NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

DECEMBER 2023 | VOLUME 2 | ISSUE 12

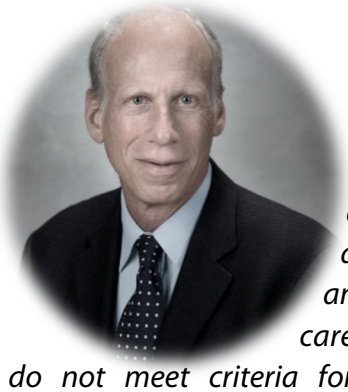
FASTEST

EVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Grotta



Clinical research is difficult. Patients arrive at the ER at inconvenient times and not frequent enough to establish an enrollment "routine"; they require careful scrutiny and more often than not do not meet criteria for inclusion; and they require the coordinated teamwork of several investigators to complete enrollment on time. Plus, our research efforts are usually not completely reimbursed and are often grafted atop our myriad clinical responsibilities. Despite these challenges, this past year has been a resounding success for FASTEST thanks to the dedication of the team-members at each enrolling site. We continue to enroll on track with our projected rate and will soon reach our first interim analysis. We are well on our way to completing the most definitive study of medical therapy for intracerebral hemorrhage!

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

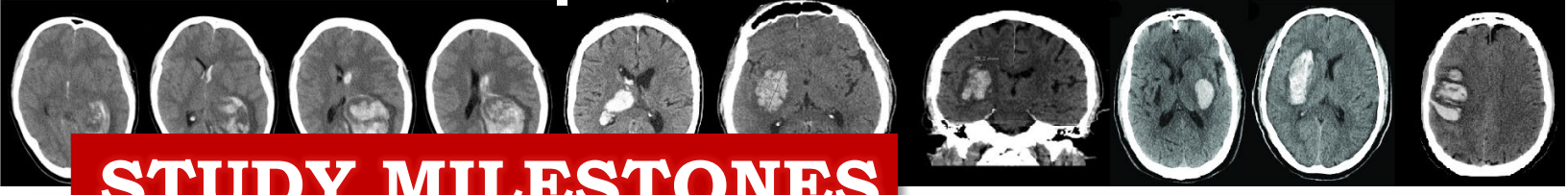
Wednesday December 20th, 2:00-3:00 pm EST

- Dr. Lauren Ng and her team from Mayo Clinic, Jacksonville, FL will be discussing case at their site.
- Dr. Sangha and his team from Kaiser Permanente Fontana Medical Center, Fontana, CA will be discussing case at their site.
- Review of sites pending EFIC approval
- Temperature Excursions and monitoring

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=E5dRFfb7oIW1z8MCqQ%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: **78** (**44** USA, **34** OUS: **6** Germany, **14** Japan, **4** Spain, **6** Canadian, **4** UK)

Total MSUs Released to Enroll: **12** (**10** US and **2** OUS)

Total Randomization = **328**

- US Randomizations: **91**
- International randomizations: **237**
  - Japan = **159**
  - Canada = **41**
  - Spain =**20**
  - Germany = **11**
  - UK = 6

Randomization last month = **19**

Total Screen Failures = **1140**

Subjects Randomized by MSU = **12**

Subjects Terminated Early = **1**

eConsent Used = **14**

Remote Consent Used = **10**

CALENDAR OF EVENTS

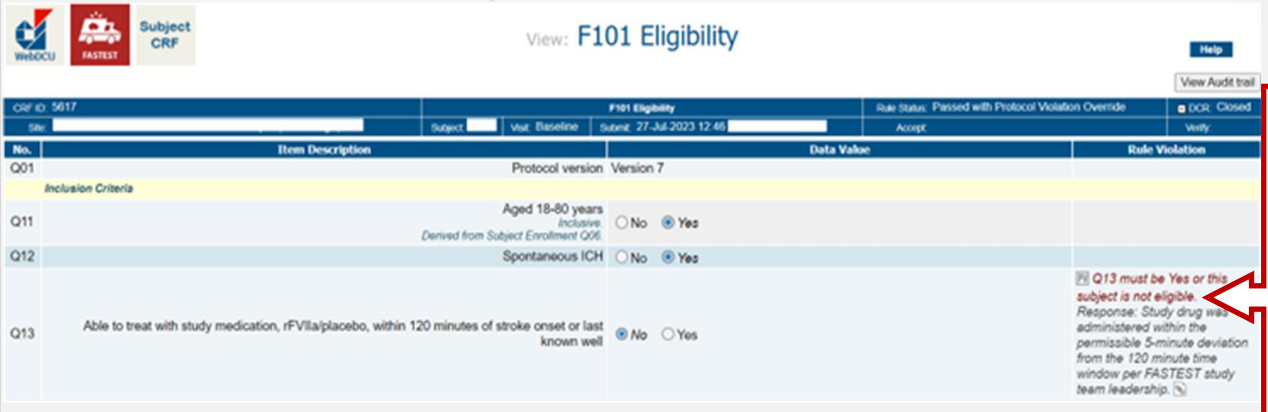
Upcoming *FASTEST* Monthly Webinar: **Wednesday, December 20th, @ 2:00-3:00 pm EST**

FASTEST study team office hours: **Monday, December 18th, @ 2:00-3:00 pm**

IMPORTANT NOTE

Enrollment Window

- Subjects enrolled **after 125 minutes** will be considered a protocol violation - ***Require prompt CIRB reporting*.**
- Subjects administered study drug/randomized **between 121-125 minutes** will be considered protocol deviation ***- do not require prompt CIRB reporting***."

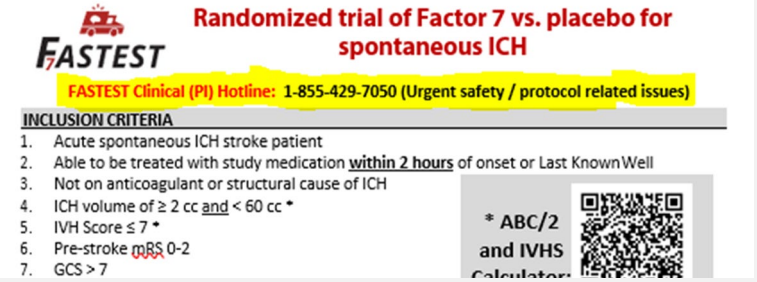


For randomization between 121-125 min select "No" for Q13 on F101 Eligibility (as shown below) and respond to the rule violation with the following language.

"Study drug was administered within the permissible 5-minute deviation from the 120-minute time window per FASTEST study team leadership".

FASTEST Hotline 1-855-429-7050

FASTEST Clinical (PI) Hotline for urgent safety, enrollment, and protocol-related matters.
You can find this number on the pocket cards (see below), the study MOP and in the monthly FASTEST newsletter.



New Sites... Welcome Aboard!

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

St. Michaels Hospital, Toronto, ON, Canada

Site PI:
Atif Zafar, MD

Kaiser Permanente Fontana Medical Center, Fontana, CA

Site PI:
Navdeep Singh Sangha, MD

Kaiser Permanente West Los Angeles Medical Center, Los Angeles, CA

Site PI:
Navdeep Singh Sangha, MD

Kaiser Permanente Downey Medical Center, Downey, CA

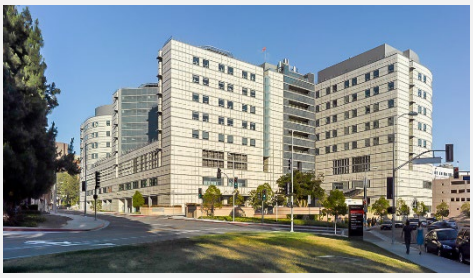
Site PI:
Navdeep Singh Sangha, MD

Congratulations on 1st Enrollment!!!

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

Congratulations to Dr. Navdeep Sangha and his team at the Kaiser Permanente Fontana Medical Center, Fontana, CA enrolling their first subject in FASTEST.

Congratulations to Dr. Christopher STREIB and his team at the M Health Fairview Southdale Hospital, Edina, MN for enrolling their first subject in FASTEST.



Congratulations to Dr. May Nour and her team at the Ronald Reagan UCLA Medical Center, Los Angeles, CA for enrolling their first subject in FASTEST.

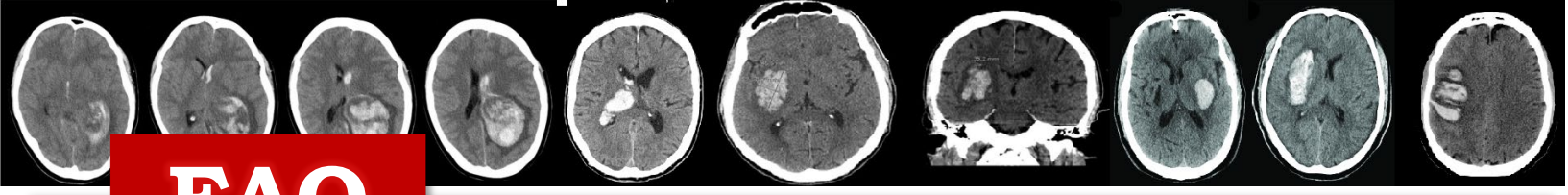
FAQ

QUESTION CORNER

Q: Pharmacy ended up mixing up the kit, thought it was not used we are short on one. Will it be shipped out automatically or do we need to do anything?

A: Dispose of the kit and complete the Study Drug Removing Form in WebDCU. Upon submission of the information, the study drug will be automatically dispatched to the site. In such instances, designate the reason as 'Other' and provide specific details in the 'Removing notes'. The identical procedure is implemented for the replacement of study kits following temperature excursions (after confirmation from NOVO) and for expired kits. (refer to the example below).

9	Removing type	○ Expired ○ Damaged ○ Missing ○ Returned ○ Recall ○ Quarantined ◉ *Temperature excursion* ○ Site closing ○ Other
10	Removing notes	Novo stating your kits are NOT fit for use due to temperature excursion.
11	Removing confirmed by	[redacted]
12	Removing confirmed on	06-Nov-2023 13:26



FAQ

Q: We had a patient yesterday but could not enroll as we weren't sure about the enrollment window/inclusion exclusion criteria/consenting situation etc. Is there a number to reach study PI for enrollment quires?

A: Kindly contact the FASTEST Clinical (PI) Hotline **1-855-429-7050** for urgent matters related to safety, enrollment, and protocol. You can locate this number on the pocket cards, in the study protocol and MOP, and within the monthly FASTEST newsletter. Please stay on the line, and one of the three study PIs will promptly attend to your inquiry.

Q: An aneurysm was identified after enrollment. Is this a n eligibility violation?

A: The identification of an incidental aneurysm post-enrollment is not considered an eligibility violation.

Q: in Form 106- Medical History the site should answer whether the subject has prior intracranial hemorrhage. In case of incidental (asymptomatic) ICH found in head CTs, how should this question be answered?

A: Since this is an incidental finding at the time of enrollment it should be answered as no prior history.

Q: in Form 106- Medical History what does it mean "excluding the qualifying stroke"? Is it excluding hemorrhagic transformation of ischemic stroke"?

A: Subject with hemorrhagic transformation of ischemic stroke should not be enrolled in the trial. Such hemorrhages do not constitute as spontaneous ICH which is the inclusion criteria for FASTEST.

Q: When reporting adverse event outcome, when would I select 'Unknown'?

A: An adverse event should only be unknown when a subject is lost to follow up and the medical record does not confirm the outcome. If a subject completes the study through the Day 180 Visit, another outcome must be selected. Remember to check-in on all previously reported ongoing events at each study visit.

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.

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 until 90 days and deaths until Day 180). 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. UPDATE?

Thank you to the sites recently released to enroll for their hard work:

1. **St. Michaels Hospital, Toronto, ON, Canada**
2. **Kaiser Permanente Downey Medical Center, Downey, CA**
3. **Kaiser Permanente West Los Angeles Medical Center, CA**
4. **Kaiser Permanente Fontana Medical Center, Fontana, CA**

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

1. **UF Health Shands Hospital, Gainesville, FL**

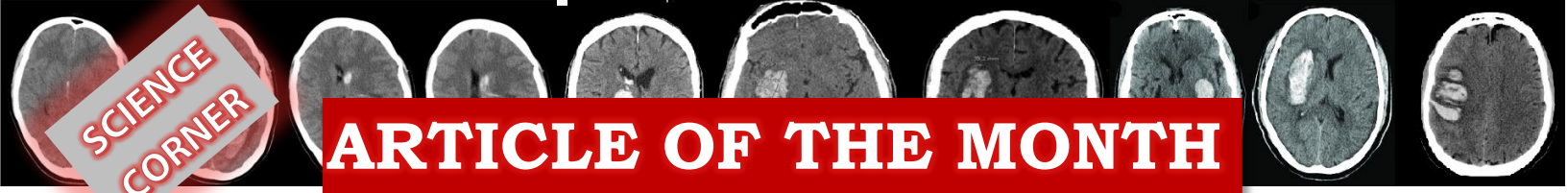
Top Enrolling Site

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

Subjects enrolled = 39!!

Congratulations to Enrolling Sites last Month!

Kobe City Medical Center General Hospital, Kobe, Japan	4 Subjects
National Cerebral and Cardiovascular Center, Osaka, Japan	3 Subject
Toranomon Hospital, Tokyo, Japan	1 Subject
Ottawa Hospital, Ottawa, ON, Canada	1 Subject
University of Calgary - Foothills Medical Centre, Calgary, AB, Canada	1 Subject
John Radcliffe Hospital, Oxford, United Kingdom	1 Subject
M Health Fairview Southdale Hospital, Edina, MN	1 Subject
Mayo Clinic, Jacksonville, FL	1 Subject
Providence St. Vincent Medical Center, Portland, OR	1 Subject
WellStar Kennestone Hospital, Marietta, GA	1 Subject
Ronald Reagan UCLA Medical Center, Los Angeles, CA	1 Subject
Mills Peninsula Medical Center, Burlingame, CA	1 Subject
Kaiser Permanente Fontana Medical Center, Fontana, CA	1 Subject
Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA	1 Subject



Intracerebral Hemorrhage Among Blood Donors and Their Transfusion Recipients

Jingcheng Zhao,MD, PhD; Klaus Rostgaard, MSc; Elsa Lauwers, PhD; Torsten Dahlén, MD, PhD; Sisse Rye Ostrowski, MD, PhD, DMSc; Christian Erikstrup,MD, PhD; Ole Birger Pedersen, MD, PhD; Bart de Strooper,MD, PhD; Robin Lemmens, MD, PhD; Henrik Hjalgrim, MD, PhD, DMSc; Gustaf Edgren, MD, PhD

JAMA. 2023;330(10):941-950. doi:10.1001/jama.2023.14445

Importance: Recent reports have suggested that cerebral amyloid angiopathy, a common cause of multiple spontaneous intracerebral hemorrhages (ICHs), may be transmissible through parenteral injection of contaminated cadaveric pituitary hormone in humans

Objective: To determine whether spontaneous ICH in blood donors after blood donation is associated with development of spontaneous ICH in transfusion recipients.

Design, Setting, and Participants: Exploratory retrospective cohort study using nationwide blood bank and health register data from Sweden (main cohort) and Denmark (validation cohort) and including all 1 089 370 patients aged 5 to 80 years recorded to have received a red blood cell transfusion from January 1, 1970 (Sweden), or January 1, 1980 (Denmark), until December 31, 2017.

Exposures: Receipt of red blood cell transfusions from blood donors who subsequently developed (1) a single spontaneous ICH, (2) multiple spontaneous ICHs, or (3) no spontaneous ICH.

Main Outcomes and Measures: Spontaneous ICH in transfusion recipients; ischemic stroke was a negative control outcome.

Results:

A total of 759 858 patients from Sweden (median age, 65 [IQR, 48-73] years; 59% female) and 329 512 from Denmark (median age, 64 [IQR, 50-73] years; 58% female) were included, with a median follow-up of 5.8 (IQR, 1.4-12.5) years and 6.1 (IQR, 1.5-11.6) years, respectively. Patients who underwent transfusion with red blood cell units from donors who developed multiple spontaneous ICHs had a significantly higher risk of a single spontaneous ICH themselves, compared with patients receiving transfusions from donors who did not develop spontaneous ICH, in both the Swedish cohort (unadjusted incidence rate [IR], 3.16 vs 1.12 per 1000 person-years; adjusted hazard ratio [HR], 2.73; 95% CI, 1.72-4.35; P < .001) and the Danish cohort (unadjusted IR, 2.82 vs 1.09 per 1000 person-years; adjusted HR, 2.32; 95% CI, 1.04-5.19; P = .04). No significant difference was found for patients receiving transfusions from donors who developed a single spontaneous ICH in the Swedish cohort (unadjusted IR, 1.35 vs 1.12 per 1000 person-years; adjusted HR, 1.06; 95% CI, 0.84-1.36; P = .62) nor the Danish cohort (unadjusted IR, 1.36 vs 1.09 per 1000 person-years; adjusted HR, 1.06; 95% CI, 0.70-1.60; P = .73), nor for ischemic stroke as a negative control outcome.

Conclusions and Relevance: In an exploratory analysis of patients who received red blood cell transfusions, patients who underwent transfusion with red blood cells from donors who later developed multiple spontaneous ICHs were at significantly increased risk of spontaneous ICH themselves. This may suggest a transfusion-transmissible agent associated with some types of spontaneous ICH, although the findings may be susceptible to selection bias and residual confounding, and further research is needed to investigate if transfusion transmission of cerebral amyloid angiopathy might explain this association.

HELPFUL REMINDERS & TIPS

For Project Managers, Study Coordinators & Study Teams

- **Imaging Reminders:** Submit all head imaging performed as SOC within 30 hours from stroke onset to IMC (i.e., NCCT, CTA, MRI if performed)
  - Baseline/first scan obtained either in ED or MSU to determine trial eligibility AND prior to study product administration.
  - 24 (+/6) hours from stroke onset follow-up scan
  - "Unscheduled" scan obtained for clinical deterioration or immediately prior to any surgical intervention (i.e., surgical removal of ICH or IVC placement) if planned prior to 24-hour scan.
    ***Failure to obtain a pre-op scan results in missing imaging endpoint (i.e., ability to calculate ICH growth between baseline scan and unscheduled pre-op scan)

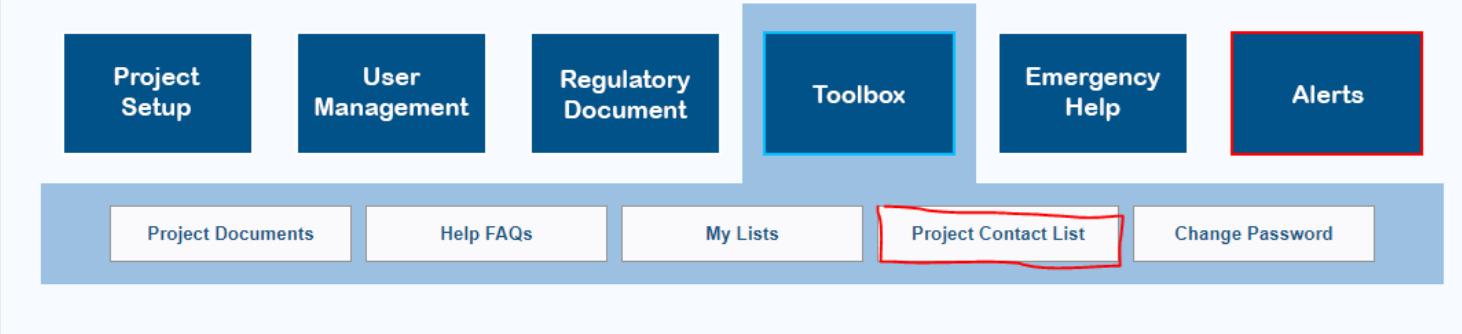
  Imaging must be submitted within 5-7 business days of subject randomization via the Ambra Health® platform.

  - Also includes submission of WebDCU F502 which is needed to process scans.

  ***Confirmation of receipt of ALL imaging is one of the requirements in triggering "Baseline through 24 hr. Payment" to your site.

- 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).

- 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

- **Recent temperature excursions in IDS Pharmacy:** There have been recent reports of temperature excursions at certain sites related to the storage of the study drug within the pharmacy. We strongly encourage all site PSCs to proactively engage with their trial pharmacist. Regular communication and periodic checks with the pharmacist will help ensure the consistent monitoring of temperature conditions and mitigate the risk of excursions.
  - The TERF needs to be submitted to the NCC project manager and Strokenet central pharmacy as soon as possible.
  - The site pharmacists should remove the effected study drug by filling out the WebDCU form in a timely manner in order to trigger a resupply. The sites are advised to add more people to the DOA in order to expedite the process of documenting things in WebDCU if necessary.

- 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.

INTERNATIONAL SITE OF THE MONTH

Gifu University Hospital, Gifu, Japan

Gifu University Hospital boasts a rich legacy, tracing its origins back to the establishment of Gifu Prefectural Hospital in 1875. The hospital has played an integral role in the healthcare landscape of Gifu Prefecture, evolving significantly over the years. In 2004, a state-of-the-art facility was inaugurated in its current location, marking a new chapter in its commitment to providing high-quality medical care.

Functioning as the sole university hospital and special function hospital in Gifu Prefecture, Gifu University Hospital holds a pivotal designation as a specialized facility for intractable diseases, including cancer, hepatitis, and AIDS. The hospital is at the forefront of addressing major health challenges, actively engaging in advanced medical care for the "five major diseases" (cancer, cardiac infarction, stroke, diabetes, and psychiatric disease) and offering specialized medical services such as Emergency Medical Care, Disaster Medical Care, Rural and Community Medical Care, Perinatal Care, and Pediatric Care.

Recognized as one of the Advanced Emergency Medical Service Centers in Japan, Gifu University Hospital's Advanced Critical Care Center is dedicated to providing tertiary emergency care for patients requiring the most advanced medical interventions. The hospital not only excels in patient care but also serves as a hub for advanced treatment technology development and research, holding certification as an "advanced treatment hospital" by the Ministry of Health, Labour and Welfare.

Gifu University Hospital takes pride in its myriad designations, including but not limited to "postgraduate education hospital," "prefectural cancer center," "Gifu prefectural incurable disease center," "AIDS treatment core center," "linked core centers for the treatment of liver disease," "advanced emergency care center," "core disaster care center," "Gifu prefectural emergency trauma center," and "nuclear disaster center." These designations underscore the hospital's pivotal role as the primary destination for patients seeking specialized care in Gifu Prefecture.

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/