

# THermoRegulation in Aneurysmal Subarachnoid Hemorrhage (THRASH)

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## **Disclosures:**

N. Badjatia

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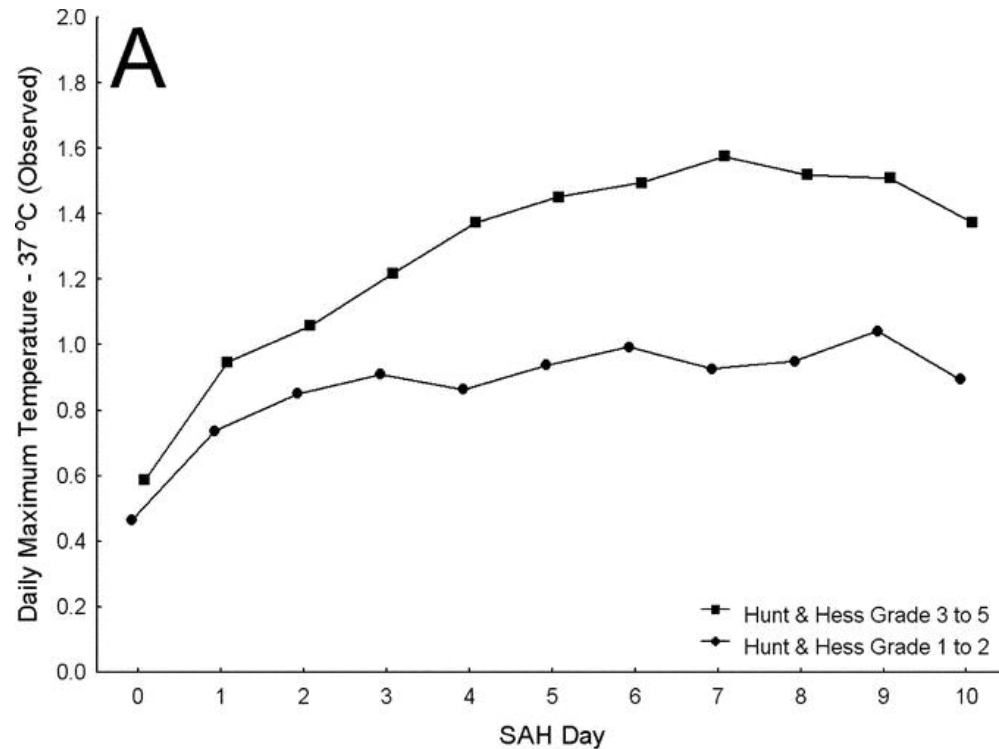
# Fever and SAH

## Experimental Evidence

- Presence of even the smallest amount of blood within the cerebrospinal fluid can induce fever

## Clinical Evidence

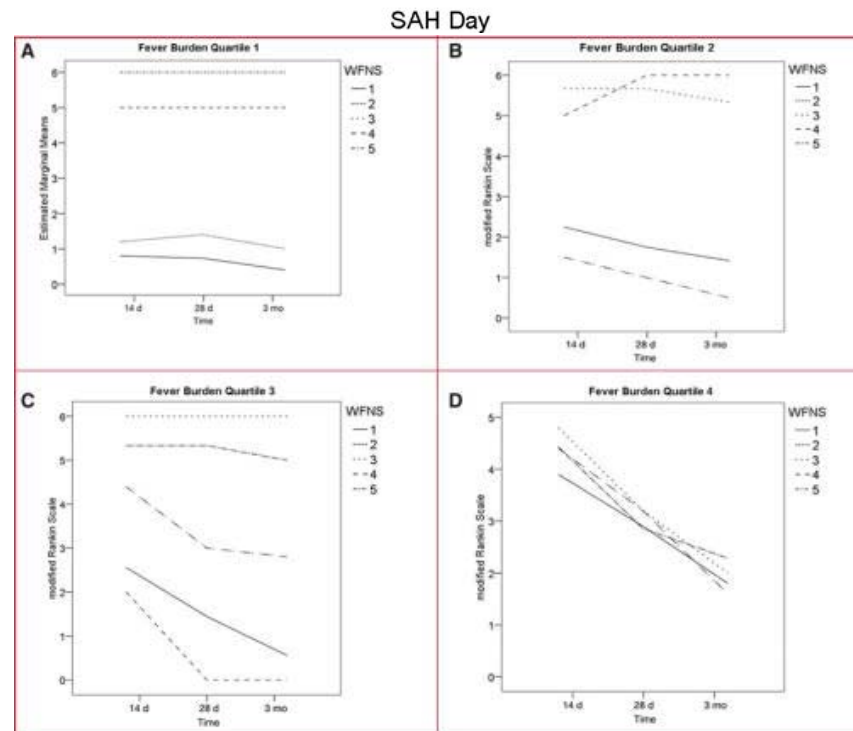
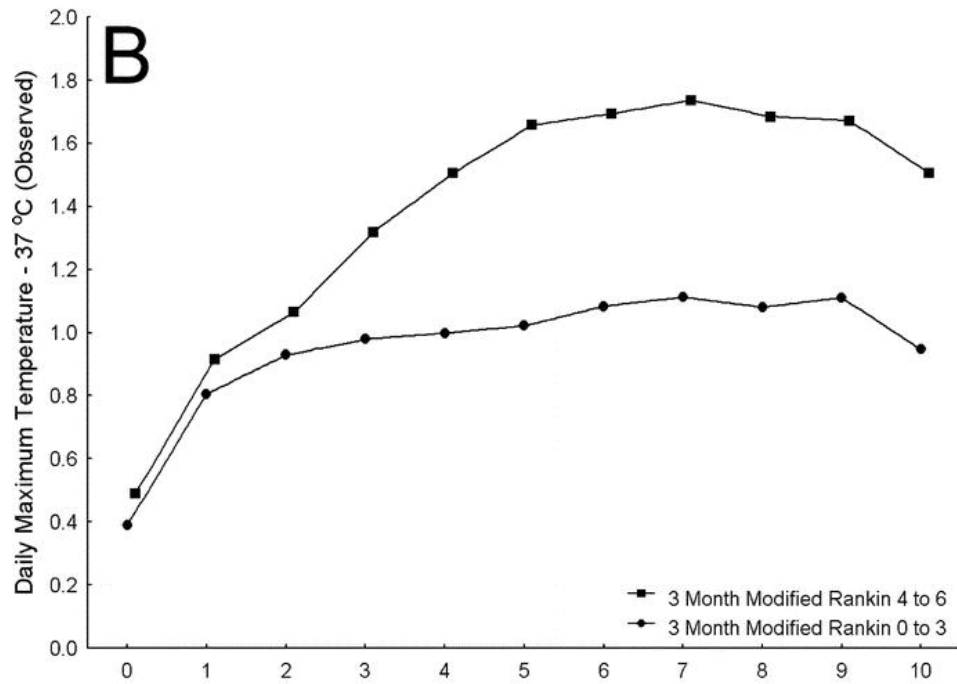
- Occurs in up to 70% of all patients in the first two weeks.
- Amount of SAH, IVH and poor initial poor grade<sup>1</sup> associated with febrile response



# Fever and Outcome

- Numerous recent studies have found that after controlling for baseline predictors of poor outcome, the **burden of fever is associated** with an increased risk of:
  - death or severe disability
  - loss of independence in instrumental activities of daily living (IADL)
  - cognitive impairment

- Oliveira-Filho J et al. Neurology. 56:1299–1304
- Fernandez A et al. Neurology. 68(13):1013-9
- Naidech AM et al. Neurosurgery. 63(2):212-7



# New surface and intravascular techniques

- Many new FDA approved devices in past few years
- ALL Target core temperature
- Target reached IN ALL via conductive heat loss in a controlled feedback mechanism
- Allow for aggressive fever control (temperature clamp) – new paradigm / treatment algorithm
  - Associated with potentially harmful effects due to shivering, heavy sedation
  - NO data to support that AFC yields improved outcomes

# THRASH Preliminary Data

## Case - Control Study

### Patient

- Patient under (AFC) after sele (CF) (HH)

### Tempe

- Hour the
- An h deriv

**Table 1. Baseline Characteristics of subarachnoid hemorrhage patients**

<b>Characteristic</b>	<b>Advanced Fever Control (n = 40)</b>	<b>Conventional Fever Control (n = 80)</b>
Age, years	58 +/- 13	58 +/-14
White (%)	20 (40)	39 (49)
Hunt Hess (%)		
1	3 (8)	6 (8)
2	1 (3)	2 (3)
3	8 (20)	16 (20)
4	14 (35)	28 (35)
5	14 (35)	28 (35)
Glasgow Coma Scale <sup>1</sup>	12 (8,14)	11 (6,13)
Aneurysm size <sup>1</sup> , mm	7 (6,10)	8 (6,11)
SAH Sum Score	18 +/- 9	19 +/- 7
Modified Fisher Score		
1	4(10)	9(11)
2	5(13)	8(10)
3	15(38)	32(40)
4	16(40)	31(39)
APACHE II	20 +/- 8	17 +/- 7
Temperature (°C)	36.7 +/- 0.4	36.7 +/- 0.2
Glucose, mg/dL	178 +/- 66	193 +/- 75

<sup>1</sup>Represents the median and 25<sup>th</sup>, 75<sup>th</sup> percentiles in parenthesis. All other continuous variables represented as mean +/- SD. No differences were found between the two groups (P > 0.1).

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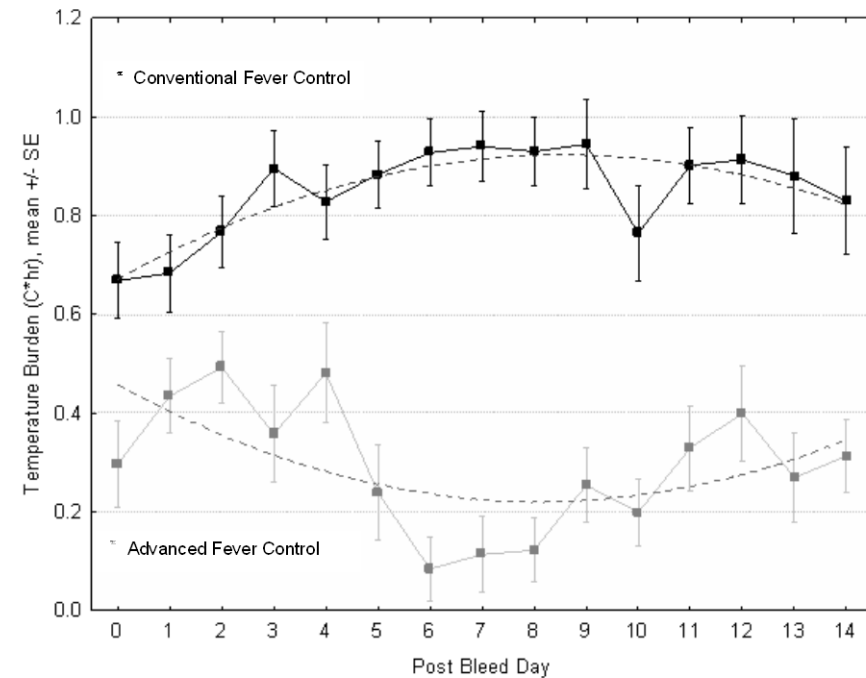
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# Preliminary Data: Temperature Burden

- Mean admission Temperature  
AFC:  $36.7 \pm 1.4$  °C v.  
CFC:  $36.7 \pm 1.5$  °C
- AFC begun on median post bleed day 3 (range: 0 – 6) and continued for 7 days (range: 1 – 13)
- The average daily temperature burden for the first two weeks
  - AFC  $0.2 \pm 0.6$  C\*hr
  - CFC  $0.9 \pm 0.5$  C\*hr ( $P < 0.001$ )
- Daily temperature burden lower in AFC patients (GEE analysis,  $P < 0.001$ )

Figure 1. Average (+/- SE) Temperature Burden for advanced fever control and conventional fever control patients



Average daily temperature burden (C\*hr) between two fever control groups. Dashed line represents the fitted polynomial line for the mean of each group.



# Preliminary Data:

## Adverse Effects of AFC

- Hyperglycemia (>200 mg/dL) most common complication
- Higher rate of arrhythmia
  - Not hemodynamically significant
  - Related to shivering
- Patients undergoing AFC were more likely to require
  - mechanical ventilation (98% v. 89%, P = 0.1)
  - intravenous sedation (100% v. 71%, P < 0.001)

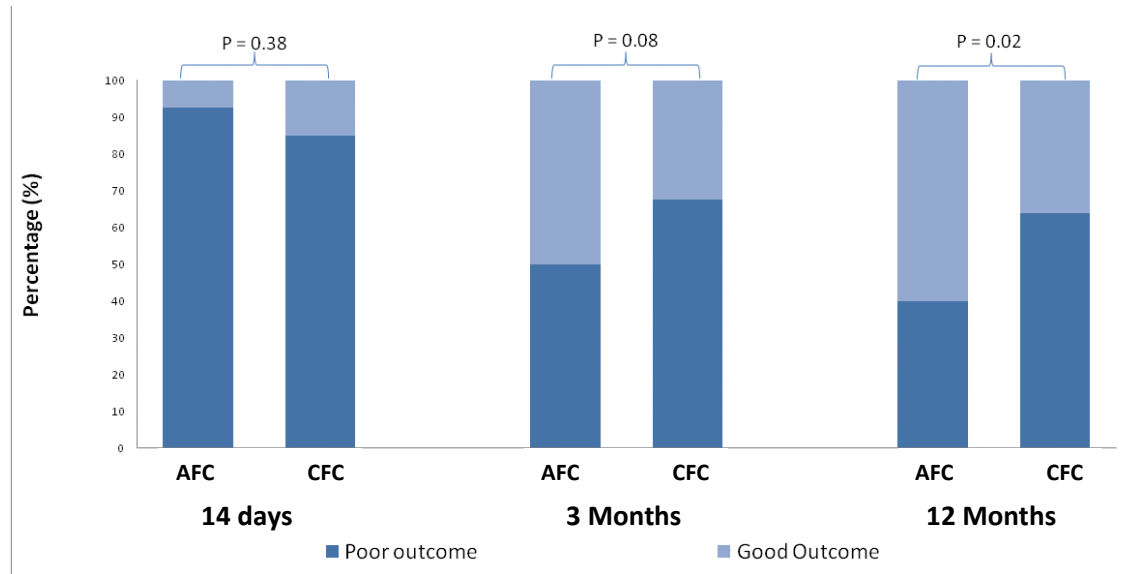
Table 2. Complications with therapeutic normothermia (advanced fever control) as compared to conventional fever control after subarachnoid hemorrhage

Complications	Advanced Fever Control (n = 40)	Conventional Fever Control (n = 80)	P value
<b>Medical</b>			
Hyperglycemia	38(95)	52(65)	<0.01
Anemia	23(58)	50(63)	0.7
Renal Failure	2 (5)	6(8)	0.7
Arrhythmia	17(43)	16(20)	0.02
Pulmonary edema	18(45)	30(38)	0.6
Congestive heart failure	8(20)	15(19)	1.0
Myocardial infarct	2 (5)	9(11)	0.3
<b>Infectious</b>			
Pneumonia	23(58)	41(51)	0.8
Urinary Tract Infection	8(20)	15(19)	0.9
Blood stream Infection			
Meningitis	7(18)	13(16)	0.9
<b>Neurologic</b>			
Symptomatic vasospasm	14(35)	25(31)	1.0
Cerebral infarction	10(25)	17(21)	0.6



# Preliminary Data: Outcome

- Longer ICU stay  
19 +/- 7 v. 14 +/- 8 days
- A higher proportion  
of tracheostomy  
60 % v. 41%



- AFC associated with lower likelihood of poor outcome ( $mRS_{\geq 4}$ ) at 12 months in after adjusting for admission Hunt Hess score, age, pneumonia, arrhythmia, and anemia



# THRASH

## Trial Design

- A two part PRCT comparing two fever control approaches for the first 14 days after SAH

### PART A: PHASE II Feasibility/Safety

- Reduction in Temperature burden
- Acceptable rate of adverse events
  - Shivering
  - Infections

### PART B: PHASE III Outcomes

- Improvement in LOC (GCS, Four Score)
- Global functional and cognitive recovery at 12 months
  - mRS, IADLs, TICS, SIP

## Treatment Protocols

### Aggressive Fever Control (AFC)

- Goal is to clamp temperature at normothermic levels for two weeks
- Aggressive shiver control
- Adequate infection surveillance

### Conventional Fever Control (CFC)

- Goal is to treat fevers as they arise with escalating therapies
  - Acetaminophen
  - Surface cooling blanket (Blanketrol, Cincinnati Sub-Zero)
- Adequate infection surveillance



# THRASH:

## Inclusion/Exclusion Criteria

### Inclusion:

1. Males and females aged 18 to 75 years (inclusive)
2. Aneurysmal repair completed within 72 hours of ictus
3. Patients with a ruptured saccular aneurysm, confirmed by angiography (digital subtraction angiography (DSA) or computed tomography angiography (CTA))
4. Hunt Hess grade 3 – 5 after resuscitation (placement of external ventricular drain or ICP monitor)
5. Women of childbearing potential must have a negative serum pregnancy test
6. Written informed consent to participate in the study must be obtained from the patient or a legal representative

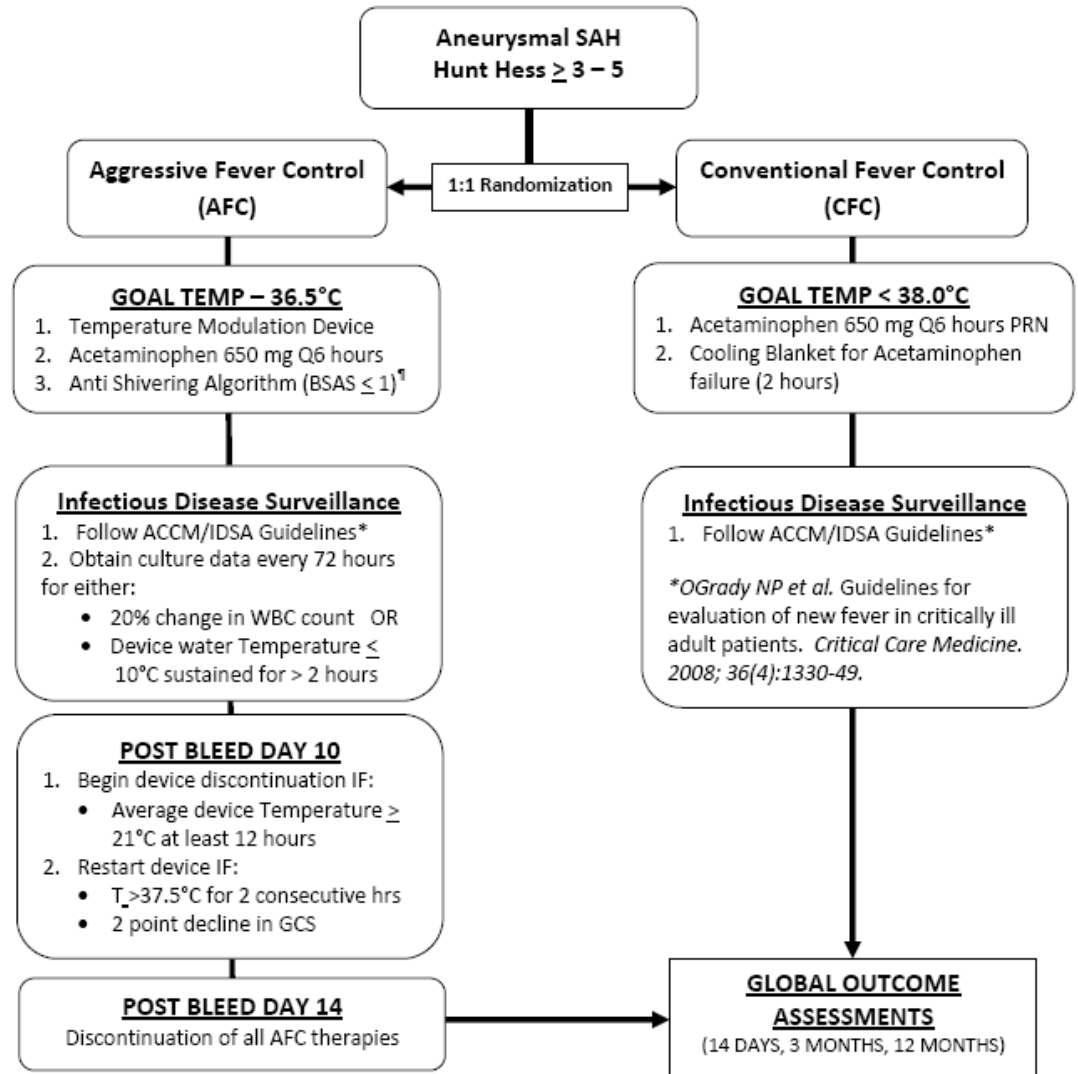
### Exclusion:

1. SAH due to causes other than a saccular aneurysm (e.g., trauma or rupture of fusiform or mycotic aneurysms).
2. Unlikely to survive one week (imminent brain death or withdrawal of care)
3. Patients for whom it is known, at time of screening, that certain follow-up protocol-mandated follow up assessments will not be feasible.
4. Requiring 2 or more vasopressors to maintain MAP > 60 at time of enrollment
5. Unable to undergo advanced fever control (severe PVD, BSA > 2.1)
6. Renal failure (assessed by  $Cl_{Cr}$ )
7. Allergy to acetaminophen, meperidine, buspirone



# Study Protocol

- Subjects randomized to one type of fever control approach after clip/coil (1:1 randomization)
- Analysis of treatment approach
  - Some ( $\leq 10\%$ ) will not have a fever
  - Some AFC subjects will fail due to shivering



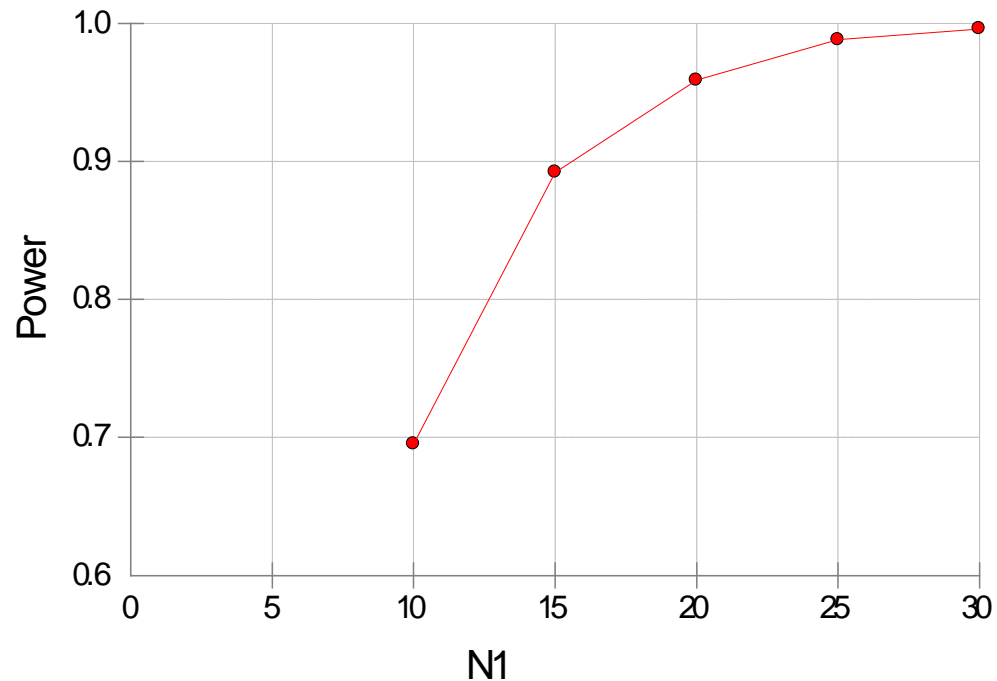
# Sample Size/Power Calculation: Temperature Burden and Adverse Effects

## Temperature Burden

- 30 total patients (15 AFC: 15 CFC) needed to detect a difference of 0.7 C\*hr between two groups<sup>1</sup>

## Adverse Effects (ID complications)

- Previous randomized studies of AFC found no difference in the rate of patients developing ID complications
- We (DSMB) plan to perform an interim analysis (N = 100; 50 AFC: 50 CFC) of ID complication rates prior to continuing enrollment

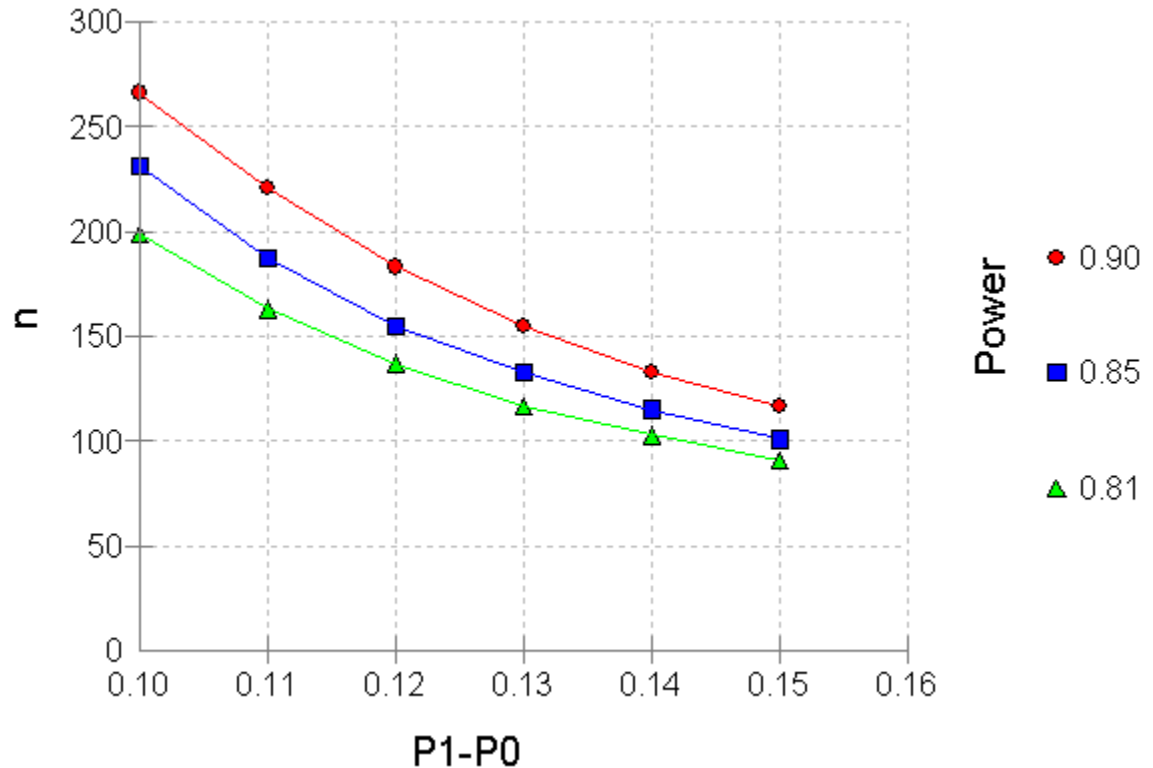


<sup>1</sup>achieves 89% power with a significance level (alpha) of 0.05 using a two-sided Mann-Whitney test assuming that the actual distribution is logistic



# Sample Size/Power Calculation: Clinical Outcome

- Sample size of 266 (133:133) needed to demonstrate an absolute 10% increase in the proportion of good outcome at 12 months with AFC<sup>1</sup>
- Assuming attrition, lost to follow up, plan to enroll 350 subjects (175:175)



<sup>1</sup>achieves 90% power using a two-sided binomial test. The target significance level is 0.05. The actual significance level achieved by this test is 0.0424.



# TIMELINE

## FALL/WINTER 2009 – 2010

- Discuss plan with the NIH/NINDS
- Invite centers to participate

## SPRING/SUMMER 2010

- Apply for independent funding (R01) from NIH/NINDS

