NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

JANUARY 2023 | VOLUME 2 | ISSUE 1

FASTEST

FVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Broderick

December was a great month for recruitment for the FASTEST Trial with 27 enrollments in 4 countries in spite of the holiday season. After 17 enrollments in November, we are on pace with our original projected recruitment rate during the last several months – and still are working to open many other sites. Japanese sites in particular have driven this randomization surge and we hope that sites in all countries will follow their lead. We already have 5 enrollments in first 7 days of January. Our goal is to have 65-70 sites of our expected 100 sites open to enrollment by beginning of February so please work hard in making this happen if your site is one of those which is getting close. We look forward to seeing those of you going to ISC in February at the Wednesday Night StrokeNet social event which includes FASTEST investigators.

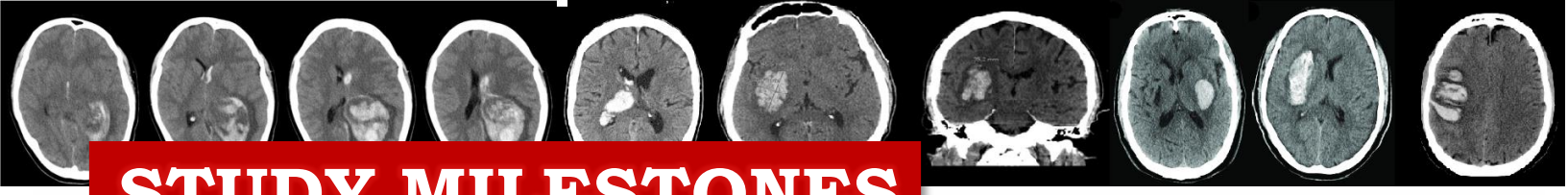
Joseph Broderick, MD
Director NIH StrokeNet
Director UC Gardner
Neuroscience Institute

There will be no *FASTEST* webinar in January.

Important Note

*** Globally, sites with high enrolling rates will receive supply to keep their inventory of **4 kits** instead of 2.

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



STUDY MILESTONES

Total Sites Released to Enroll: **49** (**24** USA, **25** OUS: **4** Germany, **14** Japan, **2** Spain, **4** Canadian, **1** UK)

Total MSUs Released to Enroll: **7** (**6** US and **1** OUS)

Total Randomization = **89**

- US Randomizations: **25**,
- International randomizations: **64** (**13** Canadian, **3** Germany, **43** Japan, **5** Spain)

Randomization last month = **27**
Total Screen Failures = **282**
Subjects Randomized by MSU = **1**
Subjects Terminated Early = **0**
eConsent Used = **2**
Remote Consent Used = **1**

CALENDAR OF EVENTS

FASTEST study team office hours: **Monday, January 16th @ 2:00 pm EST**

Congratulations on First Enrollment!!

Congratulations to Dr. Christopher STREIB and his team at the M Health Fairview Southdale Hospital, Edina, MN for enrolling their first subject in *FASTEST*.

Congratulations to Dr. Ramesh GRANDHI and his team at the University of Utah Healthcare, Salt Lake City, UT for enrolling their first subject in *FASTEST*.

Congratulations to Dr. Navdeep SANGHA and his team at the Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA for enrolling their first subject in *FASTEST*.

New Sites…Welcome Aboard!

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

Riverside Methodist Hospital, Columbus, OH

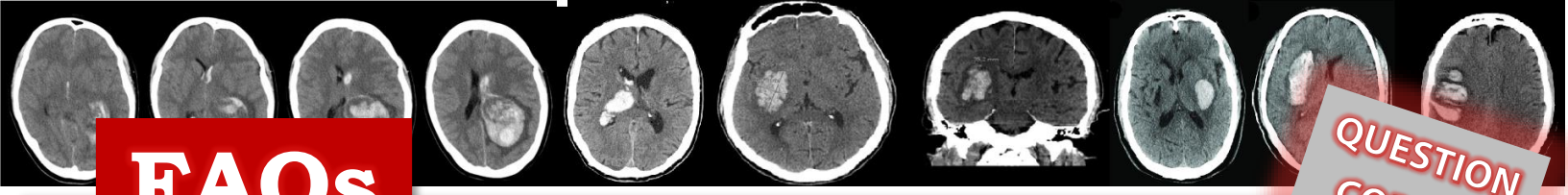
Site PI:
William J. Hicks, MD

OSU Wexner Medical Center, Columbus, OH

Site PI:
Yousef Hannawi, MD

Santa Creu and Sant Pau Hospital, Barcelona, Spain

Site PI:
Joan Martí-Fàbregas, MD, PhD



FAQs

QUESTION CORNER

Q: Can the baseline troponin be a "point of care" troponin? This is what is ordered and resulted for most of our stroke alert patients.
A: Yes, the baseline troponin is usually the "point of care" troponin done for stroke patients and is reported in F105-Laboratory Tests.

Q: Can we use the GCS from the ER staff?
A: Yes, as long as the GCS from the ER staff (licensed physician or nurse) is recorded in your EMR notes.

Q: If the data (ex. NIHSS, mRS, GCS etc.) is recorded in our EMR, you won't be expecting the hard copy NIHSS form to be in our subject binder, correct?
A: Please refer to the FASTEST Data Collection Guidelines on page 3. As per the guidelines specially the first two points (as below), the eCRFs should serve as the source document and can be used for site monitor review.

- Unless otherwise indicated, data can be directly entered into eCRFs, whereby the eCRF becomes the source document. A general comment should indicate that the eCRF is the source document to assist site monitors and reduce data clarification requests.
- eCRFs should be completed utilizing documentation from the legal medical record or other source data, whether it is paper or electronic. These source documents should be retained for site monitor review.

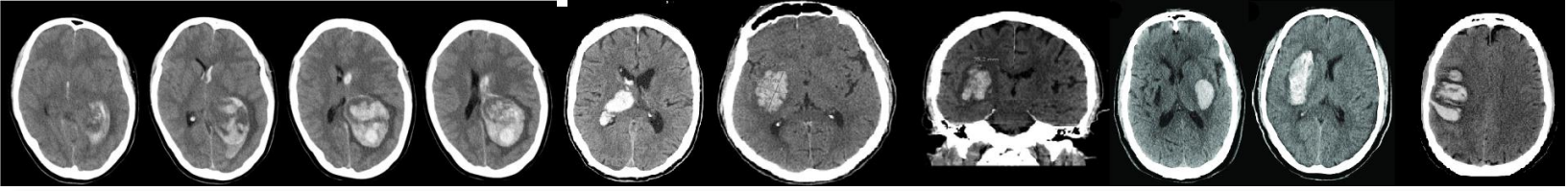
Q: If site fail to utilize the lowest kit number during the randomization, will that cause any queries when the research staff completes the enrolment form in WebDCU?
A: No, you will not get queries in WebDCU for not using the lowest kit number.

Q: Can we use estimated weight to calculate the IP dose?
A: Actual weight is preferred, but estimated weight **is acceptable.** Estimated body weight is appropriate to use for dosage determination, especially since we can't always wait for a stroke patient to be weighed. However, to ensure that there is no overdose and to calculate the dose check **we do need the sites to report the subject's actual weight** in the WebDCU. This can be done at any time during their hospitalization.

Q: Does the "rounding" rules apply to the drug dose? The patient's weight was 52.8, but we used the line for 51-52 kg for the dosing. It ended up being a 0.1 difference in dose. (The syringe only gives .5 marking, so it was hard to gauge the 0.1 anyway).
A: Yes, as explained above, **the rounding rule can be applied to the drug dose.** Estimated wait is appropriate to use, especially since we can't always wait for a stroke patient to be weighed. But since in this current example the weight of the patient was 52.8 (almost 53), it should have been rounded off as 53 kg. However, using 52 kg will not be of any harm to the patient or the study. As emphasized above, **we do require the study team to eventually enter the actual weight for the patient.**

Q: Is it required to utilize the histidine syringe provided OR it's okay to utilize our local syringe to administer study drugs for FASTEST?
A: We encourage sites to **stock appropriately sized syringes from local inventory alongside the study drug kits** (ex: 10 ml syringe) for two reasons:

1) To draw up the appropriate dose accurately - The volume on the histidine syringe provided is measured in 0.5ml increments (see picture). However. According to the dosing table and administration instructions, drug is given in 0.1 ml increments (example: for patient weight 90 kg, per USA and Canadian dosing card, dose administered should be 7.2 ml) A standard 10ml syringe is marked in 0.2ml increments and can be used for more accurate administration.



2) To administer study drug through incompatible needleless connector - The prefilled Histidine glass syringe provided in the kit (see picture) is compatible with a standard Luer-lock connector. However, some needleless connectors for intravenous catheters are incompatible with the glass diluent syringes (for example, certain connectors with an internal spike, such as Clave®/MicroClave®, InVision-Plus®, InVision-Plus CS®, InVision-Plus® Junior®, Bionector®), and their use can damage the connector and affect administration. In these scenarios, once the study drug is reconstituted (most likely you will need the two vials), leave the histidine syringe attached until it is ready for use. When it's ready to use, obtain an appropriate sized syringe from local inventory, remove the pre-filled histidine syringes from the study vials and use the "local" syringe to draw up the appropriate dose accurately.

Q: if we have a subject that needs 2 syringes, how do the other sites handle that. Do they try to put them into one syringe before doing the bolus, or do they just remove the first one and then attach the second one after the first is done.

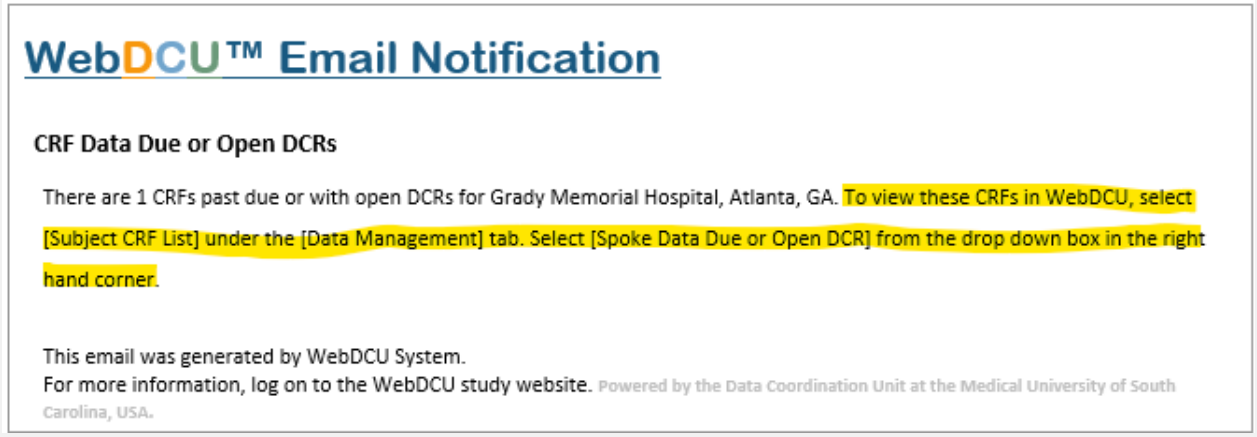
A: The two syringes issue has been confusing for some sites. We are recommending that sites use the two histidine diluent syringes for mixing the drug only. Once the vial is reconstituted with the histidine, we recommend that the histidine syringe be removed, and the actual dose of drug be drawn up with a single 10ml syringe from the site's local inventory. So, say a patient needed 8.2ml of drug, they would reconstitute the two vials with the histidine syringes, remove the histidine syringes, and then use a single 10ml syringe to draw up 5ml from one vial and 3.2ml from another. This is advantageous because you only need one syringe for the dose, and the 10ml syringes are marked in 0.2ml increments so it is easier to draw up a specific dose.

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: My site received a WebDCU email notifying us that we have data overdue and/or open DCRs. How do I find these in the database?

A: You can get to these quickly by following the directions in the email notification:



WebDCU™ Email Notification

CRF Data Due or Open DCRs

There are 1 CRFs past due or with open DCRs for Grady Memorial Hospital, Atlanta, GA. To view these CRFs in WebDCU, select [Subject CRF List] under the [Data Management] tab. Select [Spoke Data Due or Open DCR] from the drop down box in the right hand corner.

This email was generated by WebDCU System.
For more information, log on to the WebDCU study website. Powered by the Data Coordination Unit at the Medical University of South Carolina, USA.

Likewise, the email notification for overdue visits also includes directions on how to find a list of which subjects are overdue in WebDCU.

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 for their hard work

1. **Riverside and MSU**
2. **Ohio State University**
3. **Temple University**
4. **Santa Creu and Sant Pau Hospital, Barcelona, Spain**

Thank you to the sites that have gotten CIRB/REB/EC approval and preparing for readiness

1. **Mayo Clinic**
2. **Providence St. Vincent**
3. **Regions MC**
4. **Banes Jewish**
5. **St. Joseph MC**
6. **Thomas Jefferson**
7. **Medical College of South Carolina**

Top Enrolling Site

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

Subjects enrolled = 14!!

Congratulations to the December Enrolling Sites!

National Cerebral and Cardiovascular Center, Osaka, Japan	**5 Subjects**
Memorial Hermann Texas Medical Center, Houston, TX	**3 Subjects**
Kobe City Medical Center General Hospital, Kobe, Japan	**2 Subjects**
Gifu University Hospital, Gifu, Japan	**2 Subjects**
Iwate Prefectural Central Hospital, Morioka, Japan	**2 Subjects**
Vall d'Hebron Hospital, Barcelona, Spain	**2 Subjects**
University of Calgary - Foothills Medical Centre, Calgary, AB, Canada	**2 Subjects**
Kagoshima City Hospital, Kagoshima, Japan	**1 Subject**
Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan	**1 Subject**
Toranomon Hospital, Tokyo, Japan	**1 Subject**
Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA	**1 Subject**
University of Utah Healthcare, Salt Lake City, UT	**1 Subject**
M Health Fairview Southdale Hospital, Edina, MN	**1 Subject**
The Queen's Medical Center, Honolulu, HI	**1 Subject**
University of Cincinnati Medical Center, Cincinnati, OH	**1 Subject**
Ottawa Hospital, Ottawa, ON, Canada	**1 Subject**

SCIENCE CORNER

RESEARCH ARTICLE OF THE MONTH

Ischemia in intracerebral hemorrhage: A comparative study of small-vessel and large-vessel diseases

Ailing Zhang, Mengyang Ren, Wenjing Deng, Meijing Xi, Long Tian, Zhuoya Han, Weiping Zang, Hao Hu, Bin Zhang, Ling Cui, Peihong Qi , Yingjie Shang

Originally published 12 January 2022/ https://doi.org/10.1002/acn3.51497 / Ann Clin Transl Neurol. 2022 Jan; 9(1): 79–90.

Background:

This study aimed to compare effects of cerebral small-vessel disease (cSVD) burden and cerebral artery stenosis (CAS) on acute ischemia in intracerebral hemorrhage (ICH) and their interaction with mean arterial pressure (MAP) change.

Methods:

We recruited consecutive patients with acute primary ICH. Brain magnetic resonance imaging and angiography were performed to quantify diffusion-weighted imaging (DWI) lesions, CAS, and cSVD markers, which were calculated for the total cSVD score. Multivariable regression models were adopted to explore their associations by DWI lesions size (<15 vs. ≥15 mm) and median MAP change stratification.

Results:

Of 305 included patients (mean age 59.5 years, 67.9% males), 77 (25.2%) had DWI lesions (small, 79.2%; large, 20.8%) and 67 (22.0%) had moderate and severe CAS. In multivariable analysis, small DWI lesions were independently associated with higher total cSVD score (odds ratio [OR] 1.81, 95% confidence interval [CI] 1.36-2.41). and large DWI lesions were associated with more severe CAS (OR 2.51, 95% CI 1.17-5.38). This association was modified by MAP change (interaction p = 0.016), with stratified analysis showing an increased risk of large DWI lesions in severe CAS with greater MAP change (≥44 mmHg) (OR 3.48, 95% CI 1.13-10.74) but not with mild MAP change (<44 mmHg) (OR 1.21, 95% CI 0.20-7.34).

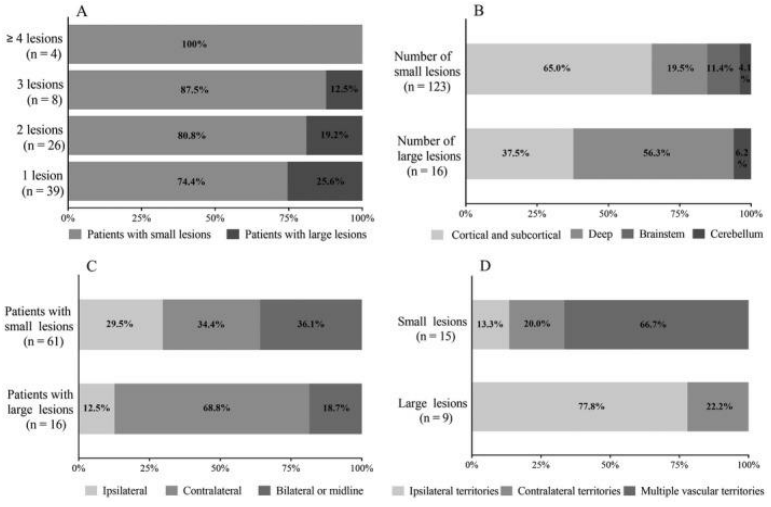


Figure 3: Number, size, location, and distribution of DWI lesions. (A) Number and size of DWI lesions; (B) location of DWI lesions; (C) laterality relative to hematoma; (D) territory distribution in moderate to severe artery stenosis. DWI, diffusion-weighted imaging.

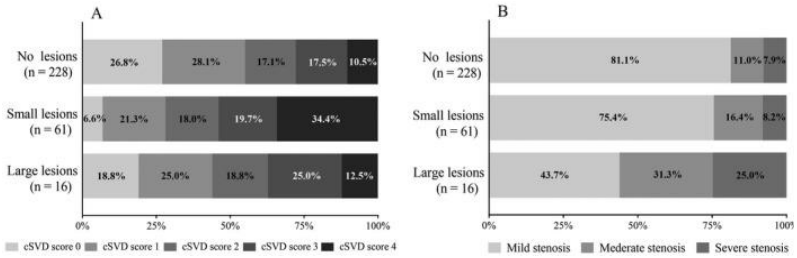


Figure 4: (A) Distribution of total cSVD burden. (B) Distribution of cerebral artery stenosis. cSVD, cerebral small-vessel disease.

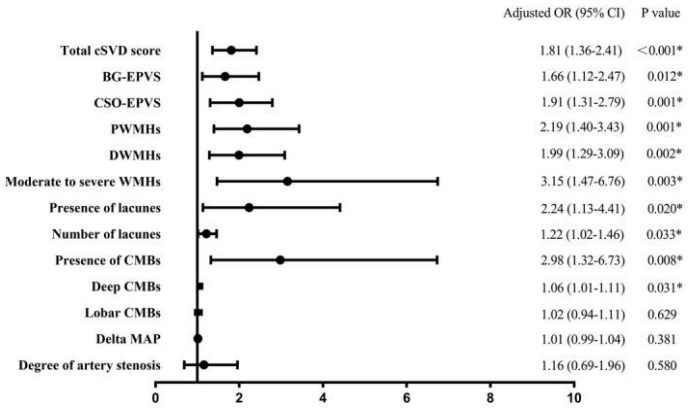


Figure 5: Multivariate analysis for the association of small DWI lesions with cSVD and CAS. Adjusted for age, sex, body mass index, hypertension, diatetes mellitus, ischemic stroke, smoking, initial systolic blood pressure, initial hematoma volume, subarachnoid extension, pneumonia, initial National Institute of Health Stroke Scale, hemoglobin A1c, delta MAP, and CAS. DWI, diffusion-weighted imaging; cSVD, cerebral small-vessel disease; CAS, cerebral artery stenosis; MAP, mean arterial pressure.

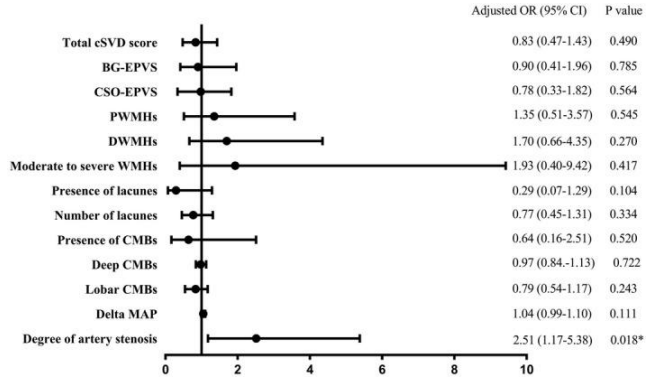
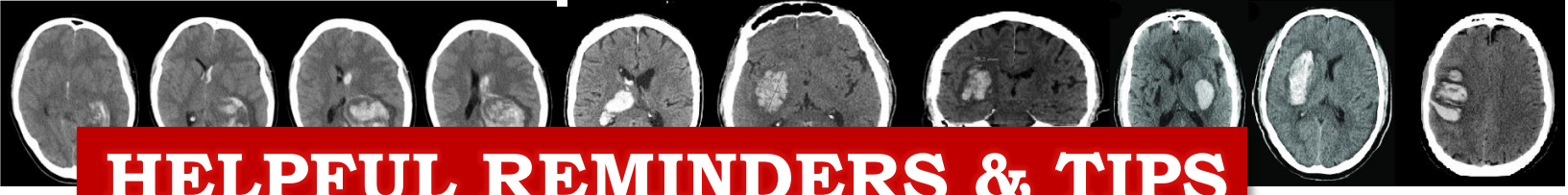


Figure 6: Multivariate analysis for the association of large DWI lesions with cSVD and CAS. Adjusted for age, sex, body mass index, hypertension, diatetes mellitus, ischemic stroke, smoking, initial systolic blood pressure, initial hematoma volume, pneumonia, initial National Institute of Health Stroke Scale, fasting blood; delta MAP, and CAS. DWI, diffusion-weighted imaging; cSVD, cerebral small-vessel disease; CAS, cerebral artery stenosis; MAP, mean arterial pressure.

Conclusions:

Total cSVD burden is associated with small DWI lesions, whereas the degree of CAS is associated with large DWI lesions, specifically with greater MAP change, suggesting that large-artery atherosclerosis may be involved in ischemic brain injury, which is different from small-vessel pathogenesis in ICH.



HELPFUL REMINDERS & TIPS

For Project Managers and Study Teams

- **WHAT IS NEW IN THE TOOLBOX?** Pharmacy TERF Example Filled out form has been added to the FASTEST toolbox in WEbDCU.
- **Follow-up labs and imaging:** The follow-up non-contrast CT of the head and Serum troponin need to be obtained at **24±6 hours from stroke onset/last known well** as per the study Table of Events.
- **Pharmacy documents in Toolbox:** Any documents that are pharmacy/drug related will be categorized as "pharmacy" in the toolbox starting on/before **2/1/2023**.
- **Adding new study members:** Please update your DOA logs and upload the training documents to WebDCU as soon as you add a new study member to your FASTEST study team. All sites currently released to enroll kindly make sure your DOAS are up to date.
- **Reporting SAE within 24 hours:** We would like to emphasize all sites on the timely reporting of the SAEs. Kindly note that all SAEs must be reported in WebDCU™ **within 24 hours** of site awareness of the event and must be followed for the duration of the study follow-up or until resolution, whichever comes first.
- **CRF Completion within 24 hours:** We would like to emphasize all sites on the timely completion of the case report forms (CRFs) **within 24 hours** of the visit (Baseline, 1-hour, 24-hour, Day 4/ Discharge). For the follow-up visits (Day 30, Day 90, Day 180, and End of study) which have a window of ±14 days please fill out the CRS as soon as the follow up visit has been completed.
- **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.**

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**

INTERNATIONAL SITE OF THE MONTH

Santa Creu and Sant Pau Hospital, Barcelona, Spain

Founded around 600 years ago, the "Hospital de la Santa Creu i Sant Pau" developed from a medieval welfare house into a modern hospital complex. It is a highly complex center which, with six centuries of existence, represents the leading hospital institution in Spain. The hospital is mainly centered in Barcelona and extends throughout Catalonia, in addition to having a notable impact in the rest of the State and an important international projection.

The Hospital de la Santa Creu i Sant Pau (Hospital of the Holy Cross and Saint Paul) has its origins in the year 1401 with the merger of the six hospitals then existing in Barcelona into one larger one that would be governed by representatives of the city and the Church through of the Very Illustrious Administration (MIA), an institution that has lasted to this day.

The architectural ensemble of the Hospital de la Santa Creu i Sant Pau is a very important reference for the heritage and culture of the city of Barcelona, in particular, and of Catalonia, in general. It is one of the most prominent works of the Catalan modernisme architect Lluís Domènech i Montaner. The complex was listed as a Conjunto Histórico in 1978 and declared a UNESCO World Heritage Site in 1998.

Site PI: Joan Marti Fabregas, MD, PhD

Dr. Joan Marti Fabregas, MD, PhD, is the Head of Neurology at Hospital de la Santa Creu i Sant Pau.

Dr. Fabregas's research is focused on clinical investigation about intracerebral hemorrhage and on reperfusion therapies in acute ischemic stroke (intravenous thrombolysis and mechanical thrombectomy).

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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