NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

MAY 2022 | VOLUME 1 | ISSUE 2

FASTEST

EVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Grotta

May is National Stroke Awareness Month. What better way to celebrate National Stroke Awareness Month than to enroll a patient into FASTEST! In Houston, we've already enrolled 4 patients. Here are the three main things that have contributed to our success so far in identifying patients and getting them enrolled within the two hour time window: pre-notification of the FASTEST team by EMS prior to ED arrival, utilization of EFIC, and the protocol's user-friendly enrollment and randomization process. I recommend that all centers network with your EMS and ED colleagues to ensure pre-notification of the FASTEST team; this "opens" the two hour time window wider allowing more time to seek consent, determine eligibility, and mix the drug. Good luck and let's make May the month that launches FASTEST enrollment at multiple centers."

James Grotta MD
Director of Stroke Research,
Clinical Institute for Research and Innovation,
Memorial Hermann - Texas Medical Center
Director, Mobile Stroke Unit Consortium.

Please join us for the *FASTEST* Monthly Webinar

Wednesday May 18th
2:00-3:00 pm EST

Zoom:
https://ucincinnati.zoom.us/j/96899791261?pwd=d1VtcEppL0RoTkFxQTV1WW54SERaZz09

To join Zoom Meeting -- Meeting ID: 968 9979 1261
Passcode: 710245 or call in. To find your local number, go to https://ucincinnati.zoom.us/u/addjGYPaHx

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

FASTEST NEWS DESK...

BREAKING NEWS

novo nordisk®

press release

NovoSeven® recommended for approval for the treatment of severe postpartum haemorrhage by the European Medicines Agency

Heavy bleeding after giving birth is globally a leading cause of death in new mothers[1]

Bagsværd, Denmark, 22 April 2022 – Novo Nordisk today announced that the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion, recommending an extension of the NovoSeven® (eptacog alfa) label to include treatment of women suffering from severe haemorrhage after giving birth, when medications used to induce uterine contractions and reduce bleeding (uterotonics) are insufficient to stop the bleeding.

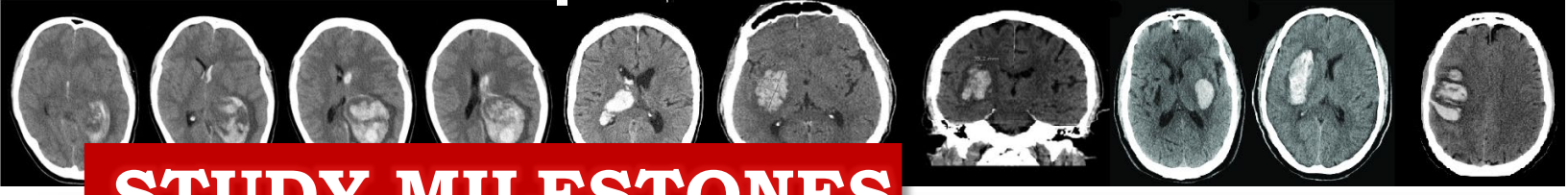
Severe postpartum haemorrhage (PPH) is when a woman suffers from blood loss of more than 1,500 mL within 24 hours after giving birth.[2] It accounts for 1 in 4 maternal deaths globally, making it a significant contributor to maternal morbidity.[1]

The positive opinion is based on data from a prospective randomised clinical trial in women with severe PPH where uterotonics had failed to control the bleeding. In the primary analysis, fewer women in the NovoSeven® arm (21 vs 35) underwent additional medical procedures, such as ligation and embolisation, to stop the bleeding, corresponding to a 40% relative reduction in risk compared to standard of care.[3]

"Postpartum haemorrhage is a serious and dangerous condition," said Martin Lange, executive vice president and head of Development at Novo Nordisk. "Reducing maternal mortality is a United Nations Sustainable Development Target and something that is very important to us at Novo Nordisk. We're pleased with the potential of NovoSeven® being able to help mothers who may need it."

Novo Nordisk expects a final approval by the European Commission within approximately two months.

For full press release please go to the following link:
https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=111903



STUDY MILESTONES

Total Sites Released to Enroll: **11** (**7** USA, **2** Germany, **1** Japan, **1** Canadian)

Total Randomization = **8**

- US Randomizations: **6**,
- International randomizations: **2** (2 Canadian)

Randomization this month = **1**

Total Screen Failures = **22**

Subjects Randomized by MSU = **0**

Subjects Terminated Early = **0**

eConsent Used = **0**

Remote Consent Used = **0**

CALENDAR OF EVENTS

Upcoming *FASTEST* Monthly Webinar: **Wednesday May 18th 2:00-3:00 pm EST**

Upcoming Advarra EFIC Panel meeting dates**: May 9th and 23rd**

FAQs

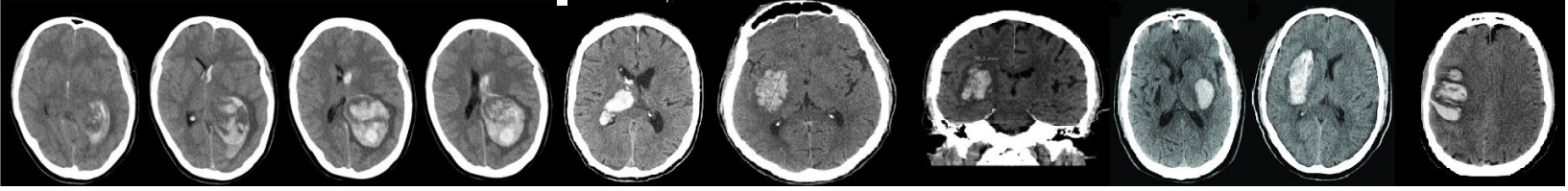
QUESTION CORNER

Q: Is Intraosseous administration is permitted for FASTEST?
A: Per FASTEST study protocol, Intraosseous administration is **not permitted**.

Q: Is the EKG at baseline (pre-drug) is the only one that is required? and how many leads are required?
A: Per FASTEST study protocol, EKG is only required once (at baseline). The number of EKG leads depends on the standard of care in the ER or MSU at that site. There is no specific requirement for the study other than standard of care.

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)



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**.

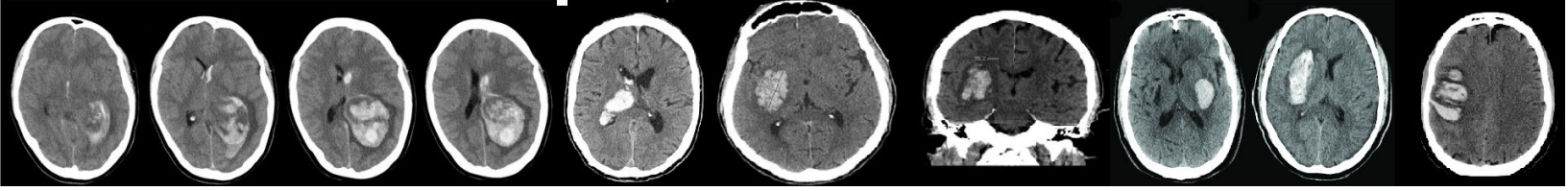
In these scenarios, once the study drug is reconstituted (most likely you will need the two vials), leave the histidine syringe attached until it is ready for use. When it's ready to use, obtain an appropriate sized syringe from local inventory, remove the pre-filled histidine syringes from the study vials and use the "local" syringe to draw up the appropriate dose accurately.

Q: What is the process for a subject enrolled into the trial via EFIC for whom consent was never obtained or if the subject expires before consent can be obtained. Does the institution pursue an effort to reach an LAR to get consent? What happens to the data if the subject dies and consent was never obtained?
A: If the subject is unable to comprehend a request for continued participation after EFIC enrollment, or the subject dies after enrollment, the investigator will attempt to inform the family members and or a LAR. Since ICH is associated with a 30-day mortality of >40%, investigators anticipate the majority of their efforts will be attempting to contact family members or LARs.

For enrolled subjects who die in the ED or the hospital, investigators will first attempt to notify a LAR of the subject. If such a representative is not reasonably available, a family member will be notified of the subject's inclusion, the details and other pertinent information regarding the study.

Notification will occur either by attempting up to two phone calls to the subject's family or sending two letters to the subject's address (as listed on the EMS run report form, hospital chart information or telephone directory). Research team members will document all efforts to contact patients and their family members and maintain records according to the same process followed for all other record keeping during the study. Telephone discussions and letters will fully inform the subject's representatives of the nature of the research project, the goals and objectives, the study protocols, the details of the EFIC regulations, and the information on the community consultation and public notification that occurred. Subject notification in each case will be documented and will become a permanent part of the study record.

For subjects who appear to have no relatives or persons responsible (e.g., homeless), investigators will make every reasonable effort, including working with the County Medical Examiner, law enforcement and hospital personnel to help identify a next-of-kin for unidentified deceased subjects so that they may be notified. The attempted consent process for each enrolled subject will be documented by the treating investigator in the WebDCU™.



Thus, these efforts at a site are documented and reviewed by the FASTEST study leadership team. If no consent was obtained because no one identified or person dies before LAR can sign (much more likely), the data are still used appropriately per EFIC. This process is documented as part of WebDCU and is always available if a local site IRB wants to review.

Health Insurance Portability and Accountability HIPAA/PIPED under EFIC

Under U.S. federal law, researchers who use information about the health of their research participants are required, except in specific circumstances, to get written permission to use their participant's protected health information (PHI) for the research study. **For the FASTEST Trial, that involves exception from informed consent (EFIC), we have requested and obtained a HIPAA waiver for the reasons listed below as per published guideline since the research could not practicably be conducted without the requested waiver or alteration. FASTEST meets the following criteria:**

1) The research could not practicably be conducted without access to and use of the PHI.

2) The PHI use or disclosure involves no more than minimal risk to the privacy of individuals based on at least the presence of:

- **A.** an adequate plan to protect PHI identifiers from improper use and disclosure (every subject will be assigned a study ID and all associated data is de-identified within a protected study database.
- **B.** an adequate plan to destroy those identifiers at the earliest opportunity, consistent with the research, absent a health or research justification for retaining the identifiers or if retention is otherwise required by law; (All study identifiers will be destroyed at earliest opportunity and prior to any public use database).
- **C.** adequate written assurances that the PHI will not be reused or disclosed to any other person or entity except (a) as required by law, (b) for authorized oversight of the research study, or (c) for other research for which the use or disclosure of the PHI is permitted by the Privacy Rule.

New Sites... Welcome Aboard!

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

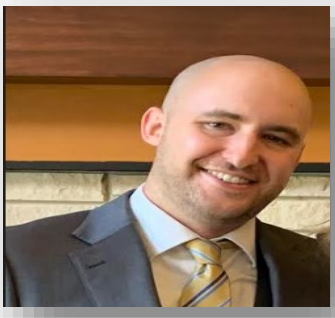
Kaiser Permanente Los Angeles Medical Center
Los Angeles, CA

Site PI:
Navdeep Singh Sangha, MD

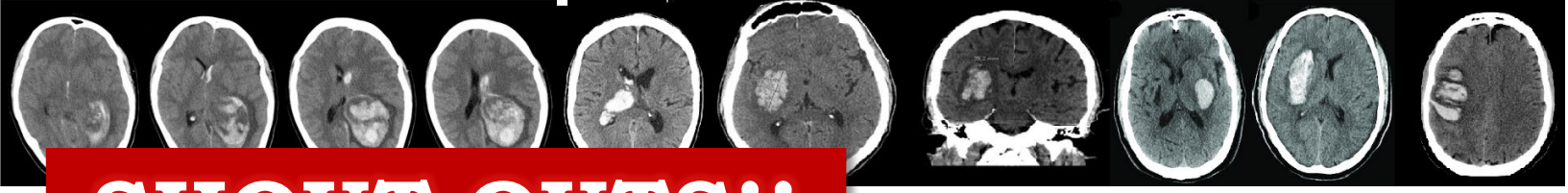
UC Irvine Medical Center,
Orange, CA

Site PI:
Jay Shah, MD

Meet our new Team Member



We would like to welcome Chris Unger PharmD aka Chris Danger to our FASTEST study team. Chris recently joined the StrokeNet NCC Central Pharmacy at University of Cincinnati and will be one of the Pharmacist working on the FASTEST study. Before joining NCC Central pharmacy, Chris was an inpatient pharmacist at the University of Cincinnati Medical Center. Chris is a new father, and welcomed his first child, Emma Rose, into the world on March 9th, 2022. In his spare time Chris enjoys visiting breweries and grilling for his friends and family at his home in Cincinnati, Ohio."



SHOUT OUTS!!

Congratulations to all our US sites that have completed their EFIC reports and gained Advarra full study approval. Advarra shared that the FASTEST sites reviewed have been strong! Well done!

Thank you to the 5 sites preparing for readiness**:**

1. **Northwestern**
2. **VCU**
3. **Stoney Brook**
4. **Central DuPage**
5. **University of Chicago**

Thank you to both sites that have submitted to Advarra for CIRB review**:**

1. **Stoney Brook**
2. **UMASS**

Thank you for the 3 sites preparing for Advarra CIRB submission**:**

1. **Mills Peninsula**
2. **University of Utah**
3. **The Queens**

Top Enrolling Site

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

Subjects enrolled = 4!!

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

1. Memorial Hermann Hospital Texas Medical Center 1 Subjects

SCIENCE CORNER

RESEARCH ARTICLE OF THE MONTH

Magnesium Sulfate and Hematoma Expansion: An Ancillary Analysis of the FAST-MAG Randomized Trial

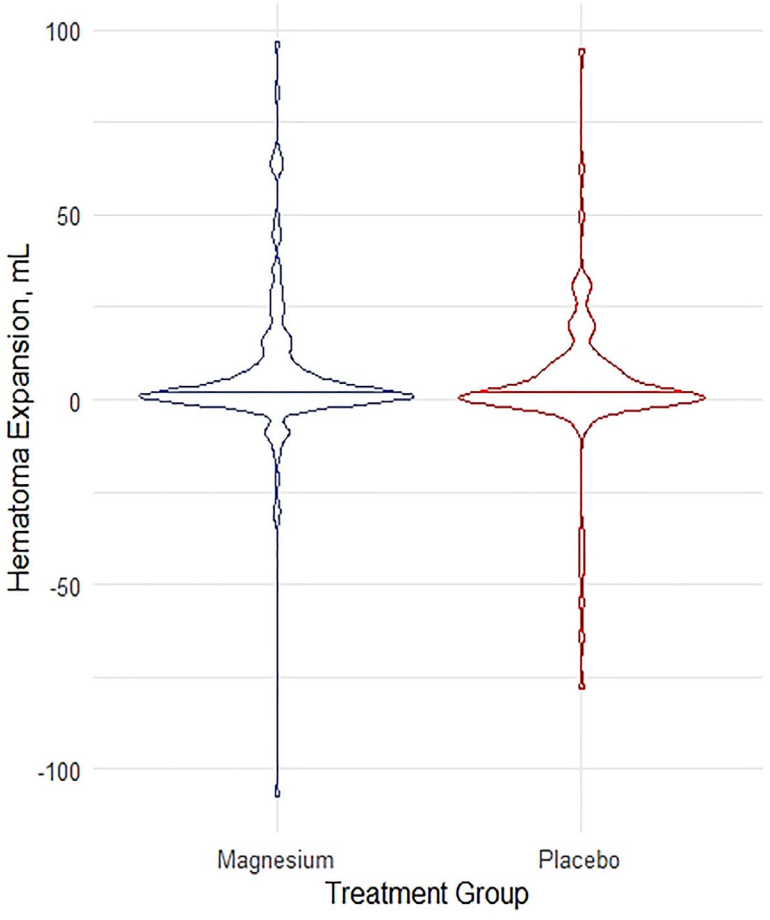
Andrew M. Naidech, Kristina Shkirkova, Juan Pablo Villablanca, Nerses Sanossian, David S. Liebeskind, Latisha Sharma, Mark Eckstein, Samuel Stratton, Robin Conwit, Scott Hamilton, Jeffrey L. Saver and for the FAST-MAG Investigators and Coordinators

Originally published5 Apr 2022 / https://doi.org/10.1161/STROKEAHA.121.037999 / Stroke. 2022;53:1516–1519

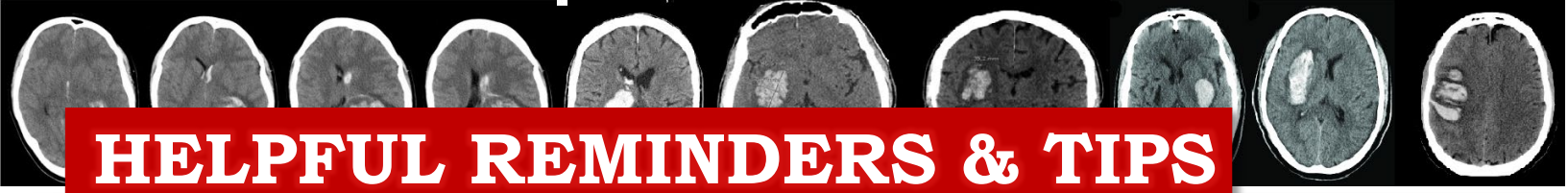
Background: Intracerebral hemorrhage (ICH) is the deadliest form of stroke. In observational studies, lower serum magnesium has been linked to more hematoma expansion (HE) and intracranial hemorrhage, implying that supplemental magnesium sulfate is a potential acute treatment for patients with ICH and could reduce HE. FAST-MAG (Field Administration of Stroke Therapy - Magnesium) was a clinical trial of magnesium sulfate started prehospital in patients with acute stroke within 2 hours of last known well enrolled. CT was not required prior to enrollment, and several hundred patients with acute ICH were enrolled. In this ancillary analysis, we assessed the effect of magnesium sulfate treatment upon HE in patients with acute ICH.

Methods: We retrospectively analyzed data that were prospectively collected in the FAST-MAG study. Patients received intravenous magnesium sulfate or matched placebo within 2 hours of onset. We compared HE among patients allocated to intravenous magnesium sulfate or placebo with a Mann-Whitney U. We used the same method to compare neurological deficit severity (National Institutes of Health Stroke Scale) and global disability (modified Rankin Scale) at 3 months.

Results: Among 268 patients with ICH meeting study entry criteria, mean 65.4±13/4 years, 33% were female, and 211 (79%) had a history of hypertension. Initial deficit severities were median (interquartile range) of 4 (3–5) on the Los Angeles Motor Scale in the field and National Institutes of Health Stroke Scale score of 16 (9.5–25.5) early after hospital arrival. Follow-up brain imaging was performed a median of 17.1 (11.3–22.7) hours after first scan. The magnesium and placebo groups did not statistically differ in hematoma volume on arrival, 10.1 (5.6–28.7) versus 12.4 (5.6–28.7) mL (P=0.6), or HE, 2.0 (0.1–7.4) versus 1.5 (−0.2 to 8) mL (P=0.5). There was no difference in functional outcomes (modified Rankin Scale score of 3–6), 59% versus 50% (P=0.5).



Conclusions: Magnesium sulfate did not reduce HE or improve functional outcomes at 90 days. A benefit for patients with initial hypomagnesemia was not addressed



HELPFUL REMINDERS & TIPS

For Project Managers and Study Teams

- **Regarding Adverse event reporting:** Please note that the responsibility **F=reporting adverse events** (AE) is synonymous with the person making **assessments** and **determinations** about AE and is to be delegated to **PIs/Sub-Is**, or medically trained team members (acceptable to delegated to NPs per FASTEST leadership).
  The primary and secondary coordinators are able to enter the AE information into the WebDCU case report form, when delegated the responsibility **G- complete case report forms**.
  The name of person who assessed an AE is entered in the **AE CRF** and **should be a qualified investigator**.

- **Regarding 24-hour CT imaging:** Also make sure that the 24-hour CT scan is requested and performed. **Some sites missed out on that as the orders were put in by the study PI at those sites but were canceled by the critical care or stroke team because they weren't aware of the study. Kindly make sure it doesn't get missed out.**

- **Regarding Troponin:** Kindly note that serum Troponin is required at **baseline (standard of care)** and **24 hours (not standard of care).**

- **Regarding CT imaging before going to the OR:** Kindly Note that if the patient is going to be taken to OR for surgery by Neurosurgery team after getting enrolled into the study, please make sure that a **CT scan is taken before going to the OR** which is also **standard of care** in this situation.

- ***FASTEST* Survey:** This survey is designed to help the FASTEST Core team understand enrollment logistics and issues associated with each site in order to help overcome any challenges with enrollment. Please submit your response to the FASTEST study survey on the given link: https://redcap.link/FASTEST.Survey

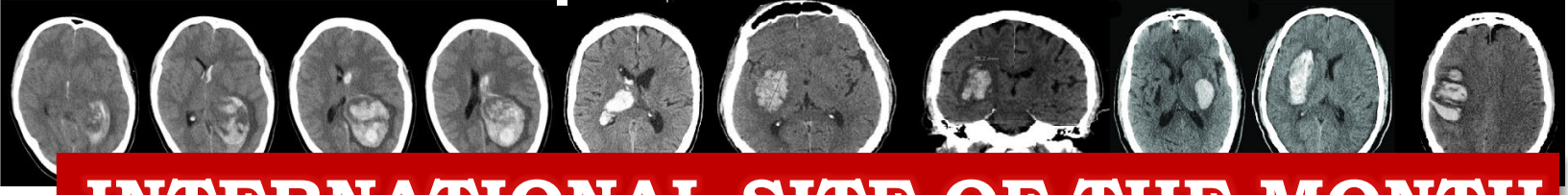
- **As you are completing EFIC events, please complete the CC and PD forms in WebDCU™**. The updated EFIC Forms Resource Guide is available in WebDCU™ (in the Toolbox under Project Documents) and is a very helpful tool for completing these forms. The FASTEST webinar from March 16th, 2021 (available at 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.

- **US Manual of Procedures v1:** Finalized version of the US MOP v1 has been distributed to all the sites but can also be found in the WebDCU Tool Box: **https://webdcu.musc.edu/nett/ViewRecord.asp?theFormID=1015&theRecordID=109**

From the ***FASTEST*** Central Pharmacy Team

- **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
  - Adding Pharmacy Personnel to WebDCU DOA



INTERNATIONAL SITE OF THE MONTH

University Hospital Augsburg (Universitätsklinikum Augsburg)
Augsburg, Germany

University Hospital Augsburg (Universitätsklinikum Augsburg) is with about 1,750 beds one of the largest medical centers in Germany located in Augsburg. It is a teaching hospital of the Universität Augsburg and the only hospital of maximal care in Swabia (Bavaria). The hospital has two locations in Augsburg. The location in the Stenglinstraße (Kriegshaber) and the location in the Sauerbruchstraße (Haunstetten).

The University Hospital Augsburg comprises a total of 23 clinics and three institutes, as well as other medical treatment areas and centers. More than 6,000 employees, including around 900 doctors and around 2,500 nurses, work for the health of patients.

Site PI: PD Dr. med. Hauke Schneider, MBA

Dr Hauke Schneider is the Senior Physician at the Clinic for Neurology and Clinical Neurophysiology. He is the PI for FASTEST at this 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 ***FASTES*** study please visit : https://www.nihstrokenet.org/fastest/home

For prior ***FASTES*** 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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