NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

APRIL 2024 | VOLUME 3 | ISSUE 4

FASTEST

FVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Steiner

Let's be clear - it's all about the whole: the hypothesis that reduction in hematoma growth equals improvement in clinical outcome has not been proven even 16 years after the publication of FAST. There are voices claiming that the hypothesis might not be correct. I don't think so. I believe that the decisive factor is that this study, with its challenges, especially with regard to the short treatment time, must be brought to an end in high quality. When I look at the latest figures, it seems to me that we are on the right track.

Professor Thorsten Steiner
Neurology and Neurointensive Care
Head of the Department of Neurology
Clinic Frankfurt Höchst, Germany
European Lead PI

Please join us for the *FASTEST* Monthly Webinar

Wednesday April 17th, 2:00-3:00 pm EST

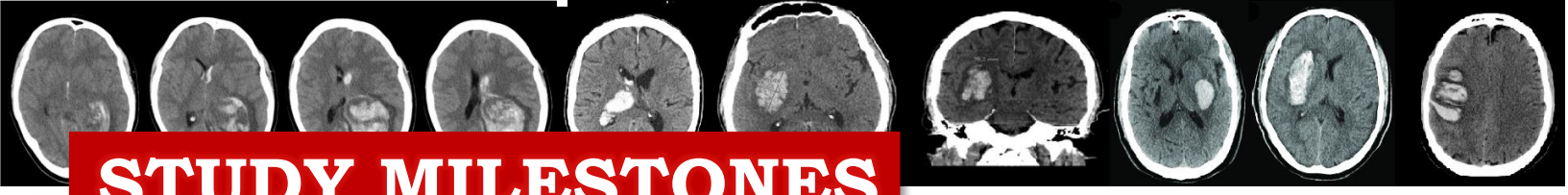
- Dr. Anna Khanna and her team from UF Health Shands Hospital, Gainesville, FL will be discussing case at their site.
- DSMB meeting update.
- Dr. Broderick will be discussing reporting requirements for SAE vs AE of special interest.
- Pharmacy update on IP shortage in US and plan for kit expiration 17 May
- NDMC will be discussing database updates

Join Zoom Meeting

https://ucincinnati.zoom.us/j/94084789726

Meeting ID: 940 8478 9726

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 = **435**

- US Randomizations: **125**
- International randomizations: **310**
  - Japan = **202**
  - Canada = **51**
  - Spain =**26**
  - Germany = **20**
  - UK = **9**

Randomization last month = **25**

Total Screen Failures = **1423**

Subjects Randomized by MSU = **16**

Subjects Terminated Early = **2**

eConsent Used = **16**

Remote Consent Used = **12**

CALENDAR OF EVENTS

Upcoming *FASTEST* Monthly Webinars: **Wednesday, April 17th, @ 2:00-3:00 pm EST**

FASTEST study team office hours: **Monday, April 22nd, @ 1:00-2:00 pm.**

IMPORTANT NOTE

FASTEST Study Drug Manufacturing Delays

We are currently experiencing delays in receiving a new study drug from Novo Nordisk for US sites, with a limited number of kits available at our central pharmacy. We are working on allocating them wisely until we receive the order from Novo.

Please note that FASTEST drug kits can be used up until their expiration date of 05/17/2024. We ask that you please **DO NOT** remove or destroy study drug **prior** to that date.

Our goal is to ensure that every enrolling location has a minimum of 1 kit available. We will resupply kits on a 1-1 basis, meaning your enrolling location must be at 0 prior to a new kit being sent out. For sites that have two enrolling locations (e.g., MSU and ED), please internally assign 1 kit to each enrolling location. For example, if your ED has no kits, but your MSU has 2, please transfer a kit from the MSU to the ED.

Note that this issue could lead to a temporary pause in enrollment at certain sites. This is a temporary issue that we are actively addressing. If you have any questions about resupply of study drug, please reach out to the StrokeNet Research Pharmacy at **FASTESTtrialRX@ucmail.uc.edu** or **513-584-3166**.

A memo from the *FASTEST* trial Pharmacy regarding this relevant information and updates was sent out last week to all PSCs.

PSCs, kindly disseminate this information among your pharmacy personnel and ensure they are informed by sharing the memo with them. It's essential to keep everyone updated.

Congratulations on 1st Enrollment!!!

Congratulations to Dr. Alejandro BUSTAMANTE RANGEL and his team at the Hospital Universitari Germans Trias i Pujol, Barcelona, B, Spain for enrolling their first subject

Congratulations to Dr. Joji KURAMATSUand his team at the University Hospital Erlangen, Erlangen, Germany for enrolling their first subject in FASTEST.

FAQ

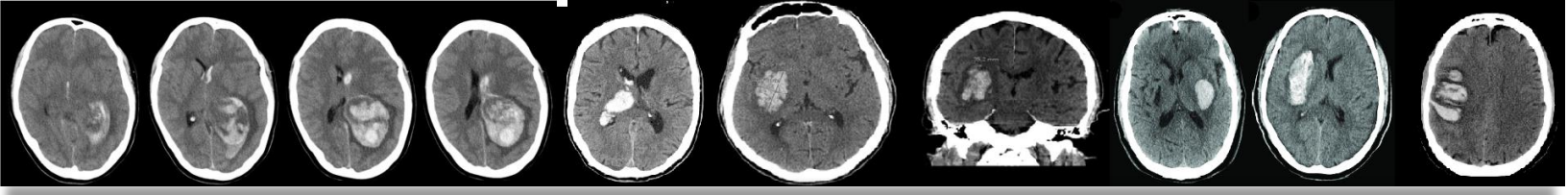
QUESTION CORNER

Q: An aneurysm was identified after enrollment. Is this a n eligibility violation?
A: The identification of an incidental aneurysm post-enrollment is not considered an eligibility violation.

Q: How many times can we preemptively begin to mix IP before it's considered a "waste" and advised we fix our workflow?
A: We will assess this on a case by case or site by site basis. Drug wastage has not been a big issue to date, and we have not had a site that seems to be wasting too much IP yet. We would prefer sites prepare the IP asap so this would not be a barrier to randomization. We have planned for IP wastage. But sites should confirm age, volume of ICH, IVH eligibility and time from onset prior to mixing medication. OK not have consented or identified family member.

Q: In WebDCU, will we be able to register a subject and release a dispensation before conferring ALL eligibility criteria since EFIC is now a factor?
A: Due to the hyper acute nature of the trial, we expect randomization to happen prior to enrollment of the subject into WebDCU. Sites are expected to enroll the subject into WebDCU within 12 hours of IP infusion. EFIC enrollments will require extra documentation in the EFIC log until written consent is obtained. Filling out the EFIC log should happen as soon as possible along with filling out the enrollment CRF's in WebDCU.

Q: We want to add the MSU manager to the DoA but I am not certain what role would be appropriate. She completed the CITI HSP but not the GCP as it is not a requirement for research in CDH. For her to be added as a sub-Investigator, she would need to complete the GCP training?
A: It really depends on what the investigator's role in the study will be. Will MSU manager be doing trial specific assessments or procedures? If so, then yes, she would need to be on the DoA and complete all the training required per her role and responsibilities. If she will be practicing standard of care duties NOT specific to the trial, then she would not be required to be on the DoA.



Q: Is there a number to reach study PI for enrollment queries?
A: Kindly contact the FASTEST Clinical (PI) Hotline **1-855-429-7050** for urgent matters related to safety, enrollment, and protocol. You can locate this number on the pocket cards, in the study protocol and MOP, and within the monthly FASTEST newsletter. Please stay on the line, and one of the three study PIs will promptly attend to your inquiry.

Q: Could you please assist me in understanding this statement and clarify whether our facility is required to initiate stroke screenings for patients already in the hospital when a "Code Stroke" is announced during their stay?
A: Yes, we are also enrolling subjects who have been admitted to the hospital and experience a stroke during their hospital stay. As mentioned in the data collection guidelines, your facility is expected to conduct stroke screenings for patients already in the hospital when a "Code Stroke" is announced. In the specific case you described, the patient should have been considered for enrollment in the FASTEST study if she met all the inclusion and exclusion criteria after screening. If the patient did not meet the criteria outlined in the inclusion and exclusion guidelines and was therefore not eligible for enrollment, they should have been documented in the screen failure log.

Q: In terms of females of child-bearing potential, is it mandatory to order the pregnancy test upon hospital admission as part of the enrollment eligibility process? or if the pregnancy test gets ordered on EPIC by the ED attending, does it need to be resulted to exclude pregnancy prior to administration of drug?
A: While the pregnancy test is recommended, it is not mandatory**.** However, it would be beneficial to conduct the test for women of childbearing age who do not have a legally authorized representative (LAR) accompanying them or do not have a confirmed pregnancy status. Notably, it is not a requirement prior to randomization because the drug **does not cross the placental barrier**, and there are no known adverse effects on the fetus.

Q: To our knowledge at the time of enrolment, the patient was not pregnant and gave birth last year. Unfortunately, we did not realize she was still lactating until after the fact. Also, her bedside exam (which included some mixed aphasia) was a bit limiting and husband did not provide additional details. Is this eligibility violation according to the exclusion criteria #22?
A: The lactation criterion is intended to identify women who have recently given birth and are at risk of venous thrombosis. Women who are lactating **beyond the 12-week postpartum period are not excluded from participation.** However, women who are breastfeeding at the time of enrollment should refrain from breastfeeding for 24 hours after drug administration, considering the study drug's half-life of 2-3 hours.

Q: Who can compound the study drug?
A: Trained Pharmacy staff, physicians (PI AND Sub-I) and RNs or trained Coordinators with a **medical license** including drug compounding within their scope of practice can compound and prepare study drug for administration. There is no need to delegate this responsibility on the DoA and should be a study team determination. Training on compounding study drug video can be found in the WebDCU training campus under the FASTEST project WebDCU™ Campus - Training Center (musc.edu).

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

SHOUT OUTS!!

Congratulations to US sites that have completed EFIC and have been approved for emergency consent

1. **Washington University Barnes Jewish, St. Louis MI**

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

1. **San Francisco General Hospital, San Francisco, CA**
2. **Kaiser Permanente Riverside Medical Center, Riverside, CA**

The Top Enrolling Site

Congratulations to **National Cerebral and Cardiovascular Center, Osaka, Japan** for being the highest enrolling site in the study.

Subjects enrolled = 52!!

Congratulations to Enrolling Sites last Month!

Kobe City Medical Center General Hospital, Kobe, Japan	1 Subject
National Cerebral and Cardiovascular Center, Osaka, Japan	5 Subject
Toranomon Hospital, Tokyo, Japan	2 Subject
Iwate Prefectural Central Hospital, Morioka, Japan	3 Subject
Kagoshima City Hospital, Kagoshima, Japan	2 Subject
Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan	1 Subject
University of Calgary - Foothills Medical Centre, Calgary, AB, Canada	1 Subject
Vancouver General Hospital, Vancouver, BC, Canada	1 Subject
University Hospital Heidelberg, Heidelberg, Germany	1 Subject
Ronald Reagan UCLA Medical Center, Los Angeles, CA	1 Subject
Barnes Jewish Hospital, St. Louis, MO	1 Subject
WellStar Kennestone Hospital, Marietta, GA	1 Subject
Toledo Hospital, Toledo, OH	1 Subject
Massachusetts General Hospital, Boston, MA	1 Subject
Riverside Methodist Hospital, Columbus, OH	1 Subject
Kaiser Permanente Fontana Medical Center, Fontana, CA	1 Subject
John Radcliffe Hospital, Oxford, United Kingdom	1 Subject

Hematoma Expansion Shift Analysis: A Novel Approach to Understanding Recombinant Factor VIIa in Intracerebral Hemorrhage

Adrian R. Parry-Jones

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Current hyperacute medical treatment for patients with intracerebral hemorrhage aims to reduce the risk of hematoma expansion.[1] However, no hemostatic or antifibrinolytic agent has thus far been shown to improve functional outcome.[2] When referring to hematoma expansion, we typically mean hematoma expansion after arrival in the hospital, which is clinically significant in ≈20% of patients.[3] Thus, the potential benefit to be gained by targeting hematoma expansion in the hospital will always be limited, as most patients will not expand anyway. In other words, we are targeting a complication that affects a minority and thus the majority cannot benefit. However, if a treatment has a risk of serious adverse effects, all patients, including the majority that would not have expanded, will be exposed to this risk. Thus, the odds are against us when targeting hematoma expansion. How then can we maximize the reduction in hematoma expansion?

It must be true that all hematomas expand in the prehospital phase so that the earlier we treat patients after onset, the greater the potential for benefit. This is supported by in hospital studies, which show an exponential increase in the probability of expansion as the time from symptom onset to baseline imaging decreases.[3] Decreasing the time from onset to treatment is thus likely to be central to maximizing benefit. Baseline hematoma volume is another key predictor of the risk of expansion, with a linear increase in risk up to ≈50 to 75 mL.[3] However, this is complicated by the fact that baseline hematoma volume is also a key predictor of functional outcome.[4] For example, those with smaller hemorrhages may be at a lower risk of expansion but may lose relatively more in terms of longer-term functional outcome. Contrast this with patients with larger hemorrhages at a higher risk of expansion but whose prognosis may be poor already, before expansion has even occurred. Another approach has been to target treatment toward those with a presumed higher risk of expansion using the computed tomography angiogram spot sign. However, this strategy has not proven beneficial in randomized clinical trials,[5,6] perhaps because the spot sign is not a strong predictor of the risk of expansion.[3] Furthermore, the spot sign is negative in many patients who later go on to expand[7] and a computed tomography angiogram adds time between onset and treatment, adding further delay to delivering treatment.

Around 80% of patients in the analysis are from the FAST trial (Factor Seven for Acute Hemorrhagic Stroke), published 15 years ago, which showed a significant reduction in hematoma expansion but no significant improvement in survival and functional outcome.[10] We have thus known for some time that this benefit in hematoma expansion seen with FVIIa does not seem to translate to clinical benefit. The FAST trial authors offered several possible explanations, including an increase in arterial thromboembolic events. Using more conventional analyses, the original article did not find a significant interaction between treatment effect and time from onset to treatment, despite a clear trend to less hematoma expansion with earlier treatment. Hematoma to less hematoma expansion with earlier treatment. Hematoma expansion shift analysis has now allowed a better understanding of how time and baseline hematoma volume may influence the treatment effect of FVIIa and has shown that hematoma expansion is similar across the spectrum of relative expansion. So, what are the implications of their findings?

Hematoma expansion shift analysis has further emphasized the importance of early treatment. The ongoing FASTEST trial (rFVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time) is aiming to deliver FVIIa within 120 minutes of onset in patients with intracerebral hemorrhage and a baseline hematoma volume of 2 to 60 mL, a Glasgow Coma Scale score of ≥8, and no more than a small volume of intraventricular hemorrhage.[11] FASTEST is using mobile stroke units to deliver treatment in the prehospital setting, a strategy likely to achieve rapid treatment. Mobile stroke units are costly and currently not available in many health care systems, so alternative, novel technologies for prehospital diagnosis of intracerebral hemorrhage will be needed to make early, prehospital treatment a reality for most patients with intracerebral hemorrhage.[12]

Second, hematoma expansion shift analysis suggests benefit for FVIIa across the spectrum of hematoma expansion. Thus, FVIIa may have synergistic effects with intensive blood pressure lowering, which appears to have the most benefit in patients at risk of high-volume hematoma expansion. Acute care bundles for intracerebral hemorrhage have already shown considerable benefit[13,14] and incorporating hemostatic treatments into future care bundles may help to increase benefit. If we are to improve outcomes for all patients with intracerebral hemorrhage, we need to consider other potential treatment targets once we have minimized the risk of hematoma expansion. Removal of larger hematomas using minimally invasive surgery has shown promise and is the subject of ongoing clinical trials. Finally, reducing secondary injury is likely to benefit all patients with intracerebral hemorrhage, targeting the universal damage that occurs when extravasated blood makes contact with brain tissue.

HELPFUL REMINDERS & TIPS

For Project Managers, Study Coordinators & Study Teams

- A new version of the **StrokeNet WebDCU User Manual** has been added to Project Documents within the Toolbox in WebDCU.

- **WebDCU CRFs updated:**
  - **F105 Laboratory Tests** – There has been a database update to (Q04) Troponin type, which added 'High sensitivity Troponin T' as a radio button. If your site reports this type of troponin, please update your CRFs.
  - **F101, F104, F126, F138, F143, F144** – These forms have had a database change that updated the assessor questions from a text field to a drop-down box. When completing these forms, please select the appropriate name for the study team member from the drop-down box.

- **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.

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/