NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

JULY 2023 | VOLUME 2 | ISSUE 7

FASTEST

FVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

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Message from Dr. Broderick

Dear FASTEST colleagues,

As we enter the middle of summer, I wanted to congratulate all of us for reaching an important milestone of 200 enrolled subjects in June. This milestone is important since we will be doing a futility analysis after these 200 subjects have been followed for 6 months and we will be looking at 6-month outcome and hemorrhage growth at 24 hours (probably close to 300 subjects) at end of year. We think it highly unlikely that we would be stopped for futility, but it is an important step. The next very important step will be 430 subjects followed up at 6 months which will be analysis for efficacy and futility. So, let's keep up and even accelerate enrollment. It is very exciting times for treatment of ICH and this is our best chance to find an effective hemostatic therapy!

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

Please join us for the *FASTEST* Monthly Webinar

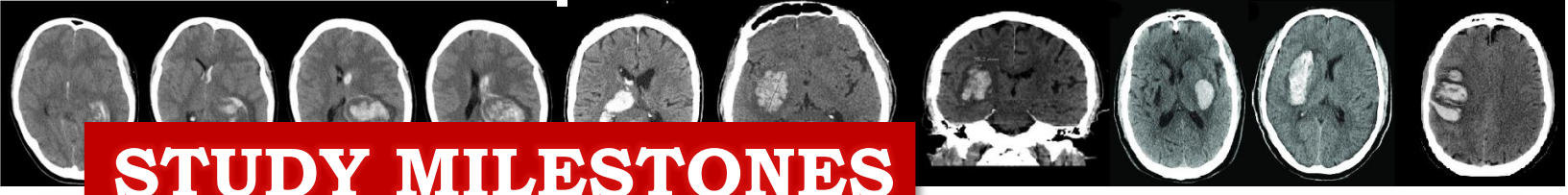
Wednesday July 19th, 2:00-3:00 pm EST

- Dr. James Grotta from Memorial Hermann, Texas Medical Center and Dr. Digvijaya D. Navalkele from Grady Memorial Hospital, Atlanta will be conducting this entirely MSU focused webinar.

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

Meeting ID: 957 6834 3105
Passcode: 111641

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 = **218**

- US Randomizations: **60**
- International randomizations: **158** (**97** Japan, **30** Canadian, **18** Spain, **11** Germany, **2** UK)

Randomization last month = **21**
Total Screen Failures = **685**
Subjects Randomized by MSU = **9**
Subjects Terminated Early = **0**
eConsent Used = **6**
Remote Consent Used = **5**

CALENDAR OF EVENTS

Upcoming *FASTEST* Monthly Webinar: **Wednesday, July 19th @ 2:00-3:00 pm EDT**

FASTEST study team office hours: **Monday, July 17th and 31st @ 2:00-3:00 pm EDT**

IMPORTANT NOTES

Webinar Invite for MSU teams

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.

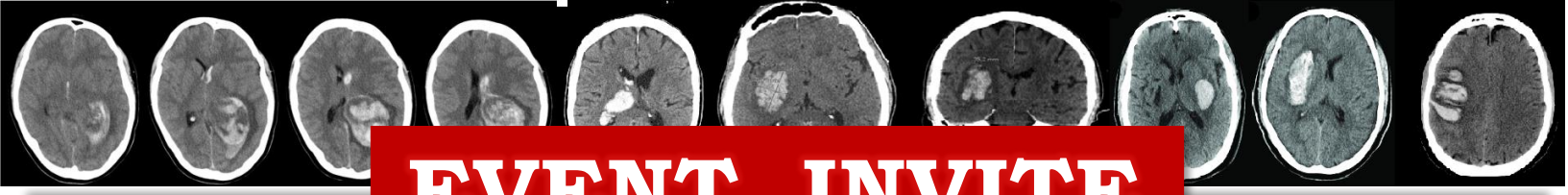
We strongly encourage attendance from all MSU teams as it promises to be an informative session for them.

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 Signature Page .

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



EVENT INVITE

Please Join Us For The

FASTEST

MOBILE STROKE UNIT WEBINAR

Wednesday July 19th
2:00-3:00 pm EDT

Join Zoom Meeting
https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fucincinnati.zoom.us%2Fj%2F97332759019&data=05%7C01%7Cquadrisd%40ucmail.uc.edu%7C5e5fbc4a050646f404c908db3ce2799c%7Cf5222e6c5fc648eb8f0373db18203b63%7C0%7C0%7C638170715624992309%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=%2FuxYHAcLPpNNr6Cv8Cf%2BYwNgejYSEWDvXIlT2dY2fkQ%3D&reserved=0

Meeting ID: 973 3275 9019

One tap mobile
+16469313860,,97332759019# US
+13017158592,,97332759019# US (Washington DC)

Join by SIP
97332759019@zoomcrc.com

Join by H.323
162.255.37.11 (US West)
162.255.36.11 (US East)
69.174.57.160 (Canada Toronto)
65.39.152.160 (Canada Vancouver)
207.226.132.110 (Japan Tokyo)
149.137.24.110 (Japan Osaka

Dial by your location
+1 646 931 3860 US
+1 301 715 8592 US (Washington DC)
+1 305 224 1968 US
+1 309 205 3325 US
+1 312 626 6799 US (Chicago)
+1 646 876 9923 US (New York)
+1 719 359 4580 US
+1 253 205 0468 US
+1 253 215 8782 US (Tacoma)
+1 346 248 7799 US (Houston)
+1 360 209 5623 US
+1 386 347 5053 US
+1 507 473 4847 US
+1 564 217 2000 US
+1 669 444 9171 US
+1 669 900 6833 US (San Jose)
+1 689 278 1000 US

New Sites...Welcome Aboard!

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

The Mount Sinai Hospital, New York, NY

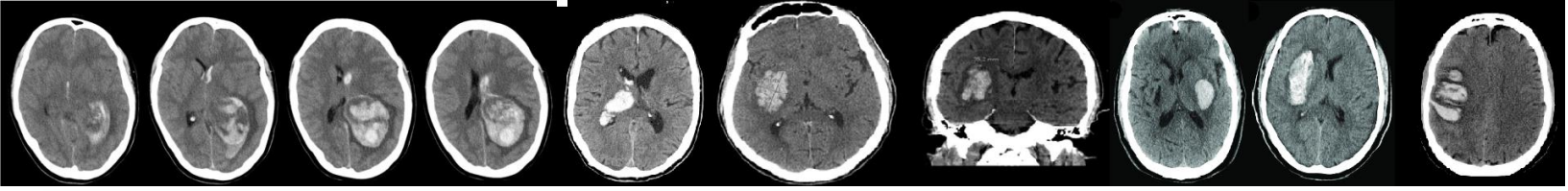
Site PI:
John Liang, MD

University of Alberta Hospital, Edmonton, AB, Canada

Site PI:
Brian H. Buck, MD, MSc, FRCPC

WellStar Kennestone Hospital, Marietta, GA

Site PI:
Raisa C. Martinez, MD



John Radcliffe Hospital, Oxford, United Kingdom

Site PI:
Philip Mathieson, MD

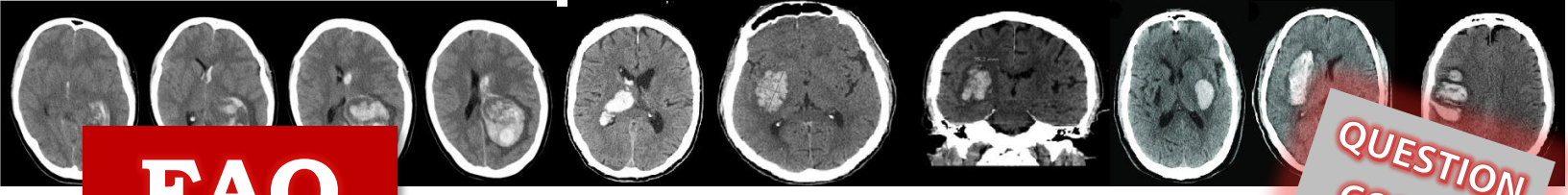
Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom

Site PI:
Indira Natarajan, MD

Congratulations on First Enrollment!!!

Congratulations to Dr. Pere CARDONA PORTELA and the team at the Bellvitge University Hospital, Barcelona, Spain for enrolling their first subject in FASTEST.

Congratulations to Dr. John Liang and the team at the Mount Sinai West, New York, NY for enrolling their first subject in *FASTEST*.



FAQ

QUESTION CORNER

Q: In WebDCU, the COVID-19 Assessment CRF is posted at the End of Study. If my subject had a positive COVID-19 test during the study, do I need to also submit an Adverse Event CRF?

A: Review the date of the positive test and the date of randomization/infusion.

- If the date of PCR test with positive results is **between randomization and Day 4**, complete Form 104: Adverse Event.
- If the date of PCR test with positive results is **after Day 4 through Day 90,** complete Form 104: Adverse Event only if the event is serious.

Q: Can a patient on novel oral anticoagulants (NOAC), such as apixaban be enrolled in the trial?

A: Anticoagulants (NOAC), such as apixaban, dabigatran, rivaroxaban and edoxaban within the past seven days are an exclusion criterion.

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.

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 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.

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. **Mt. Sinai Hospital, NY**
2. **WellStar Hosp. GA**
3. **Royal Stoke University Hospital, United Kingdom**
4. **John Radcliffe Hospital, Oxford, United Kingdom**
5. **University of Alberta Hospital, Edmonton, AB, Canada**

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

1. **Ronald Reagan, CA**
2. **Henry Ford, MI**

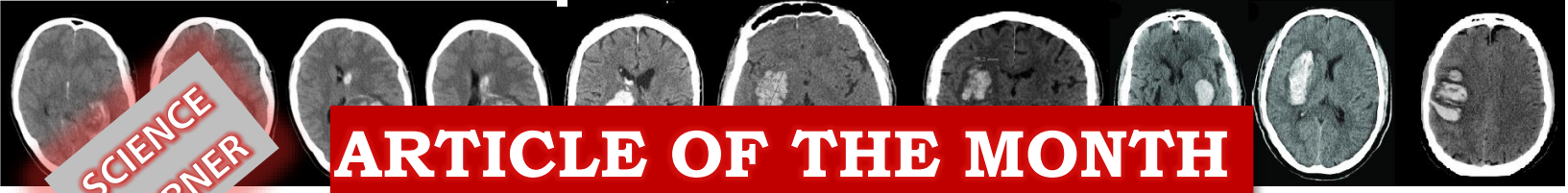
Top Enrolling Site

Congratulations to **National Cerebral and Cardiovascular Center, Osaka, Japan** and **Kobe City Medical Center General Hospital, Kobe, Japan** for being the highest enrolling sites in the study.

Subjects enrolled = 23!!

Congratulations to Enrolling Sites last Month!

Kobe City Medical Center General Hospital, Kobe, Japan	**4 Subjects**
National Cerebral and Cardiovascular Center, Osaka, Japan	**1 Subject**
Iwate Prefectural Central Hospital, Morioka, Japan	**3 Subjects**
Niigata City General Hospital, Niigata, Japan	**1 Subject**
Toranomon Hospital, Tokyo, Japan	**3 Subjects**
UCSD Medical Center - Hillcrest Hospital, San Diego, CA	**1 Subject**
Mount Sinai West, New York, NY	**1 Subject**
Central DuPage Hospital, Winfield, IL	**2 Subjects**
University of Calgary - Foothills Medical Centre, Calgary, AB, Canada	**2 Subjects**
Girona University Hospital, Girona, Spain	**2 Subject**
Bellvitge University Hospital, Barcelona, Spain	**1 Subject**



SCIENCE CORNER

ARTICLE OF THE MONTH

The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial

Lu Ma*, Xin Hu*, Lili Song*, Xiaoying Chen*, Menglu Ouyang, Laurent Billot, Qiang Li, Alejandra Malavera, Xi Li, Paula Muñoz-Venturelli, Asita de Silva, Nguyen Huy Thang, Kolawole W Wahab, Jeyaraj D Pandian, Mohammad Wasay, Octavio M Pontes-Neto, Carlos Abanto, Antonio Arauz, Haiping Shi, Guanghai Tang, Sheng Zhu, Xiaochun She, Leibo Liu, Yuki Sakamoto, Shoujiang You, Qiao Han, Bernard Crutzen, Emily Cheung, Yunke Li, Xia Wang, Chen Chen, Feifeng Liu, Yang Zhao, Hao Li, Yi Liu, Yan Jiang, Lei Chen, Bo Wu, Ming Liu, Jianguo Xu, Chao You, Craig S Anderson, for the INTERACT3 Investigators†

Lancet. 2023 Jul 1;402(10395):27-40. https://doi.org/10.1016/S0140-6736(23)00806-1

Background:

Early control of elevated blood pressure is the most promising treatment for acute intracerebral haemorrhage. We aimed to establish whether implementing a goal-directed care bundle incorporating protocols for early intensive blood pressure lowering and management algorithms for hyperglycaemia, pyrexia, and abnormal anticoagulation, implemented in a hospital setting, could improve outcomes for patients with acute spontaneous intracerebral haemorrhage.

Methods:

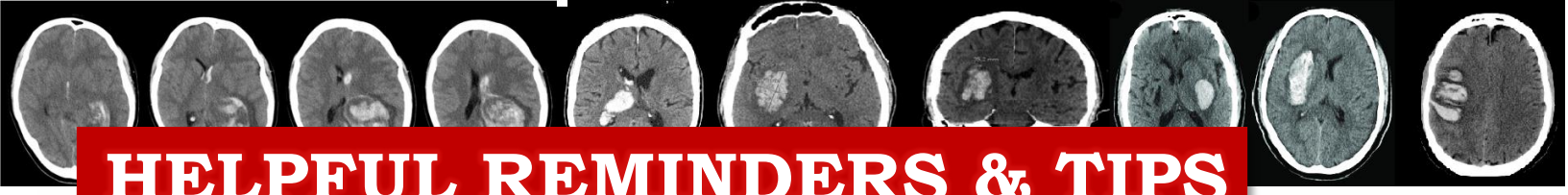
We performed a pragmatic, international, multicentre, blinded endpoint, stepped wedge cluster randomised controlled trial at hospitals in nine low-income and middle-income countries (Brazil, China, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka, and Viet Nam) and one high-income country (Chile). Hospitals were eligible if they had no or inconsistent relevant, disease-specific protocols, and were willing to implement the care bundle to consecutive patients (aged ≥18 years) with imaging-confirmed spontaneous intracerebral haemorrhage presenting within 6 h of the onset of symptoms, had a local champion, and could provide the required study data. Hospitals were centrally randomly allocated using permuted blocks to three sequences of implementation, stratified by country and the projected number of patients to be recruited over the 12 months of the study period. These sequences had four periods that dictated the order in which the hospitals were to switch from the control usual care procedure to the intervention implementation of the care bundle procedure to different clusters of patients in a stepped manner. To avoid contamination, details of the intervention, sequence, and allocation periods were concealed from sites until they had completed the usual care control periods. The care bundle protocol included the early intensive lowering of systolic blood pressure (target <140 mm Hg), strict glucose control (target 6·1–7·8 mmol/L in those without diabetes and 7·8–10·0 mmol/L in those with diabetes), antipyrexia treatment (target body temperature ≤37·5°C), and rapid reversal of warfarin-related anticoagulation (target international normalised ratio <1·5) within 1 h of treatment, in patients where these variables were abnormal. Analyses were performed according to a modified intention-to-treat population with available outcome data (ie, excluding sites that withdrew during the study). The primary outcome was functional recovery, measured with the modified Rankin scale (mRS; range 0 [no symptoms] to 6 [death]) at 6 months by by masked research staff, analysed using proportional ordinal logistic regression to assess the distribution in scores on the mRS, with adjustments for cluster (hospital site), group assignment of cluster per period, and time (6-month periods from Dec 12, 2017). This trial is registered at Clinicaltrials.gov (NCT03209258) and the Chinese Clinical Trial Registry (ChiCTR-IOC-17011787) and is completed.

Findings:

Between May 27, 2017, and July 8, 2021, 206 hospitals were assessed for eligibility, of which 144 hospitals in ten countries agreed to join and were randomly assigned in the trial, but 22 hospitals withdrew before starting to enrol patients and another hospital was withdrawn and their data on enrolled patients was deleted because regulatory approval was not obtained. Between Dec 12, 2017, and Dec 31, 2021, 10 857 patients were screened but 3821 were excluded. Overall, the modified intention-to-treat population included 7036 patients enrolled at 121 hospitals, with 3221 assigned to the care bundle group and 3815 to the usual care group, with primary outcome data available in 2892 patients in the care bundle group and 3363 patients in the usual care group. The likelihood of a poor functional outcome was lower in the care bundle group (common odds ratio 0·86; 95% CI 0·76–0·97; p=0·015). The favourable shift in mRS scores in the care bundle group was generally consistent across a range of sensitivity analyses that included additional adjustments for country and patient variables (0·84; 0·73–0·97; p=0·017), and with different approaches to the use of multiple imputations for missing data. Patients in the care bundle group had fewer serious adverse events than those in the usual care group (16·0% vs 20·1%; p=0·0098).

Interpretation:

Implementation of a care bundle protocol for intensive blood pressure lowering and other management algorithms for physiological control within several hours of the onset of symptoms resulted in improved functional outcome for patients with acute intracerebral haemorrhage. Hospitals should incorporate this approach into clinical practice as part of active management for this serious condition.



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.
- **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

Bellvitge University Hospital, Barcelona, Spain

Bellvitge University Hospital, located in Barcelona, Spain, is a renowned medical facility recognized for its excellence in patient care, research, and teaching. Established in 1972, the hospital has played a crucial role in the healthcare landscape of Catalonia and beyond.

As a tertiary hospital, Bellvitge University Hospital offers a comprehensive range of medical services across various specialties. It boasts state-of-the-art facilities and cutting-edge medical technology to provide high-quality healthcare to its patients. The hospital's commitment to patient-centered care is evident through its multidisciplinary approach, ensuring collaboration among healthcare professionals to deliver personalized treatment plans.

One of the notable strengths of Bellvitge University Hospital lies in its research capabilities. The hospital houses several research institutes and centers that focus on advancing medical knowledge, developing innovative treatments, and contributing to scientific breakthroughs. These research efforts encompass diverse fields such as oncology, cardiovascular diseases, neurosciences, and regenerative medicine, among others. The hospital's dedication to research not only enhances patient care but also fosters a vibrant academic environment.

Education and training are integral components of Bellvitge University Hospital's mission. As an affiliated teaching hospital of the University of Barcelona, it serves as a training ground for medical students, residents, and fellows. Through its collaboration with the university, the hospital provides a rich learning environment where aspiring healthcare professionals can gain practical experience and benefit from the expertise of experienced clinicians and researchers.

Site PI:
Dr. Pere CARDONA PORTELA

Dr. Pere Cardona Portela is a neurologist at the Hospital Universitari de Bellvitge. He is Associate professor at the University of Barcelona.

Dr. Cardona Portela is actively engaged in research activities at Bellvitge University Hospital. His contributions to stroke research have resulted in valuable insights and advancements in the field. Some of his primary research interests include Endovascular Thrombectomy vs Medical Management in acute stroke and Sleep-Disordered Breathing and Acute Stroke.

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/