NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

FEBUARY 2024 | VOLUME 3 | ISSUE 2

FASTEST

FVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Zafar

Together, we are onto something big: this may become the 'tpa' for hemorrhagic strokes. I am thrilled to share our team's enthusiasm for being a part of the FASTEST trial. Being located in the heart of downtown Toronto, St. Michael's is uniquely positioned to contribute significantly to this groundbreaking study.

Our involvement in FASTEST is more than just a collaboration; it's a journey of discovery and hope. For years, we have sought effective treatments for our patients suffering from intracerebral hemorrhage (ICH). Now, with the FASTEST trial, we stand on the cusp of what could be a transformative breakthrough in stroke medicine.

Our entire stroke team at St. Michael's Hospital of the University of Toronto is fully committed to this endeavor. We believe that through our collective efforts, we can uncover vital insights and develop innovative treatments that could potentially change how acute emergency care is delivered.

This journey is not just about advancing neuroscience; it's about improving patient outcomes and changing lives. We are excited to contribute, learn from our peers, and together, make strides towards developing new treatment options for ICH.

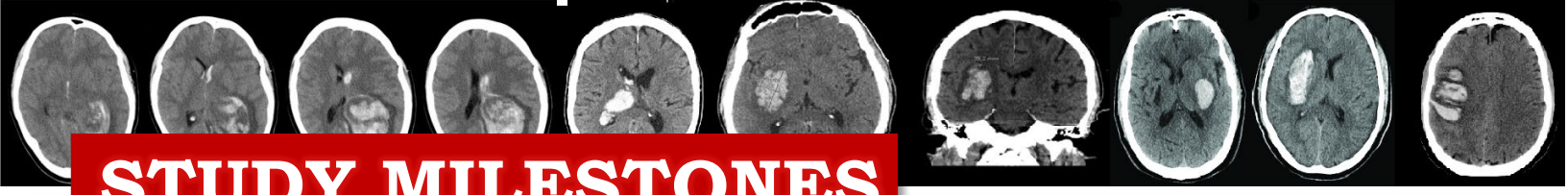
Thank you for this opportunity to be a part of something truly remarkable. We look forward to every step of this journey with optimism and determination.

Atif Zafar, MD
Medical Director of Stroke Program,
St. Michael's Hospital - Unity Health Toronto.
Faculty of Medicine, University of Toronto

Due to ISC 2024 there will be no *FASTEST* webinar in February.

Please join us for next *FASTEST* Webinar in March

Prior presentations and slides are available at,
https://www.nihstrokenet.org/fastest/webinars



STUDY MILESTONES

Total Sites Released to Enroll: **78** (**44** USA, **34** OUS: **6** Germany, **14** Japan, **4** Spain, **6** Canadian, **4** UK)

Total MSUs Released to Enroll: **12** (**10** US and **2** OUS)

Total Randomization = **373**

- US Randomizations: **103**
- International randomizations: **270**
  - Japan = **177**
  - Canada = **47**
  - Spain =**22**
  - Germany = **16**
  - UK = **8**

Randomization last month = **19**

Total Screen Failures = **1423**

Subjects Randomized by MSU = **14**

Subjects Terminated Early = **2**

eConsent Used = **16**

Remote Consent Used = **12**

CALENDAR OF EVENTS

Upcoming *FASTEST* Monthly Webinars: **Wednesday, Mar 20th, @ 2:00-3:00 pm EST**

FASTEST study team office hours: **Monday, February 26th, @ 2:00-3:00 pm.**

FASTEST @ ISC 2024

Recombinant Factor VIIa (rFVIIa) for Acute Hemorrhagic Stroke Administered at Earliest Time (*FASTEST*) Trial

Joseph P. Broderick MD, James C. Grotta MD, Andrew M. Naidech MD MSPH, Jordan J. Elm PhD, Pooja Khatri MD, Achala Vagal MD, Richard Aviv MD, Stephan A. Mayer MD, Scott Janis, Thorsten Steiner MD PhD, Heinrich J. Audebert MD, Philip M. Bath MD, Carlos A. Molina MD, Dar Dowlatshahi MD PhD, Kazunori Toyoda MD PhD

University of CINCINNATI

Objective

The objective of rFVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time (FASTEST) Trial is to establish the first treatment for acute spontaneous ICH within a time window and subgroup of patients that is most likely to benefit. The central hypothesis is that recombinant factor VIIa (rFVIIa) administered within 120 minutes from stroke onset with an identified subgroup of participants most likely to benefit will improve outcomes at 180 days as measured by mRS and decrease ongoing bleeding as compared to standard therapy.

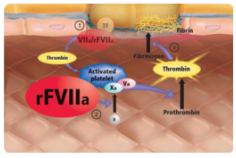
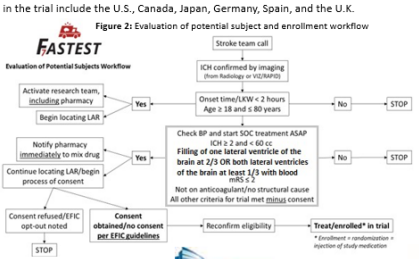


Figure 1: Mechanism of action of rFVIIa is that it binds to the surface of activated platelets in a TF-independent manner and promotes factor X (FX) activation and thrombin generation on the activated platelet surface

Study Design

Phase III, randomized, double-blind controlled trial of rFVIIa plus best standard therapy vs. placebo and best standard therapy alone. Participants with a volume of ICH ≥ 2 and < 60 cc, filling of one lateral ventricle of the brain at least 2/3 with blood, OR, filling of both lateral ventricles of the brain at least 1/3 with blood, age ≥ 18 and ≤ 80, GCS of ≥ 8, and treated within 120 minutes from stroke onset will be included. To minimize time-to-treatment, the study uses emergency research informed consent procedures (EFIC in the U.S.) and mobile stroke units (MSUs). FASTEST will include approximately 100 hospital sites including approximately 15 MSUs in the NINDS-funded StrokeNet and key global institutions with large volumes of ICH patients. Recruitment of 860 participants over 3½ years is planned. Countries participating in the trial include the U.S., Canada, Japan, Germany, Spain, and the U.K.

Figure 2: Evaluation of potential subject and enrollment workflow



Methodology

Participants are randomized in a double-blinded fashion to rFVIIa 80 µg/kg dose (maximum 10 mg dose) o placebo. Participants in both arms receive best standard therapy as per published AHA Guidelines for ICH including a target systolic blood pressure of 140 mm Hg. The primary outcome (ordinal mRS with the followir categories: 0-2, 3, and 4-6) is determined at 180 days, with additional assessments at 30 days and 90 days. measure growth of ICH, all participants have a baseline non-contrast CT of the head and a repeat scan at 24 hou Centralized volumetric measurements of ICH, IVH, and edema are performed for both time points.

Table 1: The events table illustrates participant evaluation at baseline , during hospital length of stay and follow-ups at 30, 90 and 180 days.

Event	Baseline	1-hour post-dose (±15 minutes)	24-hours from stroke onset/last known well (±6 hours)	Day 4/ Discharge, whichever is sooner	Day 30 (±14 days)	Day 90 (±14 days)	Day 180 (±14 day
Determination of eligibility	x						
Informed consent or EFIC process initiated	x						
Medical history	x						
Physical exam	x						
Vitals	x	x	x				
Demographic information	x						
NIHSS	x	x	x				
GCS	x						
mRS	x				x		
EQ-5D							
CT of head	x		x				
CTA of head	x (opt.)						
EKG	x						
Serum troponin	x		x				
Study medication administered/ Study enrollment	x						
Adverse event assessment		x	x	x	x		

Conclusion

356 participants have been enrolled as of January 20th, 2024. Currently there are 87active site MSUs and 34 OUS sites) with a per-month enrollment rate of 21.8 per month over the last year.

Trial Funding and Leadership

NINDS approved funding for trial (U01NS110772), additional funding approved in Japan. Novo Nordisk A/S providing rFVIIa/placebo and monitoring and after hour enrollments.

Protocol PIs: Joe Broderick (contact PI), James Grotta, Andrew Naidech, Jordan Elm (statistical PI).

National PIs: Thorsten Steiner (Germany), Philip Bath (U.K.), Carlos Molina (Spain), Dar Dowlatshahi (Canada), Kazunori Toyoda (Japan).

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

IND: 18150
NCT Number: 03496883
EudraCT Number: 2019-003722-25
Universal Trial Number: U1111-1201-0087
For more information regarding the FASTEST study please visit : https://www.clinicaltrials.gov/ct2/show/NCT03496883
Trial Website: https://www.nihstrokenet.org/fastest/home

NIH StrokeNet PREVENTION | TREATMENT | RECOVERY

MUSC MEDICAL UNIVERSITY of SOUTH CAROLINA

FASTEST

Northwestern Medicine Feinberg School of Medicine

New Sites... Welcome Aboard!

The following new sites were **released to enroll** in the *FASTEST* study during the last month.

Prisma Health Greenville Memorial Hospital, Greenville, SC

Site PI:
Sanjeev SIVAKUMAR, MD

UF Health Shands Hospital, Gainesville, FL

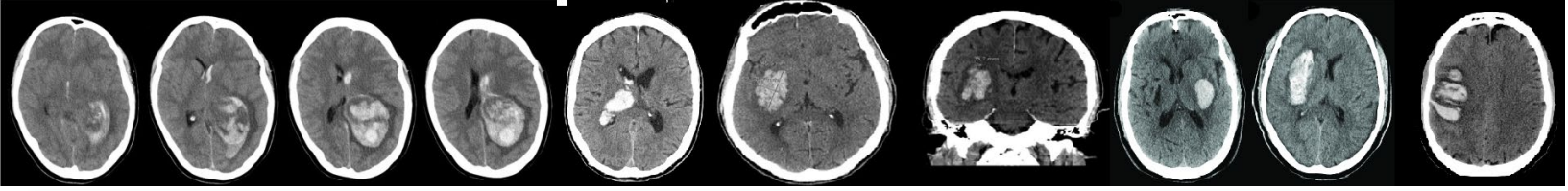
Site PI:
Anna KHANNA, MD

FAQ

QUESTION CORNER

Q: We enrolled a FASTEST Subject and during drug preparation, the wrong kit was pulled. The kit was opened, but not reconstituted. Can this kit be used for the next participant, or should we proceed with destruction/waste?
A: Kindly note that we do ask sites to use the kit with the lowest numerical number but there is no such thing as using the wrong kit. If you didn't use the lower kit number, that shouldn't be considered wrong, and you should still be able to use it. Since the kit was opened dispose of the study kit and request your pharmacist/PSC to include this in the comment section of WebDCU™ Site Drug Kit Removing form.

Q: During reconstitution our team worries about breaking the vial adapter part off. Can we use a saline vial on site and reconstitute the drug with that and a standard needle adapter vs using what is in the kit?
A: You can't utilize normal saline vials instead of histidine for reconstituting the study drug. Additionally, during reconstitution, we do not recommend adding additional punctures, especially since the drug is compounded in a non-sterile environment. However, once the drug is reconstituted and ready for use, you can obtain a syringe of the appropriate size from the local inventory. Remove the pre-filled histidine syringes from the study vials and use the "local" syringe to accurately draw up the required dose.



Q: As we were reading through the protocol, we noticed that it discusses e-consent as an option to obtain consent if the LAR is not available upon patient arrival. We were wondering if this was a process our site needs to set up/ be approved for? or is more of a matter of us obtaining access to the e-consent link? if not, is it just for us to make it available in Docusign under CFR part 11?
A: You have already agreed to use our central platform for eConsent. You can use eConsent in person or remotely. Please see the attached email that was sent to your site prior to releasing your site to enroll. Several of your study team have received eConsent training.

Q: In the event a patient is eligible and we working to obtain their data, is it necessary for us to have to enter all the data CRFs to lead to randomization? Or is it possible to submit only the most important CRFs to "launch" the randomization CRF and complete the CRFs later in the day? We are concerned that the data entry will consume critical time needed to dose the patient within the 2-hour window.
A: The expectation is that subjects will be randomized prior to being officially enrolled in WebDCU. You have 12 hours to complete the enrollment CRF post randomization.

Q: is there a specific amount contact attempts to the LAR before we proceed with enrolling under EFIC?
A: Protocol requires one attempt to reach an LAR prior to randomization but we ask sites to make all attempts to reach an LAR prior to randomization as time permits.

Q: If an LAR has been identified but they are not available to sign consent or come in person immediately, are we allowed to proceed with data collection and dosing under EFIC? or do we need a signed consent before being able to proceed with any study activity since an LAR has been identified?
A: Yes, you can leverage the use of verbal assent in this situation. Once the LAR arrives you can then get written consent. This will need to be documented as with all EFIC enrollments in the EFIC log in WebDCU until written consent is obtained from the LAR.

Q: We had a code come in today and was immediately intubated upon arrival. Do we use the GCS from prior to intubation or after?
A: GCS prior to intubation should be used.

Please send in your questions and we will address them accordingly and share with others in the next Newsletter.

SHOUT OUTS!!

Congratulations to all our US sites that have completed their EFIC reports and gained Advarra full study approval.

1. Washington University Barnes Jewish, St. Louis MI

Thank you to the sites recently released to enroll for their hard work:

1. **Prisma Health Greenville Memorial Hospital, Greenville, SC**
2. **UF Health Shands Hospital, Gainesville, FL- MSU site**

The Top Enrolling Site

Congratulations to **Kobe City Medical Center General Hospital, Kobe, Japan** for being the highest enrolling site in the study.

Subjects enrolled = 43!!

Congratulations to Enrolling Sites last Month!

Kobe City Medical Center General Hospital, Kobe, Japan	1 Subject
National Cerebral and Cardiovascular Center, Osaka, Japan	1 Subject
Kyushu Medical Center, Fukuoka, Japan	2 Subject
Iwate Prefectural Central Hospital, Morioka, Japan	1 Subject
NHO Osaka National Hospital, Osaka, Japan	1 Subject
University of Alberta Hospital, Edmonton, AB, Canada	3 Subject
Girona University Hospital, Girona, GI, Spain	1 Subject
Santa Creu and Sant Pau Hospital, Barcelona, B, Spain	1 Subject
Riverside Methodist Hospital, Columbus, OH	1 Subject
Memorial Hermann Texas Medical Center, Houston, TX	1 Subject
The Queen's Medical Center, Honolulu, HI	1 Subject
Toledo Hospital, Toledo, OH	1 Subject
Mayo Clinic, Jacksonville, FL	1 Subject
Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA	1 Subject
Charite University Medicine Berlin, Berlin, Germany	1 Subject
Tubingen University Hospital, Tubingen, Germany	1 Subject

SCIENCE CORNER

ARTICLE OF THE MONTH

Intensive Blood Pressure Reduction is Associated with Reduced Hematoma Growth in Fast Bleeding Intracerebral Hemorrhage

Qi Li, Andrea Morotti, Andrew Warren, Adnan I Qureshi, Dar Dowlatshahi, Guido Falcone, Kevin N Sheth, Ashkan Shoamanesh, Santosh B Murthy, Anand Viswanathan, Joshua N Goldstein

2023Ann Neurol. 2023 Sep 14. doi: 10.1002/ana.26795

Background: Patients with spontaneous intracerebral hemorrhage (ICH) at the highest risk of hematoma growth are those with the most potential to benefit from anti-expansion treatment. Large clinical trials have not definitively shown a clear benefit of blood pressure (BP) reduction. We aim to determine whether intensive blood pressure reduction could benefit patients with fast bleeding ICH.

Methods: An exploratory analysis of data from the Antihypertensive Treatment of Acute Cerebral Hemorrhage 2 (ATACH-2) randomized controlled trial was performed. In order to capture not just early bleeding (even if a small amount), but the rate of bleeding (ml/hour), we restricted the study to "Fast bleeding ICH," defined as an ICH volume/onset to computed tomography (CT) time >5 ml/hr. Hematoma growth, as defined as an increase of hematoma volume > 33% between baseline and 24 hours.

Results: A total of 940 patients were included (mean age = 62.1 years, 61.5% men), of whom 214 (22.8%) experienced hematoma expansion. Of these, 567 (60.3%) met the definition of "fast bleeding" with baseline ICH volume/time to presentation of at least 5 ml/hr. Intensive BP reduction was associated with a significantly lower rate of hematoma growth in fast bleeding patients (20.6% vs 31.0%, p = 0.005). In a subgroup of 266 (46.9%) fast-bleeding patients who received treatment within 2 hours after symptom onset, intensive BP lowering was associated with improved functional independence (odds ratio [OR] = 1.98, 95% confidence interval [CI] = 1.06-3.69, p = 0.031).

Interpretation: Our results suggest that early use of intensive BP reduction may reduce hematoma growth and improve outcome in fast bleeding patients. ANN NEUROL 2023.

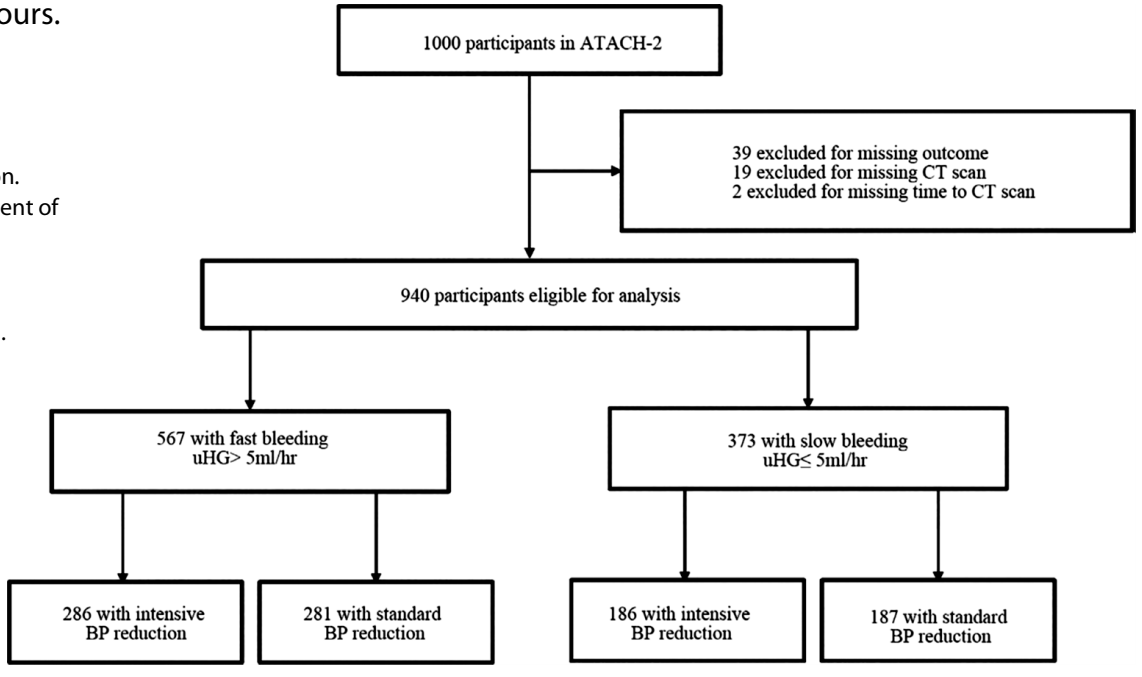


Figure: Flowchart of patient selection.
ATACH-2 = Antihypertensive Treatment of Acute Cerebral Hemorrhage 2
BP =blood pressure.
CT = computed tomography
uHG = ultra-early hematoma growth.

HELPFUL REMINDERS & TIPS

For Project Managers, Study Coordinators & Study Teams

- We have made a database change to **F144** Modified Rankin Scale. The changes are shown in the screenshot below and the new version (v3) is attached.

- If **Qd1** is answered as 'Yes', then you will be prompted to answer **Qd.**
- If **Qd1** is answered as 'No', then you will be prompted to answer **Qd2.**
- **Qd** is now a **drop-down box** that will include every study team member from your site. Select the name of the person who performed the assessment.
- Only those listed on the DOA delegated with responsibility (AB) should perform the assessment. If not, then this will be considered a Protocol Violation.

This programming update was made in hopes to reduce some data entry typos that impact data cleaning and to streamline the assessor questions across trials. This update will be implemented for a few other forms in FASTEST, and we will be in touch once those updates have been made.

Qd1		Assessment performed by study team member	○ No ○ Yes W
Qd	*If Qd1 is 'Yes'*	Study team member	R
Qd2	*If Qd1 is 'No'*	Reason assessment not performed by study team member	W 250 char.

- **Imaging Reminders:** Submit all head imaging performed as SOC within 30 hours from stroke onset to IMC (i.e., NCCT, CTA, MRI if performed)
  - Baseline/first scan obtained either in ED or MSU to determine trial eligibility AND prior to study product administration.
  - 24 (+/6) hours from stroke onset follow-up scan
  - "Unscheduled" scan obtained for clinical deterioration or immediately prior to any surgical intervention (i.e., surgical removal of ICH or IVC placement) if planned prior to 24-hour scan.
    ***Failure to obtain a pre-op scan results in missing imaging endpoint (i.e., ability to calculate ICH growth between baseline scan and unscheduled pre-op scan)

  Imaging must be submitted within 5-7 business days of subject randomization via the Ambra Health® platform.

  - Also includes submission of WebDCU F502 which is needed to process scans.

  ***Confirmation of receipt of ALL imaging is one of the requirements in triggering "Baseline through 24 hr. Payment" to your site.

From the *FASTEST* Central Pharmacy Team

- **Recent temperature excursions in IDS Pharmacy:** There have been recent reports of temperature excursions at certain sites related to the storage of the study drug within the pharmacy. We strongly encourage all site PSCs to proactively engage with their trial pharmacist. Regular communication and periodic checks with the pharmacist will help ensure the consistent monitoring of temperature conditions and mitigate the risk of excursions.
  - The TERF needs to be submitted to the NCC project manager and Strokenet central pharmacy as soon as possible.
  - The site pharmacists should remove the effected study drug by filling out the WebDCU form in a timely manner in order to trigger a resupply. The sites are advised to add more people to the DOA in order to expedite the process of documenting things in WebDCU if necessary.

INTERNATIONAL SITE OF THE MONTH

University Hospital Erlangen, Germany

The University Hospital Erlangen, Germany (Universitätsklinikum Erlangen – UKER) is the academic research and teaching hospital of the Friedrich-Alexander University Erlangen –Nuremberg (FAU). FAU is one of Germany's largest universities. The hospital is one of the leading healthcare facilities in Bavaria and offers top-class medical care distinguished by the close intertwining of clinical activities with research and training of medical students. The hospital was founded in 1815 and today is proud of its rich traditions, numerous medical achievements and an excellent reputation not only in Germany, but also in the international arena.

Since its founding in 1815, the University Hospital Erlangen has offered high-quality medical care. In the diagnostics and therapy, the latest medical research results and the most modern devices are used. The hospital has 25 specialized departments, 7 institutes and 41 interdisciplinary centers with approx. 1,378 beds. The hospital has the status of a maximum care center, and therefore it represents almost all fields of modern medicine. Oncology is represented by the Comprehensive Cancer Center Erlangen, which is one of 13 centers of excellence in Germany certified by the German Cancer Society. The university hospital has a high-tech center with high success rates for heart, liver, kidney, pancreas, cornea and bone marrow transplants. In addition, the hospital is a leader in the use of robot-assisted surgery. UKER has maintained its position in the top 100 of the World's Best Hospitals ranking in 2023.

The main focus in research and teaching is to be found at the interface between Natural Sciences, Engineering and Medicine.

Site PI: Joji KURAMATSU, MD

Joji Benjamin Kuramatsu, originally from Munich, pursued his medical studies at Friedrich-Alexander University in Erlangen-Nuremberg, Tsukuba University in Japan, and Washington University in St. Louis. Presently, he serves as the senior physician overseeing the intensive care unit at the neurological clinic, alongside his role as a trained intensive care physician. In this capacity, he oversees various prospective and randomized intensive care studies, including Investigator-Initiated Trials (IITs).

His primary research interests lie in clinical and experimental stroke research, which he conducts in collaboration with Prof. Dr. Hagen B. Huttner. Their research focuses extensively on the treatment and pathogenesis of hemorrhagic strokes. Together, they have spearheaded numerous national and international multi-center cooperation projects aimed at advancing our understanding and management of stroke-related conditions.

STUDY CONTACTS & USEFUL INFO

For any study related queries or help please reach out to ***FASTEST*** Project managers

International Sites: **Syed Quadri** (quadrisd@ucmail.uc.edu)

United States Sites: **Emily Stinson** (stinsoey@ucmail.uc.edu)

FASTEST Clinical Hotline: 1-855-429-7050

For more information regarding the ***FASTEST*** study please visit : https://www.nihstrokenet.org/fastest/home

For prior ***FASTEST*** Presentations and Webinars slides and recordings visit: https://www.nihstrokenet.org/fastest/webinars

For more information regarding the StrokeNet Trials please visit: https://www.nihstrokenet.org/