NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

SEPTEMBER 2023 | VOLUME 2 | ISSUE 9

FASTEST

EVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Tse

Greetings fellow FASTEST investigators! Our team at Vancouver General Hospital are delighted to have the opportunity to offer the FASTEST trial to eligible patients as an additional potentially lifesaving treatment.

Despite joining the FASTEST team just more than 6 months ago, we are already the third highest enrolling site in Canada with the second highest rate of recruitment in the country. This is thanks to our excellent clinical staff and hardworking research coordinators who work tirelessly to enroll all eligible patients. Our pre-notification implementation and streamlined hyperacute stroke workflow have greatly facilitated the enrolment of eligible patients as well as the administration of the study medication within the tight time window. This is an exciting time for the treatment of ICH! Thank you to everyone in the FASTEST trial for making it happen!

Dominic Tse, MBChB
Clinical Assistant Professor
Stroke Neurologist
Vancouver General Hospital
University of British Columbia
FASTEST Site PI

Please join us for the *FASTEST* Monthly Webinar

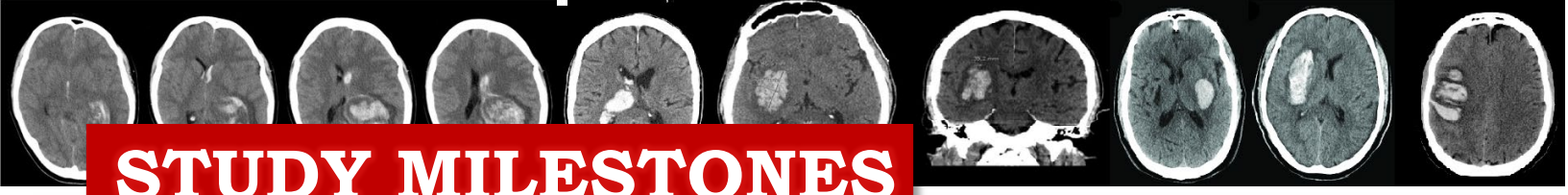
Wednesday Sept 20th, 2:00-3:00 pm EST

- Dr. TSE and his team from Vancouver General Hospital will be discussing case at their site.
- Review of EFIC.
- Review of New CRF - F246: Regain capacity consent by NDMC.
- FASTEST Pharmacy will go over the TERF form documentation process.

Join Zoom Meeting
https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fucincinnati.zoom.us%2Fj%2F91270599326&data=05%7C01%7Cquadrisd%40ucmail.uc.edu%7C59de671893534b5f411808db91e5229c%7Cf5222e6c5fc648eb8f0373db18203b63%7C0%7C0%7C638264185548573076%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=E5dRFfb7olW1z8MCqQ%2Bbz5zs%2Fb6N1KbkElfCvsgt6NQ%3D&reserved=0

Meeting ID: 912 7059 9326

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



STUDY MILESTONES

Total Sites Released to Enroll: **69** (**36** USA, **33** OUS: **5** Germany, **14** Japan, **4** Spain, **6** Canadian, **4** UK)

Total MSUs Released to Enroll: **10** (**8** US and **2** OUS)

Total Randomization = **259**

- US Randomizations: **70**
- International randomizations: **189** (**121** Japan, **34** Canadian, **20** Spain, **11** Germany, **3** UK)

Randomization last month = **20**
Total Screen Failures = **850**
Subjects Randomized by MSU = **10**
Subjects Terminated Early = **1**
eConsent Used = **6**
Remote Consent Used = **7**

CALENDAR OF EVENTS

Upcoming *FASTEST* Monthly Webinar: **Wednesday, Sep 20th @ 2:00-3:00 pm EDT**

FASTEST study team office hours: **Monday, Sep 11th and 25th @ 2:00-3:00 pm EDT**

IMPORTANT NOTE

New CRF - F246

- This new CRF - F246 is collected if a subject regains capacity to sign informed consent during study participation. Going forward, U.S. Sites and Non-U.S. Sites should complete this form. Only the U.S. sites are required to upload the re-consent document. For Non-U.S. Sites the CROs should follow up with the sites and make sure the re-consent document was filled out accordingly.
- This new form will populate in CRF binders for all current and completed subjects where a Legally Authorized Representative (LAR) or Substitute Decision Maker (SDM) (in Canada) provided informed consent on F244: Informed Consent US or F245: Informed Consent Non-US.
- If a subject does not regain capacity to sign informed consent by the end of study participation, Q30 should be answered 'No' and submit the form. The site can enter a 'General Comment' explaining the situation.
- If a subject has regained capacity to consent but is unable to physically sign the consent form due to hemiparesis or other reasons, we recommend entering Q30= Yes, then Q02=No. Then enter an explanation in Q09 that describes that particular situation why regained consent was not obtained and submit the form.
- If a subject has regained capacity to consent but is unable to consent in person, you should still complete F246. We recommend entering Q30=Yes, Q02=No, then enter an explanation in Q09 or General Comment that describes why regained consent was not obtained. However, US sites can use E-consent for consenting during remote follow-ups.
- For subjects who have already completed the study, the sites will still have to complete the form F246 and submit. We are not asking sites to go back to attempt to obtain consent for subjects who have completed the trial.
- Though F246 is posted at the Baseline visit, it can be completed at any time during study participation and does not affect the payments to the sites.

New Sites…Welcome Aboard!

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

Massachusetts General Hospital, Boston, MA

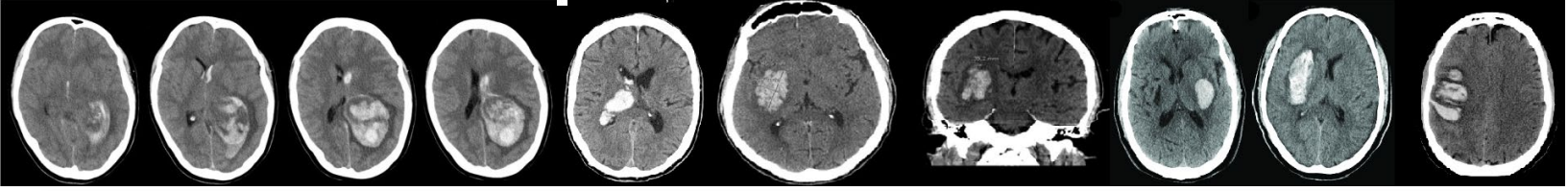
Site PI:
Pierre Borczuk, MD

Mayo Clinic, Jacksonville, FL

Site PI:
Lauren K. Ng, MD

Ronald Reagan UCLA Medical Center, Los Angeles, CA

Site PI:
May Nour, MD, PhD



Henry Ford Hospital, Detroit, MI

Site PI:
Christopher Lewandowski, MD

Congratulations on 1st Enrollment!!!

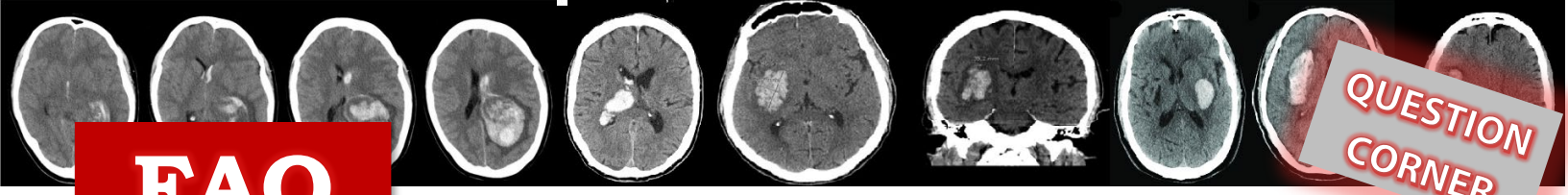
Congratulations to Dr. Theodore LOWENKOPF and the team at the Providence St. Vincent Medical Center, Portland, OR for enrolling their first subject

Congratulations to Dr. Philip MATHIESON and the team at the John Radcliffe Hospital, Oxford, United Kingdom for enrolling their first subject in FASTEST.

FAQ

Q: The 180 day follow up of our FASTEST subject. The participant has a clinic visit planned this Wednesday and is unlikely we will be able to arrange a in person follow up in October. We would need to do the follow up remote. Would it be preferred to do a mRS and EQ-5D in person out of window (3 weeks early) in the clinic as well or do we just wait to do these remote?

A: The protocol encourages in-person follow up at 180 days. However, a remote follow up can also be done if in-person is not possible.



FAQ

Q: I am trying to fill out the TERF for temperature excursion. I have the Kit ID number, the IND number but I am not sure what to put in the Lot no, shipment no, and DUN/Component code no. Please advise?

A: As per instruction provided by the pharmacy on how to fill out the TERF from these could be found in the 'Site Drug Kit Removing' section in the WebDCU.

*Product name	*Lot no/coded Lot no (if applicable)	*Kit (list all Kits for the specific lot)	*DUN/component code no (list all DUN for the specific batch)
rFVIIa/Placebo	T021/0901	12345	2366395
Histidine	L5UT989	12345	2373411

Make sure to include the product name, manufacturer lot number, and the DUN/component code. This can be found in the Site Drug Kit Removing section on WebDCU

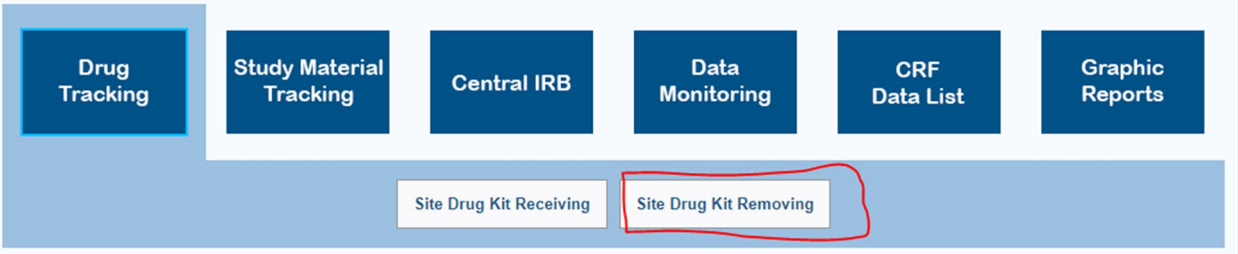
Specific for deviations during storage

*Please list all trial products involved in the deviation

*Product name	*Lot no/coded lot no (if applicable)	*Shipment no	*Kit (list all kits for the specific lot)	*DUN/ component code no (list all DUN for the specific batch)
rFVIIa/Placebo	T021/0901	UPS #	12345	2366395
Histidine	L5UT989	UPS #	12345	2373411

Always put the rFVIIa/placebo and histidine on separate lines because they are two different products/batches

IN WebDCU: Go to Drug Tracking ---- > Select Site Drug Kit Removing ----- > Select your site to review Kit, DUN and Lot numbers.



#	Site ID	Site name	Drug kit code	Expiration date	Placebo/rFVIIa 5mg component DUN	Histidine solvent component DUN	Placebo/rFVIIa 5mg manufacture lot	Histidine lot
1	1435	UCSD Medical Center - Hillcrest Hospital, San Diego, CA	30					31
2	1455	UCSD Health La Jolla, La Jolla, CA	30					31
3	1435	UCSD Medical Center - Hillcrest Hospital, San Diego, CA	30					31
4	1455	UCSD Health La Jolla, La Jolla, CA	30					31

Q: I have recently concluded the 30-Day visit for the subject and learned that they sought medical attention at an urgent care facility due to hypertension and an elevated morning blood sugar. During the visit, the healthcare provider adjusted the dosage of medications for both blood pressure and diabetes management. I am seeking clarification regarding whether this should be documented as an Adverse Event (AE). It's worth noting that both hypertension and diabetes are pre-existing medical conditions within the subject's medical history, which leads us to assume that it may not qualify as an AE. Any guidance or clarification would be greatly appreciated.

A: As per study protocol and MOP any adverse events (AE) are to be reported only during the first 4 days. However, all serious adverse events (SAE) are to be reported throughout the study period (until 180 days). In your case at 30-day follow-up, depends on if the Site PI deems this to be an SAE or just an AE. If the Site PI considers this an SAE and reportable, please report it. Otherwise, AE are not required to be reported at 30 days.

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. **Medical University of South Carolina**
2. **Henry Ford, Detroit MI**
3. **Ronald Reagan UCLA, CA MSU site**
4. **Mayo Clinic, Jacksonville FL**
5. **Mayo Clinic, Rochester MN**
6. **U of Massachusetts General, Boston MA**

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

1. **University of Colarado MSU site**
2. **San Fransisco General, San Fransisco, CA**

Top Enrolling Site

Congratulations to **Kobe City Medical Center General Hospital, Kobe, Japan** for being the highest enrolling site in the study.

Subjects enrolled = 29!!

Congratulations to Enrolling Sites last Month!

Kobe City Medical Center General Hospital, Kobe, Japan	**3 Subjects**
National Cerebral and Cardiovascular Center, Osaka, Japan	**2 Subject**
Niigata City General Hospital, Niigata, Japan	**2 Subjects**
KMU University Hospital, Osaka, Japan	**1 Subject**
Toranomon Hospital, Tokyo, Japan	**1 Subject**
Vancouver General Hospital, Vancouver, BC, Canada	**1 Subject**
University of Calgary - Foothills Medical Centre, Calgary, AB, Canada	**2 Subjects**
Bellvitge University Hospital, Barcelona, Spain	**1 Subject**
University of Cincinnati Medical Center, Cincinnati, OH	**2 Subjects**
Providence St. Vincent Medical Center, Portland, OR	**1 Subject**
WellStar Kennestone Hospital, Marietta, GA	**2 Subjects**
Mills Peninsula Medical Center, Burlingame, CA	**1 Subject**
John Radcliffe Hospital, Oxford, United Kingdom	**1 Subject**

SCIENCE CORNER

ARTICLE OF THE MONTH

Association Between Soluble Intercellular Adhesion Molecule-1 and Intracerebral Hemorrhage Outcomes in the FAST Trial

Jens Witsch, David Roh, Stephanie Oh, Costantino Iadecola, Ramon Diaz-Arrastia, Scott E. Kasner, Stephan A. Mayer and Santosh B. Murthy

Originally published25 May 2023https://doi.org/10.1161/STROKEAHA.123.042466Stroke. 2023;54:1726–1734

Background:

Neutrophil-mediated inflammation in the acute phase of intracerebral hemorrhage (ICH) worsens outcome in preclinical studies. sICAM-1 (soluble intercellular adhesion molecule-1), an inducible ligand for integrins and cell-cell adhesion molecules, is critical for neutrophil extravasation. We aimed to determine whether serum levels of sICAM-1 are associated with worse outcomes after ICH.

Methods:

We conducted a post hoc secondary analysis of an observational cohort using data from the FAST trial (Factor-VII for Acute Hemorrhagic Stroke Treatment). The study exposure was the admission serum level of sICAM-1. The coprimary outcomes were mortality and poor outcome (modified Rankin Scale score 4–6) at 90 days. Secondary radiological outcomes were hematoma expansion at 24 hours and perihematomal edema expansion at 72 hours. We used multiple linear and logistic regression analyses to test for associations between sICAM-1 and outcomes, after adjustment for demographics, ICH severity characteristics, change in the systolic blood pressure in the first 24 hours, treatment randomization arm, and the time from symptom onset to study drug administration.

Results:

Of 841 patients, we included 507 (60%) with complete data. Hematoma expansion occurred in 169 (33%), while 242 (48%) had a poor outcome. In multivariable analyses, sICAM-1 was associated with mortality (odds ratio, 1.53 per SD increase [95% CI, 1.15–2.03]) and poor outcome (odds ratio, 1.34 per SD increase [CI, 1.06–1.69]). In multivariable analyses of secondary outcomes, sICAM-1 was associated with hematoma expansion (odds ratio, 1.35 per SD increase [CI, 1.11–1.66]), but was not associated with log-transformed perihematomal edema expansion at 72 hours. In additional analyses stratified by treatment assignment, similar results were noted in the recombinant activated factor-VII arm, but not in the placebo arm.

Conclusions:

Admission serum levels of sICAM-1 were associated with mortality, poor outcome, and hematoma expansion. Given the possibility of a biological interaction between recombinant activated factor-VII and sICAM-1, these findings highlight the need to further explore the role of sICAM-1 as a potential marker of poor ICH outcomes.

Association between Soluble Intercellular Adhesion Molecule-1 and ICH Outcomes: A Post-Hoc Analysis of the FAST Trial

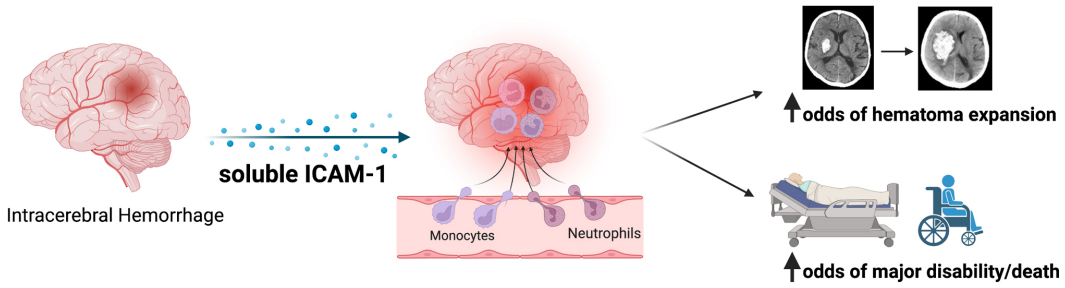
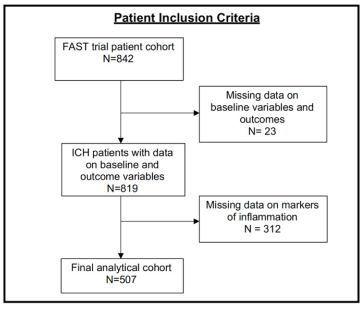


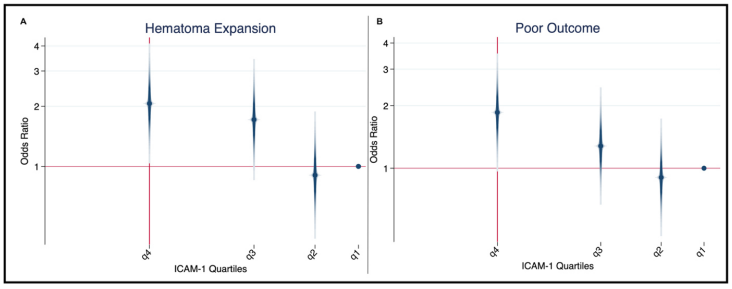
Table 3. Multivariable Analyses of sICAM-1 and ICH Outcomes

Covariate	Modified Rankin Score 4-6		Mortality	
	OR (95% CI)	P value	OR (95% CI)	P value
sICAM-1, unadjusted	1.24 (1.03=-1.49)	**0.02**	1.38 (1.13-1.70)	**0.002**
sICAM-1, per SD#	1.34 (1.06-1.69)	**0.013**	1.53 (1.15-2.03)	**0.03**

Table 4. Multivariable Analyses of sICAM-1 and Radiological Characteristics

Covariate	Hematoma Expansion# (Dichotomous Outcome)		Hematoma Expansion# (Continuous Outcome)		PHE Expansion#	
	OR (95% CI)	P value	Beta (95% CI)	P value	Beta (95% CI)	P value
sICAM-1, per SD, unadjusted	1.34 (1.11-1.61)	**0.002**	2.64 (1.26-4.01)	**<0.001**	0.14 (0.04 to 0.23)	0.22
sICAM-1, per SD#	1.35 (1.11-1.66)	**0.003**	3.83 (1.45-6.22)	**<0.001**	0.08 (-0.02 to 0.19)	0.14





HELPFUL REMINDERS & TIPS

For Project Managers, Study Coordinators & Study Teams

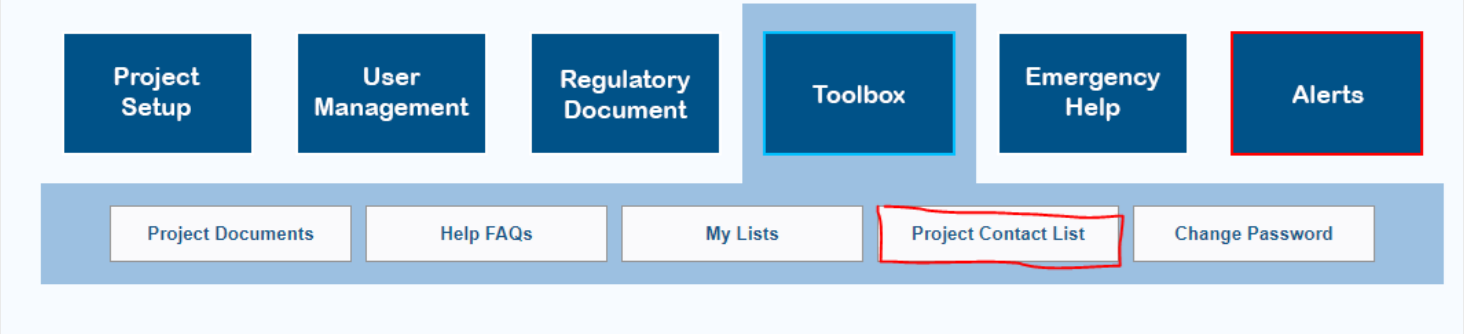
- **Updating 1572:** Compliance with regulatory requirements mandates that every modification to a 1572 form necessitates the PI signature to acknowledge the alteration. It is essential to understand that updates to an existing 1572 are not permissible; instead, a new 1572 form must be created for each update. Consequently, the PI is required to sign a new 1572 form with every update made.

- **Temperature excursion and monitoring: Please be very vigilant about temperature excursion and temperature monitoring documentation.** FASTEST sites using the ***Emerald temperature loggers*** provided by us for their MSU or ED we will be sending out weekly reminder email every Friday to the PSC. Checking once a week should ensure careful monitoring of temperature excursion and documentation, as well as avoiding the use of affected study drug.

- If kit that was affected was used for randomization it is advised to communicate with the subject to ensure that they are fully informed about the situation regarding the affected study drug. An update regarding this communication should be provided to the CIRB for their records (while reporting this deviation).

- **FASTEST is now operating under Version 7 of the Protocol.** Please sign and upload **PI Protocol v7 Training Attestation** and **new Protocol v7 Signature Page** to WebDCU.
  - It is mandatory for all PIs to sign a new **Training Attestation** for Protocol v7. By signing this attestation, the PI confirms that all individuals listed on the current DoA have received training on the updated protocol. Therefore, it is not necessary to collect a new training attestation from each investigator/study team member individually.
  - We kindly request all sites to maintain an internal training log as evidence that every individual has undergone training on the updated Protocol v7. This log will serve as documentation, which may be required during an FDA audit, to verify that the study team members have been sufficiently trained on the protocol updates.

- WebDCU have now included a "project contact list" feature, which contains all the important contact information that the site might require during the course of the trial. Sites can access it by navigating to FASTEST > ToolBox > Project Contact List.



From the *FASTEST* Central Pharmacy Team

- Instructions to fill out TERF from are in the toolbox in WebDCU.

- Kit #, DUN# and the Lot number could all be found in the 'Site Drug Kit Removing' section in the WebDCU.

- 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.

INTERNATIONAL SITE OF THE MONTH

University of Alberta Hospital, Edmonton, AB, Canada

The University of Alberta Hospital, located in Edmonton, Alberta, Canada, is a renowned medical facility and a key part of the Alberta Health Services network. It is affiliated with the University of Alberta and serves as a major teaching hospital for medical students and professionals.

The University of Alberta Hospital, located in Edmonton, Alberta, Canada, has a rich and storied history that dates back to its establishment in 1906. It was originally founded as a teaching hospital associated with the University of Alberta, making it one of Canada's earliest academic medical centers.

This state-of-the-art facility is renowned for its cutting-edge research, exceptional patient care, and a wide range of specialized medical services. It houses advanced diagnostic and treatment technologies, making it a regional center of excellence for complex medical cases, including organ transplants, cancer treatment, and neurosurgery. The UAH treats over 700,000 patients annually.

The University of Alberta Hospital is also known for its commitment to patient-centered care, medical innovation, and interdisciplinary collaboration. It plays a vital role in the Edmonton community and the broader province of Alberta, contributing significantly to healthcare advancements, medical education, and improving the overall well-being of patients in the region.

One notable milestone in its history is its involvement in pioneering organ transplant procedures. In 1984, the hospital's surgeons successfully performed Canada's first heart transplant, marking a groundbreaking achievement in the country's medical history.

Site PI:
Dr. Brian Buck

Dr. Brian Buck is an Associate Professor in the Division of Neurology at the University of Alberta and a consultant neurologist at the University of Alberta Hospital and Grey Nuns Community Hospital in Edmonton.

Dr. Buck's clinical interests include the acute stroke and telestroke service, stroke ward, and stroke prevention clinic. He is also involved in research on stroke prevention and stroke care delivery improvement, with a particular interest in stroke imaging and developing new methods of stroke detection. He is a co-principal investigator on a newly funded Canadian Institutes of Health Research clinical trial called ACT-QuICR. He is co-investigator on SECRET (Study of Early Rivaroxaban for cerebral venous thrombosis), and also the recently CIHR funded study INTERRAcT: Thrombus characteristics for predicting Reperfusion with Alteplase compared to Tenecteplase.

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/