Enhancing Enrollment in Acute Stroke Trials: Current State and Consensus Recommendations

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Abstract

Background and Purpose—The Stroke Treatment Academic Industry Roundtable (STAIR) convened a session and workshop regarding enrollment in acute stroke trials during the STAIR XII meeting on 3/22/2023.

Methods—This forum brought together stroke physicians and researchers, members of the National Institute of Neurological Disorders and Stroke (NINDS), industry representatives, and members of the U.S. Food and Drug Administration to discuss the current status and opportunities for improving enrollment in acute stroke trials.

Results—The workshop identified the most relevant issues impacting enrollment in acute stroke trials and addressed potential action items for each. Focus areas included emergency consent in the U.S. and other countries; careful consideration of eligibility criteria to maximize enrollment and representativeness; investigator, study coordinator, and pharmacist availability outside of business hours; trial enthusiasm/equipoise; site start-up including contractual issues; site champions; incorporation of study procedures into standard workflow as much as possible; centralized enrollment at remote sites by study teams using telemedicine; global trials; and co-enrollment in trials when feasible.

Conclusions— Enrollment of participants is the lifeblood of acute stroke trials and is the rate-limiting step for testing an exciting array of new approaches to improve patient outcomes. In particular, efforts should be undertaken to broaden the medical community's understanding and implementation of emergency consent procedures and to adopt designs and processes that are easily incorporated into standard work flow and that improve trials' efficiencies and execution.

Research and actions to improve enrollment in ongoing and future trials will improve stroke outcomes more broadly than any single therapy under consideration.

Abbreviations:

LAR: Legally authorized representatives

STAIR: The Stroke Treatment Academic Industry Roundtable

NINDS: National Institute of Neurological Disorders and Stroke

FDA: Food and Drug Administration

DEFUSE 3: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke Trial

MOST: Multi-arm Optimization of Stroke Trial

r-TPA: recombinant tissue plasminogen activator

TNK: tenecteplase

FASTEST: rFVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time Trial

GAINS: Global Alliance of Independent Stroke Networks

TICH 2: Tranexamic Acid for Hyperacute Primary Intracerebral Hemorrhage 2 Trial

IRB: Institutional review board

EFIC: Exception from informed consent

COVID: Coronavirus disease

Introduction:

Enrollment of participants is the lifeblood of any clinical trial, but acute stroke presents unique challenges given the time-dependent nature of the event and the variety of teams and locations in which a patient receives care (emergency management services, comprehensive stroke center and/or their affiliated spoke hospitals). The pathophysiology of ischemic and hemorrhagic strokes is very time-dependent,[1,2] narrowing the window for consent and for effective therapeutic intervention. In addition, stroke patients with more than a mild deficit often have impaired ability to provide consent and legally authorized representatives (LAR) may not be immediately available to provide consent. Because effective therapies for acute stroke are time-dependent, new experimental therapies must be incorporated into the standard workflows that minimize time to treatment. Lastly, unlike trials of prevention and chronic diseases, research and clinical teams rarely have an existing therapeutic relationship with patients, posing unique challenges regarding trust in physicians approaching them to participate in acute stroke clinical trials.

To address enrollment challenges in acute stroke trials, The Stroke Treatment Academic Industry Roundtable (STAIR) convened a workshop during the STAIR XII on 3/22/2023. This forum brought together stroke physicians and researchers, members of the National Institute of Neurological Disorders and Stroke (NINDS), industry representatives, and members of the US Food and Drug Administration (FDA) to discuss the current status and future priorities regarding enrollment in acute stroke trials. The workshop systematically reviewed, affirmed, and expanded upon enrollment issues discussed in a recent publication in the journal Stroke from a broader, international, and more diverse perspective. [3] The

workshop identified the most relevant issues impacting enrollment in acute stroke trials and addressed potential action items for each. The three broad categories affecting enrollment addressed at the workshop in order of how they occur in a trial include 1) study design, 2) infrastructure and site start-up, and 3) the process of participant enrollment by the study team.

Study Design

The determination of eligibility criteria is the most important determinant of enrollment success before initiation of the study since it defines the proportion of the stroke population that is eligible for the trial. Eligibility criteria should be as inclusive as possible unless it will substantially impact the expected effect of a study therapy or pose a potential safety risk. An example of the latter is the time from stroke onset to treatment. Expanding the treatment window for a reperfusion therapy can increase the number of eligible patients substantially. Yet, it could also reduce the likelihood to detect a beneficial effect since physiologic time is the critical determinant for preserving brain tissue by reperfusion. Some trial investigators exclude older or disabled patients who are more likely to have poorer outcomes and risks of adverse events after a stroke. Yet, older patients often will respond as well as younger patients to potential therapies.[4] Exclusion of older patients will not only decrease the rate of enrollment, but also disproportionally exclude women from a trial because the older population, where stroke rates are highest, has more women than men.[5,6] Similarly, excluding patients with some disability from to the index stroke may exclude a population that may also benefit from a therapy while decreasing the available population of eligible participants.

Stanton and colleagues recently reported the impact of expanding inclusion criteria during the feasibility planning for the DEFUSE 3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke on subsequent enrollment.[5] In response to an epidemiological assessment of the prevalence of various eligibility criteria, the DEFUSE 3 investigators expanded the originally planned inclusion and exclusion criteria (age 90 years versus 80 years, National Institutes of Health Stroke Scale score of ≥6 versus 8–25, pre-stroke modified Rankin Scale score of 0–2 versus 0–1, and time from stroke onset 6–16 hours versus 6–12 hours). Among patients enrolled in the DEFUSE 3 trial, 57% (104/182) qualified *only* via the broadened study entry criteria, a major factor leading to a faster-than-projected enrollment rate.

Another design feature to enhance enrollment is to test a proposed experimental therapy within the standard workflow for acute stroke as much as possible. The more the study protocol deviates from standard care, the higher the real and perceived burden of enrollment. For example, the ongoing Multi-arm Optimization of Stroke Trial (MOST) was initially designed to test the addition of eptifibatide or argatroban to intravenous alteplase (recombinant tissue plasminogen activator - rt-PA) begun within 3 hours of onset and followed by endovascular thrombectomy as clinically indicated.[7] After the trial began, it became clear that tenecteplase (TNK) was replacing alteplase as the standard of care at sites and communities participating in the trial, based upon accumulating data, and despite the lack of FDA approval of TNK for acute ischemic stroke in the United States (U.S.). To address this change in the standard of care, a protocol amendment was submitted and approved by the FDA. This amendment clarified that the experimental arms were to be added to “standard of care lytic therapy” that could include TNK as well as rt-PA based upon documentation of standard of

care at a participating site. FDA's flexibility with regards to this issue allowed MOST to maintain study enrollment as many U.S. sites transitioned to TNK as their standard thrombolytic agent.

Design of a stroke trial should be as simple as possible to answer a scientific question since the complexity of a trial is associated with decreased enrollment and also represents more opportunity for errors.[6] Adaptive trial designs and platform trials are more complex designs that can answer multiple study questions more quickly but should simplify operational implementation (such as simple case report forms or use of data from already ongoing stroke registries) whenever possible.[8] Efforts should be made to integrate diagnostic testing, such as imaging or blood samples, seamlessly into existing workflows to minimize disruption and optimize efficiency. Study design that allows co-enrollment in other studies, particularly studies without another intervention or without a clear scientific overlap, should be encouraged, but must be considered in light of the burden to participating patients, their families and study personnel. When there are overlapping trials at the same institution, an enrollment plan that demonstrates how multiple trial enrollments are to be determined is important. This should be developed in partnership with all stakeholders and should be agreed upon a priori. Such information, when obtained as part of trial feasibility assessments, may also determine the need for additional enrollment sites by the trial leadership team. Other methods to address competing acute stroke trials have been recently published.[3]

Acute stroke trials should include providing informed consent documents and other patient-facing materials in other languages besides English, particularly Spanish, since this enhances enrollment, diversity, and generalizability of a trial.

Trial budgets should account for these translation costs. Trial investigators should bear in mind that some Institutional Review Boards also have provisions for using generic, non-English, short form consent forms to facilitate enrollment of non-English speaking participants. Finally, having diverse and inclusive study teams could also increase recruitment, as patients who identify with study members are more likely to participate in the study. Patients who identify with the study team may be more willing to be compliant and engage with the study procedures

Infrastructure and Site Start-up

The NIH StrokeNet, and other national stroke networks, were developed to eliminate the need to build an infrastructure every time a new stroke trial is started (See Global Alliance of Independent Stroke Networks – GAINS website: https://www.globalstroketrials.org/). [9,10] Such networks include sites that have experienced investigators and study research professionals that have been successful in enrollment for past trials. The NIH StrokeNet has 27 regional coordinating centers with a potential 500 enrollment sites but only about 60-70 sites have been identified and activated in ongoing acute stroke trial sites within NIH StrokeNet. Thus, while there are many more hospitals in the U.S. with sufficient volumes of acute stroke patients, finding U.S. sites with experienced clinical trial research teams willing to enroll acute stroke patients in ongoing trials is challenging.

What makes a successful enrollment site beyond a sufficient volume of stroke patients? The workshop participants agreed that the most important marker of success is an experienced “site-investigator champion” who is passionate about clinical research and the proposed trial in particular, and who can navigate the various operational issues and local

infrastructure for efficient trial start-up and successful enrollment. These factors include maintaining and training an enthusiastic core of physician investigators and study coordinators, support from the hospital system or university for contracting and data-sharing, a responsive and experienced local IRB, a dedicated and supportive research pharmacy, and a diverse research portfolio that enhances the financial support of the team. The ideal site sees clinical research as part of the continuum of clinical care and trial enrollment as an opportunity to offer the highest level of care for every eligible patient.

Recommendations for site selection in acute stroke trials include investigators and sites with a good track-record in prior acute stroke trials, sites with appropriate local infrastructure for clinical research, and site investigators who demonstrate enthusiasm and equipoise for the treatment under study. Ideally, sites that can recruit 7 days a week and after business hours should be prioritized over those that enroll only during business hours.

Potential approaches to accelerate site start-up can include standardized contracts (as in some national stroke networks), [9] use of accelerated contracts or Master contracts by industry, the use of standardized order sets for electronic medical record system (e.g., EPIC, Cerner) that can be easily used and adapted by local sites, and providing Medicare coverage analyses to local sites by sponsors. Training and mentoring programs for local site investigators, stroke fellows, and clinical research professionals in the conduct and local management of acute stroke trials are needed to expand clinical trials and grow research at other hospitals which have ample patient populations but lack infrastructure and

experience. These programs also ensure that the accumulated wisdom of experienced clinical trialists is passed on to future generations.

Finally, adequate financial reimbursement for site start-up, screening of potential participants, and enrollment of patients, particularly after hours, provides a stronger financial basis for research in academic and community hospital settings. Furthermore, offering monetary incentives to health systems or academic centers for completing start-up activities within a 90-day timeframe can expedite the initiation of trials. When the level of support is significant, it can provide strong motivation for these organizations to successfully accomplish the task.

Some very successful enrollment sites have set up a hub-and-spoke network where a research team based at a successful hub also either provides support to research staff at nearby or regional hospitals or leads the process of enrolling subjects at those spokes, often by telemedicine as described below. This is one way to export expertise and infrastructure to hospitals with a good volume of patients but that lack the investigators, clinical research professionals, and core operational processes. A hub-and-spoke model may be one way of increasing the reach of existing trial investigators and clinical research professionals.

Recruiting, training and retaining new clinical research professionals willing to participate in acute stroke trials is a major limitation noted by workshop participants. Ideally, we need an infrastructure to train new and experienced clinical research professionals at academic centers as well as community hospitals that are new to stroke research. The NIH StrokeNet recently initiated an education/training core dedicated to on-boarding, continuing education, and retention of

clinical research professionals that mirrors the highly successful Educational Core for StrokeNet fellows and plans to leverage resources of the NIH Clinical Translational Science Awards (CTSAs). Finally, the integration of clinical research into clinical stroke care should be an expected and financially supported part of clinical work-flow at academic and busy clinical centers as it is for cancer. Without an adequate number of trained clinical research professionals, the number of recruitment sites and trial enrollment will lag.

Location and Number of Trial Sites

Enrollment is a function of the available population of eligible patients at potential sites, the estimated number of eligible patients at each site who can be successfully enrolled, the number of sites, and how quickly sites can move from identification by the sponsor to enrollment activation. As discussed above, study design and eligibility criteria drive the number of eligible patients and are the most important factors for enrollment. Data from stroke registries, in which many stroke hospitals participate (e.g., Get With The Guidelines-Stroke in the US, NVQI-QOD), and population-based studies can provide estimates of potentially eligible patients at participating sites.[5] These data then need to be adjusted for projected percentages of patients/families who will likely refuse to participate, the loss of subjects because sites only enroll during business hours, competing trials, and unique trial criteria such as special imaging, etc. After the required sample size for a trial is determined, data from this process can then be used to project the worst-case and best-case number of required sites. Yet, even with careful use of site data and careful site selection, estimates of needed sites and time needed for enrollment are almost always underestimated for a variety of reasons, the most important of which is the

inadequate bandwidth of local research teams to approach every eligible patient and take the time to thoroughly discuss the trial with potential subjects and/or their LARs. An alternative approach to this "inside view" approach of estimating sites and enrollment time is to take the "outside" view and use a reference class of comparable projects (i.e., how long has the average similar acute stroke trial taken to complete enrollment?). [11] Regardless, enrollment must be monitored carefully from trial initiation and study leadership must continually look for ways to proactively interact with sites to identify obstacles and opportunities for improvement. Additional sites should be identified at the beginning of the trial as back-up if enrollment lags in the early stages of a trial.

Global acute stroke trials are challenging from a start-up standpoint but are more likely to be successful from an enrollment standpoint. [6] Enrollment in acute stroke trials in the U.S. lags behind other countries. [6] Reasons may include larger and denser population of stroke patients (e.g., intracerebral hemorrhage in Asia) and centralized research infrastructure and financial support (e.g., China). For example, as of March 28th in the ongoing rFVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time (FASTEST) trial that enrolls ICH patients within 2 hours of onset, 14 sites in Japan without emergency consent have enrolled 65 patients (approximately 7 per site per year) as compared to 55 sites in Canada, Spain, United Kingdom, and the U.S. that have enrolled 85 patients (2.5 per site per year – personal written communication – Joseph Broderick – PI of FASTEST Trial, 4/11/2023). Cultural expectations of treating physicians and patients eligible for participation in a research study could also vary by country with more deference to physician investigators in some countries as compared to others. Thus, with only 60-70 sites in the U.S. that have

successfully enrolled in acute stroke trials within NIH StrokeNet, sponsors in the U.S. which need a larger number of sites to meet enrollment goals in a timely fashion must consider global trials.

Global trials also have challenges. Many countries now have central Research Ethics Boards (REBs)/Institutional Review Boards (IRBs) that facilitate start-up. In general, ethics review is no longer a major barrier to timely trial start up, but contractual issues dominate both within and outside the US and particularly in Europe. General Data Protection Regulation (GDPR) and relatively new data privacy laws in Europe are time-consuming for trial sponsors based in the U.S. who don't have a physical legal presence in other countries where the study is being considered.

Participant Enrollment

Obtaining Consent from Patient or LAR

The workshop participants identified obtaining consent as the most time-intensive process for enrollment of subjects in acute stroke trials and one of the most important reasons for the failure to recruit potential participants. As opposed to stroke prevention and stroke recovery trials in which discussion of a study and informed consent can occur over several visits, the time window for consent in many acute stroke trials is often minutes to several hours and every minute of delay can impact the potential efficacy of an experimental therapy. [12] Methods to address this very short-time window include an abbreviated consent form containing only critical information with an accompanying information sheet with much more detailed information that can be read by the patient and family later. [13] In the latter approach used in the Tranexamic Acid for Hyperacute Primary Intracerebral Hemorrhage 2 (TICH-2 Trial), patients provided initial consent by

signing a brief one-page information sheet (288 words) followed by a full written informed consent (four-page information sheet of 2474 words) at the earliest subsequent opportunity after enrollment. [14]

The requirements surrounding emergency consent vary by country (Table 1). In some countries emergency consent is the default process of enrollment when patients cannot provide consent and LARs cannot be immediately identified. In the U.S., emergency consent is defined as an exception from informed consent or EFIC. Under EFIC, patients who cannot provide consent or for whom an LAR cannot be identified initially can be enrolled in a trial. EFIC also allows for investigators to obtain verbal assent from LARs by phone who have yet to arrive at the hospital but cannot digitally sign an electronic consent. However, verbal assent of the LAR requires the subsequent written or digital signature on the informed consent by the LAR. Verbal assent of patient, for whatever reason such as inability to write, requires the written or digital signature of an impartial witness on the informed consent who has listened to discussion of the trial by the study investigator and verbal assessment of the patient.

While EFIC can greatly facilitate enrollment into acute stroke trials, the regulatory approval process for EFIC, particularly since the advent of COVID, is long, requires substantial engagement and time from the site investigator team, and is expensive. The FDA provides detailed guidance about the requirements for EFIC (21 CFR 50.24, https://www.fda.gov/media/80554/download) but two requirements drive the time and expense of EFIC approval in the U.S.

1) Consultation with representatives of the communities where the clinical investigation will take place and from which the subjects will be drawn, including consultation by the IRB if appropriate, concerning the proposed trial.
2) Prior to the initiation of the clinical investigation, public disclosure of plans for the investigation, as well as its risks and expected benefits, to the communities from which participants will be drawn and where the clinical investigation will be conducted.

The extent of community consultation events and methods for public disclosure of a trial can vary based on a local and central IRB's interpretation of FDA guidance, specifically in relation to the trial's target population. Before COVID, 3-6 months was a typical time course for completing these requirements before IRB approval. During and after COVID, the ability to do in-person community events was much more challenging and sites could take up to 12-18 months or longer to obtain IRB approval.

The community is defined as the geographic region from which subjects might be drawn and the population with the disease or risk factors for the disease. The former is inherently local, but the latter could be considered more broadly. If so, a centralized effort to get input nationally from the broader population at risk could be combined with local community consultation to reduce the number of required local events, thus decreasing the burden on recruiting sites . For example, a national sample of responses through social media or other sampling methods, combined with small number of local events could be ideal if the FDA and IRBs would agree on this approach.

Other countries in Europe and Canada which utilize emergency consent procedures do not have these regulatory requirements of community consultation and public disclosure. This is likely one reason why emergency consent for acute stroke trials is done more commonly in Europe, Canada, and Australia than the U.S. and enrollment in these countries has outpaced the U.S. in many ongoing global acute stroke trials. [6]

Participants of the STAIR workshop considered streamlining the EFIC/emergency consent process for acute emergencies in the U.S. a high priority. One proposed action item was organization of a conference to address this issue which should have representation from the FDA, industry, academia, the NIH, legislators/liaisons, central and local IRBs and stroke patients. Some countries, such as Japan, lack the option of emergency consent in acute stroke trials (Figure 1). Such a conference could be useful as a model for those countries who are looking to institute emergency consent within their own country for acute trials. The experience of emergency consent in other countries could be used as a backdrop for these discussions. In summary, engagement of stroke patients overall in the design and implementation of acute stroke trials is valuable. But frank discussions are needed in the U.S. regarding the currently required processes of community consultations and public disclosures in emergency research and the lack of these processes in other countries that also allow emergency deferral of consent.

Finally, because EFIC requirements take months to complete, initial approval of sites for enrollment using only prospective consent while they complete EFIC requirements is one way to begin site enrollment more quickly. This

approach involves enrollment at a much slower pace but eliminates the additional time needed to complete other requirements for site start-up after EFIC approval.

Telemedicine has accelerated the treatment of stroke patients within many hospital systems and communities, drastically reducing the time needed for physicians to assess patients. This same technology can provide an excellent mechanism for obtaining electronic and virtual consent prompted by email, rather a written signature in person. Often a LAR is not immediately available and digital platforms allow for the review and digitally signing of consent forms prior to LAR's arrival at the hospital. While some sites have become very proficient with this approach and are leading recruiters in acute stroke trials, [3] many site investigators, institutions, and trials have yet to adopt this approach. Perceived challenges are the additional regulatory steps of implementing a virtual consent process and the ability of LARs to complete the consent process digitally. The digitally signed informed consents can be configured to be only finished/signed when all necessary steps have been completed (leading to fewer potential errors and post-consent exclusions). In addition, videos and other visual aids can be incorporated into the digital consent and multiple family members in different locations can be engaged as well. The digital informed consent can be retained on platforms, such as REDCap, easily accessible to trial monitors and regulatory authorities. These platforms require expertise and training to set up. Lastly, if subjects are enrolled via telemedicine from a local emergency department, the IRB Of that local hospital may insist that the enrolling investigator hold privileges at their site, especially if data collected at that site (e.g., labs, imaging, exam findings) are used to determine eligibility.

Understanding patient perspectives on acute stroke trial consenting process is paramount, especially given the lack of pre-existing therapeutic relationship with eligible patients. All acute stroke clinical trials should consider input from patient/caregiver partners regarding a trial's consenting and enrollment processes. These inputs can be in form of consultative relationship, mock consent sessions, studios, or as involved as patient/caregiving representatives being trial co-investigators.

Availability of Site Investigators

One of the major reasons that enrollment is overestimated based on the number of eligible patients at a given site is that the study team may only enroll trial participants during business hours. This inability to enroll outside of business hours is limited less by the physician investigators who often combine research enrollment as part of their clinical call responsibilities but more by the lack of trained study coordinators and pharmacists from the research pharmacy available to take research calls in the evenings and on weekends. For example, in the ongoing Multi-arm Optimization of Stroke Trial (MOST), sites open for enrollment 7 days a week recruited participants at twice the rate of those sites open for enrolment only during business hours, Monday through Friday. [3,15] Sites who enroll in acute stroke trials only during business hours cite the challenge of paying extra for after-hour coverage and the identification, training and retention of study coordinators to do after-hour work.

The workshop participants recommended several action items that could effectively improve a site's ability to enroll at all hours. One recommendation was to adopt the payment strategy for after-hour enrollment that is currently used within

NIH StrokeNet for acute stroke trials. If all acute stroke trials, whether funded by the NIH or industry, compensate sites sufficiently for evening and weekend enrollments, more sites will be able to adequately support and retain study coordinators, which will help enrollment in all ongoing trials. Another suggestion is to train and incentivize emergency department pharmacists, or hospital pharmacists, to prepare study medications when the hospital research pharmacy is closed after hours and on the weekend. Ideally, study medication should be stored in the emergency department pharmacy whenever possible for easy and rapid availability. Some centers use a centralized group of coordinators based at the hospital and/or emergency department who are trained and enroll in many acute trials that include stroke, trauma and other emergencies. Notification of potential stroke cases via imaging applications such as RAPID and VIZ.ai can accelerate the time to enrollment. Virtual enrollment via telemedicine as noted above may help enrollment outside of business hours. Regardless, the most successful enrollment sites often involve a team of individuals to increase the likelihood of enrollment within short time windows. If full 24/7 coverage is not feasible, having the ability to enroll even in expanded such as from 7:00 am to 7:00 pm, with some flexibility for research staff to stay later if needed to complete an ongoing enrollment, may substantially increase site performance compared to a strict 8:00 am to 5:00 pm schedule.

Summary

Improving enrollment in acute stroke trials is one of the most important tasks to accelerate new treatments for stroke. Action items to enhance enrollment in acute stroke trials are listed in Table 2. We are not limited by the number of putative new therapies but by how quickly we can enroll eligible participants to test their efficacy and safety.

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Table 1: Emergency Consent for Acute Stroke in Selected Countries

Country	Emergency Consent (yes/no)	Community Consultation and Public Disclosure Required	Specific Comments about Process of Emergency Consent
United States	Yes ("exception from informed consent – EFIC")	Yes	Two IRBs usually involved in trials, a central IRB and the individual local IRBs for local context and population, often slows review. Details concerning EFIC regarding FDA guidance can be found in EFIC (21 CFR 50.24, https://www.fda.gov/media/80554/download.
Canada	Yes	No	Site IRBs and generally not central IRBs involved although there are now central IRBs in the provinces of Alberta, Ontario and Quebec. Details can be found in the Tri-Council Policy Statement-2 under Chapter 3: https://ethics.gc.ca/eng/policy-politique_tcps2-eptc2_2022.html
Mexico	Yes	No	Site IRBs and generally not central IRBs involved
Argentina			
Brazil			

Japan	No	No	
China	Yes	No	Provided the risk is low and that there are medical personal (doctors) involved in assessment and treatment assignment
India	No	No	
Australia	Yes	No	
United Kingdom	Yes	No	The law allows adults not able to consent for themselves to be recruited into Clinical Trials of Investigational Medicinal Products (CTIMPs) without prior consent in emergency situations if: • treatment needs to be given urgently • it is also necessary to take urgent action to administer the drug (IMP) for the purposes of the trial • it is not reasonably practicable to obtain consent from a legal representative • the procedure is approved by an NHS Research Ethics Committee • consent is sought from a legal representative as soon as possible. This typically refers to conditions where there is no time, e.g. cardiac arrest trials. For conditions with some time (as with FASTEST), then independent healthcare

			professional consent is allowed, usually a doctor as in many trials but can be a paramedic (as was done in RIGHT-2).
Germany	Yes	No	**As of 17-Jan-2022 EU regulation Nr. 536/2014 was formally implemented in German Drug Law with the following provisions:** Article 35 Clinical trials in emergency situations 1. By way of derogation from points (b) and (c) of Article 28(1), from points (a) and (b) of Article 31(1) and from points (a) and (b) of Article 32(1), informed consent to participate in a clinical trial may be obtained, and information on the clinical trial may be given, after the decision to include the subject in the clinical trial, provided that this decision is taken at the time of the first intervention on the subject, in accordance with the protocol for that clinical trial" and that all of the following conditions are fulfilled: (a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical trial; (b) there are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating

			the suffering and/or improving the health of the subject, or in the diagnosis of its condition; (c) it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative; (d) the investigator certifies that he or she is not aware of any objections to participate in the clinical trial previously expressed by the subject; (e) the clinical trial relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the clinical trial is of such a nature that it may be conducted exclusively in emergency situations; (f) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition. 2. Following an intervention pursuant to paragraph 1, informed consent in accordance with Article 29 shall be sought to continue the participation of the subject in the clinical trial, and information on the clinical trial shall be given, in accordance with the following requirements:

			(a) regarding incapacitated subjects and minors, the informed consent shall be sought by the investigator from his or her legally designated representative without undue delay and the information referred to in Article 29(2) shall be given as soon as possible to the subject and to his or her legally designated representative; (b) regarding other subjects, the informed consent shall be sought by the investigator without undue delay from the subject or his or her legally designated representative, whichever is sooner and the information referred to in Article 29(2) shall be given as soon as possible to the subject or his or her legally designated representative, whichever is sooner. For the purposes of point (b), where informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical trial shall be obtained from the subject as soon as he or she can give informed consent. 3. If the subject or, where applicable, his or her legally designated representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the clinical trial.”

Spain	Yes	No	For clinical trials in emergency situations Article 7 of Chapter II, of Spanish Royal Degree 1090/2015 applies: “1. Notwithstanding the provisions laid down in article 3.1.c) and articles 4 to 6 of this Royal Decree, when the clinical trial has a specific interest for the population where the investigation is conducted, and the reasons for the need to administer the investigational medicinal product are justified, a person may be included in a clinical trial without obtaining prior informed consent when all the conditions listed in article 35, paragraphs 1 and 2, of Regulation (EU) No 536/2014 of the European Parliament and of the Council, of 16 April 2014, are met. 2. In this case, whenever circumstances permit, family members or other persons close to the subject shall be previously consulted. 3. This possibility and the procedure to be followed must be provided for in the trial documentation approved by the CEIm (*Remark: Ethics committee*), and the person or his/her legally designated representative shall be informed as soon as possible and must give their consent to continue in the trial, where appropriate, or ratify it in any case.

			4. If the trial subject or, if applicable, his/her legal designated representative cannot give their consent, they shall be informed of their right to object to the use of the data obtained from the clinical trial.”
France	Yes	No	EU regulation Nr. 536/2014, Article 35 (as described for Germany) applies to all EU member states
Sweden			EU regulation Nr. 536/2014, Article 35 (as described for Germany) applies to all EU member states
Finland			EU regulation Nr. 536/2014, Article 35 (as described for Germany) applies to all EU member states
Denmark			EU regulation Nr. 536/2014, Article 35 (as described for Germany) applies to all EU member states
Israel	Yes	No	Inclusion of the patient in the trial (according the rules detailed in the trial protocol) must be approved by an independent doctor who is not part of the research team but is familiar with the protocol. It must be clarified that an independent doctor confirms the patient’s condition and his suitability and viability for the study. The independent doctor does not give consent for the patient.

Table 2: Twelve Important Actions to Enhance Enrollment and Trial Completion in Acute Stroke Trials

Actions	Specific tasks and timelines
Study Design	
Expansion of eligibility criteria whenever possible to enhance recruitment and generalizability of the trial results	Should be implemented in ongoing and all future studies
Simplification and incorporation of study design into standard workflow as much as possible	Should be implemented in all future studies
Study design that allows co-enrollment in other studies, particularly studies without another intervention.	Encouraged but must always be considered in light of the burden to participating patients, their families and study personnel.
Trial Infrastructure and Start-up	
Use of feasibility assessments to determine required number of sites. This process should include clinical databases such as "Get-with-the Guidelines" in the U.S. to determine numbers of eligible patients at participating sites.	Should be implemented in all future studies
Financial support for rapid trial start-up at study sites	Should be implemented in all future studies

Demonstration of clinical (e.g., certified comprehensive stroke centers) and research infrastructure (member of a national stroke research network) and prior successful trial enrollment.	Discussion with certifying agencies in U.S. or equivalent entities in other countries and leadership from national stroke research networks.
Global trials when more than 50 sites required and consider global trials to enhance enrollment even for smaller numbers of sites.	Strongly encouraged at beginning of all larger Phase III trials.
Training cadre of new clinical research professionals for acute stroke trials.	Establishment of funded training cores in national stroke networks.
Enrollment of Participants	
Enhancing and streamlining start-up for emergency consent in the U.S. and exploration of emergency consent in those countries not currently using this approach.	Future US conference regarding Emergency Consent for all relevant parties including FDA and open to global participants. Centralization of EFIC workload as much as possible and use of national data in conjunction with local community events.
Financial support for investigator enrollment of eligible participants outside of business hours by all sponsors in all countries.	Can be implemented now in all ongoing acute stroke trials by all sponsors.

Training of investigators in how to enroll participants via telemedicine.	National and regional workshops.
Technology (artificial intelligence) to identify potential eligible participants in prehospital and emergency department settings and rapid notification of study teams.	Already ongoing but needs greater distribution and improved processes.

Figure 1: Emergency Consent for Acute Stroke in Selected Countries

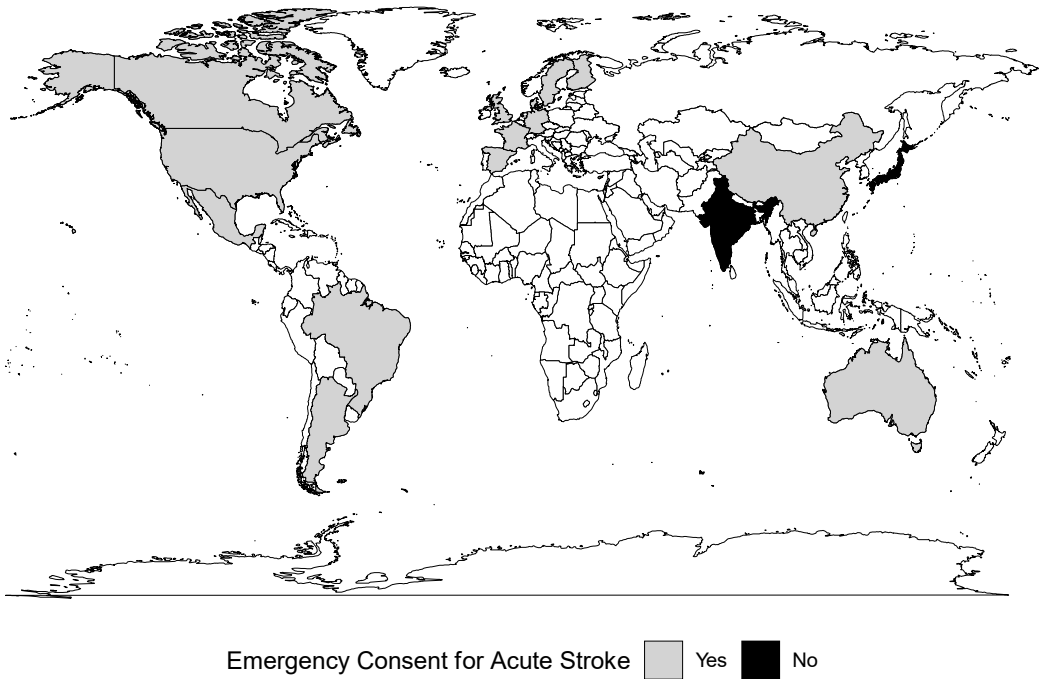

Figure 1 Legend:

Countries in white had no public information available about Emergency Consent.

Some countries depicted as having Emergency Consent have established guidelines for using Emergency Consent in clinical trials, which allow for the use of investigational drugs or medical devices without informed consent in certain circumstances; have no report of using it in acute stroke trials.

* The United States has “exception from informed consent – EFIC” for Acute Stroke