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Clinical Study Protocol

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-II:

A Phase III Randomized Multicenter Clinical Trial of Blood Pressure Reduction for Hypertension in Acute Intracerebral Hemorrhage

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1. Abbreviations

AbESTT	Abciximab in Emergent Stroke Treatment Trial
AE	adverse event
AHA	American Heart Association
ASA	American Stroke Association
ATACH	Antihypertensive Treatment of Acute Cerebral Hemorrhage
AVM	arteriovenous malformation
BI	Barthel Index
BP	blood pressure
CBF	cerebral blood flow
CCC	Clinical Coordinating Center
CLEAR-IVH	Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage
CPP	cerebral perfusion pressure
CRA	Clinical Research Associate
CRF	case report form
CT	computed tomographic
DBP	diastolic blood pressure
DCU	Data Coordination Unit
DSMB	Data Safety Monitoring Board
EAC	External Advisory Committee
ED	emergency department
EKG	electrocardiogram
EuroQOL	European Quality of Life (Group)
EUSI	European Stroke Initiative
FDA	Food and Drug Administration
GCS	Glasgow Coma Scale
h	hour(s)
HCMC	Hennepin County Medical Center
ICH	intracerebral hemorrhage
ICP	intracranial pressure
IMS	Interventional Management of Stroke
INR	international normalized ratio
INTERACT	Intensive BP Reduction in Acute Cerebral Haemorrhage Trial
IOC	Independent Oversight Committee
IRB	Institutional Review Board
ITT	intent to treat
IV	Intravenous
IVH	Intraventricular hemorrhage
JHU	Johns Hopkins University
LAR	legally authorized representative
LTFU	lost to follow-up
m	minute(s)
MAP	mean arterial pressure
ml or mL	milliliter
MMSE	Mini-Mental State Examination

MoP	Manual of Procedures
mRS	modified Rankin Scale
MUSC	Medical University of South Carolina
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NIHSS	National Institute of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
OR	odds ratio
PHI	Protected Health Information
PI	Principal Investigator
POM	proportional odds model
PROACT	Prolyse for Acute Cerebral Thromboembolism
QC	quality control
QOL	quality of life
rCBF	regional cerebral blood flow
REB	Research Ethics Board
rFVIIa	recombinant activated factor VII
RR	relative risk
SAE	serious adverse event
SBP	systolic blood pressure
SC	Steering Committee
SDCC	Statistics and Data Coordination Center
SID	subject identification number
SOC	standard of care
STICH	Surgical Trial in Intracerebral Haemorrhage
TBI	traumatic brain injury
UMN	University of Minnesota
USP	Unites States Pharmacopeia

2. ATACH-II Protocol Synopsis

Protocol Title	Antihypertensive Treatment of Acute Cerebral Hemorrhage: A Phase III Randomized Multicenter Clinical Trial of Blood Pressure Reduction for Hypertension in Acute Intracerebral Hemorrhage
Acronym	ATACH-II
Clinical Trial Phase	Phase III
Study Sites	• UMN (Clinical Coordinating Center and Fiscal Management Office) • MUSC (Statistics and Data Coordination Center) • Approximately 100 clinical recruiting centers
Study Period	Planned enrollment period – 4 years Planned duration of the study – 5 years
Study Population	Acute ICH patients.
Primary Study Objective	To determine the therapeutic benefit of intensive SBP treatment (SBP≤140 mmHg) compared with standard SBP treatment (SBP≤180 mmHg) in reducing the proportion of patients with death and disability (mRS of 4-6) at Day 90 among subjects with ICH treated within 4.5 hours of symptom onset.
Study Design	Multicenter, randomized, concurrently-controlled, parallel arms design.
Sample Size	Approximately1,280 subjects randomized in a 1:1 ratio to either intensive SBP treatment or standard SBP treatment.
Inclusion Criteria	• Age 18 years or older. • IV Nicardipine can be initiated within 4.5 hours of symptom onset • Patient can be randomized within 4.5 hours of symptom onset • Clinical signs consistent with the diagnosis of stroke, including impairment of language, motor function, cognition, and/or gaze, vision, or neglect. • Total GCS score (aggregate of verbal, eye, and motor response scores) of 5 or greater at time of ED arrival. • INR value < 1.5 • CT scan demonstrates intraparenchymal hematoma with manual hematoma volume measurement <60 cc.

- For subjects randomized prior to IV antihypertensive administration: SBP greater than 180 mmHg* prior to IV antihypertensive treatment (this includes pre-hospital treatment) AND WITHOUT spontaneous SBP reduction to below 180 mmHg at the time of randomization.

  OR

  For subjects randomized after IV antihypertensive administration: SBP greater than 180 mmHg prior to IV antihypertensive treatment (this includes pre-hospital treatment) AND WITHOUT SBP reduction to below 140 mmHg at the time of randomization.
- Informed consent obtained by subject, legally authorized representative, or next of kin.

* Note: Patients with SBP < 180 should be monitored for 4.5 hours from symptom onset as their SBP may rise to eligible levels before the eligibility window closes.

Exclusion Criteria

- ICH is due to previously known neoplasms, AVM, or aneurysms.
- Intracerebral hematoma considered to be related to trauma.
- ICH located in infratentorial regions such as pons or cerebellum.
- IVH associated with intraparenchymal hemorrhage and blood completely fills one lateral ventricle or more than half of both ventricles.
- Patient to receive immediate surgical evacuation.
- Current pregnancy, or parturition within previous 30 days, or active lactation.

- Use of dabigatran within the last 48 hours
- A platelet count less than 50,000/mm^3.
- Known sensitivity to nicardipine.
- Pre-morbid disability requiring assistance in ambulation or activities of daily living.
- Subject's living will precludes aggressive ICU management.
- Subject is currently participating in another interventional clinical trial

Study Hypothesis

Intensive SBP reduction using IV nicardipine with treatment initiated within 4.5 hours of ICH onset and continued for the next 24 hours reduces the likelihood of death or disability at Day 90 (defined by mRS of 4-6) by absolute 10% (or relative 17%) or greater compared with standard SBP reduction using IV nicardipine.

Primary Outcome Measure	Death or disability (defined by mRS of 4 to 6) at 90 days from randomization.
Statistical Analysis for Primary Outcome Measure	The primary efficacy outcome is analyzed using the generalized linear model with log link function adjusting for age, baseline GCS, and presence/absence of IVH. It is tested at the two-sided alpha level of 0.05.

3. Trial ADMINISTRATIVE organization

3.1 Clinical Coordinating Center (CCC)

The CCC provides overall scientific and project coordination and fiscal and site management of the ATACH-II Trial. The CCC is comprised of the ATACH-II Trial's Principal Investigator, Co-Investigator, Project Manager, Central Image Analyst, Financial Manager, Clinical Research Associates, Image Analysis Assistant, Research Assistant, and Administrative Assistant.

3.2 Statistics and Data Coordination Center (SDCC)

The SDCC work is conducted by the Data Coordination Unit (DCU) which is housed in the Division of Biostatistics and Epidemiology (DBE) at MUSC in Charleston, SC. The SDCC manages both the data management and statistical aspects of the trial. It also oversees the collection and maintenance of necessary regulatory documents from the clinical sites. Data management activities include CRF development, database development (including validation and maintenance), monitoring data collection activities at the sites, providing user support and training, and cleaning the data to ensure a complete and accurate final data set. Statistical activities include statistical design of the study, analysis of study data, validation and implementation of the randomization scheme, and generation and distribution of progress reports and DSMB reports in coordination with the CCC. The SDCC team consists of the PI (blinded statistician), unblinded statistician, Data Manager, Data Manager Assistant, Regulatory Documents Manager, Database Programmers, Statistical Programmer, and Administrative Assistant.

3.3 Steering Committee (SC)

The SC consists of the PI, co-PI, Project Manager, and Fiscal Manager of the CCC; the PI, Data Manager, and the Regulatory Documents Manager of the SDCC at MUSC; the NINDS Project Scientist; and a site PI. The SC is responsible for managing the day-to-day activities of the study. The SC meets via weekly teleconference and quarterly in person. The SC designs the overall plan of work for the trial, oversees the maintenance of the study protocol, informed consent template and CRFs, monitors study progress, troubleshoots problems in project implementation, generates project progress reports, and oversees compilation of final study results.

3.4 Independent Oversight Committee (IOC)

The IOC reports to the SC and its responsibilities include assessment of site investigator performance (through examination of data from the first three subjects at each site) and SAE review and adjudication over the duration of the trial. The SC and IOC meet quarterly via teleconference. The agenda for these meetings includes any concerns regarding the aggregate data at particular sites related to the principles and intensity of the overall care, and aggregation of AEs at particular sites. The IOC may recommend that the SC contact individual sites, as needed, to discuss potential remedial measures. The IOC also may make recommendations for protocol changes to the SC.

3.5 External Advisory Committee (EAC)

The EAC consultants with expertise in clinical research, particularly in clinical trials of acute stroke treatment, provide independent advice to the SC as needed. The SC and the EAC meet annually via teleconference to discuss overall study progress and issues that arise.

3.6 Data and Safety Monitoring Board (DSMB)

The DSMB is appointed by the NINDS and managed by the NINDS DSMB Liaison. Its overarching responsibility is the oversight of safety of Trial participants. They review reports on SAEs, request additional data/information as necessary, and must be cognizant of external new information regarding the safety of treatment. Upon review of periodic data, they provide recommendations to the NINDS regarding continuation of the Trial. The DSMB generally meets biannually.

3.7 Clinical Sites

Each clinical site must have a PI with expertise/certification in acute stroke care as well as clinical research, one clinician certified in NIHSS, at least one blinded medical professional certified in NIHSS and mRS assessment, and a research coordinator(s) responsible for subject recruitment and timely data entry into the study database. The site PI responsibilities include: evaluation and treatment of research subjects; ensuring signed informed consent is obtained from potential subjects; supervision and training of the study team at his/her site; providing in-service to ED staff; timely review of all clinical and laboratory data; reading and interpretation of clinical procedures; ensuring proper adverse event reporting; ensuring proper study product management; meeting with study monitors when needed; verifying subject data; and ensuring proper retention of study and regulatory documents at the site. Each clinical site should have an acute stroke treatment program with a solid track record of clinical research related to stroke.

4. STUDY OBJECTIVES

4.1 Primary Objective

The primary aim is to determine the therapeutic benefit of the intensive SBP treatment (SBP≤140 mmHg) compared with standard SBP treatment (SBP≤180 mmHg) in reducing the proportion of patients with death and disability (mRS of 4-6) at 90 days post-randomization among subjects with ICH whose treatment is initiated within 4.5 hours of symptom onset.

4.2 Secondary Objectives

- Evaluate the therapeutic benefit of intensive SBP treatment relative to standard SBP treatment in improving subjects' quality of life at 90 days post-randomization as measured by EuroQOL.

- Evaluate the therapeutic benefit of the intensive SBP treatment relative to standard SBP treatment in reducing the proportion of patients with hematoma expansion (defined as increase from baseline hematoma volume of ≥33%) at 24 hours post-randomization using serial CT scans.

- Assess safety of intensive SBP treatment relative to standard SBP treatment by comparing the proportion of subjects between the two groups with treatment-related SAEs within 72 hours post-randomization.

5. Background

5.1 Significance of the ATACH-II Trial

In 1999 and 2007, the Special Writing Group of the AHA Stroke Council[1, 2], concluded that treatment of acute hypertension in patients with ICH can be supported only by anecdotal case series (level V or Class IIa evidence) and could be considered only a Grade C recommendation. There is strong need for a randomized trial, for the following reasons:

1. It is estimated that 37,000-52,400 people in the U.S. have ICH every year[3]. The high rate of death and disability, and the high financial burden associated with this illness mandates critical analysis of treatments with therapeutic potential.
2. Elevated BP is observed in 46%-75% of patients with ICH depending on the population studied and the definition of hypertension used[4] (approximately 16,650-35,000 patients/year in U.S.)**.**
3. A variety of BP management protocols are in place for treatment of acute hypertension in ICH but lack appropriate evidence. Some strategies may have deleterious effects and need to be modified.
4. Hematoma expansion is a common and important cause of poor outcome. Elevated BP may predispose to hematoma expansion. Since expansion occurs during a time frame when therapeutic intervention is feasible, the opportunity exists to reduce BP, which ultimately may reduce hematoma expansion and subsequent death and disability.
5. Experimental and small uncontrolled clinical studies suggest that reduction of elevated BP in ICH may be tolerated and feasible.

The report from the December 2003 NINDS Workshop on priorities for clinical research in ICH[5] recommended clinical trials for evaluation of BP management in acute ICH as a leading priority.

5.2 Acute hypertension in subjects with ICH- Theoretical considerations

Treatment of acute hypertension in subjects with ICH is highly controversial[6]. Several animal studies have suggested the presence of transient reduction in rCBF in both regions surrounding and distant from the hematoma, presumably induced by compression of adjacent microvasculature[7-10]. It is further hypothesized that autoregulation is impaired in the peri-hematoma region due to local ischemia and acidosis[8]. Therefore, reduction in systemic BP theoretically may further impair blood flow in regions with reduced rCBF and provoke ischemia. In addition, reduction of systemic BP may lead to autoregulatory vasodilation of cerebral vessels and adversely affect ICP. Conversely, there is strong evidence suggesting that one-third of the subjects presenting with spontaneous intracerebral hematoma continue to demonstrate lesion expansion in the next few hours after the initial ictus, which can lead to clinical deterioration and death[11-14]. Persistently elevated BP may predispose the subject to hematoma expansion[11-14]. Furthermore, because of chronic hypertension, large proportions of subjects with ICH have cardiac hypertrophy and diastolic dysfunction and decompensate in the presence of high after-load supporting BP reduction therapy[15, 16].

5.3 Prognostic significance of acute hypertension in ICH

Acute hypertension in patients with ICH is associated with increased risk of death, dependency, and physical disability[3,17,18,19]. Quantitative estimates from two systematic reviews of the relevant studies[20,21] suggest that initial SBP>140-150 mmHg more than doubles the risk of subsequent death[20 21]. Furthermore, analyses of four studies provide estimates of the impact of a 10 mmHg higher level of SBP on early case fatality in ICH, as summarized in Table 1.

Table 1: Event rates and relative risk associated with a 10mmHg elevation in SBP

Author	Year of publication	Number of patients	Overall deaths (% of patients)	RR of 10 mmHg higher SBP
Fogelholm et al [22]	1997	425	43% dead at 28 days	28%
Vermmos et al.[23]	2004	1121	21% dead at 1 month	10%
Okumura et al [24]	2005	1097	19% dead at 30 days	19%
Carlberg et al.[19]	1993	85	14% dead at 30 days	12%

5.4 Acute elevation in BP and its association with hematoma expansion

Previous case series have suggested that a high proportion of subjects with ICH who experience expansion of hematoma have poorly controlled elevation of BP. Chen et al[14] reported persistent hypertension in 6 of 8 subjects prior to extension of the hemorrhage. A SBP of 195 mmHg or greater was recorded during the first 6 hours in five of the six subjects with hematoma expansion reported by Broderick et al.[13] Kazui et al.[12] identified factors associated with hematoma expansion in 186 subjects with ICH who had undergone an initial CT within 24 hours and a second scan within 120 hours of symptom onset. The analysis demonstrated that the following factors independently predisposed to enlargement: history of brain infarction, liver disease, and interaction of fasting plasma glucose ≥141 mg/dL, and SBP on admission ≥200 mmHg. The study concluded that subjects with high SBP (≥200 mmHg) on admission were at high risk of hematoma expansion. Maruishi et al.[25] investigated the effects of serial changes in BP in 57 subjects admitted within 6 hours of ictus whose BPs were monitored every hour from admission. Wilcoxon signed-rank analysis was used to determine the relationships between hematoma enlargement and BP. Subjects with hematoma enlargement were significantly more likely to have increased BP ($p = 0.0004$).

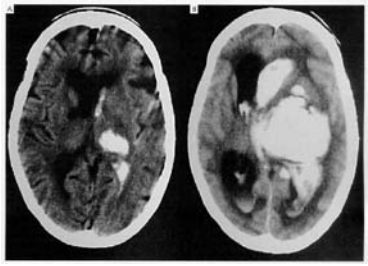


Figure 1. The first CT scan (Panel A) was obtained one hour after the patient presented and was followed by neurologic deterioration and expansion of the hematoma visible on the CT scan obtained six hours after presentation (Panel B). From: Qureshi: N Engl J Med; 344.: 2001.1450-1460[3]

5.5 Rate of hematoma expansion and its contribution to poor outcomes

Hematoma expansion occurs to a clinically significant extent in at least one-third of subjects presenting within 24 hours of symptom onset (see Figure 1)[11-14].

Brott et al.[11] performed a prospective observational study of ICH subjects within 3h of onset. Subjects had a neurological evaluation and CT scan performed at baseline, 1h after baseline, and 20h after baseline. Substantial growth in the volume of parenchymal hemorrhage occurred in 26% of the 103 subjects between the baseline and 1h CT scans. An additional 12% of subjects had substantial growth between the 1- and 20h CT scans. The 30-day mortality was higher and functional status (by BI scores) was worse in subjects with hematoma enlargement compared to those without enlargement. Table 2 outlines the four large studies that have evaluated the rate of hematoma enlargement and its association with neurological deterioration. A pooled individual patient meta-analysis involving 218 acute patients studied prospectively demonstrated that hematoma expansion is a crucial, independent determinant of both mortality and functional outcome after ICH. For each 10% increase in hematoma expansion, there was 5% increased hazard of death, 16% greater likelihood of worsening by 1 point on the mRS, or 18% greater likelihood of moving either from independence to assisted independence or from assisted independence to poor outcome on the BI.

Table 2: Hematoma expansion and associated neurological deterioration

Study	Subjects included	Definition of enlargement	Rate of enlargement	Definition of clinical deterioration	Clinical correlation
Kazui et al.[12] (1996)	204	Increase in hematoma size by 12.5 cm3; or 40% increase compared with baseline	≤ 3 h: 36% 3-6 h: 16% 6-12 h: 15% 12-24 h: 6% 24-48 h: 0%	Aggravation of consciousness or neurological deficit	66% of subjects with hematoma enlargement deteriorated (14% without enlargement deteriorated)
Brott et al.[11] (1997)	103 subjects presenting <3h	33% increase in hematoma volume compared with baseline volume	< 1h: 26% 1-20 h:12%	>2 point decrease in GCS score	31% of subjects with hematoma enlargement deteriorated (10% without enlargement deteriorated)
Davis et al. [26] (2006)	218 subjects presenting <3h	Any increase compared with baseline	73%	NA	Percentage hematoma expansion correlated with increased risk of mortality and poor functional outcome at 3 months
Silva et al. [27] (2005)	183 patients with hemispheric ICH of <12h	Volume increase >33% between the 2 CT exams w/ baseline volume <20 mL and >10% for ICH ≥20 mL	29.5%	GCS score decreased 1 or more points between admission and 48 hours after admission	Enlargement significantly associated with increased risk of early neurological deterioration, mortality, and poor functional outcome at 3 months

5.6 Inconsistent relationship between SBP and hematoma expansion

In a post-hoc analysis of 65 patients evaluated within 3 hours of symptom onset[28] and not undergoing surgery, 37% experienced hematoma expansion by 20 hours. Peak SBP was higher among those who experienced hematoma expansion (205 mmHg) than those who did not (198

mmHg). In the multivariate analysis, peak SBP demonstrated a trend for association with hematoma expansion but the relationship did not achieve statistical significance (p=0.18). In an exploratory analysis[29] from a randomized study of rfVIIa in 382 patients with ICH, SBP≥170 mmHg was associated with hematoma expansion (p=0.08). In the multivariate analysis, treatment with rfVIIa and a longer time-from-onset-to-baseline CT were related to a decrease in hemorrhage growth. However, the relationship between SBP and hematoma expansion did not achieve statistical significance in multivariate analysis. Most of the analyses are based on the initial recording and since BP treatment and targets were heterogeneous, considerable variability in BP may have occurred which is not represented by the SBP values entered in the model. These results add more controversy to the existing body of data and highlight the need for a randomized trial to address the question systematically.

5.7 Other contributing mechanisms for relationship between elevated BP and outcome

Elevated BP may exacerbate cerebral edema in the acute period of stroke. A prospective study[30] recruited 240 consecutive first-ever ischemic or hemorrhagic stroke patients within 3 hours of ictus. Patients were imaged with CT scan within 24h from stroke onset and 5d later in order to determine the presence of brain edema. The main outcome measure, brain edema formation, was present in 78 (32.5%) patients. The 24 hour SBP values were significantly higher in patients with brain edema than in the reference group (stroke patients without brain swelling). On multivariate analysis containing clinical, demographic and BP variables, 24 hour SBP remained significantly associated with brain edema. There was a 1.25 increase in odds (OR) for edema formation associated with each 10 mmHg SBP increase in 24 hours. During the first 27 hours after onset, there was a spontaneous decline of SBP in the reference group, but not in the patients with brain edema. The effect of cerebral edema on outcome was demonstrated in another study of 41 patients with ICH[31], who were imaged within 3 hours of onset, then 1 and 20 hours later. By multivariate logistic regression analysis, baseline relative edema was the strongest independent predictor of functional outcome and was associated with lesser odds of poor 3-month functional outcome OR: 0.09 per 1.0-unit [100%] increase; 95% confidence interval, 0.01 to 0.64; p=0.016).

5.8 Lack of other new treatments for ICH

There is no other promising treatment for ICH at this time. The FAST trial[33] was a phase III trial evaluating the efficacy of two doses of IV rfVIIa in patients with ICH who presented within 3 hours of symptom onset. The primary outcome was a mRS of 5 or 6 at 3 months. A total of 841 patients were randomized, and of these 821 were actually treated. Approximately 70% of the patients received treatment within 3 hours of symptom onset. Of the treated patients, 263 received placebo, 265 received 20 μg/kg, and 293 received 80 μg/kg of rfVIIa. Absolute hematoma volume change at 24 hours (compared with pre-randomization scan) was 7.6±18.7 ml, 4.7±14.8 ml, and 3.8±15.3 ml for the three study arms, respectively. At three months, the primary outcome was observed in 24%, 26%, and 29% of the three study arms, respectively. The three month mortality was 19%, 18%, and 21% among the three study arms, respectively. The rate of arterial thrombosis was higher among patients treated with 80 μg/kg of rFVII (10%) compared with placebo treated (5%) or 20 μg/kg treated (6%) groups. The study was unable to demonstrate a benefit on clinical outcome in patients with ICH treated with rfVIIa.

5.9 Expected impact of the trial

ICH remains a major public health problem, as demonstrated in a review of data from the Nationwide Inpatient Sample, which found 148,604 admissions for ICH in 1990-91 and 175,496 in 2000-01 in the U.S.[32]. In-hospital mortality rates did not change among ICH patients during the decade in the study (29.9% vs. 28.1%). The approximately 90,000 annual admissions in the U.S.(18% increase) and unchanged 7d mortality over the aforementioned 10 years, disproportionate to other stroke subtypes, suggest that both preventive and treatment strategies for ICH are lagging. A study of 45,330 patients with ICH in 2004 derived from the National Hospital Ambulatory Medical Care Survey found that 33,992 (75.0%) had an initial SBP≥140 mmHg[4]. The data were based on a national probability sample of visits in noninstitutional general and short-stay hospitals. Therefore, the ATACH-II trial will have direct implications for 75% of the patients with ICH in the U.S. BP treatment is a strategy that can be made widely available without specialized equipment or personnel, and can make a major impact on outcome in ICH patients.

6. PRELIMINARY STUDIES

6.1 Pre-Clinical Data

We performed an animal study to determine the effect of MAP reduction on rCBF and ICP in ICH[35]**.** We measured serial rCBF using radio-labeled microspheres in an experimental ICH canine model with two different volumes of injected blood: 2.8 ml (group A, n=6), and 4.4 ml (group B, n=6), and compared them with control animals (n=6). IV labetalol was administered 90min after introduction of hematoma while maintaining CPP above 65 mmHg. rCBF measurements were repeated after 10 and 30 minutes following labetalol administration. MAP and ICP were monitored continuously using intra-arterial (IA) and cisterna magna catheters, respectively. Compared to control animals, groups A and B had significant elevation in ICP and elevation in MAP was observed in group B at 45 minutes after injection of blood. These hemodynamic alterations were not accompanied by any significant differences in rCBF in any group. Administration of labetalol resulted in a decrease in MAP (mmHg±SE]) in groups A (119±9 to 103± 9) and B (125±7 to 101±5) and controls (104±4 to 85±8). In our model, pharmacological reduction of MAP within the normal autoregulatory limits of CPP, 90 minutes after onset, had no adverse effect on ICP and rCBF in regions around or distant to the hematoma. These results supported the controlled use of antihypertensive treatment in ICH in the initial time period.

6.2 Preliminary Clinical Data

6.2.1 Human studies evaluating the effect of pharmacological reduction of BP in ICH subjects

Powers et al.[34] described changes in CBF that occur globally within the brain and regionally within the clot periphery in conjunction with pharmacologic reductions in MAP in subjects with acute ICH. Fourteen subjects with acute supratentorial ICH (1 to 45 ml) were studied 6 to 22 hours after hemorrhage onset. rCBF was measured with positron emission tomography using O^{15}-water tracer. After the first rCBF measurement, subjects were randomized to receive either nicardipine or labetalol to reduce MAP by 15% followed by another rCBF measurement. Post-treatment, MAP was

lowered from 143±10 to 119±1 mmHg without any significant change in either global CBF or peri-clot rCBF. Overall, there was less than a 5% chance global CBF or peri-clot rCBF would fall by >2.7 ml/100 g/minute. They concluded that in subjects with small- to medium-sized acute ICH, autoregulation of rCBF was preserved with BP reductions in the range studied.

6.2.2 Preliminary clinical study of aggressive antihypertensive treatment in ICH patients

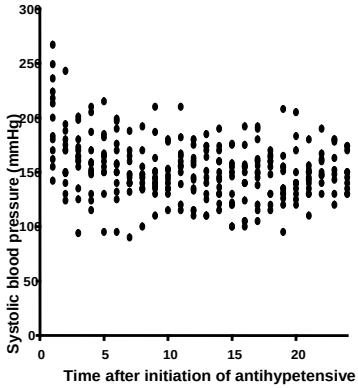


Fig **3:** Hourly SBP recordings for the 24-hour period after initiating antihypertensive treatment

Based on the animal study, we designed a prospective multi-center study to evaluate the feasibility and safety of aggressive antihypertensive treatment in subjects with acute ICH[36]. A prospective observational study was conducted at three university-affiliated hospitals. ICH subjects admitted within 24h of symptom onset were treated using a standard protocol comprised of increasing doses of IV labetalol or hydralazine (in subjects with contraindications to use of β-Blockers)**.** This was followed by IV nitroprusside infusion if required. The goal was to maintain SBP<160 mmHg and DBP<90 mmHg. Incidence of neurological deterioration, defined as decrease in GCS score of 2 or greater, was measured by neurological evaluation at 24h. A large proportion of subjects also underwent follow-up CT scan to document any hematoma size increase. Elevated BP was lowered to the target range using the antihypertensive regimen in all 27 study subjects (mean age 61±14). Mean initial SBP and diastolic BPs were 195±31 mmHg and 103 ±18 mmHg, respectively. Eight other ICH subjects without acute hypertension were followed to provide comparative information. Neurological deterioration was observed in 2 (7%) of 27 subjects who received the antihypertensive regimen and in 2 (25%) of 8 subjects who did not receive this regimen. Among subjects who underwent follow-up CT scan, hematoma expansion (>33% increase in hematoma size at 24h) was observed in 2 (9%) of the 22 who received antihypertensive medications and 1 of the 8 (13%) who did not. Among treated patients, 8 were functionally independent and 8 others had died by 1m. Those treated within 6h of symptom onset were more likely to be independent at 1m than subjects treated between 6 and 24h (8 of 18 vs. 0 of 9, p=0.03). The study results support the need for clinical trials to determine the efficacy of this approach, particularly within 6h of symptom onset. Figure 3 contains hourly recordings in 13 of the treated patients. As shown, control was not optimal (relatively high rate of SBP>160 mmHg) with the regimen used, suggesting the need for a different and more effective antihypertensive regimen.

6.2.3 IV nicardipine for treatment of hypertension associated with ICH

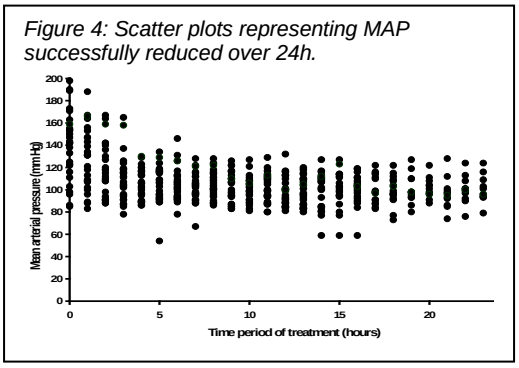


Figure 4: Scatter plots representing MAP successfully reduced over 24h.

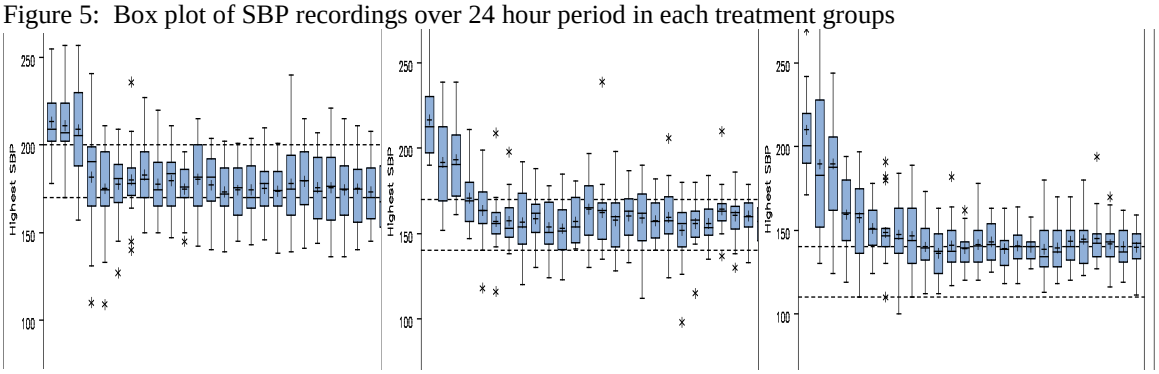
We performed a single-center prospective registry supplemented by retrospective chart review[37]**.** Patients were treated with IV nicardipine within 24h of symptom onset to reduce and maintain MAP of <130 mmHg (AHA guidelines). The primary outcome was tolerability of treatment as assessed by achieving and maintaining MAP goals for 24h after initiation of IV nicardipine infusion. Other end points were: neurologic deterioration defined by a decline in GCS from pretreatment assessment by ≥2 points or increase in NIHSS score by ≥2 points, hemorrhage growth defined as an increase in ICH volume of >33% (measured by image analysis on the 24 hours CT scan compared with the baseline CT scan), and rates of favorable outcome and death at 1 month. Of 46 ICH patients admitted to our service, 29 were treated where the primary outcome of tolerability was achieved in 25 of the 29 (86%). Neurologic deterioration was observed in 4 of 29 patients. Hematoma enlargement was observed in 5 patients. Of the 29 patients, 11 (38%) had a favorable outcome (defined as mRS of ≤2) and 9 (31%) were dead at 1 month. We observed a high rate of tolerability among ICH patients treated with IV nicardipine within 24h of symptom onset using MAP goals (see Figure 4).

6.2.4 Feasibility and safety of BP reduction using IV nicardipine: ATACH-I Trial

This trial was a multicenter open-labeled pilot trial[38] to determine tolerability and safety of 3 escalating levels of antihypertensive treatment goals for acute hypertension in 60 subjects with supratentorial ICH. Specific study aims were: (1) Determine tolerability of treatment as assessed by achieving and maintaining 3 different SBP goals with IV nicardipine infusion for 18-24h post-ictus in ICH subjects presenting within 6h of symptom onset; and (2) Define safety, assessed by the rate of neurological deterioration during treatment and SAEs, of 3 escalating SBP treatment goals**.**

Treatment feasibility: Scatter plots in Figure 5 demonstrate the distribution of hourly SBP recordings during the first 24h of infusion in the three tiers of ATACH-I. The plots show that BP can be maintained below treatment threshold within a narrow range using the proposed regimen. A prominent difference among mean SBP trends could be detected at 1h and 2-24h among all tiers.

Figure 5: Box plot of SBP recordings over 24 hour period in each treatment groups



Tier (170-200 mmHg) ***Tier (140-170 mmHg)*** ***Tier (110-140 mmHg)***

Treatment success was ascertained by MUSC after review of hourly maximum and minimum SBP. Primary treatment failure was declared if minimum SBP remained greater than the upper limit of the target range for 2 consecutive hours after initiation of nicardipine. Primary treatment failure was not observed in any patients in the first two tiers and was observed in only 6 patients in the third tier.

Safety: The safety stopping rule mandated a cessation of enrollment if the rate of neurological deterioration exceeded 45%, the upper limit of the 95% confidence interval expected for the disease based on previous published studies in the literature[61, 62]. A second review was performed by the DSMB to evaluate the nature of the neurological deteriorations and their causal relationship to the study intervention. Rates of neurological deterioration in the first 24 hours remained below the stopping rule threshold for safety in all tiers. Independent serial review by the DSMB did not identify excessive rates of causally related neurological deterioration in any of the tiers.

In any of the treatment groups, if 4 subjects developed SAEs, the study was to cease enrolling pending DMSB review. The DMSB also received reports from the CCC regarding the relationship of SAEs to the study medication. The rates of SAEs within the first 24 hours remained below the threshold for the safety stopping rule in all tiers. Furthermore, the DSMB independent serial review did not identify excessive rates of causally related neurological deterioration in any of the tiers.

6.2.5 Update from Intensive BP Reduction in the INTERACT study

In April 2007, the INTERACT trial (PI: Craig Anderson) completed recruitment, randomizing 404 patients with ICH within 6 hours of symptom onset[39]. The INTERACT study (ClinicalTrials.gov number: NCT00226096) was an investigator-initiated, blinded outcome, randomized trial that enrolled 404 patients from 44 hospitals in Australia, China, and Korea**.** Patients with ICH and elevated SBP (≥150 and <220 mmHg) were randomized to either intensive BP management (SBP <140 mmHg) or AHA-guideline based BP management (SBP<180 mmHg) using available antihypertensive agents. Patients randomized in the intensive BP management group had an average BP difference of 14 mmHg lower for the first hour and a difference of 10 mmHg lower for 1 to 24h compared with AHA-guideline based BP management. The primary efficacy end-point was proportional change (expansion) in hematoma volume at 24 hours. The results suggest that early intensive BP reduction appears to attenuate hematoma expansion in patients with ICH. In subgroup analyses, patients recruited within 3h and patients with an initial SBP≥181 mmHg appeared to have the greatest benefit with intensive SBP reduction. A differential benefit was not seen in subgroups defined by age, history of pre-existing hypertension, or initial NIHSS score. The rate of SAEs or poor clinical outcome at 90d was not different between the two groups. No significant difference in 3m mortality was observed between the groups, although the study was not powered to demonstrate a difference in rates of clinical outcomes.

6.3 Supporting Data For Selection of Treatment Targets

The ATACH-I trial proved the feasibility and tolerability of intensive SBP reduction, but was not designed to evaluate efficacy. The INTERACT study demonstrated attenuation of hematoma expansion with intensive SBP reduction. The attenuation of hematoma expansion appeared to be most prominent in patients recruited within 3 hours and those with an initial SBP≥181mmHg, a patient population that ATACH-II is targeting for inclusion.

6.3.1 SBP <140 mmHg as target for "intensive treatment"

The target for the intensive treatment group is to reduce and maintain SBP between 110 and 140 mmHg. It is not known what threshold of SBP reduction would provide the greatest benefit for reducing the rate of hematoma expansion. However, it is reasonable to consider the most aggressive SBP reduction may provide the greatest benefit, provided it can be well tolerated. This assumption is supported by INTERACT study results and by 2 studies demonstrating very low rates of hematoma expansion when SBP was maintained <140mmHg[40, 41]. Another study[42] assessed 76 consecutive patients with hypertensive ICH and attempted to lower SBP below 140, 150, or 160mmHg. Lowest rates of hematoma expansion were observed in patients with the lowest SBP. These studies suggest that the <140mmHg tier may be the most efficacious SBP range for reducing hematoma expansion.

6.3.2 Evidence of significant functional benefit in association with BP reduction.

In ATACH I, we evaluated the effect of SBP reduction (relative to initial SBP) on: (1) hematoma expansion, defined as an increase in the volume of intraparenchymal hemorrhage of >33% measured on the 24-hour CT compared to the baseline CT scan; (2) relative edema expansion, defined as an increase in the edema volume/hematoma volume ratio of >40% (where 40% cutoff is the median value of all subjects); and (3) death or disability, defined by mRS of 4-6 (moderate or severe disability or death) at 3m following treatment. In ATACH-I, we evaluated the effect of SBP reduction (relative to initial SBP) on: (1) hematoma expansion, defined as an increase in the ICH volume of >33% measured on the 24-hour CT compared to the baseline CT scan; and (2) death or disability, defined by mRS of 4-6 (moderate or severe disability or death) at 3m following treatment. A total of 60 patients were recruited (aged 62±15 yr) with 18, 20, and 22 patients recruited in each of the tiers of blood pressure reduction of increasing intensity. Baseline SBP was calculated using the average of maximum and minimum SBP recorded prior to treatment initiation. Average SBP, derived from maximum and minimum hourly recordings, was used to determine SBP reduction compared from baseline value. The overall reduction of SBP to below 140 mmHg at 6 hours from treatment initiation appears to be associated with smaller likelihood of bad outcome – hematoma expansion of >33%, relative edema expansion of >40%, and 90d mRS of 4-6 as noted with RR<1.0 Similarly, the relationship between SBP reduction of ≥ 60 mmHg at 6h also indicate reduced likelihood of bad outcomes. Approximately two-thirds of the subjects were enrolled with initial SBP above 200 mmHg (minimum=171, median=208, max=300; mean=213, sd=25.3). Of those, 65% had the SBP reduction of ≥60 mmHg at 6h, whereas those with initial SBP ≤ 200 mmHg, 30% had such a reduction.

Importantly, univariate analysis of the relationship between hematoma expansion and 90d mRS as well as between relative edema expansion and 90d mRS indicates substantial association between the % volume increase and poor outcome (mRS 4-6). The risk of poor outcome in subjects who had >33% hematoma expansion relative to those with <33% was 1.63 (95% CI: 0.86, 3.06). The RR of poor outcome in those with >40% relative edema expansion was 1.36 (95%CI: 0.65, 2.84).

In sum, due to small sample size and the pilot study nature of ATACH-I, no statistical significance would be expected. However, the direction (and to some extent, the magnitude) of the association among SBP reduction and volumetric and clinical outcomes are generally consistent with what is anticipated and hypothesized in the ATACH-II Trial.

6.3.3 SBP<180 mmHg as treatment target for "standard treatment"

Standard treatment is defined by existing recommendations from professional organizations. The European Stroke Initiative in 2006 [43] recommended that antihypertensive treatment should be initiated in patients with ICH and chronic hypertension if SBP is ≥180 mmHg. The Writing Group of the AHA Stroke Council[1] in 1999 recommended starting antihypertensive treatment if SBP is ≥180 mmHg or DBP is ≥105mmHg. The recent update from the Writing Group in 2007 recommends that if SBP exceeds 200 mmHg in a patient with ICH, continuous IV antihypertensive therapy should be considered. If SBP is ≥180 mmHg or MAP is ≥130 mmHg and there is no evidence or suspicion of elevated ICP, a modest reduction of BP is recommended [44]. With evidence or suspicion of elevated ICP, monitoring ICP and reducing BP should be considered using intermittent or continuous IV medications to keep CPP between 60 and 80 mmHg. Current guidelines acknowledge that these targets are only suggested approaches, but ongoing clinical trials of acute BP management are likely to modify and/or clarify these recommendations in the future.

6.3.4 Duration of antihypertensive infusion treatment

We chose an infusion to be up to 24 hours after randomization (24-27 hours after symptom onset), to provide adequate SBP control during the time that hematoma expansion is mostly to occur. Although the rate of hematoma expansion is highest in the first 3 hours after symptom onset[11, 12], expansion occurs in 12%-37% of patients between 3 and 24 hours after symptom onset. Early termination of antihypertensive treatment may lead to poor control of SBP, with subsequent increase in delayed bleeding. Hematoma expansion after the first 24 hours was evaluated in two studies and found to be rare[12, 45].

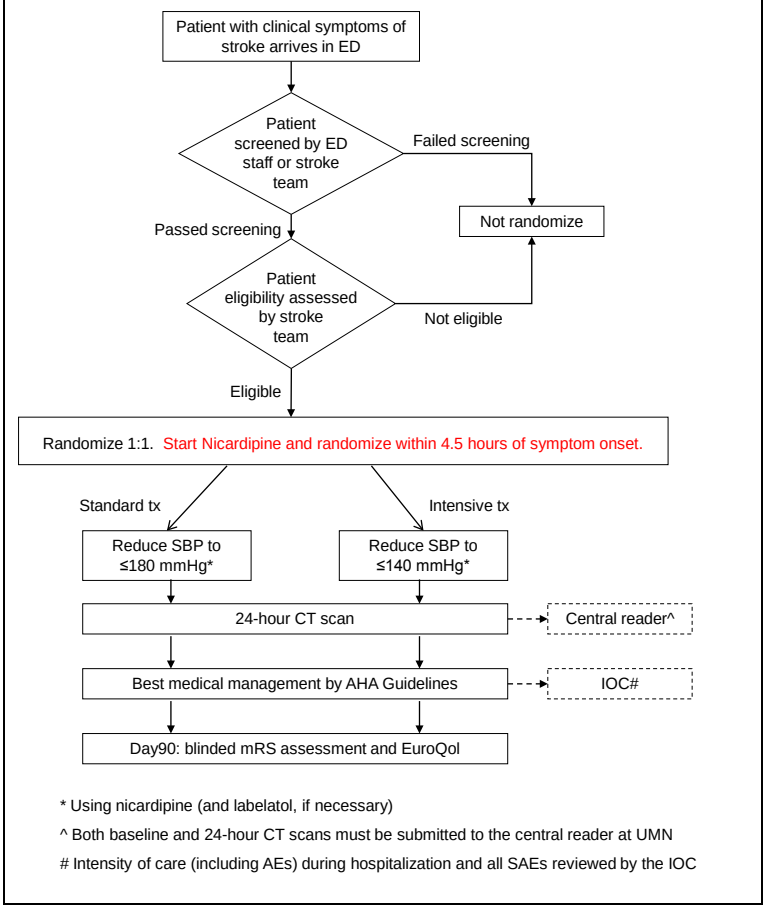
7. STUDY DESIGN

7.1 Overview

ATACH-II is a multi-center, randomized, concurrently-controlled, parallel-arm, Phase III trial designed to definitively determine the effectiveness of early (within 4.5 hours from symptom onset), intensive SBP reduction with IV antihypertensive treatment for acute hypertension in subjects with spontaneous supratentorial ICH. The design allows ascertainment of the comparative effectiveness of intensive SBP treatment and the current standard SBP treatment per the AHA guidelines.

The Trial is planned to randomize approximately1,280 subjects with ICH who meet the eligibility criteria. Subjects undergo a follow-up at 90 days post-randomization. The primary research hypothesis of the trial is that intensive SBP reduction (SBP≤140 mmHg) using IV nicardipine infusion for 24 hours post-randomization reduces the proportion of death and disability at Day 90 by ≥ 10% (absolute) compared to the standard BP reduction (SBP≤180 mmHg) among patients with ICH whose treatment is initiated within 4.5 hours of symptom onset. A pragmatic, streamlined study design evaluates the efficacy of intensive SBP reduction and its effect on outcomes measures at 24 hours and 90 days from randomization in subjects with ICH (see Figure 5).

Figure 5: ATACH-II Study Flow Chart



* Using nicardipine (and labelatol, if necessary)

^ Both baseline and 24-hour CT scans must be submitted to the central reader at UMN

Intensity of care (including AEs) during hospitalization and all SAEs reviewed by the IOC

7.2 Clinical Site Personnel Eligibility

Prior to study initiation at each site, neurologists, residents, fellows, ED physicians and nurses, involved in assessment of patients with stroke are in-serviced about ATACH-II to increase the awareness of the trial and to receive protocol instruction. Only the members of the Stroke Team and the Study Coordinator(s) listed on FDA Form 1572 as "study investigators" (which is used to monitor personnel and qualifications at each clinical site, even though this is not an investigational new drug study) are eligible to randomize and provide study treatment.

7.3 Blinding and Unblinding

In the present proposal, the infusion of nicardipine is titrated to target SBP; therefore, the treating physician cannot be blinded to treatment. Blinding of treating physicians also raises safety issues for the subject precluding early detection of relationship between hemodynamic variables and adverse neurological events and delaying corrective measures. Lack of double blinding may exaggerate estimates of treatment benefits; hence, during their planning each participating clinical site must develop strategies to minimize the bias introduced by lack of blinding. Participating centers are required to designate an individual, certified in mRS, who is blinded to treatment assignment and does not participate in randomizing or treating patients in the trial. This individual conducts the clinical assessments of treatment efficacy in a blinded manner at 30 and 90 days (± 14 days) after

randomization. All study personnel are blinded to aggregate data for the entire trial. They have access to the data only for the subjects enrolled at their sites, and not to those at other sites.

All study personnel at the CCC except Clinical Research Associates (monitors) are blinded to the treatment assignment for all subjects. The IOC members are unblinded to the treatment assignment for all subjects.

8. SELECTION AND ENROLLMENT OF SUBJECTS

8.1 Inclusion Criteria

- Age 18 years or older.
- IV nicardipine can be initiated within 4.5 hours of symptom onset.
- Patient can be randomized within 4.5 hours of symptom onset
- Clinical signs consistent with the diagnosis of stroke, including impairment of language, motor function, cognition, and/or gaze, vision, or neglect.
- Total GCS score (aggregate of verbal, eye, & motor response scores) of 5 or greater at ED arrival.
- INR value < 1.5
- CT scan demonstrates intraparenchymal hematoma with manual hematoma volume measurement <60 cc.
- For subjects randomized prior to IV antihypertensive administration: SBP greater than 180 mmHg* prior to IV antihypertensive treatment (this includes pre-hospital treatment) AND WITHOUT spontaneous SBP reduction to below 180 mmHg at the time of randomization.

  OR

  For subjects randomized after IV antihypertensive administration: SBP greater than 180 mmHg prior to IV antihypertensive treatment (this includes pre-hospital treatment) AND WITHOUT SBP reduction to below 140 mmHg at the time of randomization.
- Informed consent obtained by subject, legally authorized representative, or next of kin.

* Note: Patients with SBP < 180 should be monitored for 4.5 hours from symptom onset as their SBP may rise to eligible levels before the eligibility window closes.

8.2 Exclusion Criteria

- ICH is due to previously known neoplasms, AVM, or aneurysms
- Intracerebral hematoma considered to be related to trauma
- ICH located in infratentorial regions such as pons or cerebellum
- IVH associated with intraparenchymal hemorrhage and blood completely fills one lateral ventricle or more than half of both ventricles
- Patient to receive immediate surgical evacuation
- Current pregnancy, parturition within previous 30 days or active lactation
- Use of dabigatran within the last 48 hours
- A platelet count less than 50,000/mm^3
- Known sensitivity to nicardipine

- Pre-morbid disability requiring assistance in ambulation or activities of daily living
- Subject's living will precludes aggressive ICU management
- Subject is currently participating in another interventional clinical trial

9. Study Enrollment Procedures

9.1 Screening of Potential Subjects by ED personnel and the Stroke Team

All subjects 18 years or older who present to the study sites, within 6 hours of symptom onset with a diagnosis of *non-traumatic ICH* with ED ICD-9 code of 431 and 432.9 (ICH) are screened for study eligibility. Data collected and tests performed include demographics and vital signs, medication and medical history, and laboratory measurements required as part of standard care for ED admissions. Additionally, the patient undergoes a CT scan of the head. If ED personnel suspect an acute stroke, they should immediately call a member of the established stroke team (a pre-requisite for study sites) to the ED to evaluate the patient. A member of the stroke team could be a neurology resident, fellow, or an attending staff neurologist who arrives to the ED in an expeditious manner to evaluate the patient and determine potential study eligibility. Potentially eligible subjects identified by the stroke team are then reviewed by a study investigator or study coordinator to determine final eligibility before consent and randomization. Prior to randomization, a physician should perform a neurological assessment using NIHSS and GCS scores.

9.2 Screening/Baseline Evaluations

9.2.1 Determination of time of onset

Stroke onset is defined as time of first symptoms or signs of neurological deficits. If stroke started during sleep, onset is recorded as time the subject was last known to be intact. If an individual experiences some symptoms, returns to baseline, and subsequently experiences a focal event, onset is considered to be the time that the first symptoms manifested after the return to baseline.

9.2.2 Assessment of GCS score at the time of recruitment

Eligibility is based on the first GCS score collected. GCS scores collected in referring hospitals by non-study personnel are acceptable for this purpose. The GCS assessment is a reproducible 15-point scale on which the maximum score is 15 and the minimum score is 3. The scale has a high sensitivity and inter-observer reliability among physicians of multiple disciplines and nursing staff.[46-48] Because the verbal score maybe untestable if endotracheal intubation is necessary, we would use a predicted verbal score for subjects who are intubated, a method that has been previously validated[53].

9.2.3 Measurement of BP

A SBP > 180 must be observed after symptom onset and prior to randomization, not necessarily by study personnel, to establish eligibility for the study. BP measurements, whether taken in the EMS,

at a referring ED, or in the stroke center ED, should be taken using manual or automated cuff or an arterial line under established guidelines.[55-57] If both multiple blood pressure readings are available, select the reading in which you have the highest confidence and document why that reading was selected over other options available. See the MoP for a more in depth discussion of this issue.

9.2.4 Laboratory measurements and other procedures

The following pre-treatment tests and imaging must be performed at baseline:

- Head CT
- GCS
- NIHSS
- INR
- APTT
- EKG
- Complete blood count
- BUN
- NA
- K
- Cl
- Glucose
- Creatinine
- CO_2 (or HCO_3)

If the following additional tests and imaging are performed, please collect this information and submit the images according to the instructions on the imaging CRF:

- MRI
- CTA
- Troponin

9.2.5 Hematoma site and volume measurement prior to determining eligibility

The Study Investigator at the clinical site determines the hematoma location on review of the initial CT scan. The hematoma is classified based on location of its major component, defined as ≥50% of total hematoma from visual evaluation. In classifying by location, we use the CT atlas of Kretschmann and Weinrich[58]. The location of deep hematoma is sub-classified as: basal ganglia, thalamus, or lobar. Since hematoma volume is required for assessment of eligibility, it is determined at bedside by the stroke neurologist, in-serviced for the study. For the bedside method (length x width x height)/2, the CT slice with the largest area of hemorrhage is identified.

9.2.6 Process after screening

Patients evaluated during screening are divided into two groups: eligible and non-eligible.

9.2.7 Screen Failure Log

Any patient 18 years or older who present to the study sites, within 6 hours of symptom onset with a diagnosis of non-traumatic ICH (ED ICD-9 code of 431 and/or 432.9) are screened for study eligibility. Subjects who are screened but not randomized are tracked in the screening failure log. In addition to age, gender and race, the log captures reason(s) for non-randomization of the patient.

9.2.8 Informed Consent (for eligible subjects):

As soon as eligibility is confirmed, the subject or the legally authorized representative is asked to provide informed consent. Please refer to the MOP for more details regarding the ATACH-II informed consent policy.

After the consent is obtained from eligible patients or their LAR, randomization takes place to determine treatment assignment. Nicardipine treatment must be initiated immediately thereafter, if not done prior to randomization, and no later than 4.5 hours from the time of symptom onset.

9.2.9 Concurrent Trials

Patients enrolled in concurrent interventional studies may not be enrolled in the ATACH-II Trial, nor can active (i.e., within 3 months of randomization) ATACH-II subjects be enrolled in other interventional studies. Also, a patient may only be enrolled in the ATACH-II Trial once.
If your site is interested in running a concurrent observational study, please inform your CCC contact. Observational studies that do not interfere with ATACH-II policies and procedures, and do not impact the recruitment or outcome of the ATACH II Trial, are permissible.

9.3 Randomization procedure

Study treatment must be initiated within 4.5 hours of symptom onset. Nicardipine may be initiated prior to randomization provided the subject is still eligible at the time of randomization (*For subjects randomized after IV antihypertensive administration: SBP greater than 180 mmHg prior to IV antihypertensive treatment (this includes pre-hospital treatment) and without SBP reduction to below 140 mmHg at the time of randomization).* The covariate adaptive randomization takes place centrally via the ATACH-II Trial Website on the WebDCU^{TM}. Eligible subjects are randomized 1:1 to either the intensive or standard antihypertensive treatment group. The computer program developed by the Information Systems Managers at the SDCC balances treatment assignment based on current status of treatment group within and across clinical sites.

As with many clinical trials, timely recruitment of subjects is one of the critical concerns for the ATACH II Trial. Unlike clinical studies of chronic or progressive diseases, we cannot anticipate

when, where and how many subjects can be recruited because of the emergency nature of the ICH. Therefore, randomization takes place immediately after the Randomization CRF for the current subject is submitted into the WebDCU™ system.

The randomization procedure is implemented as follows: When an eligible patient at the clinical site is ready to be randomized, a study team member logs onto WebDCU™ and submits the Randomization CRF for the subject. The computer assesses the treatment balance with respect to the covariates, and informs the site of the treatment assigned to that subject. A subject is considered to be in the Trial when the subject is randomized into the trial (when WebDCU generates a treatment assignment), and his/her study time begins at this time point. If on a rare occasion, the internet access is unavailable due to technical problems, emergency randomization procedures are outlined in the Manual of Procedures.

10. STUDY INTERVENTION and schedule of assessments

Table 3: Summary of required activities and evaluations according to time points of ascertainment:

	Baseline	24h	48h	72h	Day 7 or D/C, (whichever 1st)	Day 30 (phone)	Day 90
Screening/Eligibility	X						
Consent and Randomization	X						
Demographics/Baseline information	X						
Medical History	X						
EKG	X						
Prior medications	X						
Blood Pressure (frequency in section 6)	X	X	X	X	X		X
GCS score	X	X					
NIHSS score	X	X					
Laboratory Tests	X	X	X	X			
CT scan	X	X					
Nicardipine administration	X	X					
Hospital discharge summary					X		
Concomitant medications		X	X		X		
Concomitant procedures		X	X		X		
Assess for recurrent stroke					X	X	X
AEs		X	X	X	X		
SAEs		X	X	X	X	X	X
mRS						X	X
Blindedness questionnaires						X	X
EuroQOL							X
End of Study							X

10.1 Initiating Study Intervention(SBP Treatment)

10.1.1 Intervention, Administration, and Duration

Patients are randomized to one of two groups; standard treatment or intensive treatment. IV nicardipine is to be started for each treatment group within 4.5 hours of symptom onset and continued for 24 hours from randomization to achieve and maintain the target SBP level for the assigned treatment arm. Protocol recommendations for nicardipine administration follow standard manufacturer's recommendations.

10.1.2 Standard treatment group

The goal for the standard BP reduction group is to reduce SBP below180 mmHg to approximately 160 mmHg for 24 hours after randomization. IV nicardipine is to be initiated at a rate of 5 mg/hr. If SBP is not reduced to <180 mmHg after 15 minutes, the infusion dose is to be increased by 2.5 mg/hr. If SBP is still not reduced to <180 mmHg after 15 minutes, the infusion dose is to be increased by another 2.5 mg/hr. The 2.5 mg/hr increments continue every 15 minutes until the

maximum dose of 15 mg/hr is reached. Once target BP is reached, the infusion rate is to be adjusted by 1 to 2.5 mg/hr to maintain SBP in the specified range.

If SBP is > 180 mmHg despite infusion of the maximum nicardipine dose for 30 minutes, a second agent can be used (Labetalol 5-20 mg IV bolus every 15 minutes) for another hour. If SBP falls below 140 mmHg, IV nicardipine is to be reduced by 2.5 mg/hr every 15 minutes until the rate of infusion is 0 mg/h. Infusion should not be restarted unless SBP rises above 180 mmHg.

10.1.3 Intensive treatment group

The goal for the intensive BP reduction group is to reduce SBP below 140 mmHg to approximately 125 mmHg for 24 hours after randomization. IV nicardipine is to be initiated at a rate of 5 mg/hr. If SBP is not reduced to <140 mmHg after 15 minutes, the infusion dose is to be increased by 2.5 mg/hr. If the SBP is still not reduced to < 140mmHg after 15 minutes, the infusion dose is to be increased by another 2.5 mg/hr. The 2.5 mg/hr increments continue every 15 minutes until the maximum dose of 15 mg/hr is reached. Once the target BP is reached, the infusion rate is to be adjusted by 1 to 2.5 mg/hr to maintain SBP in the specified range.

If SBP is >140 mmHg despite infusion of the maximum nicardipine dose for 30 minutes, a second agent can be used (Labetalol 5-20 mg IV bolus every 15 minutes) for another hour. If SBP falls below 110 mmHg, IV nicardipine is to be discontinued. If SBP does not achieve target goals 15 minutes after discontinuation of nicardipine, fluid boluses may be given to raise BP. Infusion should not be restarted unless SBP is >140 mmHg.

10.1.4 Second agents outside of the United States

An alternative second agent, diltiazem, should be used in countries where labetalol is not available. It is recommended that diltiazem be administered in IV bolus doses of 5 mg (5mg/ml, diluted in 0.9% sodium chloride, 5% dextrose, or 5% dextrose and 0.45% sodium chloride) to a maximum dose of 15 mg per hour. Diltiazem can also be administered as a continuous infusion starting at initial infusion rate of 5mg/hour. The drip rate may be increased in 5 mg/hour increments up to 15 mg/hour as needed. Investigators may deviate from these guidelines if best interests of patient care require a different administration.

If neither labetalol nor diltiazem is available in the country, urapidil should be used as the second agent. It is recommended that uriapidil be administered via intravenous bolus; with starting dose of 12.5 mg and repetitive administration of 12.5 mg every 15 min until response or a maximum dose of 50 mg is reached. Investigators may deviate from these guidelines if best interests of patient care require a different administration. If labatelol is not available, but both diltiazem and urapidil are available, investigators may choose either diltiazem or urapidil.

10.1.5 Initiating nicardipine when a subject's SBP has been reduced to target levels pre-randomization through the use of other anti-hypertensive agents

If the subject's SBP is at or below the target SBP at the time of randomization, the initial nicardipine dose should be 0 mg/h. If the subject's SBP subsequently rises above the assigned target, the titration

schedule described in section 10.1.2 (standard treatment group) or 10.1.3 (intensive treatment group) of this protocol should be followed. Other IV anti-hypertensive agents that may have been initiated before the patient was randomized must be discontinued at the time of randomization.

10.1.6 Randomizing subjects at referring hospitals

Given the short recruitment window in this study, clinical sites are encouraged to work closely with community hospitals that will transfer ICH patients to enrolling ATACH-II sites. Team members from an enrolling site may randomize a subject at a referring hospital provided the following requirements are met:

- Transport time from the community hospital to the ATACH-II site is estimated to be less than 20 minutes
- The transferring EMS carries infusion pumps and cardiac monitors
- An ATACH-II team member, coordinator or investigator, can travel to the community hospital to confirm eligibility, obtain informed consent, and to randomize the patient (If a telemedicine connection is available an in-person presence at the community hospital is not required.)
- Randomized treatment can be initiated before the patient is transferred to the ATACH-II Site

The transporting EMS provider must maintain compliance with the ATACH-II protocol when possible. This will not always be feasible, since some providers may not be able to titrate the nicardipine infusion during transport. In these cases, it is acceptable for one titration to be missed (e.g. for 30 minutes to pass between the last titration at the community hospital and the first titration at the ATACH-II site) as a result of transport related issues. Lapses of more than 30 minutes between titrations will be considered a protocol violation.

EMS providers should be instructed to terminate the nicardipine infusion if SBP drops below 140 for subjects in the standard treatment group and 110 for subjects in the intensive treatment group.

10.2 Drug Availability, Manufacturer, and Preparation

EKR Therapeutics (Bedminster, NJ) will supply Cardene® (nicardipine hydrochloride), a calcium ion influx inhibitor. EKR will supply nicardipine to sites in the United States.
Sites are allowed to make their own arrangements for the supply of nicardipine with other manufactures if the premixed bags are not appropriate for their site. All international sites will need to make their own arrangements as our agreement with EKR only applies to sites in the United States. Sites that choose to do so will not receive additional compensation. Please note, if another source of nicardipine is used, the informed consent template will need to be altered with respect to the brand used and how it will be paid for.

A specific concentration of nicardipine is not mandated for the ATACH-II trial, but it is recommended that nicardipine be administered according to manufacturer recommendations. Manufacturer recommendations call for a continuous infusion with a starting dose of 5 mg/hr, and then increased by 2.5 mg/hr every 15 minutes as needed, up to a maximum of 15 mg/hr. Once target SBP is reached, the

infusion rate is to be gradually decreased to the minimal effective dose. Investigators may depart from these recommendations if they determine that doing so is in the best interest of the patient. Formulation of solutions of any concentration in Dextrose is to be avoided.

10.3 Distribution to clinical sites

EKR Therapeutics will distribute nicardipine to the clinical sites in the United States. Each clinical site is required to provide documentation of current pharmacy licensing for their facility in order for drug to be received. More details are provided in the site initiation checklist. Alternative arrangements may be made to supply nicardipine to sites outside of the United States.

10.4 Storage and Disposition

Per the package insert instructions, nicardipine is to be stored at controlled room temperature 20º to 25ºC (68º to 77ºF). Protect from freezing. Avoid excessive heat. Protect from light, store in carton until ready to use.

10.5 Potential risks with treatment

The most important side effect of the study drug is hypotension. Severe or prolonged hypotension may cause hypoperfusion of organs which can result in ischemic injury. The study protocol institutes the infusion with a low dose of nicardipine and increases it gradually with BP monitored at least every 30 minutes. The infusion rate is to be adjusted according to SBP readings. If SBP is below the target range, either the infusion rate is to be decreased until SBP goes up to target range again or the nicardipine infusion should be discontinued. If SBP ≤110 mmHg, or if the subject develops symptoms of hypotension even after stopping nicardipine infusion, IV fluids should be given. Nicardipine has a rapid onset (within 1-5 minutes) and short half-life of 10-15 minutes, so most subjects should show an increase in BP within 10-15 minutes after stopping the infusion. If SBP remains < 110 mmHg with signs of organ hypoperfusion, the treating physician may start vasopressor agents. Symptoms of hypoperfusion include changes in level of consciousness, new or worsening of focal neurological deficits, myocardial ischemia, and oliguria.

Another important side effect is non-responsiveness to nicardipine. According to the study protocol, if SBP is higher than the target range for longer than 30 minutes despite the maximum dose of nicardipine, IV boluses of a protocol-approved second agent can be used for another hour. If SBP still remains above the target range, further management is left to the discretion of the treating physician.

Other side effects of nicardipine are headache (the most commonly reported side effect), nausea or vomiting, and tachycardia.

10.6 Management during study intervention (SBP Treatment)

10.6.1 BP measurement and monitoring

Once study drug is initiated, heart and respiratory rates and transcutaneous oxygen saturation are to be monitored continuously. BP should be monitored regularly according to the below schedule with an automated BP monitor. It is recommended that BP measurements are taken with subjects in a recumbent position and with elevation of the head of the bed not exceeding 15°. Intra-arterial BP recording is not mandated but can be used by the treating physician based on medical indications. BP measurements are to be taken on the following schedule:

- During the first hour after nicardipine started:
    a) Every 5 minutes for the first 15 minutes after nicardipine is started
    b) Every 15 minutes for the remainder of the first hour, unless the dose is being adjusted (see next bullet point)

- Every 5 minutes (recommended) to 15 minutes (mandatory) during dose adjustments

- At least every 30 minutes while receiving nicardipine

- After the 24-hour study drug maintenance infusion period has ended, every 30 minutes until SBP is increased by 10 mmHg over the SBP measurement taken at the end of infusion, alternate antihypertensive therapy is initiated, or a maximum of 24 hours has elapsed.

More frequent measurements are recommended if prominent BP changes are observed as determined by the treating physician.

10.6.2 SBP unresponsive to treatment regimen (SBP above target range)

If the SBP remains higher than the upper limit of the target range after the first 2.5 hours of treatment despite use of the maximum dose of nicardipine and the protocol approved second agent, the investigators are allowed to use another agent if considered clinically necessary. Be aware that the recommended protocol for increasing nicardipine allows achievement of the maximum dose over 1 hour. Lack of adequate response for 30 minutes to the maximum dose of IV nicardipine and lack of response for one hour to a second agent defines unresponsiveness to treatment regimen. We expect this scenario to be uncommon, based on results observed in ATACH-I.

10.6.3 SBP unresponsive to treatment regimen (SPB declines below target range)

Nicardipine has a short half-life and the fall in SBP below specified goals is expected to be transient.

In the standard treatment group, if the SBP falls below 140 mmHg, IV nicardipine is to be reduced in a stepwise pattern until SBP returns to target range (140-180mmHg) or nicardipine is discontinued. Saline boluses should not be given to raise BP unless SBP <110 mmHg.

In the intense treatment group, if the SBP falls below 110 mmHg, IV nicardipine is to be discontinued and fluid boluses are to be given to raise BP. Vasopressor agents should not be used unless a subject develops symptoms related to or possibly exacerbated by hypoperfusion. Symptoms of hypoperfusion include changes in level of consciousness, new or worsening of focal neurological deficits, myocardial ischemia, and oliguria.

Acute hypertension and hypotension can be a result of new or increased injury to the brain. Therefore, great care must be taken not to miss early signs of neurological deterioration.

10.6.4 SBP decline reduces CPP below 70mmHg

Another scenario may be if a subject has high ICP and lowering BP reduces CPP below 70 mmHg (the minimum level of acceptable CPP according to AHA guidelines[44]). In this case, nicardipine infusion should be stopped and standard treatment for elevated ICP must be initiated. We expect this scenario to be very uncommon.

In one of the largest studies of ICP monitoring in 41 ICH patients[59], the mean value of maximum ICP elevation was 16 mmHg in patients who did not deteriorate and 30 mmHg in patients who deteriorated in the first 24 hours after symptom onset. Approximately 40% of these patients had a hematoma volume >60 cc, a population excluded from our study. In the last tier of ATACH-I (SBP <140 mmHg), MAP was very rarely under 100 mmHg, the value below which CPP could be compromised in the presence of the highest expected values of ICP. In ATACH-I, only 2 patients required ICP monitoring and SBP reduction did not compromise CPP in any of the patients (ICP range for patients: 12-18 mmHg and 0-19 mmHg).

10.6.5 Use of other antihypertensive medication

Concomitant use of other antihypertensive medication can introduce an unidentified bias. Therefore, antihypertensive medications other than those specified in the protocol are not allowed in the first 24 hours unless considered necessary for patient safety by the treating physician. Some patients may be on antihypertensive medication prior to admission with varying degree of compliance. Some patients with history of congestive heart failure or coronary artery disease may be using medication, such as beta-blockers, which have hypotensive properties. These subjects may be continued on the same dose of beta-blockers they were using prior to admission. An increase in dose is not recommended, unless mandated for patient safety.

10.6.6 Off-Intervention Requirements

All randomized subjects are followed until 90 days, death, or withdrawal of consent, whichever comes first. Thus, regardless of whether or not a subject has received and/or completed the study intervention, all follow-up procedures are to be performed according to the specified schedule.

10.7 Management upon drug discontinuation through discharge

10.7.1 Post-intervention clinical assessment

Neurological status is to be assessed by the NIHSS by the Study Investigator at 24 (±3) hours post randomization. The trial also mandates a non-contrast head CT scan at 24 (±6) hours post-randomization. Additionally, brain-imaging studies are performed at the discretion of the treating physician as a part of routine care.

A CT scan may be done as part of standard of care for an episode of neurological deterioration. If the standard of care CT is done within 6 hours of the protocol specified time of 24 hours post-randomization, it is not necessary to repeat the CT scan at 24 hours.

As standard of care, brief history and physical examinations should be performed daily while the subject is in the hospital.

Routine daily labs must be collected for the first three days of hospitalization. These labs are discussed as the 24, 48, and 72 hour labs elsewhere in the protocol. The 24 hour lab must be collected ±12 hours post-randomization.

- Complete blood count
- BUN
- NA
- K
- Cl,
- Glucose
- Creatinine
- CO_2 (or HCO_3)

10.7.2 Blood pressure management

The maximum SBP measurement of the day for Days 2, 3, and 7 (or discharge, whichever occurs first) and Day 90 must be recorded on the study CRFs. Clinical management after the first 24 hours is at the primary physician's discretion. BP should be maintained in the intermediate range (approximately 160/110 mmHg), consistent with recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP[62]. Oral antihypertensive agents may be introduced after the first 24 hours.

Optimal drug regimen remains uncertain; however, available data support the use of diuretics and the combination of diuretics and an ACE-inhibitor (Class I, Level of Evidence A) for patients with ischemic stroke or transient ischemic attack[63]. Data for ICH patients is limited, but a similar medication paradigm is recommended. Choice of specific drugs and targets are to be individualized on the basis of reviewed data and consideration of specific patient characteristics (e.g., extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and diabetes) (Class IIb, Level of Evidence C).

When BP is >20 mmHg above SBP goal or 10 mmHg above SBP goal, consideration should be given to initiating therapy with two drugs. Once neurological stability is achieved, more aggressive BP reduction using oral antihypertensive agents should be targeted, consistent with guidelines. Since most subjects with hypertension, especially those >50 years of age, reach the DBP goal once the SBP goal is achieved, the primary focus should be on attaining the SBP goal. Treating SBP and DBP to targets that are <140/90 mmHg is associated with a decrease in cardiovascular events and should be the target goal. In patients with hypertension and diabetes or renal disease, the BP goal should be <130/80 mmHg. Once antihypertensive drug therapy is initiated, most patients should return for

follow-up and adjustment of medications until the SBP goal is reached. More frequent visits may be necessary for patients with stage 2 hypertension or with complicating comorbid conditions.

10.7.3 In-hospital management and post-discharge care

Broad principles of in-hospital management after the first 24 hours are outlined in the MOP.

Regardless of whether or not a subject has completed the study intervention, all follow-up procedures are to be performed according to the schedule specified in this protocol.

10.8 Management After Hospital Discharge

10.8.1 Post-discharge care

Long-term care and rehabilitation after discharge should be based according to principles outlined in previous guidelines[64-67] particularly the AHA clinical practice guidelines[65] which provide a comprehensive review of evidence-based principles of post-hospitalization care.

10.8.2 Post-discharge follow-up

Post-discharge follow-up is planned at 30 days (±7 days) by telephone and at 90 days (±14 days) in person. All follow-up exams are to be performed by a medical professional, certified in assessment of mRS scores, who is blinded to the subject's assigned treatment arm. At the time of site activation, clinical sites are required to designate an individual who is blinded to treatment assignment for the duration of the trial. The designated individual must be familiar with the care of stroke patients, but not be a part of the acute care stroke responder team at their respective institution. The PI at each site is responsible for ensuring integrity of blinded follow-up exams.

The main components of the Day 90 follow-up include measurement of BP, assessment of patient disability using mRS, and quality of life using Euro-QOL. The assessor and the subject, or his/her representative, will also be asked to complete a blindedness questionnaire. Additional assessments are to be made as necessary after discharge for any new neurological or non-neurological events.

All subjects are followed to 90 days (±14 days), death, or withdrawal of consent, whichever comes first. Thus, regardless of whether or not a subject has completed the study intervention, all follow-up procedures are to be performed according to the standard schedule.

11. GENERAL PRINCIPLES OF MONITORING AND TREATMENT

11.1 Intensive care monitoring

Each subject is to be admitted in the intensive care unit for a 24-hour observation period. The patient's heart rate and oxygen saturation is to be continuously monitored. The respiratory rate is to be measured hourly.

11.2 Neurological evaluation

Subjects are to be examined, per clinical standard of care at the site, every 30 minutes by nursing staff or investigator. A comprehensive neurologic examination must be performed at 2-hour intervals throughout the treatment period. As soon as any episode of neurological deterioration is recognized, a site study investigator and the treating physician (if not the same) should be notified.

11.3 Management of neurological deterioration

Neurological deterioration is defined as a decrease of ≥2 on GCS OR increase of ≥4 points on NIHSS (from baseline) that is not related to sedation/hypnotic use and is sustained for at least 8 hours. Each episode of neurological deterioration is to be evaluated and managed under the direct supervision of a stroke neurologist or neurointensivist. After neurological deterioration is detected, sedating medications should be discontinued (if being used) to ensure that an adequate neurological examination can be performed. A non-contrast CT scan is to be performed; based on the results, appropriate neurological or neurosurgical intervention should be performed.

When neurological deterioration is identified, the treating physician is responsible for completing an AE CRF. Depending on the severity of the AE, information recorded may include vital signs, ICP, CPP, narrative account, and, if ascertained, the cause of the episode. The GCS and NIHSS scores should be included if the event occurs within the first 24 hours. The emergent CT scan results must be recorded in a standardized format and forwarded to and reviewed by the image analyst at the CCC.

If a standard of care CT scan is completed at the time of neurological deterioration, the research CT scan required at 24 hours post-randomization may not be necessary depending on the timing of the CT collected for neurological deterioration.

11.4 Principles of monitoring and treatment of ICP

The Principles are based on the 2007 AHA Writing Group update[44], stating that patients with smaller ICHs are likely not to have increased ICP and require no measures to decrease ICP[44]. Monitoring and management of ICH patients must take place in an ICU setting because of the acuity of the condition, frequent elevations in ICP and BP, frequent need for intubation and assisted ventilation, and multiple complicating medical issues (Class I, Level of Evidence B). If there is evidence or suspicion of elevated ICP, then monitoring ICP and reducing BP using intermittent or continuous IV medications to keep CPP between 60-80 mmHg should be considered. Suspected elevation in ICP is based on decreased level of consciousness (GCS score of <8), impaired pupillary reactivity, or radiological evidence (midline shift or obliteration of basal cisterns on computed tomography). Treatment of elevated ICP should include a balanced and graded approach that begins with simple measures, such as elevation of the head of the bed and analgesia and sedation. More aggressive therapies to decrease elevated ICP, such as osmotic diuretics (mannitol and hypertonic saline solution), drainage of cerebrospinal fluid via ventricular catheter, neuromuscular blockade, and hyperventilation generally require concomitant monitoring of ICP and BP with a goal to maintain CPP >70 mmHg (Class IIa, Level of Evidence B). Indiscriminate use of hyperosmotic agents is discouraged because benefit was not observed in a randomized trial among ICH patients [60]. Due to

the hyposmotic effects of, and potential for increase in cerebral edema, the use of fluids containing dextrose should be avoided as much as possible.

11.5 Principles of sedation

Sedation is sometimes required to avoid pain and discomfort, even though it can obscure neurological examination and cause hypotension. It is imperative that the physician and staff first rule out significant and potentially life-threatening physiologic disturbances that may manifest as restlessness and agitation. Emergent conditions such as hypoxia, hypercarbia, acidosis, hemodynamic shock, or cerebral ischemia must be dealt with promptly and their signs and symptoms should not be masked with sedative agents. Additional patho-physiologic processes to consider in the critical care population are electrolyte disturbances, uremia, infection, hyperammonemia, temperature dysregulation, and drug intoxication.

When sedation is necessary, the treatment described below is recommended but not required. Fentanyl is to be initiated as a bolus of 0.25-1.25 μg/kg followed by an infusion of 0.3-1.5 μg/kg/hour in subjects if required. Each subject started on IV fentanyl must be closely monitored for bradycardia, hypotension and respiratory depression. If any of these occur, the infusion rate of fentanyl is to be progressively reduced or stopped. With its short half-life, the effects are expected to be transient. IV midalozam is to be used as the second choice if fentanyl can't be tolerated due to hypersensitivity or adverse effects. It should be initiated as 0.02-0.08 mg/kg bolus followed by 0.05-0.1 mg/kg/hour infusion. The subject must be monitored for hypotension and respiratory depression during midazolam infusion. The goal of sedation is to titrate infusion rate to achieve Ramsey sedation grade of 2 or 3[61].

11.6 Renal evaluation

Urine output volumes are to be collected and recorded with a urinary catheter and graduated urimeter each hour for the first 24 hours after the initial dosing. Renal impairment is identified by oliguria defined by <30 ml of urine in 1 hour.

IV 0.9% sodium chloride (20 mEq/KCl added) is recommended to be administered at 1ml/kg/hour, unless contraindicated, as determined by the treating physician. The use of fluids containing dextrose should be avoided whenever possible and the use of which will be captured in the CRFs.

11.7 Cardiac monitoring

An EKG is to be performed at baseline. Continuous monitoring is to be performed for 24 hours during the infusion of nicardipine. Significant ST-segment shift suggestive of myocardial ischemia is defined as horizontal or downsloping ST depression ≥ 0.1 mV below baseline or upward ST elevation ≥0.1 mV above baseline, lasting ≥1 minute, and separated from other episodes of ST-segment shift by ≥1 minutes. Additional creatinine kinase and troponin-T samples is to be drawn when clinically indicated or when EKG changes suggest myocardial ischemia.

11.8 Management of AEs

The investigators must use their best clinical judgment to decide what specific management must be undertaken to treat an AE. Specific AEs reported with IV nicardipine, which are well known, are described in the nicardipine package insert and discussed later in the AE section.

12. CRITERIA FOR INTERVENTION DISCONTINUATION

Study agent should be discontinued if any of the following occur:

- Suspected anaphylactic reaction.
- Need for emergency surgery.
- Investigator determination that discontinuation is in the subject's best interest (for example, suspected study drug-related SAE)
- Withdrawal of consent by the subject (or the subject's legally authorized representative).

For the occasional participant who withdraws consent, the date and reason for consent withdrawal must be documented in the End of Study CRF. Otherwise, all subjects are followed for 90 days regardless of whether or not a subject has completed the study intervention. All follow-up procedures are to be performed according to the schedule specified in this protocol.

13. PREMATURE TERMINATIONS, TREATMENT FAILURES, CROSSOVERS, LOST TO FOLLOW-UP

13.1 Adherence and retention

The ATACH II Trial recruits patients with acute medical problems, who at study entry are hospitalized ensuring initial adherence. Retention is enhanced post-discharge by providing education with clear and easy-to-follow written instructions for subjects and their families and reviewing these instructions at the time of discharge and during follow-up visits. These efforts are to be coordinated and overseen under the direction of the PI at each clinical site.

13.2 Inability to initiate allocated treatment

A subject may meet eligibility requirements and be randomized, and might be unable to proceed to the study treatment. This could be due to progression of neurological deficits or need for emergent surgery prior to the study intervention, subject/LAR request to terminate the study treatment, subject/LAR withdrawal of consent, or occurrence of new medical events such as cardiac arrest, respiratory failure, or severe hypotension. Events such as these may render the subject no longer medically fit to receive allocated treatment as determined by the site investigator or treating physician. We expect such events to be uncommon. However, if the subject is randomized, he/she must complete the required study assessments and procedures through Day 90 unless the subject withdraws consent prior to that point. In addition, subjects who request to terminate from the study treatment, but who do not withdraw from the study protocol, should be followed until Day 90.

13.3 Treatment failure and crossover

Spontaneous reduction in SBP in the standard treatment group may result in their SBP entering the SBP range of the intensive treatment group. Similarly, inability to reduce SBP in the intensive treatment group may result in their SBP entering range of the standard treatment group. If the goals of the assigned treatment cannot be met as defined earlier, the subject is considered a treatment failure but is considered in the original allocation group per the ITT principle.

13.4 Deviations from the protocol

Investigators should not deviate from the protocol except in medical emergencies. The IRB must be informed of all protocol changes by the site PI in accordance with the IRB's established procedures. Reporting of protocol deviations must be done in compliance with established IRB procedures.

13.5 Withdrawal of consent

A subject or their legally authorized representative may decide at any time during the study to no longer participate in either the treatment portion of the protocol or the follow-up portion. Every study subject has the right to withdraw voluntarily from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The subject data collected prior to the time of withdrawal remain as part of the study records.

13.6 Lost to follow-up

For the Day 30 follow-up telephone contact, the Study Coordinator, or designee, must make at least three attempts over the course of two weeks.

All efforts, above and beyond those described for the Day 30 follow-up, must be made to contact the subject who fails to show up at the scheduled Day 90 follow-up visit since the assessments made at this visit provide the primary outcome measure for the Trial.

Study Coordinators, or designees, must make at least five attempts to contact the patient over the course of two weeks. The Study Coordinator must also send a certified letter. When all methods have been tried and have failed, the subject is coded as lost to follow-up in the End-of-Study CRF.

13.7 Procedure and documentation for premature terminations

A premature termination includes withdrawal of consent or death. The procedure to be followed at the time of premature termination is: (1) to check for the development of adverse events; and (2) to complete the End-of-Study CRF with explanation of why the subject is terminated. In case of death of a subject, additional data on the date and causes of death must be collected.

Because primary analysis of trial data is conducted under the Intent To Treat principle, data must be collected for all randomized subjects, except those who specifically withdraw consent to continued

participation in the trial. Thus, it is imperative to complete all required research evaluations during hospitalization and post-discharge for all subjects whether or not they received complete treatment with the study drug. All study procedures must be carried out per the protocol whether or not a subject receives treatment according to the protocol or is transferred to another facility.

14. MONITORING OF ADVERSE AND SERIOUS ADVERSE EVENTS, ADHERENCE TO TREATMENT PROTOCOL **AND STANDARD OF OVERALL CARE**

14.1 Independent Oversight Committee (IOC)

The IOC's responsibilities include assessment of site investigator clinical care and SAE review and adjudication for the duration of the trial. The IOC members are not directly involved with the trial.

The IOC monitors the principles of organ specific care and intensity of overall care at each site by reviewing the clinical care profile of the first three patients recruited at the site to assess the adequacy of "intensity of overall care." The SDCC generates the clinical care profile and provides access to pertinent data that allows the IOC's assessment of the principles of care. Examples of relevant data are the medical history, NIHSS and GCS scores at baseline and 24 hours, BP measurements, medications with dosages, and procedures performed.

The IOC reviews the intensity of care and compliance for the post-24-hour period by subject and site for approximately 300 subjects. It reviews standards of care and submits a quarterly report and recommendations to the SC.

The IOC's responsibilities also encompass SAE review and adjudication initiation throughout the duration of the trial. All AEs that meet the SAE definition provided are reported to the IOC, with initial notification by an automated system triggered when SAEs are entered into the study database. The IOC adjudicates the relationship of the SAEs to both the "study intervention" and the "principles and intensity of overall care". The IOC also reviews aggregated SAE data and related site performance and make recommendations to the SC on a quarterly basis. All reports to the SC contain only aggregate data so the SC remains blinded to treatment group.

The SC and IOC meet by teleconference periodically. During these meetings, discussions include, among other items, any concerns regarding the principles and intensity of the overall care at particular sites and aggregation of AEs at particular sites. The IOC may recommend that the SC contact individual sites, as needed, to discuss potential remedial measures. Also, the IOC may make recommendations to the SC for protocol changes if serious safety concerns are raised.

Table 4: A Summary of Oversight for Quality of Data Ascertainment, Protocol Adherence, and Overall Care Parameters

	Methodology	Review	Identify	Report
Clinical monitors (CRAs)	Site visits	Review regulatory documents and source documents	Protocol violations; accuracy of source-to-database documentation	SC
IOC	1) Data entered into the WebDCU™ system 2) Site contact for additional information, as needed	1) Review of care principles in the following organ specific domains; 1/. Other cardiac care (particularly the initiation of long term anti-hypertensive care); 2/. Management of mass effect, IVH, and ICP; 3/. Respiratory care 4/. Management of medical complications (particularly hyperglycemia and DVT prophylaxis); 5/. SAE related Post-ICU care.	Adherence to "AHA guidelines" and "best practices"	SC
DCU	Data entered into the WebDCU™ system	Review of inconsistencies and missing data	Deficiencies in data collection and entry	SC

14.2 Definition of Adverse Events

An adverse event is defined as any untoward event or complication that was not previously identified, or that occurs with greater frequency or severity than previously reported. The event occurs during the protocol intervention or during the follow-up period, and may or may not be considered related to the protocol intervention. Abnormal laboratory findings considered by the reporting physician to be clinically significant are included as adverse events. The investigator, on the basis of his or her clinical judgment and the following definitions, determines the relationship of the adverse event to the protocol intervention as one of the following:

Unrelated

- The temporal relationship between treatment exposure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)

Unlikely (must have 2)

- May have reasonable or only tenuous temporal relationship to intervention.
- Could readily have been produced by the subject's clinical state, or environmental or other interventions.
- Does not follow known pattern of response to intervention.
- Does not reappear or worsen with reintroduction of intervention.

Possibly (must have 2)

- Has a reasonable temporal relationship to intervention.
- Could not readily have been produced by the subject's clinical state or environmental or other interventions.
- Follows a known pattern of response to intervention.

Probably (must have 3)

- Has a reasonable temporal relationship to intervention.
- Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions.
- Follows a known pattern of response to intervention.
- Disappears or decreases with reduction in dose or cessation of intervention.

Definitely (must have all 4)

- Has a reasonable temporal relationship to intervention.
- Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions.
- Follows a known pattern of response to intervention.
- Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure.

Adverse events are further graded as mild, moderate, severe, life-threatening, or fatal. Adverse events that are non-serious must be followed through the discharge. Only SAEs are reported and followed beyond hospital discharge or Day 7 (whichever occurs first).

An SAE is one that results in any of the following outcomes:

- death due to any cause;
- a life-threatening adverse experience (at immediate risk of death from the event as it occurred)
- in-patient hospitalization or prolongation of existing hospitalization. (Hospitalizations scheduled before enrollment for elective procedures or treatment of a pre-existing condition that has not worsened during study participation is not considered a serious adverse event)
- a persistent or significant disability/incapacity (i.e., a substantial disruption of one's ability to conduct normal life functions)

14.3 Reporting of Adverse Events and Serious Adverse Events

All AEs, including SAEs, deaths and abnormal and clinically significant laboratory values, occurring to the subject from enrollment through Day 7 or hospital discharge (whichever occurs first) are recorded on the case report form on the study website. After Day 7 or discharge, only SAEs are collected and followed. For each event, date of onset, severity, duration, and relationship to the prescribed drug regimen are recorded. All AEs are monitored until they are adequately resolved or explained until the subject reaches the end of study.

For each AE, the clinical site staff records the event in WebDCU™, providing relevant information such as the AE description and seriousness. For SAEs, clinical site staff, in consultation with the site investigator, must provide the date of onset and resolution, severity, suspected relationship to study treatment, and a narrative description of the SAE.

All deaths are to be reported within 5 days of first knowledge of event using the AE CRF. All deaths are to be reported to the IOC and DSMB by the SC. In the event of a subject death during the

study, all possible efforts are to be made to obtain relevant records, including death certificate, from the hospital or the subject's family physician to determine the cause of death.

14.4 Review and Reporting of Serious Adverse Events

All serious AEs must be entered by the site into the WebDCU™ system within 5 days of first knowledge of the SAE. Additionally, all current study data for that subject must be entered to allow for timely review. Upon entry of an SAE, WebDCU™ triggers notification of the SAE to the SC and the IOC Safety Specialist. The narrative section of the SAE report is reviewed by the IOC Safety Specialist. If the narrative is satisfactory the SAE is forwarded to the IOC physician.

The IOC physicians conduct independent reviews, blinded to 3 month outcomes, of all SAEs entered into WebDCU™. Should any medical reviewer need additional subject data to conduct his review, those data may be accessed on the WebDCU™. Opinions are then given regarding whether the AE was a) serious, b) unexpected, and c) related to the study drug. The IOC Safety Specialist may contact the site for more information. If two or more of the parties involved with the reporting and/or reviewing of the SAE (i.e., site investigator and any of the IOC physicians) believe the AE is serious, study drug-related (possibly, probably or definitely), and unexpected, the SAE is likely to require reporting to the DSMB (depending on the guidelines established by the DSMB for reporting safety events).

Each clinical site PI is responsible for reporting SAEs to its own IRB/REB per their policy.

14.5 Follow-Up Reporting of Serious Adverse Events

The clinical site staff is responsible for obtaining any follow-up information about the SAE. All follow-up information should be actively sought by the clinical site and must be submitted via WebDCU™ as soon as the information becomes available.

Table 5: Summary of Adverse Event Definitions and Overview of SAE Reporting and Adjudication

Events	Definitions	Ascertainment	Monitoring	Frequency of review
AEs	See Adverse Event Coding Guide in the MoP	Site Investigators, from enrollment through hospital discharge or Day 7 (whichever is first)	DSMB, SC	Aggregated review by DSMB
SAEs	An AE that results in any of the following criteria[119]: Death; A life-threatening adverse event; In-patient hospitalization or prolongation of existing hospitalization; Persistent or significant disability/incapacity	Site Investigators, from enrollment to hospital discharge or Day 7; and then from discharge/Day 7 to Day 90	IOC, SC, and DSMB	Reported within 5 days, quarterly review of aggregate events
Deaths	N/A	All deaths are SAEs	IOC, SC, and DSMB	Protocol defined

14.6 Additional Safety Measures and Review

14.6.1 Safety Monitoring Plan

The unblinded study statistician provides blinded quarterly safety reports to the SC and unblinded safety reports to the IOC (except Day 90 outcomes) and DSMB (interval to be determined in consultation with the DSMB). Both reports contain summary statistics on the AEs, SAEs, and deaths in aggregate in the blinded report, and by treatment code (A vs. B) in the unblinded report. In addition, in the unblinded report, relative risks and their 95% confidence intervals are provided for deaths, overall SAEs, pre-specified type of SAEs and AEs.

14.6.2 Safety-related stopping rules

To ensure that antihypertensive therapy does not present any safety risk to study subjects, a careful review (masked to treatment assignment) by the SC is mandated after every 20 treatment-related SAEs during the first 72 hours from randomization.

15. STATISTICAL CONSIDERATIONS

15.1 Randomization Scheme

Each eligible subject is randomized to either the intensive or standard antihypertensive treatment group using a covariate adaptive randomization. Randomization takes place centrally through the WebDCU™. The centrally-controlled randomization helps ensure the treatment balance at any interim analysis as well as in the final analysis.

15.2 Outcomes

15.2.1 Primary Outcome

The primary outcome is death or disability, defined by mRS (see Table 6) of 4-6 at 90 days following treatment. The 90 day mRS assessment is made only by blinded study investigators trained and certified in the use of the structured interview method of obtaining the mRS score.

Table 6: Components of modified Rankin Scale score

Scale	Criteria
0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability requiring some help, but able to walk without assistance
4	**Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance**
5	**Severe disability; bedridden, incontinent, and requiring constant nursing care and attention**
6	**Death**

15.2.2 Secondary Outcomes

Quality-of-Life at Day 90:

EuroQOL, designed in Europe in 1987[72], is a simple, standardized non-disease-specific instrument for describing and valuating health-related quality of life. One of its components is a printed 'thermometer'-type visual analogue scale on which respondents indicate how good or bad their health is today. Its other component, EQ-5D, consists of 5 questions in 5 different domains and allows for responses from 1 (the best outcome) to 3 (the worst). The original version contained 6 dimensions: mobility, self-care, chief activity, social ability, pain, and state of mind, each with 3 levels. The modified EQ-5D version has reduced the dimensions to 5, combining chief activity and social ability into "everyday activities."

Hematoma expansion at 24 hours:

Hematoma expansion is defined as an increase in the volume of intraparenchymal hemorrhage of ≥33% as measured by image analysis on the 24-hour CT scan compared with the baseline CT scan. The cutoff for hematoma enlargement is based on the cutoff defined by Brott et al.[11] which is the change in size associated with significant neurological deterioration. All volumetric analysis is conducted centrally by CCC staff blinded to the treatment assignment and the clinical outcome (mRS). Data is entered into the trial database by the CCC staff.

15.2.3 Safety Outcome

The safety outcomes of interest for the analysis at the end of the trial are: (1) all deaths; and (2) the proportion of subjects who experienced any treatment-related SAEs during the first 72 hours from randomization. The clinical site investigator must determine whether each event meets the SAE definition by established regulatory definitions. Furthermore, neurological deterioration identified within 24 hours of randomization is a SAE. Neurological deterioration is defined a decrease of ≥2 on GCS OR increase of ≥4 points on NIHSS (from baseline) that is not related to sedation/hypnotic use and is sustained for at least 8 hours. The adjudication of site-reported relatedness of an SAE to treatment is performed by the IOC. Any SAE judged possibly, probably or definitely related to the study treatment is counted as a treatment-related SAE. The timeframe for SAE is based on the rapid onset (within 1-5 minutes) and short half-life (10-15 minutes) of nicardipine. Therefore, most subjects should show an increase in BP within 10-15min after stopping the infusion. Late SAEs are not expected to be related to treatment; however, these SAEs also are ascertained (by site investigators) and adjudicated by the IOC for transmittal to the SC and potential forwarding to the DSMB for review.

15.3 Sample Size

The total sample size for the effect size of 10% (the absolute difference between the two treatment groups in the proportion of subjects with poor outcomes) assuming the control group's proportion of 60% (obtained from the literature), and Type I and Type II error probabilities of 0.05 and 0.10, respectively, is 1,042 with two interim analyses for overwhelming efficacy and concurrently, for futility. We assume a group sequential design of O'Brien and Fleming boundary. The ITT principle

is applied to the primary analysis, and therefore, to safeguard against an approximate 10% drop-in/out and missing data in the two treatment groups, we inflate the sample size by a factor of 1.23 which is derived from $1/(1-R)^2$, where R is the proportion of dropouts. Therefore, the maximum sample size for the trial is 1,280.

15.4 Data Analysis

15.4.1 Analysis of Primary Efficacy Outcome

The primary analysis for the trial is to test, under the ITT principle, the hypothesis of superiority of intensive SBP treatment over the standard SBP treatment in eligible ICH subjects, adjusting for age, baseline GCS, and IVH (present or absent). The analysis model for the primary efficacy outcome is:

$$g\{P|Y_i=1|\underline{x}\} = \alpha + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4$$

where Y= primary clinical outcome (0=mRS of 0-3, 1=mRS of 4-6), βi is the regression coefficient, x_1= treatment assignment (0=standard, 1=intensive), x_2= baseline GCS score, x_3= age, and x_4= IVH (0=absent, 1=present).

The primary analysis of the main efficacy outcome is the generalized linear model with log link function which yields relative risk, rather than the logit link function which yields odds ratio. It is tested at the two-sided alpha level of 0.05. In addition, relative risk and its 95% confidence interval are calculated.

15.4.2 Analysis of Other Outcomes

See SAP for the analysis of the two continuous outcome measures.

15.5 Handling of Missing Outcome Data

Under the ITT principle, all patients who are randomized are included in the analysis. Therefore, missing data, especially in the outcome measures, can be problematic. Every effort is to be made to keep all missing data, particularly the Day 90 mRS assessment, to a minimum. Despite the clinical sites' best efforts, some missing data may be inevitable mainly due to lost-to-follow-up (LTFU).

As the primary approach, we plan to use the multiple imputation method. This is generally considered the least biased method since it incorporates the uncertainty to the imputed value. As a sensitivity analysis, we plan to impute the missing primary outcome data by assuming the missing mRS score at Day 90 to be unfavorable (i.e., 4-6). If the treatment effect is robust, we expect analysis using these imputation methods would yield similar inferences, particularly if the missing data are minimal (<5%).

15.6 Data Monitoring

15.6.1 Statistical Stopping Guidelines for Overwhelming Efficacy

For the interim analyses of the primary outcome, the alpha spending function approach with O'Brien and Fleming type stopping boundaries is adopted. Currently, two interim analyses, after approximately 1/3 (or 425) and 2/3 (or 850) of subjects complete the Day 90 follow-up, and one final analysis are tentatively planned.

15.6.2 Statistical Stopping Guidelines for Futility

For assessment of futility, we adopt the stochastic curtailment method based on conditional power. The informal criterion for determination of futility is that at each interim look, if the conditional power (defined as the probability of rejecting the null hypothesis at the final analysis given the data accumulated so far and under the assumption that the alternative is true) falls below a certain value, for example 10%, then the DSMB may evaluate all study information (such as overall recruitment rate and secondary outcome assessment data) to consider stopping the study for futility. Depending upon the DSMB request, additional interim analyses may be conducted.

At any interim analysis, if we cross the stopping boundary, the DSMB may recommend (to the NINDS) stopping the study for overwhelming efficacy of one treatment over the other, although the better treatment may not necessarily be the intensive SBP treatment. Only if the stopping boundary is crossed, prior to making the final decision for recommendation to stop the study, it is expected that the DSMB would request thorough analyses of secondary outcomes and subgroup analyses to confirm the findings of the primary outcome results.

15.6.3 Statistical Monitoring for Safety

In addition to analyzing the treatment-related SAEs within 72 hours of randomization as a safety outcome upon completion of the study, the SDCC continuously monitors and reports all SAEs, and specifically:

- Neurological deterioration within 24 hours of randomization. Neurological deterioration is defined as a decrease of≥2 on GCS OR increase of ≥4 points on NIHSS (from baseline) that is not related to sedation/hypnotic use and is sustained for at least 8 hours
- All SAEs by body system during the subject's study period (see MoP for a list of anticipated AEs)
- All deaths by cause (broad categories) within 90 days of randomization

Other specific SAEs to be monitored may be added in consultation with the DSMB.

15.7 Data and Safety Monitoring Board (DSMB) Reports

The SDCC Study Statistician is the ATACH II Trial liaison to the DSMB and is responsible for the preparation of the DSMB reports. The comprehensive Open Reports include aggregated demographic and baseline characteristics of the randomized subjects and data quality (e.g.,

timeliness of data submission, number of data clarification requests generated and resolved) for each clinical site, and data listings on safety outcomes in a blinded fashion. The Closed Reports include information from the Open Reports plus more detailed information on safety and, if requested by the DSMB, on efficacy outcomes. On a schedule determined by the DSMB, the Study Statistician meets with the DSMB to present the Closed DSMB reports.

16. DATA COLLECTION AND MANAGEMENT OVERVIEW

16.1 Electronic data capture and database management

Data management is handled by the DCU, which is housed in the Division of Biostatistics and Epidemiology at MUSC. All activities are conducted in coordination with the clinical sites, CCC and the IOC. Case Report Forms (CRFs) have been developed by the DCU with input from the SC. An electronic copy of the CRFs is made available to the clinical sites prior to initiation of the study to be used as worksheets for capturing data for the Trial.

The clinical site staff is responsible for timely entry of required data into the database via the WebDCU™ System. The WebDCU™ is a user-friendly menu-driven system with built-in warnings and rules to facilitate the data collection process and ensure sufficient quality control. Upon confirmation of an eligible subject, the Eligibility and Randomization form must be submitted to obtain the treatment assignment. All other study data must be entered **within 5 days** of each subject's completion of each phase of the study. The details of the data entry requirements for the clinical site staff are provided in the MoP.

The study database, WebDCU™ System, has been developed in Microsoft SQL Server based on the approved CRFs. This system allows for a web-based data entry and management. The data are captured and entered (single keyed) at the clinical sites via the web interface. The data are managed (including data queries) by the DCU using a secured ATACH-II Trial website. During the design of the database, automated consistency checks and data validation rules were programmed to check for potential data errors, including missing required data, data out of pre-specified range, data conflicts and disparities within and among the CRFs. All validation rules are outlined in the Data Management Plan maintained by the DCU.

The validation procedure is implemented in two stages. First, automated data-checks flag the items that fail pre-programmed logic checks. The Study Coordinator sees on the data entry screen a validation error and he/she is requested to address it. His/her choices are to: (1) correct the entry immediately; (2) correct the entry at a later time; or (3) if the entered data are correct, dismiss the rule violation. This last option is not allowed for gross logic discrepancies such as a violation of a skip pattern. Any changes made on the website have a full audit trail. Secondly, for some checks that are more complicated, such as inter-CRF data-checks, additional validation takes place. This process involves the running of the consistency-check (validation rules) program that was prepared during the development of the database. All data items that fail the programmed consistency checks are queried via the data clarification request (DCR) process initiated by the DCU. The DCRs are generated, communicated between DCU and the clinical sites, and resolved on the secured study website.

In addition to the study database, the DCU provides the clinical site staff access (via password) to a standard set of web-enabled tools, including subject visit calendar, subject accrual reports, CRF completion status, and outstanding DCR status pertaining to their respective sites. These tools allow the staff to receive regular updates on overall study status.

The DCU has maintained fully networked and dedicated computing resources to provide a high performance and mission-critical system. The servers at DCU are configured to have RAID 1/5 hard drive arrays, redundant components, alternative power sources and multiple backup systems (Windows Shadow Copy Service, MS SQL Backup Plans, Windows 2003/2008, and IBM® TSM Tape Backup). This ensures the web-based DCU runs the WebDCU clinical trial management system for large multi-center clinical research studies at all times. The database and web system architecture is scalable and system resources are measured against usage to ensure top performance. The DCU also employs several layers of hardware firewalls in cooperation with MUSC to ensure system security. MUSC maintains hardware and software firewall protection between the university and outside computer systems. The DCU maintains an additional firewall on web servers because access is not limited to within MUSC. In addition to the firewall protection, two levels of software security are in place at DCU. The first is antiviral protection: Microsoft Forefront® is being used to protect all servers and workstations from infection. Virus definitions and system patches are updated on a daily basis. The second component is password protection. MS SQL, Access, and Windows all include password protection features to prevent unauthorized activated and kept fully functional by the DCU.™ access. All WebDCU systems adopt Secure Sockets Layer (SSL) protocol to enable encrypted, authenticated communications across the Internet and require the user to log-in at the beginning and log-out at the completion of the system session. The user authentication process is based on the combined identification of a user ID and strong password. The user is required to change their password periodically or their account will expire. When an internet user tries to log-in to the WebDCU™ system, the user's browser type, IP address, log date and time are collected for security reasons. If any suspicious log-in attempt is detected, the system begins to trace the possibly malicious attack, immediately refuses any more system access, and automatically notifies the incident to an IS Manager or designee.

16.2 Collection of image analysis data

Electronic copies of baseline and 24 hour CT scans must be forwarded by the clinical site to the CCC imaging lab for volumetric analysis. Please refer to the imaging CRF, form 22, for instructions on de-identifying, labeling, and shipping the CDs to the CCC. The neuroimaging specialist is blinded to treatment assignment, clinical findings, and CT scans from different time points.

The CCC neuroimaging specialist, who is blinded to treatment assignment, clinical findings, and baseline vs 24 hour, reviews the CT scan and record findings on a CRF. The following data is extracted by the core laboratory from subject CT scans: (1) site of hemorrhage; (2) ventricular extension by assessing CT scans for presence or absence of blood in the ventricles; (3) parenchymal hematoma volume calculated by computerized image analysis; and (4) presence of hydrocephalus.

When MRIs and CTAs are performed on ATACH-II subjects, the CCC requests that sites submit these images to the CCC with the required CT scans. Please refer to the imaging CRF, form 22, for

instructions on de-identifying, labeling, and shipping these additional scans to the CCC. These scans will enable the conduct of important ancillary studies.

17. HUMAN SUBJECTS

17.1 External DSMB

An external DSMB is responsible for monitoring safety data and subject recruitment. The DSMB and its chair are established by NINDS. The study PI, study statistician and designated staff attend DSMB meetings and present progress reports. The DSMB chair's role is to help the DSMB identify problems early and seek corrective action. The DSMB meets at 6-month intervals and as necessary to discuss safety data, recruitment, the timelines, accuracy of data collection, frequency and nature of AEs, and mortality rates. At any time, the DSMB may recommend to NINDS to discontinue the study if there is compelling evidence from it or other studies regarding adverse effects of study treatment sufficient to override any potential benefit of the BP reduction to the target population.

17.2 Institutional Review Boards

The IRB at each institution reviews and approve the proposal for the study. Researchers using Protected Health Information in their projects are required by federal law and CCC Policy to have a study-specific HIPAA form approved by the IRB and signed by each subject or LAR. Federal regulations [45CFR46.103(b)(5) and 21CFR56.108(b)(1)] require the IRB to ensure that investigators promptly report “any unanticipated problems involving risk to subjects or others.” Unanticipated events are defined as any problem or event which in the opinion of the local investigator is unanticipated, serious and at least possibly related to the research procedures. These must be reported to the IRB in accordance with local IRB requirements. Regulations state that the IRB must conduct Continuing Review of an approved study at intervals appropriate to the degree of risk, but not less than once per year. The purpose of this process is to review an entire study and determine that it’s anticipated risks and benefits are reflected in the actual experience of subjects and that safeguards in place at the time of original approval are, in fact, adequate to ensure subject safety.

17.3 Institutional Review Board /Research Ethics Board Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications are reviewed and approved by the IRB/REB or ethics committee responsible for oversight of the study. A signed consent form must be obtained from the subject. For subjects who cannot consent for themselves, a legally authorized representative , or person with power of attorney, may sign the consent form. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form must be given to the subject, the legally authorized representative , or the person with power of attorney; and this fact must be documented in the subject’s record.

17.4 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site are identified only by the Subject ID Number to maintain subject confidentiality. All records are kept in a locked file cabinet. All computer entry and networking programs are done using SIDs only. Clinical information is not released without written permission of the subject, except as necessary for monitoring by IRB/REB, the NINDS, the OHRP, the sponsor, or the sponsor's designee.

All study investigators at the clinical sites must ensure that the confidentiality of personal identity and all personal medical information of study participants are maintained at all times. Additionally, the U.S. clinical sites must follow privacy obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA). On the CRFs and other study documents or image materials submitted to the DCU, the subjects are identified only by study identification codes.

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRF by the site monitors. Other properly authorized persons, such as the regulatory authorities, may also have access to these records. Personal medical information is always treated as confidential.

17.5 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the NINDS, the sponsor, the OHRP, or other government agencies as part of their duties to ensure that research subjects are protected. Additionally, the IRB/REB at any site may discontinue the trial at that site, but only at that site, should it be deemed necessary.

17.6 Site Assessment and Monitoring

Prior to study initiation, clinical sites are required to complete a site application. In addition, site visits of teleconferences with the CCC, or its designee, may be scheduled prior to the candidate site being accepted as an official recruiting site. The application, site visit, and calls serve to verify site-specific components such as the likelihood of successful subject recruitment, research team composition, and patient care facilities.

Sites that are accepted to enroll subjects are visited periodically by a team of clinical research associates (CRAs or "monitors") that perform onsite data verification for the trial. Clinical data submitted to the ATACH-II database are verified against source documents at the performance sites prior to locking of the database. Complete source data verification is done for the first subject enrolled at any site. For subsequent subjects, a checklist of key outcome and safety data variables for source monitoring has been developed based on the trial's safety and efficacy endpoints. All data monitored on site are verified for accuracy and thoroughness using the most appropriate source documents for all subjects. In addition, 100% of subjects enrolled are monitored for the presence of signed consent.

Additional on-site monitoring verification includes: ongoing evaluation of the adequacy of site facilities and staff, site recruitment, subject randomization, the presence of regulatory documents, and specific review of documents and data as requested by the CCC or SDCC staff. Generally, each

site is monitored at least twice a year. Sites are evaluated in an ongoing manner by site monitors, CCC, and the SDCC to determine if there is a need to monitor more frequently or more thoroughly.

During the monitoring visit, any omissions and corrections to data submitted to the database are noted and queries are generated by the monitor onsite or within 72 hours via the WebDCU™ system.

The Investigator guarantees direct access to all source documents and will co-operate with the monitor to ensure that any discrepancies identified are resolved. Investigators and coordinators must make themselves available to monitors to answer questions that may arise during the site visit.

The close-out monitoring visit by a monitor takes place at the completion of subject enrollment at the performance site. At that visit, the monitor again reviews the presence of a regulatory file and verifies documents for currency and completion. Sites are instructed in the record retention of all trial documents. Site Principal Investigators are directed to close the trial and issue a final report to the IRB/REB. Finally, any additional special consideration for the auditing of any additional safety issues are made during this final monitoring visit.

17.7 Investigators' Meetings

The first ATACH-II Trial Investigators' Meeting serves as the initiation of all site investigators and staff able to attend. If a center joins the Trial after the initial Investigators' Meeting has occurred, the CCC, CRAs, SDCC staff, or some combination thereof, initiates and trains the site after the site had been successfully screened by the SC. At the time of a personal visit, those conducting the visit verify the presence and completeness of regulatory documentation at the performance site, and perform a review of the study protocol, and electronic data entry worksheets with the appropriate clinical site personnel. In addition, we anticipate holding annual investigators throughout the course of the trial.

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