UC Health | UC Neuroscience Institute

UNIVERSITY OF Cincinnati

FVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time (FASTEST) Trial

Joseph P. Broderick, MD

James Grotta, MD

Jordan Elm, PhD

Background

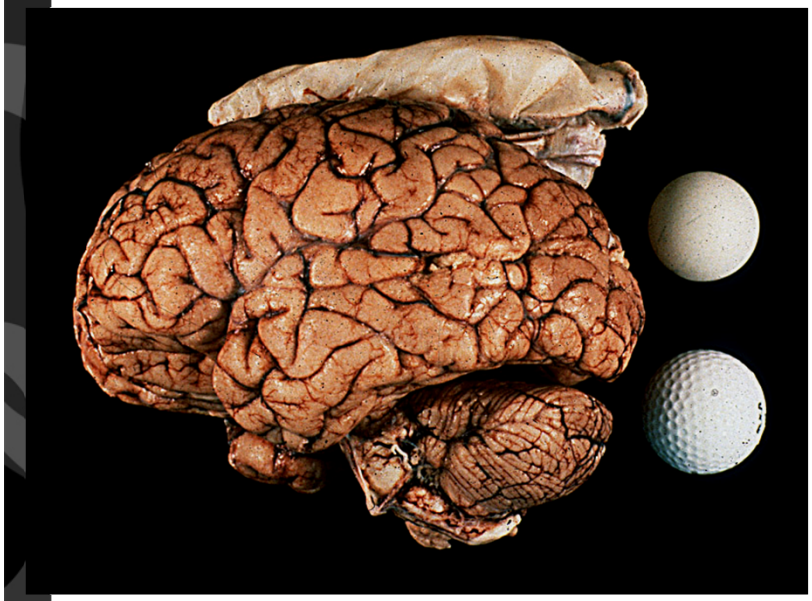
- Intracerebral hemorrhage (ICH) accounts for more than 10% of the estimated 17 million strokes worldwide each year or about 1,700,000 cases per year.
- Mortality of more than 40% and only 20% of survivors are functionally independent at 6 months
- There is no scientifically proven effective treatment for ICH.

Background

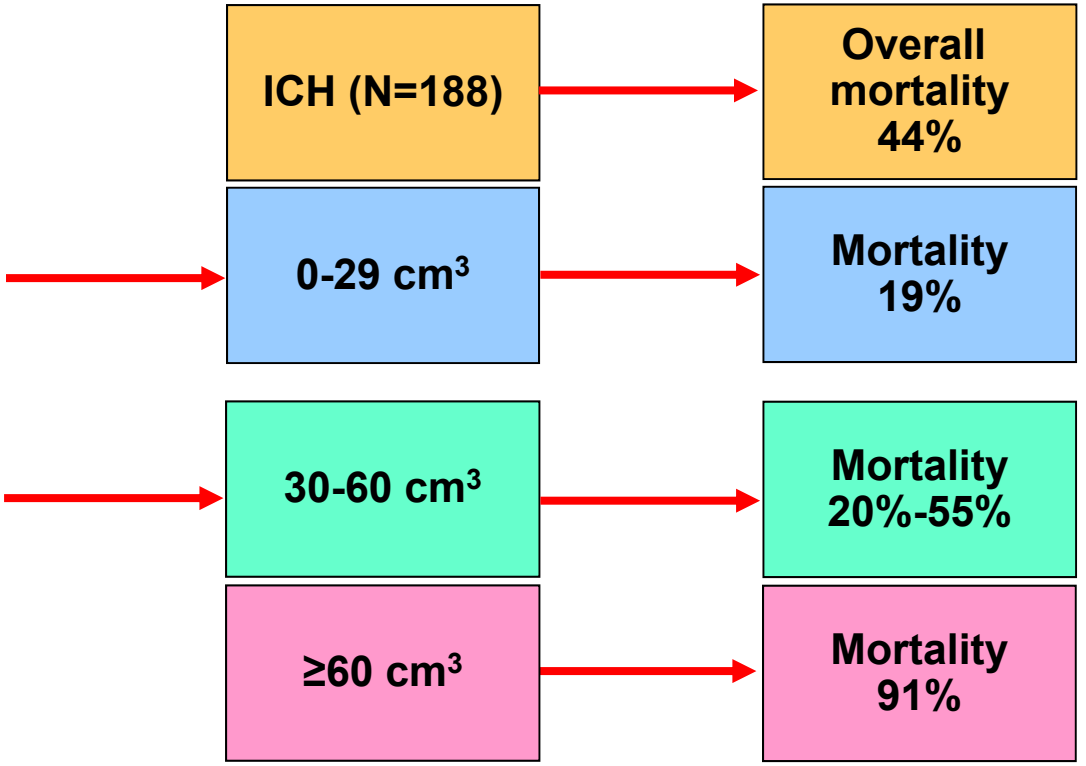
- The baseline factors associated with ICH mortality and functional outcome are volume of ICH, volume of intraventricular hemorrhage (IVH), growth of ICH during first hours of onset, age, Glasgow Coma Scale (GCS), and infratentorial location.
- Of these, only growth of ICH and the resulting volumes of ICH and IVH are biologically modifiable.

SIZE MATTERS!

Small Increases in ICH Volume Cause Significant Increase in Mortality



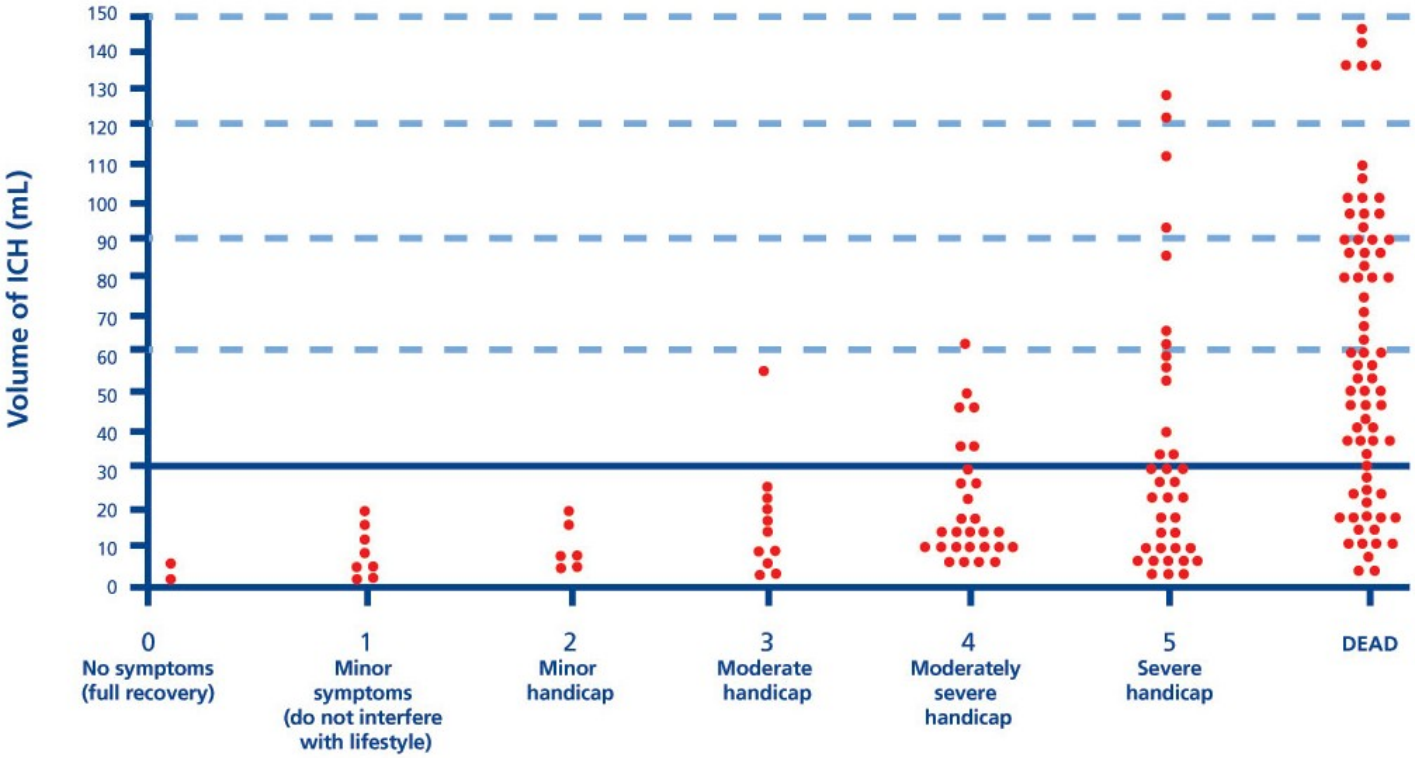
Ping-pong ball vs Golf ball
28.0 mL 40.8 ml



Only 1 of 71 patients with ICH volume ≥30 cm^3 functioned independently at 30 days (Oxford Handicap Score ≤3)

(Broderick, *Stroke*. 1993;24:987-993)

30-day outcomes for 162 patients with intracerebral hemorrhages (ICH) (Oxford Handicap Scale)



Good recovery with volume >30 mL does not occur

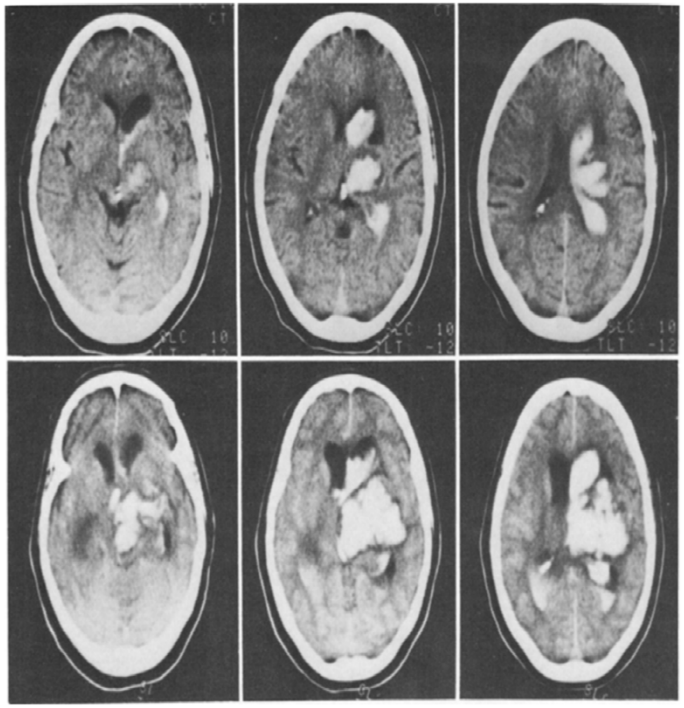


FIG. 2. Serial computerized tomography (CT) scans in Case 3. An increase in volume of hemorrhage from 8 to 35 cc was recorded between the first CT scans *(upper)*, obtained 50 minutes after onset of symptoms, and the second CT scans *(lower)*, obtained 210 minutes after onset.

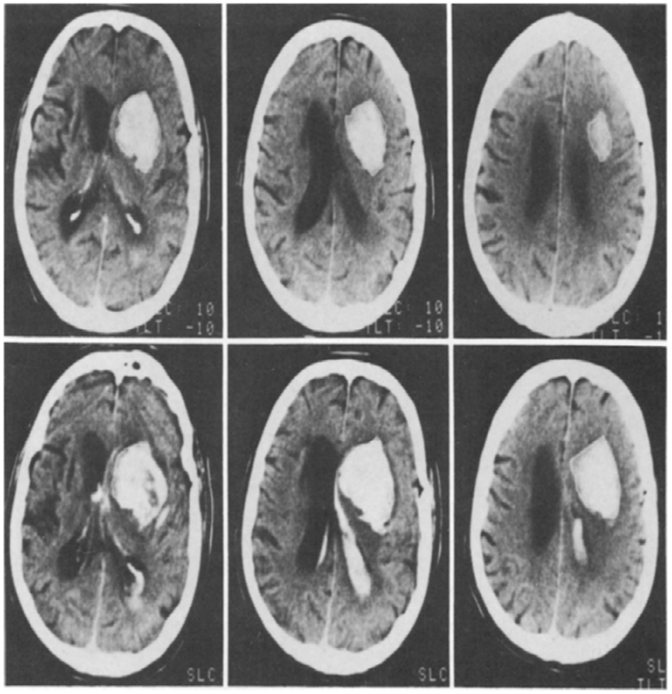


FIG. 1. Serial computerized tomography (CT) scans in Case 1. Measurement of the volume of hemorrhage revealed an increase from 25 to 44 cc between the first CT scans *(upper)*, obtained 35 minutes after onset of symptoms, and the second CT scans *(lower)*, obtained 105 minutes after onset.

TABLE 1

Times and results of serial computerized tomography (CT) scans

Case No.	Time of CT Scan*		Hemorrhage Volume (cc)		Origin of Bleed
	1st	2nd	1st CT	2nd CT	
1	35	105†	25	40	lt putamen
2	50	6000	20	36	rt putamen
3	50	210	8	35	lt thalamus
4	55	110†	71	72	lt frontal lobe
5	60	110†	14	20	rt putamen
6	75	105†	41	47	rt frontal lobe
7	95	185	17	48	rt thalamus
8	140	690	18	44	rt thalamus

* Time (in minutes) measured from onset of symptoms.
† Second CT scheduled prospectively, prior to deterioration.

J. Neurosurg: 72: 195-199, 1990

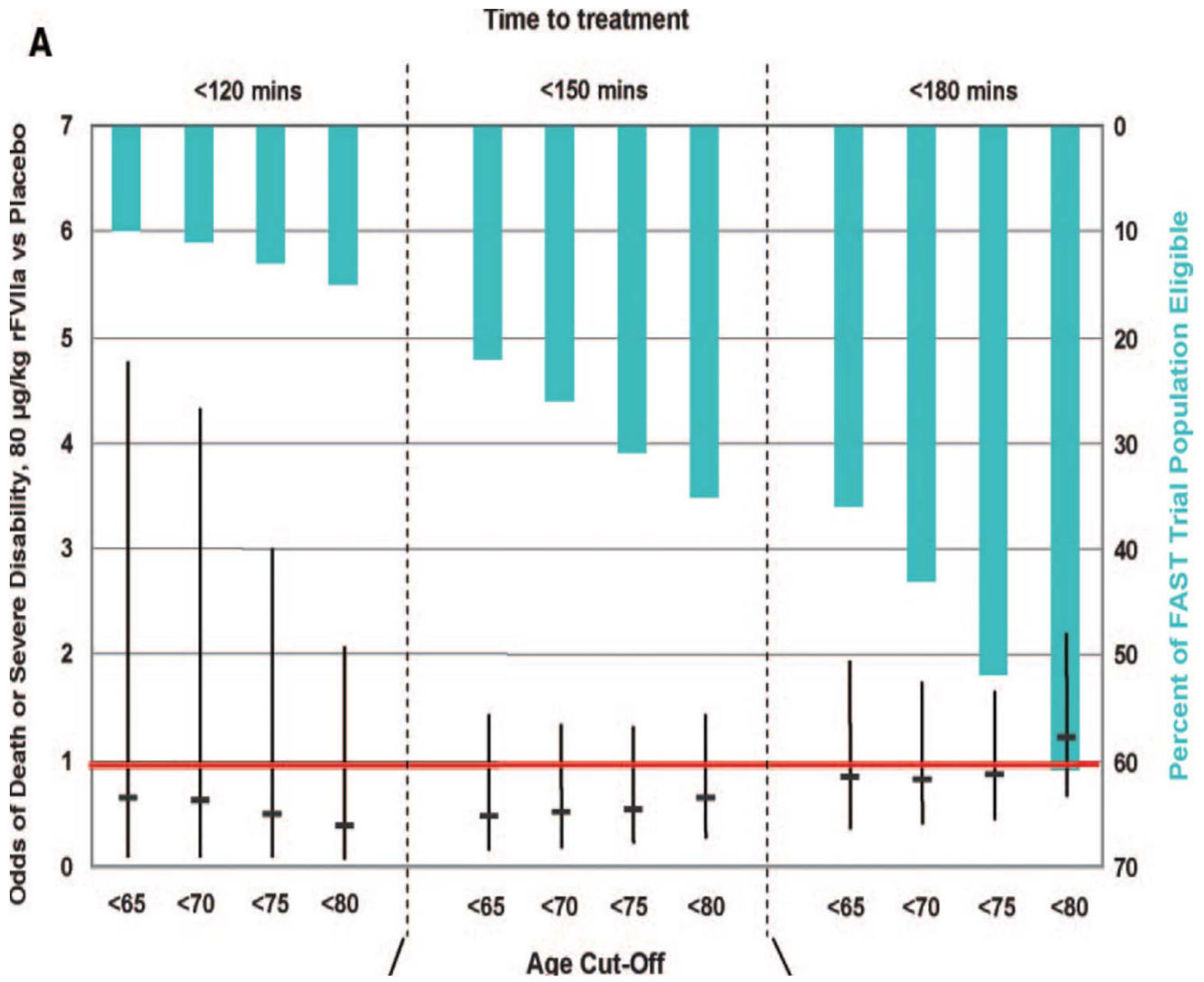
Background

- Growth of ICH has a rapid time course with the large majority of bleeding completed within 3 hours of onset.
- The only medical treatment consistently demonstrated to decrease ICH growth in spontaneous ICH is recombinant FVIIa.
  - 6 cc absolute decrease in the volume of ICH as compared to placebo within 2 hours of onset (FAST)
  - 3.5-6.3 cc within 3 hours of onset (FAST, FVIIa 2b, SPOTLIGHT/SPOT-IT)
  - 0.7 cc within 3-4 hours of onset (FAST IIb)
  - No signal beyond 4 hours

SPOTLIGHT Trial: Volume of ICH+IVH at 3 time Points

Scan	Stroke onset to CT (h)	rFVIIa ICH+IVH vol (ml) Median (IQR) n=19	Placebo ICH+IVH vol (ml) Median (IQR) n=25
Baseline CT	1.4 (1.2,2.6)	24.1 (16.0,41.4)	23.1 (11.5,53.0)
Immediate Post-dose CT	3.0 (2.5,4.3)	35.9 (20.8,63.0)	30.4 (21.4,63.1)
24 hour CT	26.6 (26.1,27.8)	31.3 (17.4,64.8)	33.3 (18.5,59.6)

Post-hoc analysis of Subgroup from FAST and Phase IIb Trials



FASTEST Subgroup from FAST

Minutes from onset to treatment in patients age ≤ 80	mRS 0-2 FVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of FVIIa at 90 days
≤ 150	42%	42%	0%
≤ 140	46%	41%	5%
≤ 130	49%	41%	9%
≤ 120*	52%	38%	14%

Minutes from onset to treatment in patients age ≤ 70	mRS 0-2 FVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of FVIIa at 90 days
≤ 150	53%	39%	14%
≤ 140	59%	38%	21%
≤ 130	62%	38%	24%
≤ 120	69%	33%	36%

*N=25 in FVIIA and 32 in placebo group

FASTEST Subgroup from Phase IIb

Minutes from onset to treatment in patients age ≤ 80	mRS 0-2 FVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of FVIIa at 90 days
≤ 150	42%	32%	10%
≤ 140	47%	30%	17%
≤ 130	50%	25%	25%
≤ 120	50%	20%	30%

Serious Adverse Events

Trial	Placebo	80µg/kg
Phase IIb FVIIa Trial	2%	4%
FAST Trial	4%	9%*
FASTEST Subgroup	6%	4%
STOP-IT/SPOTLIGHT**	3%	0%

*P = 0.04

**Within 4 days. DWI asymptomatic infarct

Primary Specific Objective

- The *objective* of the FVIIa for Acute hemorrhagic Stroke Administered at Earliest Time (FASTEST) Trial is to establish the first treatment for acute ICH within a time window and subgroup of patients that is most likely to benefit.

Design

- Randomized, double-blind controlled efficacy trial of FVIIa plus best standard therapy vs. placebo plus best standard therapy (including INTERACT 2 goal of target BP of 140 mm Hg).
- Includes subjects:
  - Baseline volume of ICH < 60 cc,
  - No or small volume of IVH (IVH score ≤ 7)
  - Age ≤ age 80
  - Treated within 120 minutes from stroke onset (goal ½ within 90 minutes).

Minimize Time to Treatment

- Mobile stroke care units
- Exemption from informed consent
- Improved Acute Stroke Treatment Processes

Mobile Stroke Units

- 13 MSUs now in U.S. At least 4 outside of US (first were in Germany).
- PRESTO organization identified ICH trial as highest priority. (Int. Journal of Stroke, 2017)
- MSUs cover 3% of all strokes already in U.S. Two thirds of stroke patients treated with tPA in Houston are treated within the first 90 minutes from onset

Intervention

- We will randomly assign patients in a 1:1 ratio to intravenous FVIIa or placebo at a dose of 80 µg/kg (maximum 8000 µg or 8 mg) and administered intravenously over 1 minute. All investigators and patients will be blinded throughout the course of the study.
- Only baseline non-contrast CT required.

Efficacy Outcomes

- The primary outcome measure is the distribution of the ordinal mRS at 90 days.
- Secondary endpoints include the utility-weighted Rankin Score, mRS of 0-2, and EQ-5D at 90 days; telephone mRS at 6 months and a year, and change in the volume of ICH and ICH +IVH between baseline CT and 24 hour CT.
- Will collect spot sign data but only if CTA done as standard of care.

Safety Outcomes

- The primary safety measures of the study will be life-threatening thromboembolic complications during the first four days after completion of study drug. A significant life threatening complication will be defined as development of: 1) acute myocardial ischemia 2) acute cerebral ischemia and 3) acute pulmonary embolism.
- Secondary safety measure for these events at 90 days.

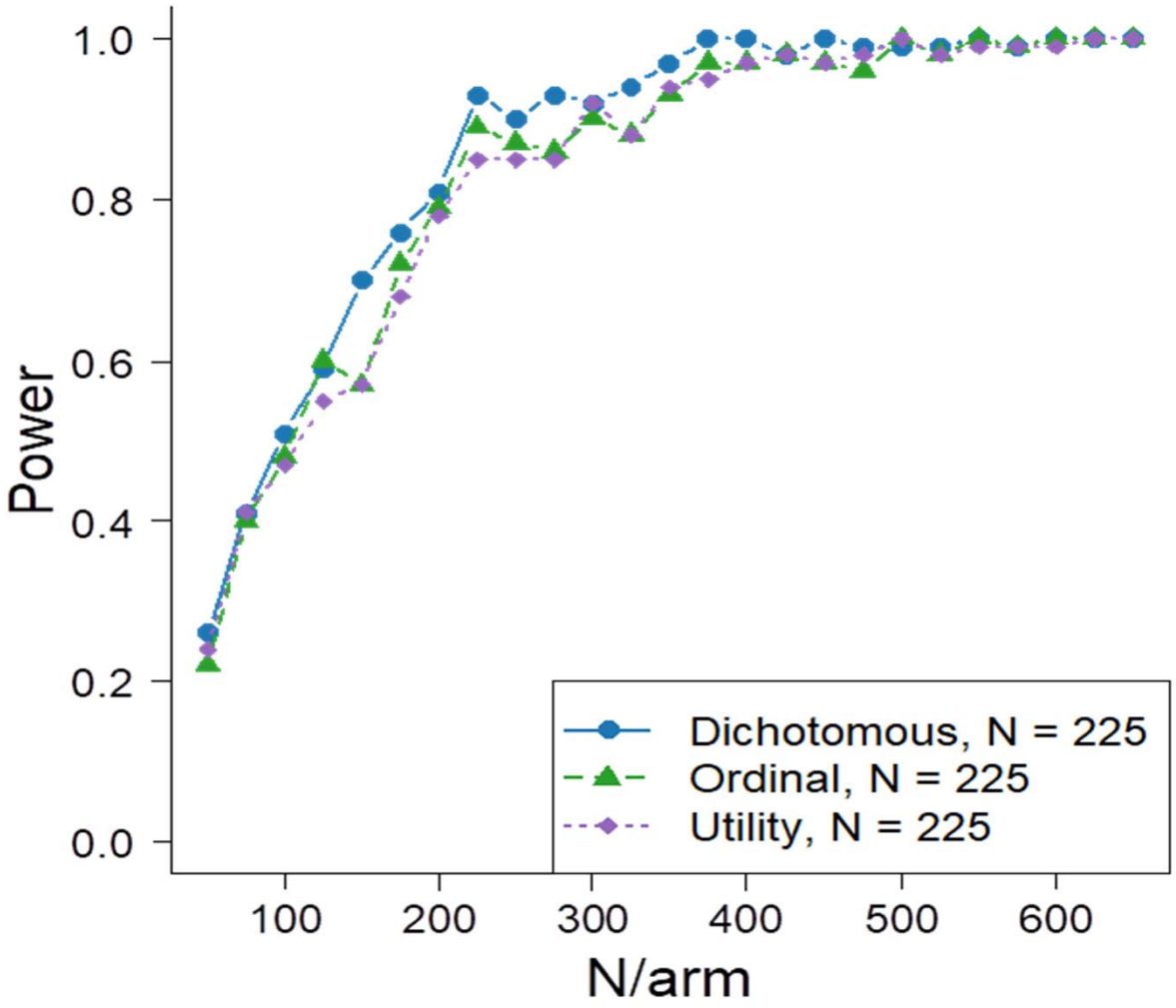
Enrollment of Study Population

- Subjects to be enrolled - 680.
- Anticipated number of trial sites – 100 hospitals (2 subjects per 100 ICHs per year at participating hospitals and 10 mobile stroke units (8 subjects per MSU per year).
- Anticipated number of subjects to be randomised/started on trial medication(s) at each trial site over 3 ½ years of recruitment – 24 subjects per mobile stroke unit and 6 subjects per hospital site.
- Country(ies) planning to participate. USA, Canada, Australia, Germany, Japan. Other European countries, Korea, and China are also possible.

Statistical Methods

- The primary analysis will be using the intent-to-treat (ITT) analysis population. We will compare the ordinal values of the 90 day mRS by treatment group via an ordinal logistic regression adjusted for age, baseline ICH volume, baseline IVH volume, and pre-stroke mRS. If the proportional odds assumption does not hold, then we will rely on a generalized ordered logit (partial proportional) model.

Sample Size Estimation



Next Steps

- Await Novo Nordisk Global final review about protocol to supply study medication
- IND to FDA for EFIC proposal

Questions?