NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

AUGUST 2022 | VOLUME 1 | ISSUE 5

FASTEST

FVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Steiner

I am very excited to see the FASTEST trial running as we still do not have a treatment for acute intracerebral hemorrhage (ICH). This did happen after many years of trying to find an intervention for hematoma expansion using hemostatic agents and in particularly recombinant factor VIIa. The history behind this and the efforts needed were nicely summarized by Joe Broderick in Stroke last year. It tells you a lot about the background of the study, its design and the pathophysiological concepts of the primary treatment target - hematoma expansion. I encourage all investigators to try the best you can even with the short time window of 2 hours – it can be done, as shown in NINDS-trial on thrombolysis for ischemic stroke that build the base for key treatment in stroke today.

Thorsten Steiner, MD, PhD
Head of the Department of Neurology
Clinic Frankfurt Hoechst,
Frankfurt, Germany
FASTEST German National PI

Please join us for the *FASTEST* Monthly Webinar

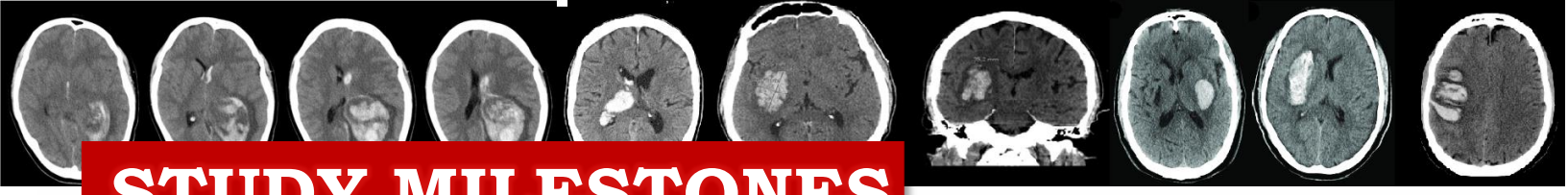
Wednesday August 24th, 2:30-3:30 pm EST

- Dr. Andrew Naidech will be discussing "Management of ICP and monitoring in ICH".
- Dr. Sven Poli and his team from Tübingen University Hospital, Tübingen, Germany will be presenting their recent case and sharing their experience of first enrollment at their center.
- We will review the payment process for recent updates to the payment schedules.

Zoom:
https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fucincinnati.zoom.us%2Fj%2F95468027963&data=05%7C01%7Cquadrisd%40ucmail.uc.edu%7C11cb65abc22f47dd781908da7ec43e47%7Cf5222e6c5fc648eb8f0373db18203b63%7C1%7C0%7C637961678567448550%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=vZR6FRMnzQAHFc3s%2Ba8EkReXtg4ZXdRMex%2B3jpBjas0%3D&reserved=0

Meeting ID: 954 6802 7963

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



STUDY MILESTONES

Total Sites Released to Enroll: **30** (**13** USA, **3** Germany, **11** Japan, 1 Spain, **2** Canadian)

Total Randomization = **16**

- US Randomizations: **9**,
- International randomizations: **7** (2 Canadian, 3 Germany, 1 Japan, 1 Spain)

Randomization this month (last 30 days) = **3**

Total Screen Failures = **65**

Subjects Randomized by MSU = **0**

Subjects Terminated Early = **0**

eConsent Used = **0**

Remote Consent Used = **0**

CALENDAR OF EVENTS

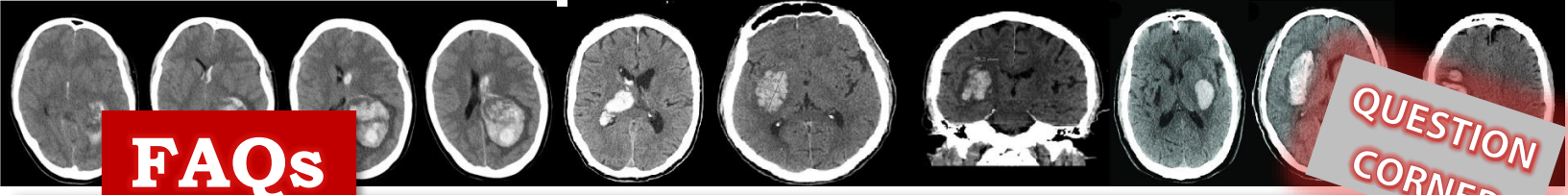
Upcoming *FASTEST* Monthly Webinar: **Wednesday, August 24th @ 2:30-3:30 pm EST**

FASTEST study team office hours: **Monday, August 15th @ 2 pm EST**

Congratulations on First Enrollment!!

Congratulations Dr. Kenichi Morita and his team at the Niigata City General Hospital, Niigata, Japan for enrolling their first subject in *FASTEST*.

Congratulations Dr. Carlos Molina and his team at the Vall d'Hebron Hospital, Barcelona, Spain for enrolling their first subject in *FASTEST*.



FAQs

QUESTION CORNER

Q: Are there any issues using glass versus plastic syringes (electrostatic properties of glass versus plastic)?
A: The histidine syringes provided in the kit are glass syringe provided by Novo and the package insert allow to utilize the Lure-Lock plastic syringe for administration if needed.

Q: If the kits are stored in a 10C fridge, how long would it take to come to room temperature?
A: Novo recommends the rule of thumb of 15 minutes (thaw time) for the refrigerated study drug. Therefore, we recommend sites to store IP at room temperature if possible, if not, we recommend that site pull the kit from fridge as soon as they have a potential patient to allow for "thaw time". The kits can be put back in the fridge if the patient deemed not eligible AND the kit is still sealed.

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.

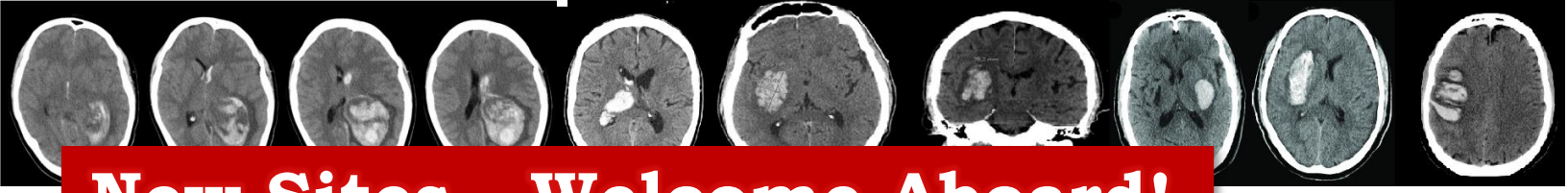
Q: Do we also report AE and what is the timeline to report the Non-serious AEs?
A: All non-serious adverse events observed by the investigator or reported by the participant will be recorded from the time of randomization through **Day 4.** Kindly make note that these non-serious adverse events need 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.

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).

Q: What is the timeline to report SAEs?
A: All SAEs must be reported in WebDCU™ within **24 hours** of site investigator's awareness of the event and must be followed for the duration of the study follow-up or until resolution, whichever comes first. Kindly note that all SAEs will be recorded from the time of randomization through **Day 90**. However, mortality is reported through end of study **(day 180).** Kindly remember that Death due to the natural history of ICH will be recorded as a non-related SAE. Additionally, all serious but known complications of ICH (i.e., malignant brain edema) will be recorded as non-related SAEs. Please refer to our study MOP sent to all the participating sites earlier.

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

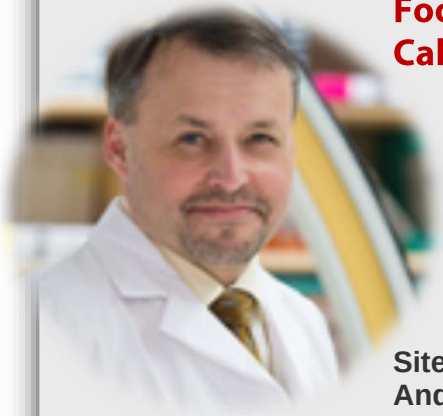


New Sites... Welcome Aboard!

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

Clinic Frankfurt Hoechst, Frankfurt, Germany

Site PI:
Thorsten Steiner, MD, PhD



University of Calgary - Foothills Medical Centre, Calgary, Canada

Site PI:
Andrew M. Demchuk, MD

Kansai Medical University (KMU) Hospital, Osaka, Japan

Site PI:
Yusuke Yakushiji, MD, PhD

New Sites…Welcome Aboard!

Memorial Hermann Memorial City Medical Center, Houston, TX

Site PI:
Ritvij Bowry, MD,

NHO Osaka National Hospital, Osaka, Japan

Site PI:
Toshiyuki Fujinaka, MD

Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan

Site PI:
Yoshinari Nagakane, MD

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 preparing for readiness:

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 to sites that have submitted to Advarra for CIRB review:

1. **Mills Peninsula**
2. **Providence St. Vincent**

Thank you for the sites preparing for Advarra CIRB submission:

1. **North Shore**
2. **Prima Health**
3. **Cedar Sinai**
4. **Ohio Health (OSU, Riverside, Mt. Carmel)**

Top Enrolling Site

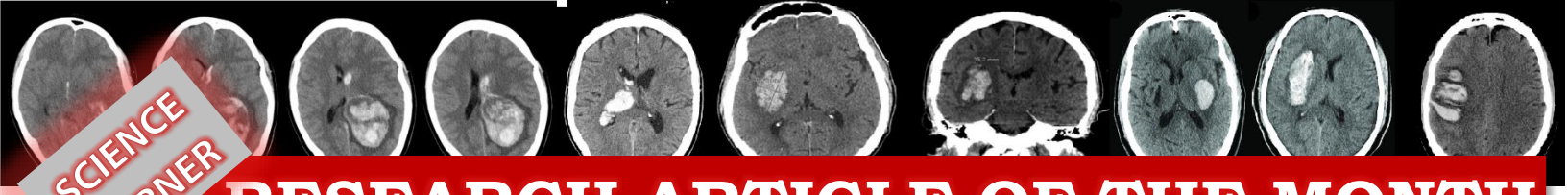
Congratulations to **Memorial Hermann Hospital-Texas Medical Center** for being the highest enrolling site in the study.

Subjects enrolled = 5!!

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

1. Vall d'Hebron Hospital, Barcelona, Spain — 1 Subject
2. Niigata City General Hospital, Niigata, Japan — 1 Subject
3. Tubingen University Hospital, Tubingen, Germany — 1 Subject

Looking forward to 1st Enrollment from UK!



SCIENCE CORNER

RESEARCH ARTICLE OF THE MONTH

Intracranial Pressure Monitoring in Patients With Spontaneous Intracerebral Hemorrhage - *Insights From the SYNAPSE-ICU Study*

Stefania Dallagiacoma, MD, Chiara Robba, MD, Francesca Graziano, PhD, Paola Rebora, PhD, J. Claude Hemphill, MD, Stefania Galimberti, PhD, Prof, and Giuseppe Citerio, MD, Prof, on behalf of the SYNAPSE-ICU Investigators

Originally published May 4, 2022, / DOI: https://doi.org/10.1212/WNL.0000000000200568 /Neurology Jul 2022, 99 (2) e98-e108

Background: Uncertainties exist regarding the indications, management, and effect of intracranial pressure (ICP) monitoring and treatment on outcome in patients with spontaneous intracranial hemorrhage (ICH).

Methods: We performed an analysis of patients with spontaneous ICH enrolled in the SYNAPSE-ICU study, an international prospective observational study on the use of ICP monitoring. This study aimed to describe, in a large cohort of patients with spontaneous ICH admitted to the intensive care unit (ICU), the clinical practice of ICP monitoring, the occurrence of intracranial hypertension, and its therapeutic management. We assessed in-hospital mortality and the association between ICP monitoring and 6-month mortality and outcome by a propensity score approach with inverse probability weighting.

Results: A total of 587 patients with ICH were included in this study; 281 (47.9%) received ICP monitoring. ICP-monitored patients, compared with nonmonitored patients, were younger (61 vs 67 years; $p < 0.001$), presented more frequently with both reactive pupils (67.2% vs 55.2%; $p = 0.008$), with better neurologic status at admission (Glasgow Coma Scale ≤8, 82.3% vs 88.8%; $p = 0.038$), and received higher therapy intensity level during the ICU stay. In 70.5% (170 out of 241) of ICP-monitored patients, the ICH score was equal to 3 or 4. Nearly half of monitored patients (46.6%) had at least one episode of ICP ≥20 mm Hg during the first week. An intraventricular catheter (53.6%) was the most frequently used device and was associated with fewer episodes of intracranial hypertension compared with the other monitoring devices (43.7% vs 64.9%, respectively). At weighted Cox regression model, ICP monitoring was associated with a significant reduction of 6-month mortality (hazard ratio 0.49 [95% CI 0.35–0.71; $p = 0.001$), but not with neurologic outcome (odds ratio 0.83 [95% CI 0.41–1.68]; $p = 0.6077$).

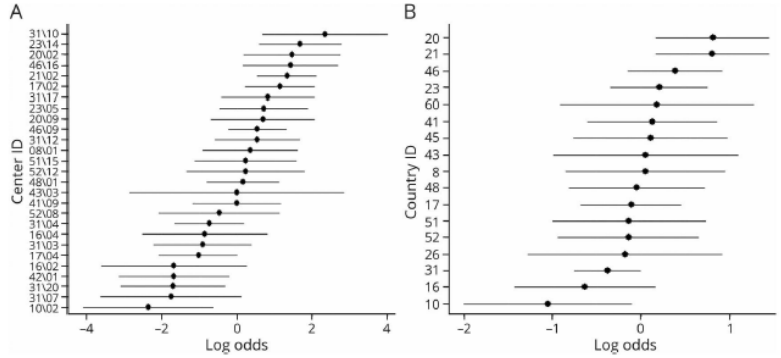


Figure 1 Variability in the Use of ICP Monitoring: Variability in the use of intracranial pressure (ICP) monitoring among centers (A) and countries (B). Caterpillar plot of predicted random intercept for each center/country corresponding to the adjusted log odds of ICP monitoring use (median odds ratio 4.02 and 1.78, respectively). Predicted random intercepts with corresponding prediction intervals (higher values indicate higher propensity to use ICP monitoring) are given on the horizontal axis; center ID (A) and country ID (B) are given on the vertical axis. A total of 28 centers and 17 countries enrolled >10 patients.

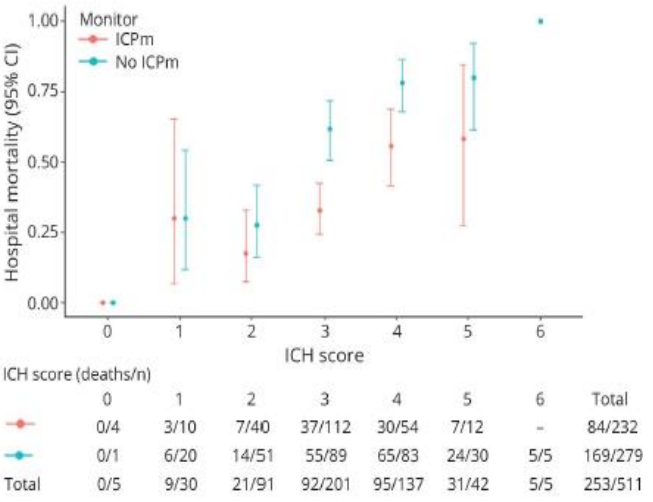


Figure 2

In-Hospital Mortality: Observed in-hospital mortality (95% CI) by intracranial hemorrhage score in intracranial pressure monitored and not monitored patients.

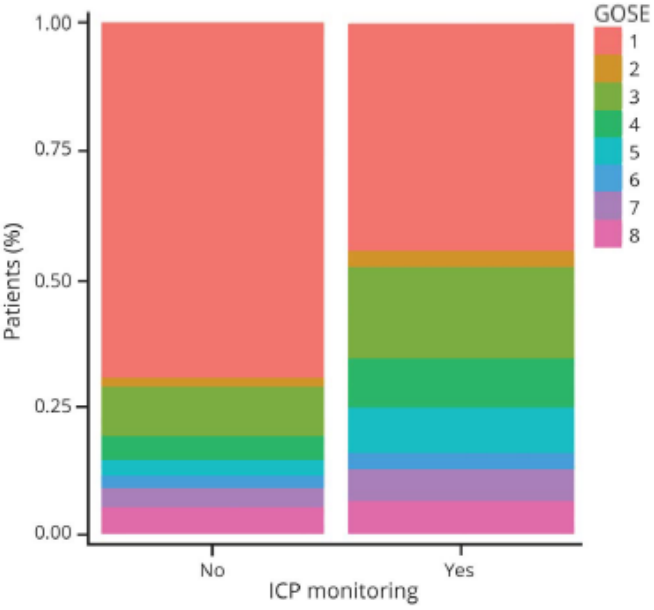


Figure 3

Six-Month Outcome: Distribution of Extended Glasgow Outcome Scale scores at 6 months.

Conclusions: ICP monitoring in ICH was utilized mainly in moderately severe cases. ICP monitoring was associated with a reduction of in-hospital and 6-month mortality but did not improve 6-month functional outcomes. Further research and randomized controlled trials to generate higher-level medical evidence to support guidelines regarding ICP use and treatment in patients with ICH are needed.

Trial Registration Information

SYNAPSE-ICU: ClinicalTrials.gov NCT03257904.
https://clinicaltrials.gov/ct2/show/NCT03257904

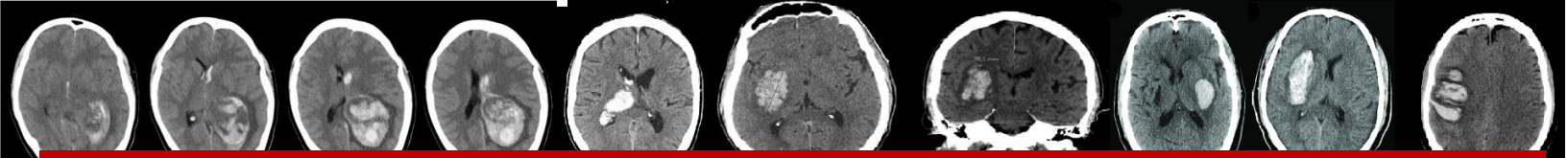
HELPFUL REMINDERS & TIPS

For Project Managers and Study Teams

- Newly approved study wide documents available in the Tool Box in WebDCU
  - **Condensed Radio advertisement** less than 60 sec. Can be used for sites still working on EFIC public disclosures. **REMINDER:** All radio advertisements recordings need to be submitted for CIRB approval prior to ad running.
  - **Consent conversation script**- This is **NOT** a consent document but a script of a conversation that can be used to help explain EFIC and emergency consent to LAR's and/or subjects.
- **Screen failure logs: Please update the screen failure logs in WebDCU screen failure data is very important to the study.**
- **CTA Amendments:** Please make sure the amended CTA's have been returned to UC for execution.
- eICD templates are being sent to CIRB approved sites that have the amended CTA's fully executed.
- **Uploading of documents:** Please remember to pull approval letters and CIRB approved documents from the CIRBI portal and upload them to WebDCU. It is the sites responsibility to keep their site documents updated and uploaded to WebDCU. If you have questions about where to upload your documents please reach out to Emily Stinson stinsoey@ucmail.uc.edu
- **Study team office hours:** Please join the FASTEST study team office hours. Calendar invites have been sent out. This is an informal meeting to answer questions and provide additional training and support. We will meet biweekly on **Monday's at 2pm EST each month.** We highly recommend that you attend regularly as we plan to touch on many topics. We especially encourage new study coordinators to join to help get acclimated to FASTEST as well as spend time collaborating with different FASTEST study sites.
- **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

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

Ottawa Hospital, Ottawa, ON, Canada

The Ottawa Hospital (French: L'Hôpital d'Ottawa) is a hospital system in Ottawa, Ontario, Canada. The system was formed through the merger of the former Grace Hospital, Ottawa Riverside Hospital, Ottawa General Hospital and Ottawa Civic Hospital. The system is affiliated with the University of Ottawa, and its three campuses are all non-profit, public teaching hospitals (the University of Ottawa Heart Institute is located at the hospital's Civic Campus). The Ottawa Hospital's General campus is home to the Ottawa Hospital Cancer Center, the main site of the Ottawa Hospital Cancer Program and the Champlain Regional Cancer Program. The General Campus provides specialized in and outpatient services for hematological diseases, as well as radiation and medical oncology.

The Ottawa Hospital Research Institute (OHRI) is a non-profit academic health research institute that is part of The Ottawa Hospital, and a major part of the University of Ottawa Faculties of Medicine and Health Science. It is one of the largest hospital-based research institutes in North America. OHRI scientists are working on an array of questions in the fields of cancer therapeutics; clinical epidemiology; diseases of ageing; hormones, growth, and development; molecular medicine; neuroscience, and vision. The OHRI's mandate is to advance knowledge of health and disease on multiple fronts, ranging from increasing understanding of what is happening at the molecular and cellular level in complex disease states, to elucidating best practices in the delivery of health care.

Site PI: Dr. Dar Dowlatshahi, MD PhD

Dr. Dowlatshahi is a Stroke Neurologist and professor in the Department of Medicine, and Cross Appointed to Epidemiology and Community Medicine, University of Ottawa. He is the Scientific Director of the Ottawa Stroke Program and recently promoted to Scientist, Neuroscience, Ottawa Hospital Research Institute. He is also a member of the Faculty of Graduate and Postdoctoral Studies.

Dr. Dowlatshahi joined the University of Ottawa and OHRI in July 2010 and is both a Clinician Scientist and the Scientific Director of the Ottawa Stroke Program. In 2014 he was awarded the inaugural Department of Medicine Clinician-Scientist Chair Award, and a Heart & Stroke Foundation of Canada New Investigator Award. His clinical research program in acute stroke and intracerebral hemorrhage focuses on multi-modal neuroimaging. Through collaborative trials and observational studies, Dr. Dowlatshahi hopes to discover a treatment for intracerebral hemorrhage.

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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