NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

OCTOBER 2022 | VOLUME 1 | ISSUE 7

FASTEST

FVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Broderick

We want to announce very good news and also a strong plea to accelerate efforts to get your sites activated and recruiting. Advarra has approved sites to be opened for enrollment using only prospective consent until EFIC materials are approved. This allows sites to get up more quickly while EFIC efforts are ongoing. Our Data Safety Monitoring Board has also strongly recommended that we have 70 sites open for enrolment by end of 1/2023. Finally, we will be having a virtual investigator meeting for site PIs and coordinators on November 7th where we will discuss upcoming changes to the protocol and study progress.

September was our best month of enrollment so far with 8 randomizations and we strongly encourage continued enrollment as we move forward.

Joseph Broderick, MD
Director UC Gardner Neuroscience Institute
Director NIH StrokeNet
FATEST PI

Please join us for the *FASTEST* Monthly Webinar

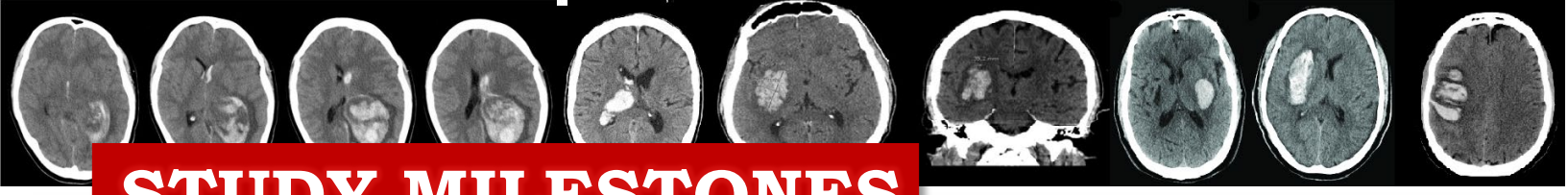
Wednesday October 19th, 2:00-3:00 pm EST

- Dr. Sven Poli from Tubingen University Hospital, Tubingen, Germany will be presenting their case and sharing their experience of enrollments at their center.

Join Zoom Meeting
https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fucincinnati.zoom.us%2Fj%2F95768343105%3Fpwd%3DZjYwZ0tNakxsN01qMmhPOE15N21Jdz09&data=05%7C01%7Cquadrisd%40ucmail.uc.edu%7C7b2505f4647443dd6b2e08da7ec1eb4c%7Cf5222e6c5fc648eb8f0373db18203b63%7C1%7C0%7C637961668587750683%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=40q90l8dB9QtZj9P5aZ0BeWkvzCsNx1WgQL9cFmISHQ%3D&reserved=0

Meeting ID: 957 6834 3105
Passcode: 111641

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



STUDY MILESTONES

Total Sites Released to Enroll: **39** (**18** USA, **3** Germany, **13** Japan, **1** Spain, **3** Canadian, **1** UK)

Total Randomization = **30**

- US Randomizations: **12**,
- International randomizations: **18** (6 Canadian, 3 Germany, 7 Japan, 2 Spain)

Randomization this month (last 30 days) = **7**

Total Screen Failures = **112**

Subjects Randomized by MSU = **1**

Subjects Terminated Early = **0**

eConsent Used = **0**

Remote Consent Used = **0**

CALENDAR OF EVENTS

Upcoming *FASTEST* Monthly Webinar: **Wednesday, October 19th @ 2:00-3:00 pm EST**

FASTEST study team office hours: **Monday, October 10th @ 2:00 pm EST**

FASTEST Investigator's Meeting: **Monday November 7th, 2022 @ 2:00 - 4:00 pm EST**

Important Update

During our July meeting with the DSMB the status of site activation was of concern. The DSMB is asking that all sites that have an approved EFIC plan, complete their EFIC activities and be activated by the end of this year, 2022.

Emily Stinson stinsoey@ucmail.uc.edu NCC Project Manager is the point of contact for EFIC. Please reach out to her for assistance if your site has not completed the EFIC process. The FASTEST study team is committed to help all remaining sites finish with EFIC and get open for enrollment as soon as possible.

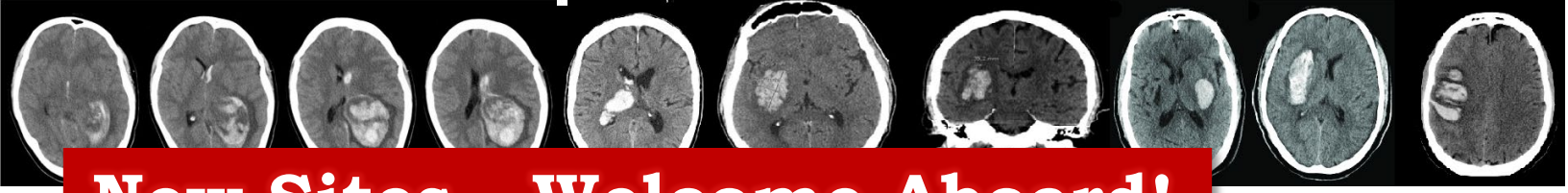
Please reach out us for guidance and updates.

SAVE THE DATE!!

FASTEST Investigator's Meeting

Monday November 7th, 2022
2:00 - 4:00 pm EST

Dr. Broderick and the StrokeNet NCC would like to invite all *FASTEST* investigators to attend the Annual *FASTEST* Investigator's Meeting to be held in the November 2022. The meeting will be held virtually. The invite and meeting link will be sent to all *FASTEST* investigators in November.



New Sites... Welcome Aboard!

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

Toranomon Hospital,
Tokyo, Japan

Site PI:
Takayuki Hara MD

Congratulations on First Enrollment!!

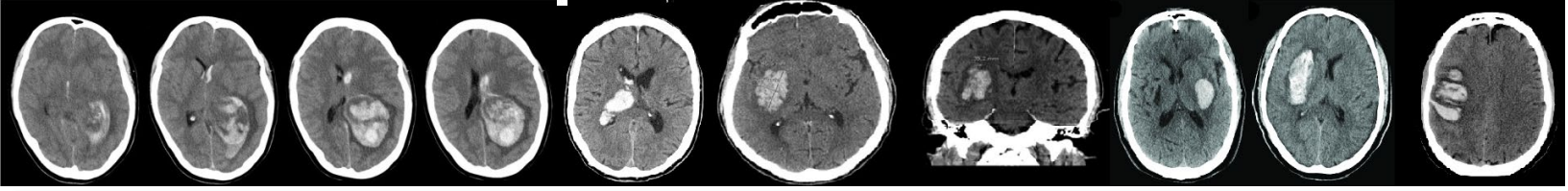
Congratulations Dr. Fumio Miyashita and team at the Kagoshima City Hospital, Kagoshima, Japan for enrolling their first subject in *FASTEST*.

FAQs

QUESTION CORNER

Q: In the Inclusion/Exclusion Criteria, anticoagulants are an exclusion and thrombocytopenia is addressed but how about antiplatelets such as aspirin, Plavix, Brillinta etc.?
A: No antiplatelet agents are an exclusion for the *FASTEST* trial.

Q: For BP management, how close to the target SBP of 140 mm Hg would be acceptable prior to initiating treatment? Should we follow the parameters (range 130-150 mm Hg) outlined in the concomitant medication section for medical management of ICH in the ICU?
A: The 140 systolic pressure is a target value. You can use what is listed in the American Heart Association guidelines for management of intracerebral hemorrhage as a guide. That is our reference. If you target 140, a little on the higher side of 140 is probably better.



Q: The MSU team is requesting for specific parameters for BP management for the trial. According to the team, it will be challenging to hit the specific target BP of 140 when the rig is on the move. They do not want to limit treating a patient with the study drug if they cannot stabilize BP to that target of 140. For example, if SBP decreases to 138 after BP management, will this potentially exclude the patient?

A: No, SBP around 140s is a target number over first hours when treatment starts. It is a guideline, not a requirement. Range is broad (140-160) and really is not what is expected in MSU. **Treatment with study medication should and can occur before any blood pressure medication is even administered.** In general, we aim for SBP around 150 and not much lower while in the MSU, and if SBP starts off really high (like > 220), maybe even 160s. However, kindly note that the BP treatment can be done in parallel with, or after getting the FASTEST study started, rather than requiring that the BP be controlled first.

Q: The consent form mentions that the study will be trying to keep systolic blood pressure at 140, but doesn't state why or how this will be done? Assuming with fluids and standard of care medications, it may be helpful to explain this further.

A: Blood pressure (BP) is the most important modifiable risk factor for intracerebral hemorrhage (ICH). Elevation in BP is common in acute ICH and is associated with greater hematoma expansion and poor clinical outcomes after ICH. Therefore, with BP management in acute spontaneous ICH the goals are to reduce hematoma expansion and perihematomal edema, improving the functional outcome. As explained above, try to keep systolic blood pressure at 140s. Systolic blood pressure (the first number) indicates how much pressure your blood is exerting against your artery walls when the heart beats. Keeping the systolic BP around a target of 140s will be done **using standard of care blood pressure medications that are used at a local institution**. BP in patients with ICH is usually elevated beyond this range.

Q: There is hematoma expansion/growth in our patient without clinically significant neurological deterioration/ worsening (24 hrs. NIHSS unchanged from baseline NIHSS?

A: Hematoma expansion/growth without clinically significant neurological deterioration/worsening should be documented as non-serious AE. This is similar to how we document the rise in troponin levels without clinically significant deterioration as non-serious AE.

Q: Do we also report AE and what is the timeline to report the Non-serious AEs?

A: All non-serious adverse events observed by the investigator or reported by the participant will be recorded from the time of randomization through **Day 4.** Kindly make note that these non-serious adverse events need to be reported in WebDCU™ within **5 days** of the site investigator's awareness of the event.

Q: Can we use our own temp. monitoring logs?

A: All areas where study drug is stored (including MSUs) must be monitored continuously for temperature excursions and the temperature monitoring system, at a minimum, must provide a daily minimum and maximum temperature. Sites may use their own institution-specific or electronic study drug temperature monitoring log to document temperature readings if such temperature log is deemed equivalent. The original Study Drug Temperature Log must be filed in the master file at the site and available for monitoring visits. There is a confusion among sites receiving emerald loggers from StrokeNet NCC that the NCC is responsible to to note any temperature excursion and inform us accordingly so that NOVO can be informed.

Q: Who can compound the study drug?

A: Trained Pharmacy staff, physicians (PI AND Sub-I) and 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 all our US sites that have completed their EFIC reports and gained Advarra full study approval.

Thank you to the sites recently released to enroll.

1. **Central DuPage**
2. **University of Utah**
3. **Memorial City**
4. **The Queens MC**
5. **University of Minnesota**
6. **M Health Fairview Southdale**

Thank you for sites scheduled for Readniness Calls

1. **Mills Peninsula**
2. **Promedica Toledo**

Thank you that have submitted to Advarra for CIRB review

1. **Providence St. Vincent**
2. **Cedar Sinai**
3. **Mayo Clinic Rochester**
4. **Regions**
5. **Temple**
6. **MUSC**
7. **Wake Forest**
8. **UAB**

Top Enrolling Site

Congratulations to **Memorial Hermann Hospital-Texas Medical Center** for being the highest enrolling site in the study.

Subjects enrolled = 6!!

Congratulations to the Enrolling Sites Past Month (30 days)!

Kyorin University Hospital, Tokyo, Japan	**2 Subject**
National Cerebral and Cardiovascular Center, Osaka, Japan	**1 Subject**
Memorial Hermann Memorial City Medical Center, Houston, TX	**1 Subject**
Memorial Hermann Texas Medical Center, Houston, TX	**1 Subject**
University of Calgary - Foothills Medical Centre, Calgary, AB, Canada	**1 Subject**
Kagoshima City Hospital, Kagoshima, Japan	**1 Subject**

Looking forward to 1st Enrollment from UK!

Focused Update on Vascular Risk and Secondary Prevention in Survivors of Intracerebral Hemorrhage

Kevin N. Sheth, MD; Magdy Selim, MD, PhD

Originally published27 Jun 2022 / https://doi-org.uc.idm.oclc.org/10.1161/STROKEAHA.122.039819 / Stroke. 2022;53:2128–2130

Intracerebral hemorrhage (ICH) is the most disabling and deadly stroke subtype globally. However, an improved understanding of the natural history of ICH, coupled with advances in neurocritical and stroke systems of care, have led to the possibility of higher rates of survival during the index hospitalization. Stroke caregivers, families, and patients now reckon with identifying and successfully implementing strategies for secondary prevention. Many of the clinical and scientific questions in recent years focus on the interplay between thrombosis and recurrent bleeding. ICH survivors and the stroke community struggle with determining these competing risks, applying available therapies, and communicating decision making in both domains. This Focused Updates summarizes the current knowledge of cardiovascular events after ICH, the clinical management of blood pressure, antithrombotics, and lipid-lowering medications. Surviving an ICH is the first step toward converting a potentially devasting acute condition into a disease of chronic management. Identifying and implementing strategies that optimize chronic disease management is the next.

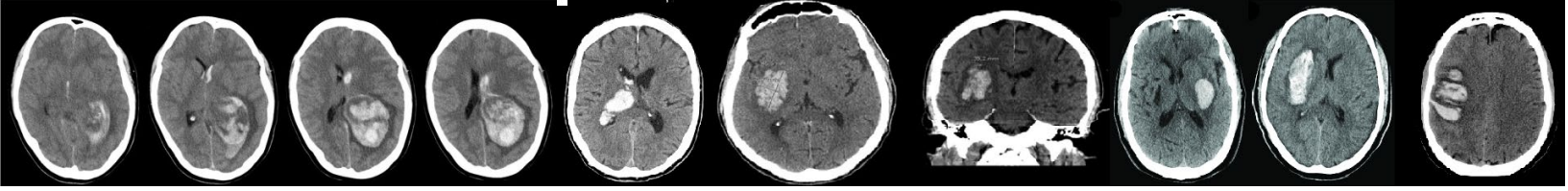
In this Focused Update, ICH survivors take center stage, and by definition, they have already defied the odds of not succumbing to the acute hospitalization. In contrast to ischemic stroke, where at least 50% of survivors have no or mild disability, ICH survivors on average have moderate to severe disability. The acute period following an ICH is often marked by an inability to ambulate independently, requiring assistance with activities of daily living, and cognitive decline. Transitions of care frequently include a recovery unit or a skilled nursing facility during a period in which coordination of care between primary care providers, neurologists and frequently cardiologists is needed. It is easy to see how this portrait can lead to pessimism and disengagement for chronic disease management, on the part of either the patient and family or the providers. Because prospective studies have demonstrated that an upward trajectory is possible in ICH survivors,1,2 we suggest that ICH survival is a moment when the stroke community should increase their engagement. In this Focused Update, as the contributors outline the current state of science for vascular management, we urge you to ask—how can this state of science reach my patient?

CARDIOVASCULAR EVENTS AFTER ICH

After ICH, recurrent vascular events, ischemic or hemorrhagic, are a leading cause of mortality, recurrent hospitalizations, and further decline. This is not altogether a surprise because many of the vascular risk factors that were present and led to the index ICH have not disappeared and as Li and Murthy articulate,3 the ICH may actually increase the probability of a recurrent event. Further, ineffective prevention of a recurrent event is likely to alter any recovery trajectory since a second event is usually not simply additive and could be fatal. Recurrent events are common for both lobar and non-lobar locations. Although rates of subsequent ischemic events are higher for non-lobar ICH, suggesting a stronger link between systemic vascular risk factors and recurrence, the rates of hemorrhagic events are higher after lobar ICH. Emerging evidence demonstrates the appearance of covert ischemic infarcts seen on diffusion weighted magnetic resonance imaging after ICH; their appearance is associated with an increased risk for recurrent clinical events and worse outcome. A second ICH can provide cumulative devastation, and the mechanism is often similar to that of the index ICH. This Focused Update places into context the systemic vascular events that occur after ICH as well, especially myocardial infarction, venous thrombosis, and pulmonary embolism. The risk assessment and communication of that assessment represents borderlands between primary care, neurology, and cardiology. To date, few recent investigations have assessed the potential for improved delivery of care in this area. In daily practice, we think that patients and providers are familiar with this challenge in communication across these borderlands.

BLOOD PRESSURE CONTROL AFTER ICH

In the majority of ICH survivors, blood pressure remains the most important modifiable risk factor. As Mullen and Anderson4 summarize in this Focused Update, elevated blood pressure is associated with a continuum of central nervous system and systemic events after an ICH. Blood pressure control is often categorized in terms of the acute emergency or inpatient management and the chronic or outpatient component. In the acute setting, clinicians are guided by the 2 most important phase III trials of blood pressure management, INTERACT2 (The Second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial) and ATACH-2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage II). The 2 clinical trials tested different interventions in varied populations, and results differed between them as well. However, individual pooled patient level meta-



analyses suggest that intensive treatment towards stable blood pressure can lead to improved outcomes.5 Treatment should be initiated within the first 2 hours of ICH onset. In patients with systolic blood pressure above 220 mm Hg or severe ICH, the safety and efficacy of lowering is less clear. The Focused Update further clarifies the role of ICH location in effect modification of these results. For example, patients with non-lobar ICH may be more likely to benefit from an intensive regimen. Recent analyses also suggest that reducing blood pressure from extreme levels and suggest that reducing blood pressure from extreme levels and to significant levels can cause kidney injury or neurological deterioration, so individual patient context and timing should be carefully considered. With regards to long-term prevention, in secondary analyses of stroke prevention trials such as PROGRESS (The Perindopril Protection Against Recurrent Stroke Study) and SPS3 (Secondary Prevention of Small Subcortical Strokes), there was a clear causal link between blood pressure reduction and less frequent ICH. Blood pressure management for ICH survivors has often been extrapolated from broader vascular risk populations. Mullen and Anderson provide a rationale to justify doing so, especially considering the consequence of persistent hypertension in ICH survivors and the dose-response link to recurrent ICH, as well as vascular events and a high frequency of cognitive decline. Suboptimal control of blood pressure and its consequences disproportionately affect under-represented populations. In this Focused Update section, the authors place in context ongoing pragmatic trials that focus on low-cost interventions and home blood pressure monitoring as potential strategies.

ORAL ANTICOAGULANT USE AFTER ICH

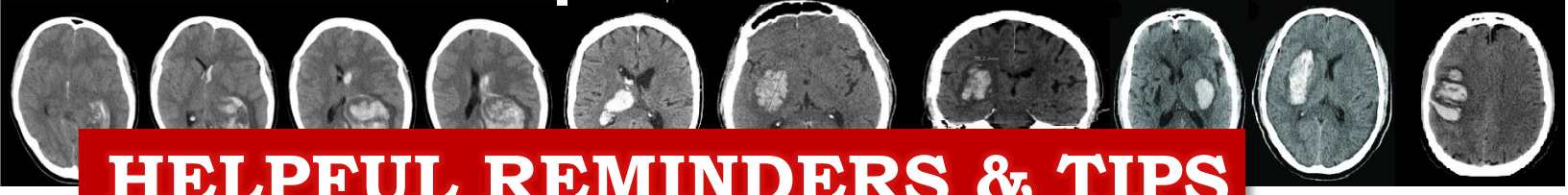
Atrial fibrillation coexists in as many as 20% of ICH survivors, and with the increase in aged population, this estimate has and will continue to increase. For patients and providers, the competing risks of recurrent ICH and thrombotic events such as ischemic stroke have led to great consternation.7 In this population, the mortality rate is particularly high, given that each of the 2 cardiovascular conditions (ICH and atrial f fibrillation) increase with age. For several decades, prior decision analyses and observational studies have yielded varying results, leading to significant practice variation for whether to initiate or resume anticoagulation. In routine non-ICH populations with atrial fibrillation, anticoagulation is under prescribed, in part because causing a hemorrhage may be perceived as "active" harm while the more common ischemic stroke is a "passive" harm. In an ICH population, in the context of a prior brain hemorrhage, the limbic weight of this dilemma takes even greater prominence. To date, until recently, there have been no randomized clinical trial data to provide the community with high quality information. Prior studies suggesting that anticoagulation may be associated with improved outcomes are likely highly susceptible to confounding by indication. Still, independent cohorts seem to suggest that even high-risk patients with cerebral amyloid angiopathy may benefit. In recent years, newer oral anticoagulants have an improved safety and efficacy profile in broad populations, and so the stage has been set for multiple randomized controlled trials in ICH survivors with atrial fibrillation. The first trials to report, SoSTART (Start or Stop Anticoagulants Randomized Trial) and APACHE-AF (Apixaban After Anticoagulation-Associated Intracerebral Hemorrhage in Patients with Atrial Fibrillation), show that the dilemma is real. Exposure to anticoagulation showed increased bleeding and reduced thrombotic events but both trials were underpowered to make any definitive claims on these end points. Finally, while left atrial appendage closure is a seemingly attractive treatment option since many feel that long-term anticoagulation may be avoided, but to date, few patients with ICH have been enrolled in previous trials. This treatment option is currently being investigated in ongoing trials in ICH populations.

USE OF LIPID-LOWERING DRUGS AFTER ICH

Hyperlipidemia is common in patients with ICH and is a risk factor for ischemic cardiovascular events. While intensive statin therapy is often recommended to reduce ischemic cardiovascular events, there is considerable uncertainty and lack of consensus regarding the optimal strategy for managing hyperlipidemia after ICH because only a handful of ICH survivors were enrolled in previous randomized controlled trials of various lipid-lowering therapies including stains' trials. In this focused updated, Shomanesh and Selim review existing literature to outline the competing risks of increased propensity for ICH and benefits of reducing ischemic events of lipid lowering treatments in ICH population. They suggest a treatment paradigm based8 on available data, but appropriately note that data from dedicated randomized trials are needed to build the necessary evidence to guide optimal lipid-lowering strategy in patients with a history of ICH.

CONCLUSIONS

We hope that this focused update will raise awareness of the heightened risk of future ischemic and hemorrhagic vascular events among ICH survivors and highlight best practices and current knowledge and evidence gaps for secondary prevention in this vulnerable population. While this focused update does not explicitly address the role of antiplatelet drugs, as well imaging predictors of future stroke risk, both topics will be covered in future issues. We emphasize the need for more coordination and collaboration between primary care providers, neurologists, and cardiologists caring for these patients; and endorse the participation of patients in ongoing randomized controlled secondary prevention ICH trials whenever possible to derive the necessary evidence to guide future preventive strategies.



HELPFUL REMINDERS & TIPS

For Project Managers and Study Teams

- **Clarification regarding Emerald Temp Loggers:** We would like to clarify the misperception among sites receiving the Emerald loggers from StrokeNet NCC for their MSUs and EDs that the NCC is not responsible to track or note any temperature excursions. We are ONLY providing technical assistance to set up the loggers for the respective sites. Like any other trial, **it is the sole responsibility of the site to note any temperature excursions** and inform us duly so that NOVO can be informed accordingly.

- **Syncing & Accessing Data from the Cloud:** Kindly ask the MSU staff to sync the Temp loggers regularly so that the data can be uploaded to the cloud. **You can download the PDF of the monthly temp log from the cloud for study records and internal or external audits.** No need to fill out a temp log manually. If the PSC or the MSU staff having any issues with the device kindly notify FASTEST Project Manager, Syed Quadri quadrisd@ucmail.uc.edu to further assist you with troubleshooting the device.

- **Requesting 48 hrs recording from the data logger:** We are asking all sites receiving the Emerald loggers to send us a 48 hrs recording/data after placing the device in the MSU or ED and before moving the study drug. This is to make sure that the temp. logger is set up properly and recording the data. Once we give approval you can move the drug to the MSU or ED.

- **Screen failure logs: Please update the screen failure logs in WebDCU screen failure data is very important to the study. As you are aware we will be reimbursing the sites for their screen failures.**

- **As you are completing EFIC events, please complete the CC and PD forms in WebDCU™**. The updated EFIC Forms Resource Guide is available in WebDCU™ (in the Toolbox under Project Documents) and is a very helpful tool for completing these forms. The FASTEST webinar from March 16th, 2021 (available at https://www.nihstrokenet.org/fastest/webinars) can provide additional tips. If you have questions in completing the forms, please feel free to reach out to the NCC. The NCC is also happy to review the forms and provide guidance and feedback along the way to ensure completeness.

From the *FASTEST* Central Pharmacy Team

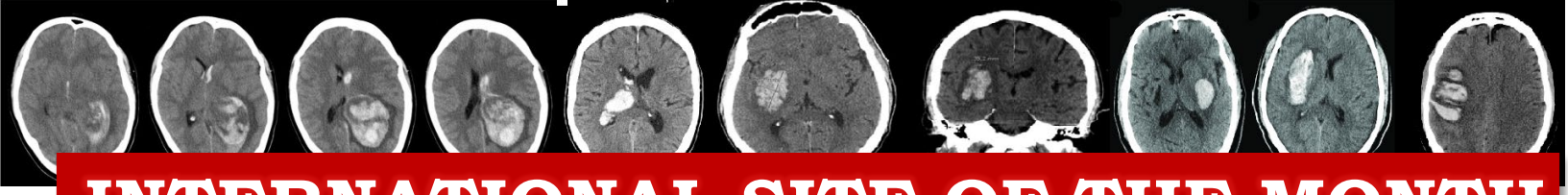
- While the IP has a wide temperature range and could be stored either refrigerated OR room temperature, we highly encourage sites to **choose one range** and **keep this range for the duration of the trial**.

- **Temperature excursion and monitoring: Please be very vigilant about temperature excursion and temperature monitoring documentation.**

- Please make sure to disseminate this newsletter to you site pharmacist/s too as it may contain helpful information regarding drug compounding, storage, accountability, etc.

- **Study Drug Shipment:** The Central Pharmacy will ship FASTEST study drugs few days prior to the readiness call. *FASTEST* IP will be shipped refrigerated. The initial study drug shipment will contain a total of two study drug kits to sites with one enrolling location (ED or MSU) and four study drug kits to sites that have two enrolling locations (ED+MSU) or 2 Eds

- **For the US sites**: Please upload the following regulatory documents into WebDCU for your site pharmacy to receive IP:
  - Institutional Pharmacy License
  - Institutional Drug Destruction Policy/SOP
  - Clinical Site Drug Shipping Address, Phone Number, and Contact Person



INTERNATIONAL SITE OF THE MONTH

Kyorin University Hospital, Tokyo, Japan

Site PI: Teruyuki Hirano, MD

Kyorin University Hospital is the only university hospital main campus in the Tama area of western Tokyo; an advanced acute care hospital that provides advanced medical treatment; and one of 85 special functioning hospitals in Japan with development, assessment, and training capabilities.

Kyorin University Hospital a key regional hospital for Tama area in western Tokyo, Kyorin University Hospital has been designated as an "advanced treatment hospital" by the Ministry of Health, Labor and Welfare in recognition recognition of its role as a center for advanced treatment, medical research and development, and education. Its Trauma and Critical Care Center is one of the largest emergency medical facilities in Japan, and its Maternal and Perinatal Center provides services around the clock in collaboration with obstetrics and neonatology.

The hospital's regular clinical divisions consist of 33 departments representing all major specialties of internal medicine and surgery, along with psychiatry and neurology, pediatrics, dermatology, radiology, anesthesiology, and rehabilitation. The Central Clinical Division consists of special units, including the Cancer Center, Stroke Center, Renal Dialysis Center, and Cognitive Disorder Center, as well as the Trauma and Critical Care Center, where teams of specialists use state-of-the-art equipment to provide advanced care and conduct clinical training. Altogether more than 2,000 medical professionals work in teams, in close communication, to deliver the kind of high-quality, conscientious care patients can trust.

Dr. Hirano and his team at the Kyorin University Hospital have been the highest enrolling Japanese site for FASTEST trial with 3 subjects enrolled so far.

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/

NIH StrokeNet
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