

# MR RESCUE: Primary Results

(Mechanical Retrieval and REcanalization of Stroke Clots

Using Embolectomy)



Funded by NIH-NINDS UCLA SPOTRIAS Grant: P50 NS044378

Clinical Trials.gov Number NCT00389467

FDA IDE Number: G050077

# MR RESCUE Investigators



# Additional Acknowledgements

- **Data Safety and Monitoring Board**
  - Colin Derdeyn, MD – Chair; Washington University, St. Louis, MI
  - Kyra Becker, MD; University of Washington, Seattle, WA
  - Scott Hamilton, MD; Stanford University, Palo Alto, CA
  - Larry Brass, MD (deceased); Yale University, New Haven, CT
- **Medical Monitor**
  - Gene Sung, MD; University of Southern California, Los Angeles, CA
- **Catheter Angiography Core Laboratory**
  - Reza Jahan, MD; David S. Liebeskind, MD
- **Neuroimaging Core Laboratory**
  - Chelsea S. Kidwell, MD; Jeffry R. Alger, PhD; Timothy J. Schaewe, DSc; James Norman;
  - Laura Russell, BS; Reva Stidd, BA; Gina Norato, BS
- **NIH/NINDS**
  - Scott Janis, PhD – Program Officer
  - Claudia Moy, PhD – DSMB Liaison
- Philips Healthcare (Cleveland, OH) provided the Advanced Brain Perfusion Software employed in the CT perfusion analyses

# Study Design

Multicenter, randomized, controlled, blinded outcome trial

Target sample size = 120 patients

Acute Stroke < 8 Hours Screened



Multimodal Images Acquired; Target ICA/MCA Occlusion Shown



Randomization (stratified by pattern in real time using study specific software)



Favorable Penumbral Pattern



Non-Penumbral Pattern



Standard Care



Embolectomy



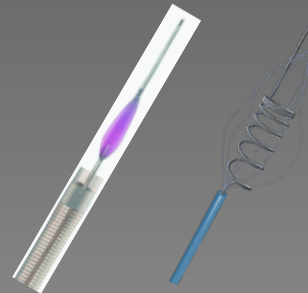
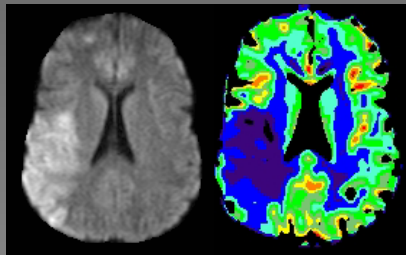
Standard Care



Embolectomy

# Background

- Main goals
  - Demonstrate that presence of substantial penumbral tissue predicts patients most likely to respond to mechanical embolectomy
  - Demonstrate that embolectomy patients have improved functional outcome compared to randomized controls



# Enrollment Criteria

## **Inclusion**

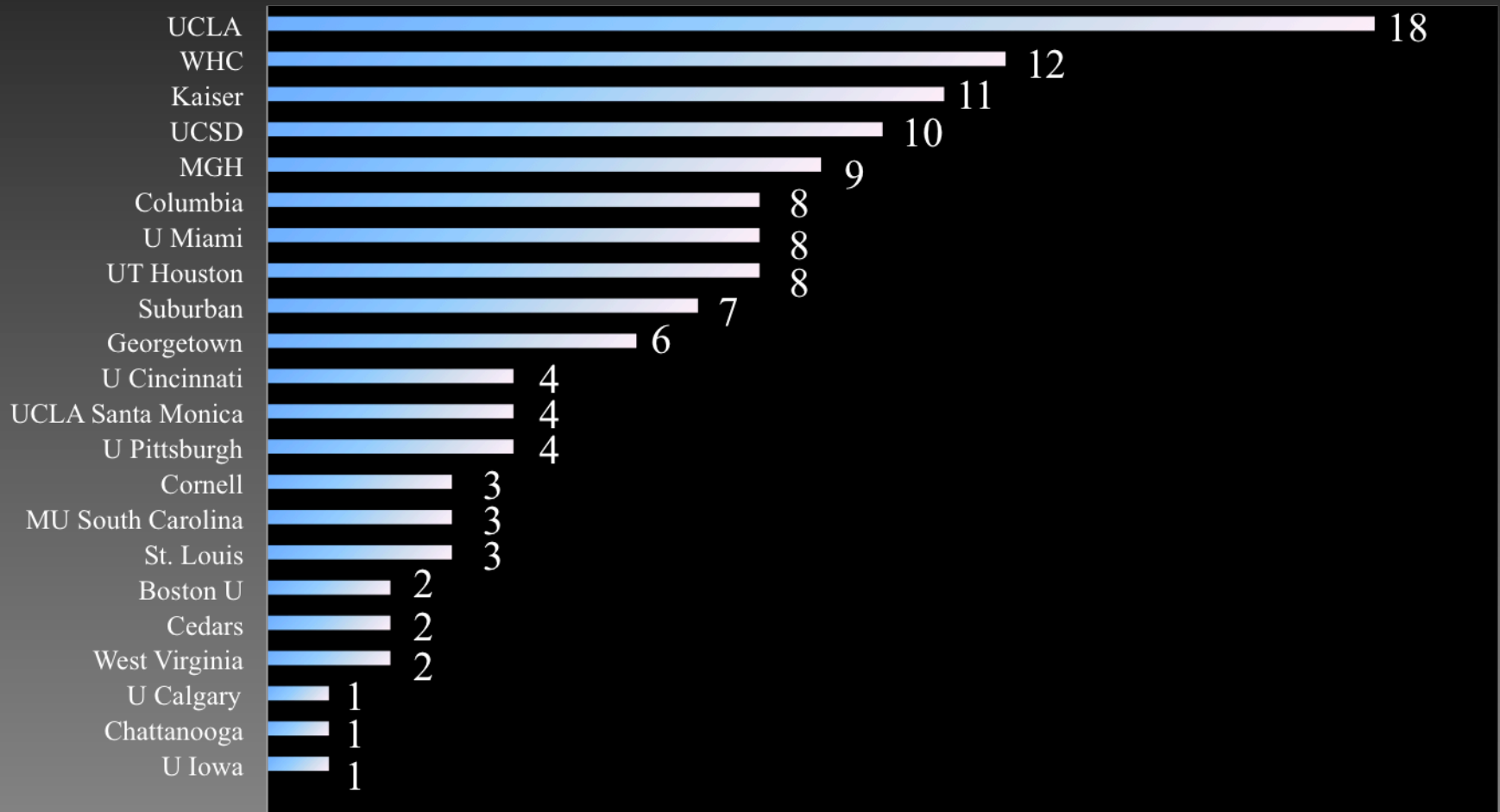
- NIHSS  $\geq 6$
- Age  $\geq 18 \leq 85$
- Procedure initiated within 8 hrs from onset
- ICA, M1 or M2 MCA occlusion
- Premorbid mRS 0-2
- Allowed: IV tPA (if vessel imaging post-tPA infusion showed persistent target occlusion)

## **Exclusion**

- NIHSS  $\geq 30$
- Acute intracranial hemorrhage
- Rapidly improving symptoms
- Pregnancy
- Refractor iodine allergy
- Proximal carotid stenosis  $> 67\%$ , or dissection
- INR  $> 3.0$  or PTT  $> 3$  x normal
- Renal failure (Cr  $> 2.0$  or GFR  $< 30$ )

# Results

127 subjects were enrolled between 2004-2011; of these, 118 were fully eligible



# Patient Characteristics

	<b>Total Cohort</b>
Age – yr	65.5 ± 14.6
Median NIHSS (IQR)	17 (13-21)
Time to enrollment – hr	5.5 ± 1.4
IV tPA administration – no. (%)	44 (37)
MRI imaging modality – no. (%)	94 (80)
Target occlusion site – no. (%)	
Internal Carotid Artery	20 (17)
M1 Middle Cerebral Artery	78 (66)
M2 Middle Cerebral Artery	20 (17)



# Safety and Embolectomy Outcomes

	Safety
Mortality	21%
Symptomatic Hemorrhage	4%

	Revascularization (Embolectomy Arm)*
<b>TICI 2a-3– no. (%)</b>	<b>67%</b>
TICI 2b-3– no. (%)	27%

\*Mean time to groin puncture = 6.2 hrs

# Primary Outcome Analyses

Primary Hypothesis: Test for Interaction between treatment assignment and penumbral pattern by shift analysis

	<b>E/Pen n=34</b>	<b>S/Pen n=34</b>	<b>E/Non-Pen n=30</b>	<b>S/Non-Pen n=20</b>	<b>p value</b>
Mean (95% CI) Day 90 mRS	3.9 (3.3-4.4)	3.4 (2.8-4.0)	4.0 (3.4-4.6)	4.4 (3.6-5.2)	0.14

➤ As such, the trial failed to demonstrate that penumbral imaging identifies patients who will differentially benefit from endovascular therapy for acute ischemic stroke

# Primary Outcome Analyses

Nested Hypothesis 1: Test for treatment efficacy in Penumbral Patients

	<b>E/Pen n=34</b>	<b>S/Pen n=34</b>	<b>p value</b>
Mean (95% CI) Day 90 mRS	3.9 (3.3-4.4)	3.4 (2.8-4.0)	0.23

Nested Hypothesis 2: Test for absence of treatment efficacy (equivalency) in Non-Penumbral Patients

	<b>E/Non-Pen n=30</b>	<b>S/Non-Pen n=20</b>	<b>p value</b>
Mean (95% CI) Day 90 mRS	4.0 (3.4-4.6)	4.4 (3.6-5.2)	0.38

Nested Hypothesis 3: Test for treatment efficacy in Embolectomy vs. Standard Care Patients

	<b>Embolectomy n=64</b>	<b>Standard Care n=54</b>	<b>p value</b>
Mean (95% CI) Day 90 mRS	3.9 (3.5-4.3)	3.9 (3.4-4.4)	0.99

# Primary Analyses: Age Adjusted

Primary Hypothesis: Test for Interaction between treatment assignment and penumbral pattern by shift analysis

	<b>E/Pen n=34</b>	<b>S/Pen n=34</b>	<b>E/Non-Pen n=30</b>	<b>S/Non-Pen n=20</b>	<b>p value</b>
Mean (95% CI) Day 90 mRS	3.8 (3.2-4.4)	3.4 (2.9-3.9)	4.3 (3.8-4.7)	4.2 (3.7-4.8)	0.30

Nested Hypothesis 1: Test for treatment efficacy in Penumbral Patients

	<b>E/Pen n=34</b>	<b>S/Pen n=34</b>	<b>p value</b>
Mean (95% CI) Day 90 mRS	3.8 (3.2-4.4)	3.4 (2.9-3.9)	0.26

Nested Hypothesis 2: Test for absence of treatment efficacy (equivalency) in Non-Penumbral

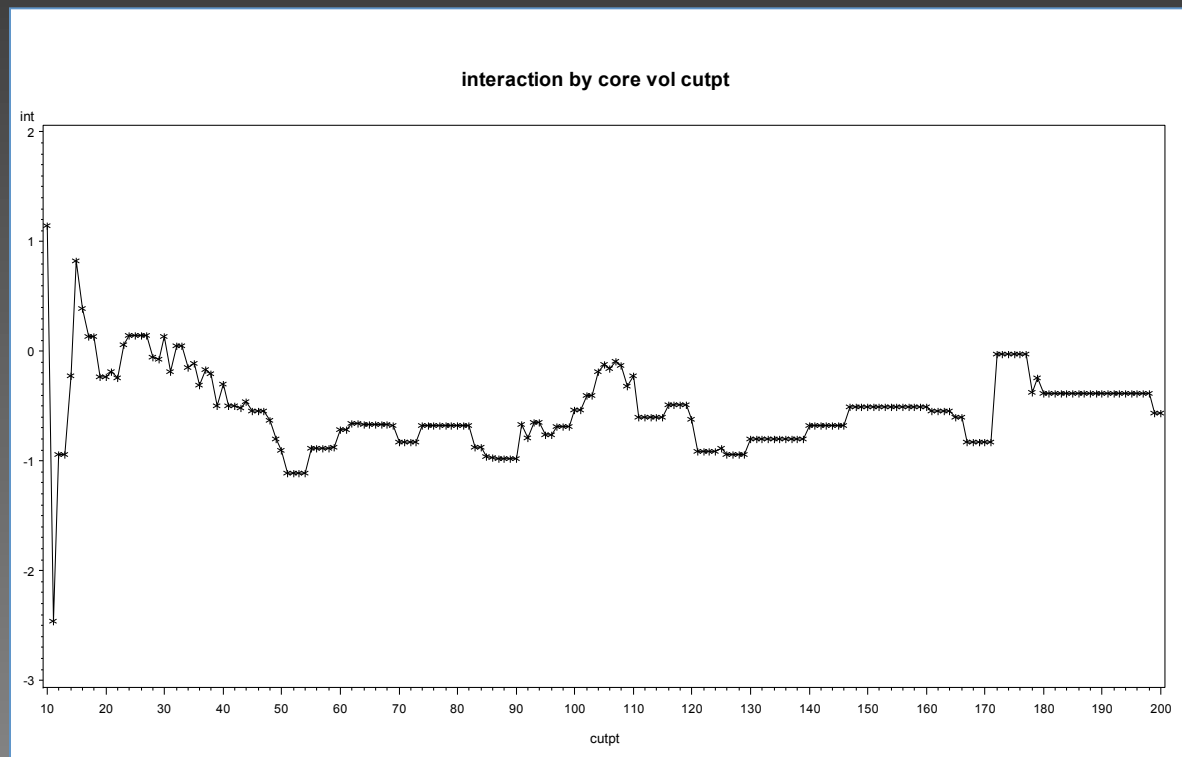
	<b>E/Non-Pen n=30</b>	<b>S/Non-Pen n=20</b>	<b>p value</b>
Mean (95% CI) Day 90 mRS	4.3 (3.8-4.7)	4.2 (3.7-4.8)	0.85

Nested Hypothesis 3: Test for treatment efficacy in Embolectomy vs. Standard Care Patients

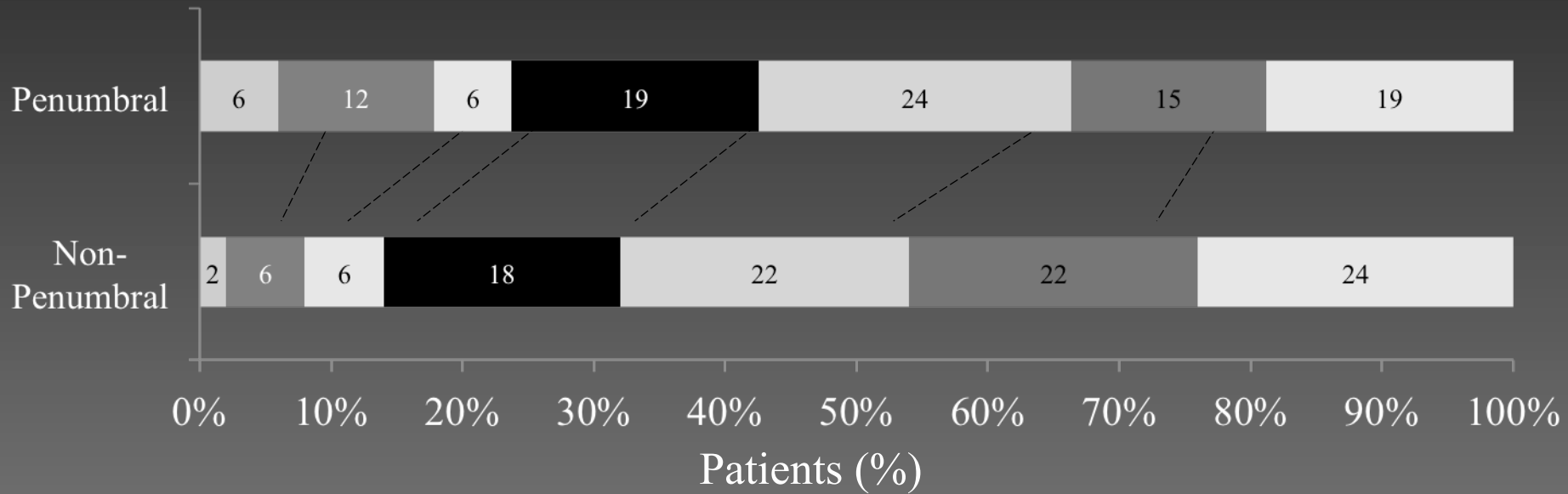
	<b>Embolectomy n=64</b>	<b>Standard Care n=54</b>	<b>p value</b>
Mean (95% CI) Day 90 mRS	4.0 (3.7-4.4)	3.8 (3.4-4.2)	0.36

# Best Cutpoint Analysis

A receiver operator curve exploratory analysis failed to identify a threshold of predicted core volume that would have yielded a significant difference in outcomes based on treatment assignment and favorable penumbral pattern.



# Day 90 mRS by Imaging Pattern



p=0.01

# Trial Limitations

- Long duration for study recruitment (8 years)
- Inclusion of only first generation devices
  - Modest recanalization rates
- Baseline imaging: single snapshot in time
- Relatively late time to enrollment (whole cohort) and time to groin puncture (for the embolectomy arm)

# Conclusions

- MR RESCUE failed to confirm the primary hypothesis of penumbral imaging selection of patients for endovascular therapy for acute ischemic stroke
- MR RESCUE failed to support the hypotheses of
  - Treatment efficacy in favorable penumbral pattern patients
  - Equivalency in non-penumbral pattern patients
  - Efficacy of embolectomy vs. standard care



# Conclusions

- Possible reasons for neutral results include
  - Low recanalization rates with 1<sup>st</sup> generation devices
  - Introduction of two imaging modalities, which may differ in penumbral prediction
  - Potential for favorable outcomes in penumbral patients regardless of treatment (due to collateral support until spontaneous recanalization)
  - Flawed penumbral imaging selection hypothesis (as currently conceived)

# Implications and Future Directions

- MR RESCUE underscores importance of confirming hypotheses in randomized, controlled trials prior to implementing treatment approaches in clinical practice
- Further randomized, controlled trials with new generation devices are needed
  - To test the full spectrum of the penumbral imaging selection hypothesis
  - To test clinical efficacy of new generation stent-retriever devices

