FASTEST:
Recombinant Factor VIIa for Acute Hemorrhagic Stroke Administered at Earliest Time

Exception from Informed Consent Requirements in Certain Emergency Research

University of Cincinnati
Model EFIC Proposal – Community Consultation and Disclosure Plan

Supported by:
The National Institute of Neurologic Diseases and Stroke

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INTRODUCTION

The goal of this document is to provide a logistical outline for the implementation of the additional protections associated with 21 CFR 50.24, Exception from Informed Consent (EFIC) Requirements in Certain Emergency Research, as related to the FASTEST study of spontaneous intracerebral hemorrhage (ICH) at the University of Cincinnati. The implementation of this plan is the first phase of conducting the proposed trial and the data acquired from the planned activities will be presented to the Advarra IRB and assist in the deliberations regarding the approval process for the study to take place.

The Advarra IRB will serve as the Central Institutional Review Board (CIRB) for all participating sites in the United States. The CIRB serves as the reviewing IRB for all sites. It has regulatory responsibility for assuring the protection of the rights and welfare of research participants in accordance with all Standard Operating Procedures of the Advarra IRB. The National Institute of Neurological Disorders and Stroke (NINDS) selected the Advarra IRB to serve as the CIRB for this trial.

To meet the FDA guidance that *"The IRB that is responsible for finding and documenting that community consultation and public disclosure will take place (as required by 21 CFR 50.24(a)(7)) should be knowledgeable about local conditions in order to evaluate the community consultation and public disclosure plan"*, the Advarra IRB will work with the National Clinical Coordinating Center, the Regional Coordinating Centers (RCCs), the protocol principal investigators, the local investigators, and local IRBs to develop community consultation (CC) and public disclosure (PD) plans for the geographic areas in which the research will take place, and the Advarra IRB will ensure that the study is in compliance with state or local laws and regulations.

The Advarra IRB must review the plans for community consultation and public disclosure before the plans are implemented. The local investigators, possibly in conjunction with the local Regional Coordinating Centers (RCCs), will execute the plans. The Advarra IRB, in consultation with the local IRBs, will consider the concerns and objections raised during community consultation activities when they deliberate on whether to approve, require modifications in (to secure approval), or disapprove the research sites. The Advarra IRB must approve the plans and results of the CC/PD prior to approval of the research sites. The FASTEST Trial is also performed under an FDA-approved IND and the FDA will review study data, as needed.

Research involving ICH participants presents a challenging dilemma. Protecting participant autonomy through the informed consent process is one of the cornerstones of ethical research. However, evidence from prior trials of ICH indicate that hemostatic therapy for ICH must be started within 2 hours of stroke onset/last known well

if it is likely to benefit participants. ICH patients are often somnolent or aphasic and unable to provide informed consent. In cases where patients are incapable of giving informed consent, consent by a legally authorized representative (LAR) has been substituted, even though the true wishes of the patient are rarely known. This has been an accepted practice and is adequate for most research interventions proposed. However, in many cases of ICH the LAR is often not readily available. The resulting delay in obtaining consent can significantly affect the efficacy of hemostatic therapy and limits patient eligibility for inclusion in such time-critical studies. Yet new treatments for ICH are needed since there is no current scientifically proven treatment for acute ICH.

This study proposes 2 approaches to informed consent for patients with spontaneous ICH: 1) if the patient is alert and oriented, or without capacity to consent but with a family member/legally authorized representative (LAR) present, within the first 120 minutes of onset/last known well and within 30 minutes of baseline CT imaging, delegated research personnel will approach the patient/LAR and obtain prospective informed consent, either in-person or remotely (as per FASTEST Trial Standard Operating Procedures), followed by paper or electronic documentation; and 2) if the patient is without capacity to consent and a family member/LAR is not present within the given therapeutic window (following repeated attempts by research and clinical staff to contact the LAR), the participant will be enrolled/randomized under HHS regulation 21 CFR 50.24, Exception from Informed Consent in Certain Emergency Research. The attempted consent process for each enrolled subject will be documented by the treating investigator in the WebDCU™.

APPLICABILITY OF EFIC (21 CFR 50.24) TO THE FASTEST TRIAL

The specific regulations for justification of research EFIC are listed below:

> ***1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.***

Intracerebral hemorrhage (ICH) accounts for more than 10% of all strokes worldwide or about 1,700,000 cases per year. It is the deadliest type of stroke with a mortality of more than 40% at 1 month and only 20% of survivors are functionally independent at 6 months. There is no scientifically proven effective treatment for ICH.

> ***2. Obtaining informed consent is not feasible because the subjects will not be able to give their informed consent as a result of their medical condition, the intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible, and there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.***

Stroke patients have significant limitations in providing informed consent in the acute setting. In the NINDS t-PA stroke trials investigating tissue plasminogen activator (t-PA) for acute ischemic stroke, surrogate consent was used to enroll 439 of 624 (70%) of participants. These trials included participants with very mild strokes (0-5 on NIHSS) which would be highly unlikely in the FASTEST Trial of ICH. Compared to NINDS t-PA Trial subjects who provided their own consent, those enrolled by surrogate consent generally were about 5 years older, with higher NIH stroke scale (NIHSS) scores (median 17 versus 9, $p < 0.001$), and less likely to have a good recovery (26% versus 53% had a modified Rankin score of 0-1 at 90 days, $p < 0.001$).

> ***3. Participation in the research holds out the prospect of direct benefit to the subjects.***

The post-hoc data from the FAST Trial, and replicated in the rFVIIa IIb Trial, indicate a high likelihood of potential benefit for participants with the characteristics who are enrolled in the trial. All of the trials show that rFVIIa slows bleeding and its benefits are most noted within the first 2 hours of stroke onset/last known well.

4. Subjects are facing a life-threatening situation that necessitates intervention.

As noted above, patients with ICH are facing a life-threatening situation that requires timely intervention.

5. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

ICH is a disease with high morbidity (only 20% of survivors are independent) and mortality (> 40%). rFVIIa is associated with an absolute increase of thrombotic events (myocardial infarction, ischemic stroke, and pulmonary embolus) of about 5% in the prior trials, the majority of which are not fatal. For comparison, t-PA use in ischemic stroke is associated with a 6% risk of symptomatic ICH, of which 50% are fatal.

6. The clinical investigation could not practicably be carried out without EFIC.

The major issue here is the therapeutic window for rFVIIa. Minimization of time from onset to treatment with rFVIIa is critical since clinical trial data indicate that the time window for stopping or slowing growth of ICH is smaller than that for IV t-PA (≤ 2 hours). In the SPOTLIGHT Trial, subjects with a positive "spot sign" on CT angiography indicating ongoing bleeding had imaging at baseline, immediately after start of study medication, and 24 hours. *Almost all additional bleeding occurred between the baseline CT imaging and the CT scan immediately after treatment during when informed consent and randomization occurred.* Thus, there was little opportunity for rFVIIa to biologically modify ongoing bleeding.

7. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

This study proposes 2 approaches to informed consent for patients with spontaneous ICH: 1) if the patient is alert and oriented, or without capacity to consent but with a family member/legally authorized representative (LAR) present, within the first 120 minutes of stroke onset/last known well and within 30 minutes of baseline CT imaging, delegated research personnel will approach the patient/LAR and obtain prospective informed consent, either in-person or remotely (as per FASTEST Trial Standard Operating Procedures), followed by paper or electronic documentation; and 2) if the patient is without capacity to consent and a family member/LAR is not present within the given time window (following repeated attempts by research and clinical staff to contact the LAR) the patient will be enrolled/randomized under HHS regulation 21 CFR 50.24, Exception from Informed Consent in Certain Emergency Research. The attempted consent process for each enrolled subject will be documented by the treating investigator in the WebDCU™ and will be made available to the Advarra IRB at time of continuing review.

ADDITIONAL PROTECTIONS

The 5 additional protections associated with conducting a trial under 21 CFR 50.24 are the following:

1. Community Consultation
2. Public Disclosure before the trial – including methods by which patients can "opt-out" or refuse participation in the trial
3. Public Disclosure after the trial
4. Plan for contact of legally authorized representatives (LARs) or family members to seek informed consent for the patient's participation in the trial within the therapeutic window, if feasible, or after enrollment as soon as possible when feasible
5. Formation of a Data Safety Monitoring Board to oversee the trial

The plan for each of these activities will be discussed in detail. The regulatory language is included for convenience and reference as well as some text taken from the FDA Guidance Document (April 2013) that offers an interpretation of the regulations to assist investigators, sponsors, and IRBs.

COMMUNITY CONSULTATION PLAN

The federal regulations for community consultation (21 CFR 50.24) state:

> *Additional protections of the rights and welfare of the subjects will be provided, including, at least: (i) Consultation (including where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn.*

The goals of community consultation are the following:

1. To ensure that all relevant communities have the opportunity for input into the IRB's decision-making process before initiation of the study at a research site.
2. To present information so that community members understand the proposed investigation, its risks and benefits.
3. To be sure community members understand that the investigation will take place without informed consent.

Community consultation is not community consent for the trial to take place. If community consultation were viewed as community consent, this would imply that the input came from a large proportion or essentially all the members of the community as opposed to representatives of the community. The process is meant to solicit input from the community regarding the study. The IRB makes the final determination as to study approval based on the information obtained from the community consultation. For the purposes of EFIC, the definition of community includes "the community in which the research will take place," which includes the geographic area where the hospital or study site is located, and the "community from which subjects will be drawn," which includes the group of patients who share particular characteristics (i.e., patients with the disease of interest or those "at-risk" for the disease or condition of interest).

The **content** of community consultation will inform the communities that informed consent may not be obtained for most (or all) research participants. Specifically, the goal will be to:

- Inform the community about all relevant aspects of the study including its risks and expected benefits
- Hear the perspective of the community on the proposed research
- Provide information about ways in which individuals wishing to be excluded may indicate this preference

The **type and frequency** of community consultation will:

- Provide opportunities for broad community discussion
- Ensure that representatives from the communities involved in the research participate in the consultation process
- Use the most appropriate ways to provide for effective community consultation
- Be based on numerous factors, including the size of the community, the languages spoken within those communities, the targeted research population, and the heterogeneity of the population

Description of the NIH StrokeNet Network

FASTEST will be conducted at approximately 70 StrokeNet hospitals and 13 mobile stroke units within the NIH StrokeNet within the United States as well 37 non-U.S. hospitals and 2 mobile stroke units in Canada, Japan, Germany, Spain, and the U.K. Each institution was selected because of their ability to care for a large volume of ICH patients and prior experience in acute stroke trials. This network provides the basis for conducting efficient studies in these environments.

The National Coordinating Center (NCC) for this multicenter trial is the University of Cincinnati and the National Data Management Center (NDMC) is the Medical University of South Carolina (MUSC).

We are seeking to conduct FASTEST under 21 CFR 50.24 and will include patients who present following ICH within 2 hours of stroke onset/last known well and who have a volume of ICH $\geq$ 2 cc and $<$ 60 cc, no or small volume of IVH (IVH score $\leq$ 7), age $\geq$ 18 and $\leq$ 80, and a Glasgow Coma Scale of $\geq$ 8.

Development of Study Presentation Materials

Templates for materials for community consultation (e.g., focus group script, interview, surveys, and other educational materials) and public notification are developed by the FASTEST study team. Material presented for community consultations will include: a) background information on ICH, b) current lack of any proven treatment for ICH, c) profile of patients who would qualify for FASTEST, d) protocol description, e) experimental intervention rationale, f) randomization definition, g) potential study risks, h) potential study benefits, i) differences between research and treatment, j) rationale for EFIC, and k) the ethical constructs of EFIC. The PI or a research team designee will be available at all community consultation activities to answer questions and hear concerns regarding the project.

The requirements of EFIC also include informing the community that a research project will be done that may impact members of the local population. This public disclosure will be made prior to the initiation of the project and after the project is completed. The content of the public disclosure messages will include: a) the nature of the trial and that it involves victims of ICH, b) the trial involves EFIC under emergency circumstances, c) the trial involves specific potential risks and benefits, and d) contact information on where to receive answers to concerns or questions as well as further information. The types of public disclosure will be determined by the PI and local IRB. The suggestions listed here are consistent with the public notification content suggested by the FDA 2013 Guidance Document.

If a local IRB determines the need for unique community EFIC activities, the FASTEST team will assist the local institution’s site investigators in developing appropriate materials and processes.

Definition of Community

For the purposes of EFIC, the definition of community includes “the community in which the research will take place” and the “community from which subjects will be drawn”. In other words, the community includes the geographical area from which patients will be drawn and the group of patients with, or at-risk for, the disease of interest, in this case, intracerebral hemorrhage. Communities have many subgroups that can be defined by innumerable characteristics such as race, ethnicity, religion, age, gender, wealth, education, employment, neighborhood, and other factors. Community consultation should consider the heterogeneity of the community and seek diverse input. It is understood, however, that it is impracticable to reach every possible subgroup, but each site will complete activities that reflect a sufficient portion of the spectrum of their relevant communities.

Content

The content of community consultation (CC) will inform the community participants that informed consent will be obtained for any research participants prior to enrollment whenever possible, and may not be obtained when no LAR is available. Informational materials developed for FASTEST activities are subject to IRB approval. Additional materials developed later will be submitted to the IRB for approval before being used in any CC/Public Disclosure (PD) activities. Specifically, the content of all CC activities will:

- Tell the community about the most relevant aspects of the trial including its potential risks and potential benefits, and the therapeutic window of 2 hours
- Hear the perspective of the community on the proposed research and elicit values and experiences
- Explain how individuals wishing to be excluded may indicate this preference

Types of Events

Based on our interpretation of the regulations and their proposed ethical basis, we have prepared a menu of the types of events and activities that FASTEST sites may use to meet their requirements for CC. Sites will prepare a site plan that lists all the events and activities that they will use to engage the community. Each site plan will:

- Provide opportunities for broad community discussion
- Ensure that representatives from relevant communities participate in the consultation process
- Include more than one type of event or activity to provide for effective community consultation
- Consider multiple factors including, but not limited to, the size of the communities, the languages spoken within those communities, and the heterogeneity of the population

Community Consultation Plan (Table of Activities):*

A (Interactive - Direct)**	B (Asynchronous - Delegated)****
A presentation and discussion by an investigator visiting a meeting of an existing group (visits to existing meetings)	
Focus group (moderated small group session)* **	Web-based survey
In-person individual interviews or meetings	Social media messaging
A booth or table at community events involving interactive discussions (not just surveys) [A booth/table discussion of sufficient length to meet Column A criterion (as opposed to Column B) is approximately 5 minutes of interaction.]	In-person solicited survey (e.g., waiting room survey, without other interaction)
Meetings convened by the investigators inviting the targeted audience (preferably with RSVP)	A booth or table at community events handing out study materials and surveys with limited interactive discussions

* required mix is at least 6 total CC events or activities
** at least 2 events must be from column A
*** at least 1 of the events from column A must be a focus group
**** at least 1 event or activity must be of a type in column B

Required mix is at least 6 total CC events or activities. Among these 6 events or activities, at least 2 events or activities must be of a type in column A, and at least 1 event or activity must be of a type in column B. One of the 2 events in column A, 1 must be a focus group. The other events may be of the same type, for example, they could both be focus groups or visits to existing groups. Events should include participants representing a sufficient breadth of the diversity of both the geographic community primarily served by the enrolling site's institution and the community either at-risk for, or familiar with, stroke. There is no expectation that all of the subgroups of either community can be engaged.

<u>Visits to Existing Meetings or Existing Groups</u>
In this method of community consultation, members of the study team, sometimes accompanied by representatives of their participating institutional research leadership, ask to present the study and lead a discussion about the study at a regularly scheduled meeting of a relevant community group. Sometimes, the existing group may hold a special meeting for this purpose, but the study team still goes to the group (rather than asking members of the group to come to the study team).

Existing groups that might be consulted using this method may include, but are not limited to: disease-related support or interest groups, civic groups, neighborhood groups, service organizations, faith-based organizations, political or governmental bodies, business groups, social clubs, and retiree groups. Examples of disease-related support groups include: stroke support networks. Examples of governmental bodies include: law enforcement and fire department groups, city councils, and community boards. This approach may also include: study team visits to senior centers or stroke rehabilitation facilities. Participation in an existing meeting shows respect for community by bringing the information to the community, reduces inconvenience to the community, and

exposes the study to a diverse audience. Community members may be more comfortable expressing their opinions in a known setting. Investigators may have to travel, attend multiple meetings, and conform to the community group's schedule. Using this method can encourage more involvement by co-investigators and other members of the study team, which can be advantageous.

Prior to and during the visit, the study team must clearly communicate that being allowed to attend the meeting does not imply any implicit approval or endorsement by the group being visited.

Best Practices:

- An investigator should be present to take and answer questions from the community.
- Presentation should be brief (i.e., 10-15 minutes).
- If a presentation is longer than 15 minutes, it should be interactive throughout the presentation.
- The presenter should be knowledgeable about the study and comfortable with the group.
- Allow ample time for community discussion (at least 15-30 minutes).
- Often best to ask for 30 minutes on an existing meeting agenda to allow 10 minutes to present, 15 minutes for discussion, and 5 minutes to hand-out and get back evaluation surveys. Insufficient time for solicitation of feedback greatly reduces the utility of this method.
- Probe for discussion using open-end questions. Ask participants about their experiences and what they care about.
- Ensure that the discussion includes feedback from the participants on EFIC.
- Light refreshments may be sponsored; direct monetary incentives are uncommon.
- An anonymous survey for group participants to indicate their thoughts, feelings, and opinions about the EFIC regulations and the study is typically collected at the end of the event.

Focus Groups

In this approach, a study team member interviews and moderates a discussion in several small groups (generally about 6 to 8 participants). Unlike focus groups designed for other research purposes, these focus groups are performed as community consultations. They are an opportunity for investigators to directly listen to community members, and to show their respect by listening humbly. The scientific presentation of the study to the focus group will be made by study staff, typically a physician. The remainder of the focus group will be led by a moderator who has experience in conducting focus groups. This could include the leader of, for example, the support group; a separate individual that accompanies the study staff; or study staff who have this particular experience. The study team member runs the meeting and facilitates the discussion using the FASTEST focus group moderator guide approved by the Advarra IRB. The study team member elicits the group's views, questions, concerns, and comments about the study. The interaction is generally audiotaped (and possibly videotaped) for review by the investigative team to allow subsequent analysis and reporting of the session. Focus groups could solicit feedback from any relevant focus of the community, including: the general public, individuals affiliated with particular organizations or subgroups, or specific patient populations. Emergency Medical Service providers and Emergency Department physicians should also be interviewed. Information should be collected about participants' basic demographics. In addition, if taping is to be conducted, focus group facilitators will ask for verbal consent to tape the focus group session prior to starting the discussion. This portion of the consent process will include a description of the confidentiality protections associated with the focus group discussion. Light refreshments may be provided at each focus group session.

Recruitment methods for focus group participants will depend on the targeted population. Participants may be recruited by mail or telephone, at random from volunteer banks or public data sets, or from special populations (such as patients with stroke or their families, advocacy group representatives, or other vested interest groups).

Compared to other methods of community consultation, focus groups may allow for more in-depth discussion of the study because of their small size. They also allow for interaction not only between the facilitator and participant but between participants. For these reasons, focus groups offer a rich set of information and have often been found by investigators and IRB members to be a high-quality source of information.

Best Practices:

- The meeting should be at an accessible location and time for the population included.
- The session should generally be run by a study team member; sometimes it is helpful if it is someone who is also demographically concordant with the focus group participants (experience, race, ethnicity, or gender).
- Sessions should be small, generally including 6-8 participants.
- Focus groups generally run 1-2 hours in length.
- Refreshments should be provided.
- Participants are generally paid for participation in focus group sessions in an amount and form appropriate to the participant population.
- An anonymous written survey for group participants to indicate their thoughts, feelings, and opinions about the study and the focus group session should be conducted at the end of the event.

Convened (Invited) Meeting

Sometimes called a "Town Hall Meeting", this type of CC uses the same structure and best practices as visits to regularly scheduled meetings, but invites a target audience to a meeting convened by the study team. The potential advantage of this method is that multiple groups of attendees can be invited to the meeting, and have a chance to interact with each other and the investigator. Because the meetings are typically open to the public, there is the potential to involve everyone. The disadvantage with this method is that organizing such a meeting and attaining adequate attendance can be burdensome and difficult. To be successful, however, an intensive effort to diligently invite several potential attendees and secure their commitment to participate is needed. Merely advertising a public meeting and seeing who shows up leads to events with very few community members. Such low attendance events have been commonly held in prior EFIC trials, but are not acceptable for FASTEST. The use of invited meetings, therefore, is discouraged unless the site has a track record of successfully using this method in the past.

Community Events – interactive or survey

In this type of event, the study team and investigator typically set up a booth or table at an existing community event and interact with individuals one at a time as they browse or stop by the booth. Events of this kind have occurred at the American Heart Association Mini Marathon, Steps for Stroke, State Fairs, Fire and Emergency Services Open Houses, Farmers Markets, Art Festivals, Music Concerts, Health Fairs, Ice Cream Socials, Disease-Related Fundraising Events, Tailgates, and other Sporting Events. This kind of event often allows exposure to a large number of community members. Depending on the kind of event, it may allow investigators to reach a focused or very diverse group, and a large number of participants. Because conversations are typically one-on-one, this method often allows more intimate and revealing opportunities for the investigator and members of the public to interact. Disadvantage of this approach is that most of the contacts are very brief, usually limiting the opportunity to exchange information. Also, the time commitment from the study team to staff the booth for the duration of the event may be significant, making this potentially inefficient. This type of event can be conducted in a way that is more interactive (a column A event), in which an investigator or other study team member primarily engages participants in conversations, often concluding with having the participant fill out a survey either through an interview or by completing a written tool. The event can also be conducted in a way that is primarily driven by only giving out written information about the study and asking participants to fill out a written survey (a column B event). In this case, the booth can be staffed without an investigator present, which can be more efficient for the study team.

Best Practices:

- Booths should have good signage that attracts passers-by.
- Have small treats or "swag" to attract participants and thank them for taking time to talk to you.
- Have enough staff at the booth to engage with anyone who wants to talk.
- Have enough clipboards and pens to make certain no one has to wait to complete written feedback.
- It is often effective to make this kind of event a fun social team-building exercise for the study team.

Simple Solicited Surveys like those Performed Online, in Waiting Rooms, or at Booths

Simple individual surveys, whether performed online or in-person, can also be used to solicit community questions and views. This method can be used to reach large numbers and a wide variety of respondents. Online surveys can be linked to social media platforms or can be easily solicited by e-mail. Respondents can also be recruited to complete surveys distributed in-person in relevant clinical settings like emergency departments or clinic waiting rooms. Internet and paper surveys also allow respondents to see visual aids and diagrams. Waiting room surveys may allow focus on populations with stroke. Careful writing and testing of surveys remains critically important. If surveys are distributed in-person, surveyors need to be well-trained in the study protocol and in the EFIC regulations. Specific examples related to the FASTEST Trial are detailed below:

A. Face-to-Face Interviews/Surveys at Neurology Stroke Clinics

Patients in the neurology clinic waiting rooms and their family members could be asked to complete the survey. The survey will inform the individuals that participation is voluntary and completion of the survey implies consent. The survey participation must not interfere with patient care. Each survey will take approximately 10-15 minutes to complete and will be delivered by a designee of the study team.

B. Advocacy Groups and Online Surveys – community at-risk

Local chapters of the American Heart Association will be approached to solicit assistance to link FASTEST study online surveys.

C. Online Surveys

Post the link to online surveys on a health system website.

D. Face-to-Face Interviews/Surveys in the Emergency Department – geographic population, ethnic minorities, and at-risk populations

Investigators will approach stable patients in the ED and their families. Investigators will not interfere with medical care. Members of the study team will identify potential survey participants from the ED electronic patient tracking board. A study team member will approach the patient or family member to see if they are willing to complete the survey. If the patient/family member agrees, the study team member will obtain verbal informed consent and proceed with conducting the interview. Each survey will take approximately 10-15 minutes to complete. Because investigators will conduct these surveys during the patient's ED visit, they will not provide compensation for any expenses incurred. Investigators will perform this survey at various times of the day and on different days of the week to ensure that this sample is representative of the community of individuals that utilize the hospital ED. Investigators will also include targeted surveys of ethnic minorities. Experience with other studies has shown that larger broad venues, while representative of the overall state population, include few respondents who are minorities and who are members of lower socioeconomic groups. To reduce this bias, investigators will include as many Emergency Department and clinic patients as possible from public and county hospitals and clinics, who traditionally fall into lower socioeconomic groups and who disproportionately represent racial and ethnic minorities.

Best Practices:

- Whenever possible, these surveys should be conducted by members of the study team, and/or delegated surveyors with medical knowledge and training in the protocol and EFIC. Medical students and residents can sometimes be recruited as surrogates for the investigative team.

Other Social Media

Social media offers a low cost, potentially far-reaching, and potentially interactive, method to exchange information with members of a community. Recent data suggest that the penetrance of social media is very high, with 80% of adults in the U.S. accessing Facebook, YouTube, Instagram, Pinterest, Snapchat, LinkedIn, Twitter, or WhatsApp daily (while only 29% read print newspapers daily). Social media may also allow messages to be directed to selected subgroups and demographics. However, investigators should still be aware that despite the high prevalence of social media overall, that use is still somewhat weighted toward younger adults, those living in suburbs, those with higher incomes, and those with more education. Also, different platforms are favored by different demographics. Social media is a medium that blurs the line between one-way communication (as used in public disclosure) and dialogue (as used in community consultation). The former type of use is probably more common, but truly interactive social media communications are also possible. If chosen as a CC activity, the content of the presentation, the methods to allow interaction, and gaps in the available population should be clearly described.

Opt-Out

During each community consultation event, and in public disclosure efforts, instructions will be given on how to inform the study team of the desire to opt-out of the FASTEST Trial. Patients who request opt-out cards will be provided at the time of the meeting. Community members who can be identified as having opted-out will not be enrolled in the study.

IRB Activities and Review

The local IRBs may choose to appoint an IRB member to oversee community consultation activities. This IRB liaison will be invited to attend the focus group sessions and all other community consultation activities, and may provide an in-depth review of the results obtained. An example of proposed community consultation activities that could be performed are described below:

Group	Description	Materials
Individuals with the condition of interest, at-risk individuals, and advisory group of medical providers	**Focus groups** of at-risk persons (i.e., stroke or TIA patients) each with approximately 6-8 participants will meet at the institution or other public forums within the context of support groups **Advisory committee** (professionals) Additional professional health care provider focus groups **Surveys** will be conducted at stroke neurology clinics	PowerPoint presentations, flyers, brochures, verbal informed consent, audio (or video) tape and recorder, feedback forms, information on opt-out option, etc. Surveys after one-on-one discussion about FASTEST and of informed consent

Individuals in the geographic area	**Focus groups** in existing community group meetings, PTA, church groups **Surveys** to be conducted in the emergency departments or patient clinics of participating hospitals	PowerPoint presentations, flyers, brochures, verbal informed consent, audio (or video) tape and recorder, feedback forms, information on opt-out option, etc. Surveys after one-on-one discussion about FASTEST and of informed consent

PUBLIC DISCLOSURE BEFORE AND AFTER THE TRIAL

Objectives of Public Disclosure – applies to both before and after the trial

The requirements of 21 CFR 50.24 include informing the community of the performance of a research study that may impact members of the local population. Public disclosure will be done prior to the initiation of the project and after the project is completed. The content of the public disclosure messages will be implemented following the Advarra IRB's approval of the public disclosure plan.

Public Disclosure requirements state:

21 CFR 50.24

> *Additional protections of the rights and welfare of subjects will be provided, including at least:*
> *(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;*
> *(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;*

Public disclosure is defined as the "dissemination of information about the research sufficient to allow a reasonable assumption that communities are aware of the plans for the investigation, its risks and expected benefits, and the fact that the study will be conducted". It also includes "dissemination of information after the investigation is completed so that communities and scientific researchers are aware of the study's results".

Appropriate public disclosure includes:

- Clear statement that informed consent may not be obtained for most (or all) participants
- Information about the study medications use, including a balanced description of the risks and benefits
- Synopsis of the research protocol and study design
- How potential study subjects will be identified
- Participating sites/institutions
- Description of the attempts to contact an LAR
- Suggestions for opting-out of the study

We will work to reach a maximum number of people through events and media for Public Disclosure within our study budget.

Development of Study Presentation Materials

Methods of announcing information about the trial and the development of advertising and other materials about the trial will take place both locally and at the other regional sites. Standard materials for use in public disclosure activities will be developed by the national study team members and approved by the Advarra IRB. The local study team will coordinate local public disclosure efforts with local public relations offices, as appropriate. Public service announcements, press releases, paid print and broadcast advertising, community access cable TV, postings in existing hospital and community publications and mailings, social media, and other modalities will be considered as well.

Content of Public Disclosure

It is impossible for a single public announcement or disclosure method to include all information that is found in the informed consent documents, the investigator's brochure, and the research protocol. We propose that the following are the most important issues for community understanding:

a) the nature of the trial and that it involves victims of ICH;
b) the trial involves exception from informed consent under emergency circumstances;
c) the trial involves specific potential risks and benefits; and,
d) contact information on where to receive answers to concerns or questions as well as further information.

The type of public disclosure will be determined by the PI and the local IRB.

Documentation of IRB Reporting

Investigators will document all inquiries from the public or interested parties on an Initial Public Notification Feedback Form. E-mail questions, comments, and feedback will also be documented. Investigators will collate and report results to the Advarra IRB before the start date of the study.

Public Disclosure Methods and Activities – table of examples below

Community and In-Hospital Activities

Prior to the start of the trial, the site PI or designee will present the proposed study to Neurology, Emergency Medicine, and Neurosurgery residents, faculty, and staff, as appropriate.

If allowed by these various entities, brochures, posters, and flyers, will be displayed in the Emergency Department, and the Neurology and Neurosurgery Clinics before and during the trial. These materials will provide a description of the study, local contact numbers, study website address, and opt-out information. It will indicate that the study will be conducted with EFIC. All materials will be reviewed by the Advarra IRB for approval prior to dissemination.

Pending approval by the Public Relations Department of each institution, an announcement will be made on the institutional intranet informing hospital staff of the proposed trial. Contact information for the site PI and study personnel will be provided in the announcement. An e-mail announcement of the trial may also be made to the faculty and staff of relevant clinical departments.

The site PI and study coordinator will provide study training sessions for the emergency clinicians who will be identifying potential participants in the ED or mobile stroke units. The investigators will also train the attending/fellow physicians and nurses who treat ICH/stroke patients within each institution. Study updates will periodically be provided to these providers by e-mail or in-person.

Key Community Contacts

The investigators will work with the local chapters of the American Heart Association (AHA) to develop information for public notification aimed at the general public about FASTEST and EFIC, and will ask permission to post this information on their website as part of a public disclosure method. This will be done both for local chapters of the AHA as well as the national organization (Dr. Broderick is a past-chair of the Stroke Council). Some rehabilitation hospitals sponsor support groups for stroke survivors. These meetings present a great opportunity for distribution of public disclosure materials as well.

Information about ICH, the FASTEST Trial, and EFIC will be distributed to those who choose not to participate in interviews/surveys.

Media Announcements

With the assistance of a public relations office, the PI and study team may develop and publish public media announcements in local outlets with broad reach. The content of these announcements will mirror those items listed above and will appear before and during the duration of the trial. The content of the media announcements will be first approved by the Advarra IRB.

Summary Table Example: Public Disclosure Pre-Trial

A (networking)	B (paid advertising)	C (conventional outlets)
National or local study website	Newspaper advertisement (and similar print advertising)	Press release
Social media postings	Television and radio ads (broadcast advertising)	News stories, interviews (print, radio, or television)
Mailings (including e-mail circulars/bursts and direct paper mailings)	Outdoor advertising (placards, bus ads, billboards, etc.)	Newsletters (articles or informational ads, print or electronic)
Booth/table community event	Paid online advertisements (banner, block, or video ads purchased from Google, Facebook, YouTube, etc.)	Brochures, flyers, handouts, bulletin boards
		Radio or television PSA (public service announcements)

Many different channels of public disclosure should be used. This will increase the depth and breadth of market penetration. The required mix is at least 6 total PD activities including at least 2 of a type in column A, and at least 1 of a type in column B or column C. Distribution of activities should be cognizant of the anticipated audiences, and should include audiences representing a sufficient breadth of the diversity of both the geographic community primarily served by the enrollment site, and the community either at-risk for, or familiar with, stroke. There is no expectation that all potential audiences will be reached. It is expected that PD efforts will represent a good faith effort to provide transparency across the relevant communities.

Timeline for Community Consultation and Public Disclosure Activities

The community consultation activities will be conducted over the course of approximately 3 months. PD will be initiated prior to the start of the trial, will continue during enrollment, and will conclude with the dissemination of study results after the trial is completed. The investigators plan to initiate PD activities at least 4 weeks prior to the start of the proposed trial. PD will continue beyond the end of study enrollment and through disclosure of study results, which is anticipated to be within a 5-year timeframe.

Reporting of CC results will be provided by the study team to the Advarra IRB. Summaries of the data will be made available to the Advarra IRB and the National Coordinating Center for NIH StrokeNet.

The data collected regarding CC and PD will include the following elements:

- Consultation methodology used
- Community type: geographic or condition-specific
- Participants involved: number and demographics
- Duration, content, format of information presented
- Free text log of comments, questions, and responses to open-ended questions
- Log of pre-determined closed-ended survey questions and responses

All group discussions will be reviewed by the study team, and general themes will be summarized. The results of all local community consultation efforts will be summarized and submitted to the Advarra IRB. If appointed, and if present at CC activities, an IRB liaison will provide an in-depth review of the discussions and additional feedback to the IRB, as needed. Summaries of responses from PD will be reported to the Advarra IRB prior to approval, and then at least annually or upon request from the Advarra IRB.

A provision of the protocol has been made to allow participants who learn of the trial through public disclosure efforts or other means, and who would not want to participate, to communicate that decision to treating physicians without causing any delay in treatment. This will be indicated by opt-out cards available from the study team that will say “FASTEST declined”.

ANALYSIS AND PRESENTATION OF RESULTS FROM COMMUNITY CONSULTATION AND PUBLIC DISCLOSURE

Reporting of CC results will be standardized across the FASTEST StrokeNet sites. A simple web-based data entry form will be included in WebDCU™. WebDCU™ is the data management system used for the study. It is a web-based database that uses an encrypted data transfer mechanism and secure user privilege control. No protected health information (PHI) will be entered into WebDCU™.

The web-based data entry form will collect the following elements:

- Consultation methodology used
- Community type: geographic or condition-specific
- Participants involved: number and demographics
- Duration, content, format of information presented
- Free text log of comments, questions, and responses to open-ended questions
- Coding of free text using qualitative research methodologies
- Log of pre-determined closed-ended survey questions and responses, if used
- Log of site customized closed-ended survey questions and responses, if used

The information collected using the community consultation surveys will be compiled. Reports will be generated to provide both site-level summaries and trial-level summaries. These summaries will all be made available to any IRB and will be reported to the FDA.

Reporting of PD efforts will be through a web-based interval report completed by each site-spoke complex in the WebDCU™ regulatory management system. Summaries of PD will be reported to the Advarra IRB prior to approval and as required by the Advarra IRB. Composite reports of local and national public disclosure at the trial-level will be provided to the FDA annually.

CONTACT OF AN LAR OR FAMILY MEMBERS

The federal regulations for contact of a legally authorized representative 21 CFR 50.24 state:

21 CFR 50.24

> *Additional protections of the rights and welfare of the subjects will be provided, including, at least:*
> *(iv) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.*
> *(v) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.*

DEFINITION OF AN LAR OR FAMILY MEMBER

The definition of an LAR is determined by local state regulations. An LAR is defined as:

- An individual or body authorized under applicable law to provide permission on behalf of a prospective Human Subject to the Human Subject’s participation in the procedure(s) involved in the Research. For the purposes of this Policy, a Legally Authorized Representative includes not only a person appointed as a health care agent under a Health Care Proxy, a court appointed guardian of the person with specific authority to consent to participation in the Research study, but also next-of-kin in the following order of priority unless otherwise specified by law: spouse, adult child (18 years of age or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older).

PROCESS TO CONTACT AND OBTAIN INFORMED CONSENT FROM A LEGALLY AUTHORIZED REPRESENTATIVE (LAR)

Consent

A written (paper or electronic) consent form that complies with the policies of the Advarra IRB and local context requirements has been developed and approved for the FASTEST Trial. It includes the following elements:

- Title of the protocol
- Name of the PI
- Study objectives and purpose
- Detailed description of the procedure and interventions
- Explanation of the responsibilities of the participant
- Any foreseeable risks, anticipated benefits, available alternatives
- An explicit statement of confidentiality
- Non-compensation for participation
- Right to withdraw at any time
- Signature section
- Number to contact the PI or a member of the study team with any questions

The PI, co-I, and/or research staff will identify the LAR by leveraging a number of information sources. First, the investigator will check to see whether an LAR is present on hospital property by communicating with the emergency department (ED) front desk, communicating with the ED social worker, and by checking the ED waiting areas. If no LAR is found, the participant's medical records (both ambulance transfer records and hospital electronic medical records) will be analyzed for any contact information for an LAR. If no LAR is identified by either of the first two methods, the investigator will check with the ED staff to see whether the participant's belongings contain any phone numbers or other contact information where a possible LAR might be found.

Follow-Up Consent for Participants Enrolled under EFIC

If the participant is enrolled without written (paper or electronic) informed consent and the LAR arrives at the hospital at any time during the hospital course, or becomes available remotely, (or if the participant becomes able to consent), then written (paper or electronic) informed consent will be obtained. The study team will check for an LAR and the subject being capable of consenting daily. At any time, the LAR (or the subject, if able) can withdraw from continuing in the study.

Documentation

All attempts to contact the LAR will be documented in a specialized Case Report Form (CRF) kept in each enrolled subject's file within the WebDCU™ managed by the National Data Management Center for NIH StrokeNet. This documentation will include number of attempts made and actions taken for each subject.

Post-Enrollment Disclosures

A procedure for prospective informed consent has been be developed, as is required by the regulations, in the unlikely event that an LAR can be identified within the presumed short therapeutic time window for the intervention and is able to provide a meaningful prospective surrogate consent for patient enrollment. In circumstances in which is it impossible to identify an LAR within the therapeutic time frame, EFIC will be applied.

Prior to enrolling an eligible patient into the proposed trial with EFIC, the emergency/mobile stroke unit physician will see if the eligible participant has refused study participation by checking if the patient has a card

with the phrase “FASTEST declined”. If the words “FASTEST declined” are listed on the card, the person will not be enrolled in the clinical investigation. If no “opt-out” is identified, the patient will be entered into the study.

Subjects who are enrolled in FASTEST with EFIC or by their LAR/family, will be informed of their inclusion in the clinical investigation at the earliest possible opportunity. This will be done in-person, after the patient is hospitalized. A study team member will speak with the senior clinician to determine the stability of the subject and the appropriate time for speaking with the subject, or if not alert or capable of making informed decisions (and the subject was enrolled with EFIC and not by an LAR/family), an LAR or family member. A delegated study team member will approach the subject or LAR/family about the subject’s enrollment, provide information about the study, about the subject’s rights, the responsibilities of the investigators, and answer any questions about the study. At that time, the subject or the LAR will be asked to provide consent for continued participation in the study. An informed consent document, either in paper form or electronic, will be used to document the subject’s (or LAR/family’s) decision to either continue in the study or to not participate any further, with the process conducted either in-person or remotely (as per FASTEST Trial Standard Operating Procedures). A copy of this form will be provided to the subject and another copy will be placed in the subject’s research record. Subjects who do not wish to continue to participate will be excluded from all further aspects of the study except for the collection of data required by federal agencies and permitted by the IRB to determine safety and efficacy.

If the subject is unable to comprehend a request for continued participation after EFIC enrollment, or the subject dies after enrollment, the investigator will attempt to inform the LAR/family members. Since ICH is associated with a 30-day mortality of > 40%, investigators anticipate the majority of their efforts will be attempting to contact LARs or family members.

For enrolled subjects who die in the ED/mobile stroke unit or the hospital, investigators will first attempt to notify an LAR of the subject. If such a representative is not reasonably available, a family member will be notified of the subject’s inclusion and the details and other pertinent information regarding the study.

Notification will occur either by attempting up to two phone calls to the subject’s family or sending two letters to the subject’s address (e.g., as listed on the EMS run report form, hospital chart information, or telephone directory). Research team members will document all efforts to contact subjects and their family members and maintain records according to the same process followed for all other record keeping during the study. Telephone discussions and letters will fully inform the subject’s representatives of the nature of the research project, the goals and objectives, the study protocols, the details of the EFIC regulations, and the information on the community consultation and public notification that occurred. Subject notification in each case will be documented and will become a permanent part of the study record.

For subjects who appear to have no relatives or persons responsible (e.g., homeless), investigators will make every reasonable effort, including working with the County Medical Examiner, law enforcement, and hospital personnel to help identify a next-of-kin for unidentified deceased subjects so that they may be notified.

In the rare case where no LAR consent is obtained, the LAR is never available, and the subject remains incapable of consent at 6 months, documentation of the attempt process and condition of the subject will be documented.

POST STUDY DISCLOSURE OF RESULTS

Disclosure of study results will be made both locally and nationally. The study results will be announced on local websites and the health system website, and in e-mails and letters to hospital personnel, community

physicians, and the AHA. Press releases will be coordinated by the StrokeNet National Coordinating Center and the NINDS. The study results will also be disclosed through peer-reviewed journals and presentations at national meetings, as well as listed on clinicaltrials.gov.

DESCRIPTION OF REFUSAL OF PARTICIPATION PROCEDURES (OPT-OUT)

Prior to and throughout the duration of the clinical trial, members of the specific geographic community will have various methods through which they can refuse participation in the trial. The investigators will include this information on the brochures and posters for public disclosure. Sites will provide cards with the words "FASTEST declined" to those individuals who decide to refuse participation in the trial.

DATA SAFETY MONITORING BOARD

An independent Data Safety Monitoring Board (DSMB) approved by the NINDS will provide safety and monitoring throughout the trial.