NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

NOVEMBER 2022 | VOLUME 1 | ISSUE 8

FASTEST

FVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Broderick

It is an exciting time for the FASTEST Trial. We just had a day in the last week where we randomized 3 patients in 24 hours in 3 different countries! We have also considered how we can make the enrollment of patients easier for physician investigators in terms of imaging. As described in our virtual investigator meeting on November 7th, we are submitting a protocol amendment to the FDA this month that changes the IVH exclusion from an IVH score > 7 to "Blood filling 2/3 or more of one lateral ventricle of the brain, OR blood filling at least 1/3 of both lateral ventricles". This won't go into effect until after the FDA and CIRB approval (likely in late winter of 2023) so please continue to use the IVH > 7 until that time. If you didn't attend the meeting, please review the presentation on the StrokeNet FASTEST website that provides a lot of examples. Go FASTEST!

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

On National Pharmacy Week last October!

To all our site pharmacists and pharmacy technicians, **THANK YOU** for striving to do what's best for our patients. You are vital to the overall success of FASTEST trial, and you are much appreciated!

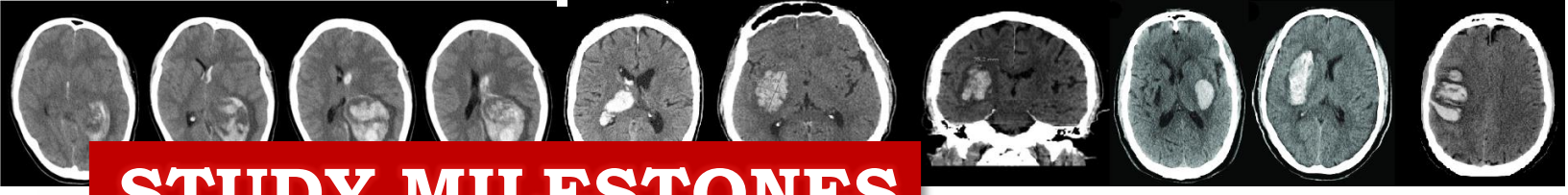
Best,

NIH StrokeNet pharmacy team
NIH StrokeNet National Coordinating Center

There will be no *FASTEST* Monthly Webinar In November

Next webinar will be held on December 21st, 2022

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



STUDY MILESTONES

Total Sites Released to Enroll: **45** (**21** USA, **24** OUS: **4** Germany, **14** Japan, **1** Spain, **4** Canadian, **1** UK)

Total MSUs Released to Enroll: **6** (**5** US and **1** OUS)

Total Randomization = 46

- US Randomizations: **14**,
- International randomizations: **32** (9 Canadian, 3 Germany, 18 Japan, 2 Spain)

Randomization last month = **9**
Total Screen Failures = **165**
Subjects Randomized by MSU = **1**
Subjects Terminated Early = **0**
eConsent Used = **0**
Remote Consent Used = **0**

CALENDAR OF EVENTS

FASTEST study team office hours: **Monday, November 21st @ 2:00 pm EST**

Important Update

FASTEST investigators meeting 2022

We recently had the 2022 FASTEST investigator's meeting in which the PI Dr. Broderick presented the summary of study progress so far. The investigators were briefed about the proposed changes in the protocol and statistical analysis plan. The IVH criteria change and changes in Troponin case report form were also discussed with the study investigators.

The video of this webinar can be accessed at https://www.nihstrokenet.org/fastest/webinars. The password for the video is *Faster*.

DSMB

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.

New Sites... Welcome Aboard!

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

Charite University Medicine Berlin, Berlin, Germany

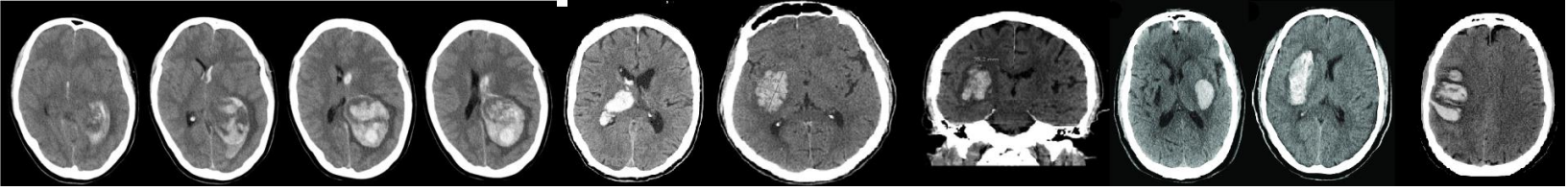
Site PI:
Christian Nolte MD

Wake Forest Baptist Medical Center, Winston-Salem, NC

Site PI:
Mustapha A. Ezzeddine MD

Iwate Prefectural Central Hospital, Morioka, Japan

Site PI:
Naoto Kimura



Wake Forest Baptist Medical Center, Winston-Salem, NC

Site PI:
Mouhammad Jumaa, MD

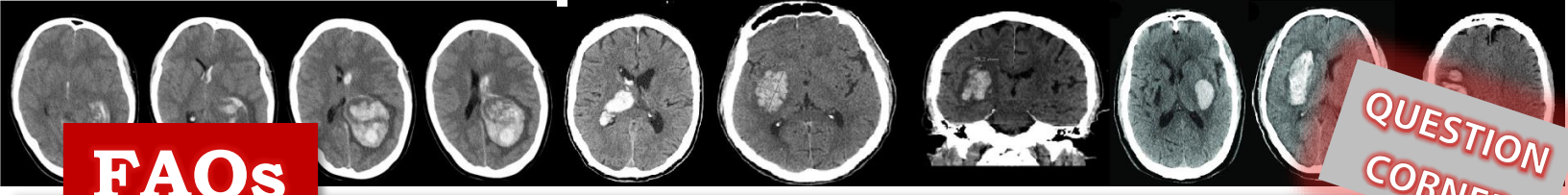
Mills Peninsula Medical Center, Burlingame, CA

Site PI:
Ilana Spokoyny, MD

Congratulations on First Enrollment!!

Congratulations Dr. Toru IWAMA and his team at the Gifu University Hospital, Gifu, Japan for enrolling their first subject in *FASTEST*.

Congratulations Dr. Yoshinari NAGAKANE and his team at the Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan for enrolling their first subject in *FASTEST*.



FAQs

QUESTION CORNER

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 queriers 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.

Q: For site with two enrolling sites (ED and MSU) how the study team should distribute the four kits provided by StrokeNet pharmacy?
A: Site will determine the flow that works best for managing their inventory and documenting which kit is in which location utilizing the accountability and chain of custody forms. Generally, since we assume that the randomization rate will be higher at the MSUs, we encourage that each MSU (depending on space) to always keep two kits (with the lowest kit numbers), once one kit is used for randomization on an MSU, the inventory should come from the emergency room supply (or investigational pharmacy) to substitute the used kit.

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 like 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 note any temperature excursion and inform us accordingly so that NOVO can be informed.

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. **Sunnybrook Health Sciences Center**
2. **Charite University Medicine Berlin**
3. **Iwate Prefectural Central Hospital**
4. **Toledo Hospital**
5. **Wake Forest Baptist Medical Center**
6. **Mills Peninsula Medical Center**

Thank you for sites scheduled for Readiness Calls

1. **Mayo Clinic Rochester**

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 **Foothills Medical Centre, Calgary, AB, Canada** for being the highest enrolling site in the study.

Subjects enrolled = 7!!

Congratulations to the October Enrolling Sites!

Kobe City Medical Center General Hospital, Kobe, Japan	**2 Subject**
Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan	**1 Subject**
Gifu University Hospital, Gifu, Japan	**1 Subject**
Memorial Hermann Texas Medical Center, Houston, TX	**1 Subject**
University of Calgary - Foothills Medical Centre, Calgary, AB, Canada	**2 Subject**
University of Cincinnati Medical Center, Cincinnati, OH	**1 Subject**

Looking forward to 1st Enrollment from UK!

SCIENCE CORNER

RESEARCH ARTICLE OF THE MONTH

Prehospital transdermal glyceryl trinitrate in patients with presumed acute stroke (MR ASAP): an ambulance-based, multicentre, randomised, open-label, blinded endpoint, phase 3 trial

Sophie A van den Berg*, Simone M Uniken Venema*, Hendrik Reinink, Jeannette Hofmeijer, Wouter J Schonewille, Irene Miedema, Puck S S Fransen, D Martijn O Pruissen, Theodora W M Raaijmakers, Gert W van Dijk, Frank-Erik de Leeuw, Jorine A van Vliet, Vincent I H Kwa, Henk Kerkhoff, Alex van 't Net, Rene Boomars, Arjen Siegers, Tycho Lok, Klaartje Caminada, Laura M Esteve Cuevas, Marieke C Visser, Casper P Zwetsloot, Jooske M F Boomsma, Mirjam H Schipper, Roeland P J van Eijkelenburg, Olvert A Berkhemer, Daan Nieboer, Hester F Lingsma, Bart J Emmer, Robert J van Oostenbrugge, Aad van der Lugt, Yvo B W E M Roos, Charles B L M Majoie, Diederik W J Dippel, Paul J Nederkoorn†, H Bart van der Worp†, for the MR ASAP Investigators‡

Originally published September 01, 2022 / DOI: https://doi.org/10.1016/S1474-4422(22)00333-7 / Lancet Neurol 2022; 21: 971–81

Background: Pooled analyses of previous randomized studies have suggested that very early treatment with glyceryl trinitrate (also known as nitroglycerin) improves functional outcome in patients with acute ischaemic stroke or intracerebral haemorrhage, but this finding was not confirmed in a more recent trial (RIGHT-2). We aimed to assess whether patients with presumed acute stroke benefit from glyceryl trinitrate started within 3 h after symptom onset.

Methods: MR ASAP was a phase 3, randomised, open-label, blinded endpoint trial done at six ambulance services serving 18 hospitals in the Netherlands. Eligible participants (aged ≥18 years) had a probable diagnosis of acute stroke (as assessed by a paramedic), a face-arm-speech-time test score of 2 or 3, systolic blood pressure of at least 140 mm Hg, and could start treatment within 3 h of symptom onset. Participants were randomly assigned (1:1) by ambulance personnel, using a secure web-based electronic application with random block sizes stratified by ambulance service, to receive either transdermal glyceryl trinitrate 5 mg/day for 24 h plus standard care (glyceryl trinitrate group) or to standard care alone (control group) in the prehospital setting. Informed consent was deferred until after arrival at the hospital. The primary outcome was functional outcome assessed with the modified Rankin Scale (mRS) at 90 days. Safety outcomes included death within 7 days, death within 90 days, and serious adverse events. Analyses were based on modified intention to treat, and treatment effects were expressed as odds ratios (ORs) or common ORs, with adjustment for baseline prognostic factors. We separately analysed the total population and the target population (ie, patients with intracerebral haemorrhage, ischaemic stroke, or transient ischaemic attack). The target sample size was 1400 patients. The trial is registered as ISRCTN99503308.

Findings: On June 24, 2021, the MR ASAP trial was prematurely terminated on the advice of the data and safety monitoring board, with recruitment stopped because of safety concerns in patients with intracerebral haemorrhage. Between April 4, 2018, and Feb 12, 2021, 380 patients were randomly allocated to a study group. 325 provided informed consent or died before consent could be obtained, of whom 170 were assigned to the glyceryl trinitrate group and 155 to the control group. These patients were included in the total population. 201 patients (62%) had ischaemic stroke, 34 (10%) transient ischaemic attack, 56 (17%) intracerebral haemorrhage, and 34 (10%) a stroke-mimicking condition. In the total population (n=325), the median mRS score at 90 days was 2 (IQR 1–4) in both the glyceryl trinitrate and control groups (adjusted common OR 0·97 [95% CI 0·65–1·47]). In the target population (n=291), the 90-day mRS score was 2 (2–4) in the glyceryl trinitrate group and 3 (1–4) in the control group (0·92 [0·59–1·43]). In the total population, there were no differences between the two study groups with respect to death within 90 days (adjusted OR 1·07 [0·53–2·14]) or serious adverse events (unadjusted OR 1·23 [0·76–1·99]). In patients with intracerebral haemorrhage, 12 (34%) of 35 patients allocated to glyceryl trinitrate versus two (10%) of 21 allocated to the control group died within 7 days (adjusted OR 5·91 [0·78–44·81]); death within 90 days occurred in 16 (46%) of 35 in the glyceryl trinitrate group and 11 (55%) of 20 in the control group (adjusted OR 0·87 [0·18–4·17]).

Interpretation: We found no sign of benefit of transdermal glyceryl trinitrate started within 3 h of symptom onset in the prehospital setting in patients with presumed acute stroke. The signal of potential early harm of glyceryl trinitrate in patients with intracerebral haemorrhage suggests that glyceryl trinitrate should be avoided in this setting.

RESEARCH IN CONTEXT

Evidence before this study

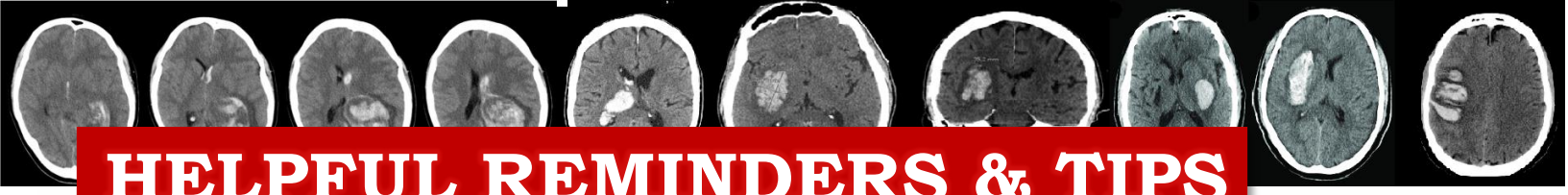
We searched PubMed and Embase for relevant articles published between database inception and April 28, 2022, using the terms "nitric oxide donor", "glyceryl trinitrate", "stroke" and "randomised controlled trial", and comparable terms. No language restrictions were used. Our search was restricted to the effects of glyceryl trinitrate treatment in humans within 6 h of stroke symptom onset on functional outcome and death. Meta-analysis of five randomised trials, including data from one ambulance-based feasibility trial, and a predefined subgroup analysis of a large hospital-based trial, found that glyceryl trinitrate treatment started within 6 h of stroke onset improved outcomes in patients with ischaemic stroke or intracerebral haemorrhage. In 2019, a large, randomised ambulance-based trial (RIGHT-2) of glyceryl trinitrate treatment within 4 h of symptom onset found no benefit of glyceryl trinitrate in patients with stroke or transient ischaemic attack, and possible harm of glyceryl trinitrate in patients with intracerebral haemorrhage. Analysis of the combined results of the above-mentioned trials resulted in neutral effects for death or functional dependency.

Added value of this study

The findings of MR ASAP are consistent with previous findings that ambulance-delivered glyceryl trinitrate does not seem to alter functional outcome in patients with presumed acute stroke. In patients with intracerebral haemorrhage, there was evidence of a greater risk of death within 7 days in patients allocated to glyceryl trinitrate versus standard treatment alone.

Implications of all the available evidence

Transdermal glyceryl trinitrate treatment does not seem to improve outcomes if given within 3 h after stroke onset. The signal of early harm of glyceryl trinitrate in patients with intracerebral haemorrhage suggests that glyceryl trinitrate should be avoided in the prehospital setting in patients with presumed stroke.



HELPFUL REMINDERS & TIPS

For Project Managers and Study Teams

- **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 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

INTERNATIONAL SITE OF THE MONTH

Charite University Medicine Berlin, Berlin, Germany

The Charité – Universitätsmedizin Berlin (Charité – Berlin University of Medicine) is one of Europe's largest university hospitals, affiliated with Humboldt University and Free University Berlin. With numerous Collaborative Research Centres of the German Research Foundation, it is one of Germany's most research-intensive medical institutions. From 2012 to 2022, it was ranked by Focus as the best of over 1000 hospitals in Germany. In 2019 to 2022 Newsweek ranked the Charité as the 5th best hospital in the world, and the best in Europe. More than half of all German Nobel Prize winners in Physiology or Medicine, including Emil von Behring, Robert Koch and Paul Ehrlich, have worked at the Charité.

Complying with an order of King Frederick I of Prussia from 14 November 1709, the hospital was established north of the Berlin city walls in 1710 in anticipation of an outbreak of the bubonic plague that had already depopulated East Prussia. After the plague spared the city, it came to be used as a charity hospital for the poor. On 9 January 1727, King Frederick William I of Prussia gave it the name "Charité", French for "charity. In 1990, with the reunification of Germany, and in the years following, Charité became one of the world's leading research and teaching hospitals.

Site PI: Prof. Christian Nolte, MD

Dr. Nolte is the head of CSB Trial Team, Head of Research Group Nolte (Heart-Brain Interaction). His main interests are Cardiac markers (troponin, heart rate) and autonomic balance in stroke patients (HEBRAS, TRELAS, PRAISE studies) Biomarkers/ prognostic markers/ complications after thrombolysis and thrombectomy for acute ischemic stroke (German Stroke Registry) - Frequency and Risk factors for new vascular events (after stroke) on neuroimaging (DWI, CMB) - pre- and intrahospital delays; knowledge of patients and lay persons on stroke (BASS-Study).

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/

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