NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

JUNE 2023 | VOLUME 2 | ISSUE 6

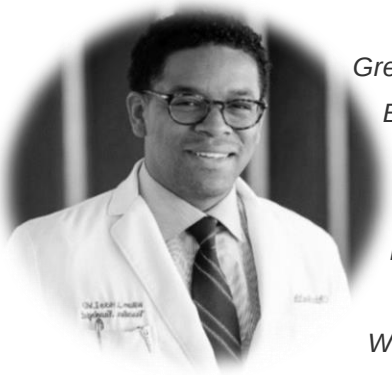
FASTEST

FVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Hicks



Greetings fellow FASTEST participants! Believe it or not, I am currently writing this impactful group of investigators from an undisclosed vacation location (my first in 5 years).

We should all feel energized by the positive outcome of the ENRICH surgical trial. ENRICH is an example of why we need to remain vigilant. We can do this by proactively seeking enrollment of hemorrhagic stroke patients presenting within two hours of symptom onset. The faster we close enrollment, the faster we potentially have an accompanying treatment option to impact more lives.

While we are in prime summer vacation season, the 2nd highest enrolling site in the US (my OhioHealth Riverside Methodist Hospital research team) thinks we can improve enrollment. Anyone up for a challenge to see who's the FASTEST!?

William J. Hicks II, MD
Medical Staff President
Vascular Neurologist & Co-Director,
Comprehensive Stroke Program
OhioHealth Riverside Methodist
Columbus, OH

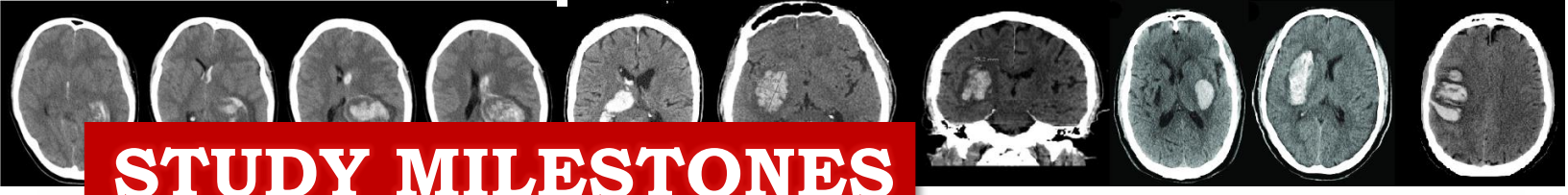
Please join us for the *FASTEST* Monthly Webinar

Wednesday June 21st, 2:00-3:00 pm EST

- Dr. William Hicks and his team from Riverside Methodist Hospital, Columbus will be discussing the MSU case at their site.
- DSMB meeting review.
- Review of ENRICH and INTERACT3 trails.
- The process and documentation for LTFU (lost to follow up).

Join Zoom Meeting
https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fucincinnati.zoom.us%2Fj%2F95768343105%3Fpwd%3DZjYwZ0tNakxsN01qMmhPOE15N21Jdz09&data=05%7C01%7Cquadrisd%40ucmail.uc.edu%7C7b2505f4647443dd6b2e08da7ec1eb4c%7Cf5222e6c5fc648eb8f0373db18203b63%7C1%7C0%7C637961668587750683%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=40q90l8dB9QtZj9P5aZ0BeWkvzCsNx1WgQL9cFmISHQ%3D&reserved=0

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



STUDY MILESTONES

Total Sites Released to Enroll: **63** (**33** USA, **30** OUS: **5** Germany, **14** Japan, **4** Spain, **5** Canadian, **2** UK)

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

Total Randomization = **197**

- US Randomizations: **56**
- International randomizations: **141** (**71** Japan, **28** Canadian, **14** Spain, **11** Germany, **2** UK)

Randomization last month = **25**
Total Screen Failures = **632**
Subjects Randomized by MSU = **8**
Subjects Terminated Early = **0**
eConsent Used = **5**
Remote Consent Used = **5**

CALENDAR OF EVENTS

Upcoming *FASTEST* Monthly Webinar: **Wednesday, June 21st, @ 2:00-3:00 pm EDT**

FASTEST study team office hours: **NO office hours this month due to scheduling conflicts**

IMPORTANT NOTES

Webinar Invite for MSU teams

The upcoming July FASTEST webinar scheduled for **07-19-2023** will focus on various topics related to MSU. We have extended invitations to Principal Investigators (PIs) from lead enrolling MSU sites to discuss important matters, including enrollment in MSU and other relevant subjects that will provide significant value to MSU personnel at your site.

The webinar offers a unique opportunity for MSU personnel to engage with other esteemed MSU teams, fostering interaction, enabling the exchange of knowledge, and encouraging the sharing of experiences. Attendees will have the chance to ask questions, gain insights, and participate actively in the session.

It is kindly requested that all MSU site PIs and PSC inform their respective MSU teams about the July webinar, scheduled for **Wednesday, July 19th, 2023, from 2-3 PM EDT**. Please share the Zoom invitation with your team, ensuring their access to this valuable and enlightening session. It is the same invitation link as for the recurring monthly webinar.

We strongly encourage attendance from all MSU team as it promises to be an informative session for them.

Protocol Training Signatures

Please sign and upload these two documents to WebDCU

1. PI Protocol Traning Attestation attesting to study team training for the updates to the new Protocol v7
2. The new Protocol v7 Signatre Page .

Please reach out to Emily Stinson stinsoey@ucmail.uc.edu if you have any questions.

New Sites…Welcome Aboard!

The following site was **released to enroll** in the *FASTEST* study with a new PI during the last month.

University of Chicago Medical Center, Chicago, IL

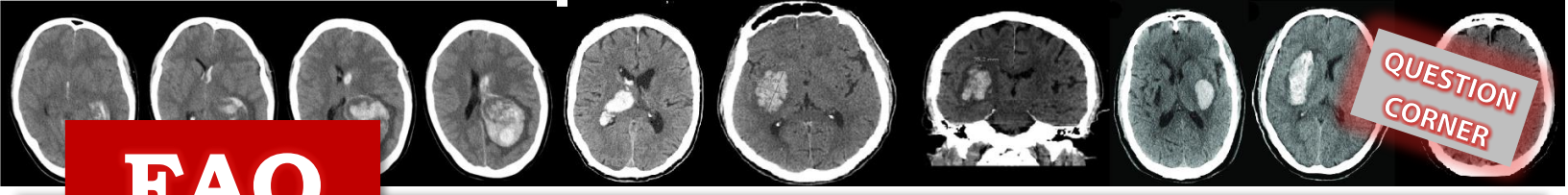
Site PI:
Ali Mansour, MD

Congratulations on First Enrollment!!

Congratulations to Dr. Ilana SPOKOYNY and her team at the Mills Peninsula Medical Center, Burlingame, CA for enrolling their first subject in *FASTEST*.

Congratulations to Dr. Tudor GHEORGHIU and his team at the Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom for enrolling their first subject in *FASTEST*.

Congratulations to Dr. Ganesh SUBRAMANIAN and his team at the Queens Medical Centre, Nottingham, United Kingdom for enrolling their first subject in *FASTEST*.



FAQ

Q: We have 2 drug kits that expired, would we be able to keep these kits and use them for training? Or do you need proof that they were destroyed by our pharmacy? It would be great to be able to use the kits for training our new fellows, it's really helpful when they can actually practice and mix drug, as they routinely do not do this.

A: In order to maintain the integrity of our drug accountability process, it is essential to document the destruction of study drugs in both the accountability log and WebDCU system.

If you intend to use an expired kit for demonstration or training purposes, we kindly request that you first inform the *FASTEST* pharmacy and obtain their approval. Once approval has been granted, please remove the expired kit from WebDCU, selecting the "Others" option as the reason for removal. In the comment section, please clearly indicate that you will be utilizing this kit for demonstration purposes and confirm that you have received approval from our pharmacy team to do so.

Q: Do we need to keep the tell-tale monitors that are sent with each drug shipment?

A: No, you do not need to keep those monitors. You can discard them.

Q: Do we need to keep paper copies of our screen failure pts? We've been entering all screen failures directly into WEBDCU, do we also need to keep our own log? It was requested by the auditor reviewing but it seems redundant.

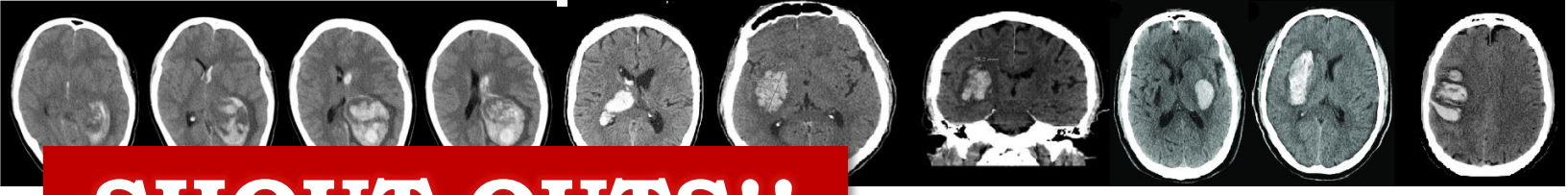
A: Our requirement is to include screen failures in the WebDCU system. The WebDCU serves as an electronic source document for this purpose. However, if the auditors from specific countries deem it necessary, we highly recommend adhering to their advice regarding this matter.

Q: While enrolling our last subject we noticed that the kit was missing the vial adapters. We opened an expired kit and used those vial adapters to be able to mix the drug. We've also taken the vial adapters from the other expired kits and placed them with our study drug just in case we come across this situation again. Is this acceptable?

A: Vial adapters have an expiration date. If the vial adapter expiration date is prior to the drug/placebo expiration date, then it is imperative that those vial adapters must be discarded immediately. Under no circumstances should they be replaced in another kit or used in the future.

Furthermore, this incident must be thoroughly documented as a "note to file" for record-keeping purposes. We request that you report this issue, along with the corresponding "note to file," in the Issues Table within 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. **University of Alabama (UAB)**
2. **UC Davis, CA**
3. **St. Joesph AZ, MSU site**
4. **Mt. Sinai, NY**
5. **Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom**
6. **University Hospital Heidelberg, Heidelberg, Germany**

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

1. **Cedar Sinai, CA**
2. **WellStar, GA**
3. **Ronald Reagan, CA**

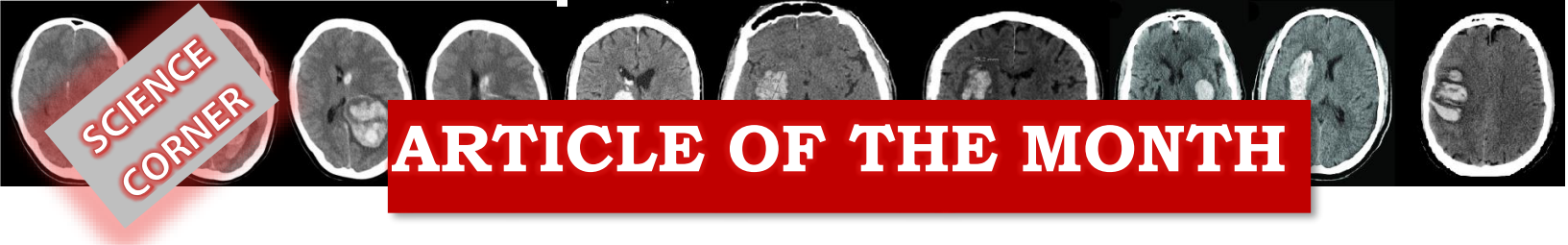
Top Enrolling Site

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

Subjects enrolled = 22!!

Congratulations to Enrolling Sites last Month!

Kobe City Medical Center General Hospital, Kobe, Japan	**3 Subjects**
National Cerebral and Cardiovascular Center, Osaka, Japan	**3 Subjects**
Iwate Prefectural Central Hospital, Morioka, Japan	**3 Subjects**
Kyorin University Hospital, Tokyo, Japan	**1 Subject**
Niigata City General Hospital, Niigata, Japan	**1 Subject**
Toranomon Hospital, Tokyo, Japan	**1 Subject**
Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA	**3 Subjects**
UCSD Medical Center - Hillcrest Hospital, San Diego, CA	**1 Subject**
Mills Peninsula Medical Center, Burlingame, CA	**1 Subject**
Riverside Methodist Hospital, Columbus, OH	**2 Subjects**
University of Calgary - Foothills Medical Centre, Calgary, AB, Canada	**2 Subjects**
Vancouver General Hospital, Vancouver, BC, Canada	**1 Subject**
Clinic Frankfurt Hoechst, Frankfurt, Germany	**1 Subject**
Queens Medical Centre, Nottingham, United Kingdom	**1 Subject**
Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom	**1 Subject**



Seasonal Variation in Neurologic Hospitalizations in the United States

Ali G. Hamedani, MD MHS , Dylan Thibault and Allison W. Willis, MD MSCI

Ann Neurol. 2023 Apr;93(4):743-751. https://doi.org/10.1002/ana.26579

Background:
Certain neurologic diseases have been noted to vary by season, and this is important for understanding disease mechanisms and risk factors, but seasonality has not been systematically examined across the spectrum of neurologic disease, and methodologic guidance is also lacking.

Methods:
Using nationally representative data from the National Inpatient Sample, a stratified 20% sample of all non-federal acute care hospitalizations in the United States, we calculated the monthly rate of hospitalization for 14 neurologic diseases from 2016 to 2018. For each disease, we assessed seasonality of hospitalization using chi-squared, Edward, and Walter-Elwood tests and seasonal time series regression models. Statistical tests were adjusted for multiple hypothesis testing using Bonferroni correction.

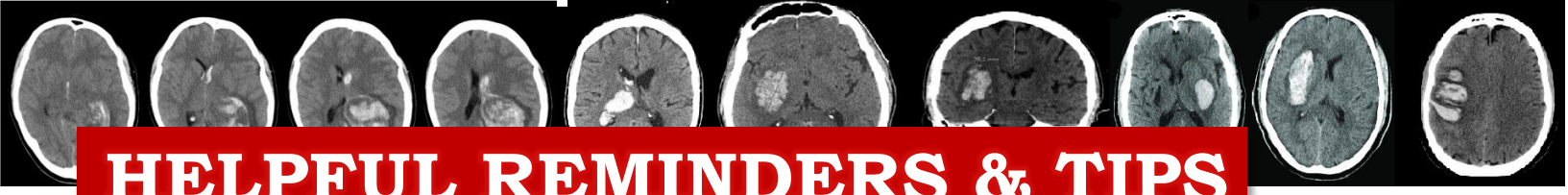
Results:
Meningitis, encephalitis, ischemic stroke, intracerebral hemorrhage, Guillain-Barre syndrome, and multiple sclerosis had statistically significant seasonality according to multiple methods of testing. Subarachnoid hemorrhage, status epilepticus, myasthenia gravis, and epilepsy had significant seasonality according to Edwards and Walter-Elwood tests but not chi-square tests. Seasonal time series regression illustrated seasonal variation in all 14 diseases of interest, but statistical testing for seasonality within these models using the Kruskal-Wallis test only achieved statistical significance for meningitis.

Interpretation: Seasonal variation is present across the spectrum of acute neurologic disease, including some conditions for which seasonality has not previously been described, and can be examined using multiple different methods.

TABLE. Results of Non-Regression and Seasonal Time Series Analyses of Seasonality in Neurologic Hospitalizations, NIS 2016 to 2018

Diagnosis	Number of Hospitalizations	Chi-squared	Edwards Test	Edwards Test, Month-Adjusted	Walter-Elwood Test	Walter-Elwood Test, Month-Adjusted	Seasonal Time Series Regression		
							Peak-to-Trough Ratio (95% CI)[a]	Kruskal-Wallis Test Statistic	*p*-Value
Ischemic stroke	1,497,670	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	1.055 (1.047–1.064)	14.57	0.2029
Intracerebral hemorrhage	209,305	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	1.114 (1.090–1.137)	17.56	0.0923
Subarachnoid hemorrhage	69,570	0.0200	<0.0001	<0.0001	<0.0001	<0.0001	1.124 (1.084–1.166)	12.55	0.3235
Dural sinus thrombosis	2,190	0.3500	0.0144	0.0358	0.0112	0.0109	1.341 (1.087–1.653)	13.15	0.2837
Epilepsy; convulsions	579,755	0.2400	0.0295	<0.0001	0.0003	0.0004	1.054 (1.012–1.037)	18.43	0.0722
Status epilepticus	122,600	0.1300	<0.0001	0.0027	<0.0001	<0.0001	1.074 (1.045–1.103)	19.07	0.0598
Myasthenia gravis	25,365	0.3100	<0.0001	0.0045	<0.0001	<0.0001	1.162 (1.093–1.234)	12.78	0.3082
Guillain-Barre syndrome	23,005	0.0020	<0.0001	<0.0001	<0.0001	<0.0001	1.16 (1.089–1.236)	11.28	0.4199
Multiple sclerosis	68,410	0.0020	<0.0001	<0.0001	<0.0001	<0.0001	1.12 (1.080–1.162)	10.15	0.5173
Optic neuritis	7,415	0.2400	0.4356	0.1546	0.4765	0.4819	1.046 (1.000–1.169)	4.85	0.9382
Transverse myelitis	8,480	0.3500	0.8828	0.8025	0.7074	0.7153	1.023 (1.000–1.135)	10.48	0.4874
Neuromyelitis optica	4,905	0.1900	0.2805	0.1256	0.2899	0.2999	1.085 (1.000–1.244)	15.84	0.1471
Meningitis	79,050	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	1.925 (1.853–2.000)	29.38	0.002
Encephalitis	32,595	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	1.280 (1.213–1.351)	19.92	0.0465

[a]Obtained from sine curves fitted to monthly hospitalization frequencies (corresponding to the Edwards test).[12, 13] The minimum peak-to-trough ratio is 1 (indicating an equal incidence of hospitalization during each month without seasonal variation), and higher values indicate greater degrees of



HELPFUL REMINDERS & TIPS

For Project Managers, Study Coordinators & Study Teams

- **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.
- Please respond to all the pending open DCRs for our site. We also will be reaching out to sites with pending protocol deviation and violations to help them file these in the Issue table accordingly with a NTF.
- **Things to make sure with DOA changes**: We have noticed that there is an increase in DoA changes, and we understand that many sites are adding or removing investigators from the DoA. Considering this, we would like to emphasize the following points. We kindly request your attention to ensure the following:
  1. Update **box 6** of the **FDA 1572** to make sure it aligns with investigators listed on your current DoA
  2. Make sure if you are adding investigators to the DoA that you are also uploading their required documents in a timely manner.
  3. Investigators must do all trainings and have all documents uploaded and approved in WebDCU before performing study procedures.
  4. Please make sure that your study team has been updated on the recent changes to the protocol. Promptly upload the **PI attestation** form and the new **Protocol v7 Signature Page** if you have not done so already.
- Jama Olsen from NDMC will be working with the international CRO monitors to be sure they are familiar with the Issues Table in the WebDCU and will be able to instruct sites what to report in it if need be. Kindly reach out to Jama for any queries or clarification about the Issues Table at olsen@musc.edu.
- **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.

INTERNATIONAL SITE OF THE MONTH

Queens Medical Centre, Nottingham, United Kingdom

The Queens Medical Centre, located in Nottingham, United Kingdom, is a renowned and leading medical facility known for its exceptional healthcare services and commitment to patient care. As one of the largest hospitals in Europe, it offers a wide range of specialized medical services, cutting-edge technology, and a highly skilled team of healthcare professionals. The Queens Medical Centre is a major teaching hospital affiliated with the University of Nottingham, attracting top medical talent, and fostering an environment of innovation and research. With its state-of-the-art facilities, comprehensive medical departments, and dedication to delivering outstanding healthcare, the Queens Medical Centre plays a pivotal role in providing high-quality medical services to the community it serves.

The hospital is recognized for its extensive research activities that contribute to advancements in healthcare and medical knowledge. The medical center has a robust research program that encompasses a broad range of fields, including clinical trials, biomedical sciences, and healthcare innovation. Collaborating with renowned academic institutions and industry partners, the Queens Medical Centre conducts groundbreaking research studies and trials that aim to improve patient outcomes and shape the future of medicine. The research activities at the center encompass various disciplines, such as cancer research, cardiovascular studies, neuroscience, genetics, and regenerative medicine. The dedicated team of researchers, scientists, and clinicians at the Queens Medical Centre are committed to pushing the boundaries of medical knowledge through their innovative research initiatives, ultimately leading to enhanced diagnostics, treatments, and healthcare practices.

Site PI:
Dr. Ganesh Subramanian

Dr. Subramanian chairs the Clinical Advisory Group in Stroke in East Midlands and leads the development of mechanical thrombectomy pathway as well as co-leading the deployment of artificial intelligence (AI) software for stroke imaging regionally. He provides injection service (for management of spasticity) in adults. He is one of the select few peer-reviewer of stroke services in the Country.

Dr Subramanian is an Associate Post Graduate Dean in East Midlands and Training Program Director for the Specialist Registrars in General Internal Medicine. He chairs a registration/fitness to practice panel in the General Medical Council. He also undertakes medico-legal work in stroke, geriatrics, and general medicine.

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/