E&HR

Ethical Considerations during the Informed Consent Process for Acute Ischemic Stroke in International Clinical Trials

Tiffany Bellomo, Jennifer Fokas, Noah Tsao, Clare Anderson, Christopher Becker, Rachel Gioscia-Ryan, and William Meurer

ABSTRACT We sought to investigate the experiences of researchers in existing active-control trials in acute ischemic stroke comparing investigational therapy to tissue plasminogen activator (tPA) in order to identify the approaches and challenges in obtaining informed consent. Out of 401 articles evaluated, 14 trials met inclusion criteria. Trial representatives were contacted to complete a survey concerning the consent process. None of the 14 trials published materials related to the informed consent process. Trials with 75% to 100% of patients directly consented had shorter door-to-treatment (DTT) times than trials that directly consented less than 50% of patients. Trials that had translators available (for recruiting participants who were not native speakers in the local language) and translated consent documents had longer DTT times. The study findings suggest that differences in the standards of informed consent internationally may allow more patients with moderate strokes to provide direct consent without delaying DTT time. Future trials should emphasize transparency to the public and scientific community in the informed consent process.

KEYWORDS human research ethics, human subjects research, acute ischemic stroke, informed consent, randomized controlled trials, literature review

Bellomo, T., J. Fokas, N. Tsao, C. Anderson, C. Becker, R. Gioscia-Ryan, and W. Meurer, "Ethical Considerations during the Informed Consent Process for Acute Ischemic Stroke in International Clinical Trials," *Ethics & Human Research* 44, no. 4 (2022): 14-25. DOI: 10.1002/eahr.500133

Although the purpose of medical research involving human subjects is to generate knowledge that will potentially benefit a target population, this purpose should not take precedence over the rights of the individual research subjects.[1] Before conducting research with human participants, researchers must obtain their informed consent (or consent from a legally authorized surrogate) to receive an investigational drug or device in a clinical trial. In the consent process, prospective participants are informed of the aims, methods, risks, potential benefits, alternative treatments, and other relevant aspects of the study. The process of informed consent becomes challenging when a study is designed to intervene in an urgent and time-sensitive setting, such as when an individual is experiencing a stroke.

In the United States in 2016, the prevalence of stroke was 2.5%, and this is projected to increase to 3.9% by 2030.[2] Given this increasing burden, a large effort has been made to improve upon stroke treatments. Intravenous administration (IV) of tissue plasminogen activator (tPA) within 4.5 hours and mechanical thrombectomy for large vessel occlusions within 6 hours of onset of stroke symptoms are the standard of care for eligible patients according to the American Heart Association guidelines for acute ischemic stroke with significant functional deficits.[3] Reperfusion therapies in acute stroke show a clear time-dependent effect, being more effective the earlier treatment is initiated or reperfusion is achieved.[4] Therefore, time constraints on informed consent make the consent process difficult and may

pose a barrier to examining new and potentially more beneficial therapies in clinical trials.[5]

Studying an alternative to tPA involves randomizing patients between tPA and investigational therapy; however, the brief informed consent process for administering tPA alone without the added time burden of a formal consent process for a non-standard-of-care therapy has been reported to delay treatment.[6] In addition, patients with severe stroke symptoms may not have the capacity to consent for research and thus require consent by proxy (i.e., surrogate consent).[7] This has also been shown to delay treatment, especially when consensus is needed among family members.[8] Delays can also occur with elderly patients who have cognitive impairment, a population that commonly suffers from stroke. Not only do cognitive impairments complicate determination of capacity, but elderly patients may present to the emergency room unaccompanied, making it difficult to ascertain if they have a surrogate decision-maker.[9] Although there has been investigation of alternative consent approaches such as a targeted or briefer consent model focusing only on high-level information to reduce delays in treatment,[10] ethical considerations involved in conducting clinical research in the urgent setting with respect to the process of obtaining informed consent has been an area of ongoing deliberation.[11]

In our study, we investigated the experiences of researchers in existing active-control trials in acute ischemic stroke comparing investigational therapy to tPA in order to identify the approaches and challenges in obtaining informed consent in this unique patient population. To assess barriers to informed consent for trials that were specifically designed to study a completely alternative therapy to IV tPA, we selected trials in which the patient population would be eligible for IV tPA administration within 4.5 hours of symptom onset based on current recommendations for acute ischemic stroke and that compared IV tPA to an alternative treatment.[12] In evaluating approaches to informed consent, we were interested in, among other things, whether study team members who obtained informed consent were first required to complete formal training specific to their trial and the methods of obtaining direct consent of patients, defined as informed consent provided by the patients on behalf of themselves (without a proxy) (see appendix 1, available online, along with table 3 and the figures, as explained in the "Supporting Information" section below). To evaluate the impact of research study factors on patient care, we also collected information on door-to-treatment (DTT) times of both experimental and control arms of trials. This information can serve not only to identify potential barriers and ethical considerations of performing such studies but also to promote new approaches in the acute setting for a more efficient informed consent process that balances being patient centered with the need to develop new interventions. This research study was reviewed by the University of Michigan Institutional Review Board (IRB) for Human Subjects Research and determined to be exempt under IRB #HUM00180410.

Information about how consent was obtained, consent forms, and the personnel involved across the trials we examined was highly variable and often could not be located publicly through protocol papers or within the published manuscripts.

STUDY METHODS

Literature search. Literature searches with the aid of a University of Michigan research librarian were performed using the following platforms: PubMed, ClinicalTrials.gov,[13] Japan's National Institute of Public Health Clinical Trials Search,[14] Europe PMC,[15] the EU Clinical Trials Register,[16] the Australian New Zealand Clinical Trials Registry,[17] and the World Health Organization's International Clinical Trials Registry Platform[18] (see figure 1). Peer-reviewed scientific articles published in the English language were identified using the following search terms: "alteplase" OR "tPA" OR "Activase" and "ischemic stroke" OR "acute ischemic stroke." Publication dates were restricted to January 1991 through March 2020. The PubMed search was fur-

ther filtered by selecting the terms "clinical trials" and "humans." The ClinicalTrials.gov search was further filtered by excluding recruitment status listed as "suspended," "terminated," "withdrawn," or "unknown." The Australian New Zealand Clinical Trials Registry search was further filtered by selecting "interventional" trial type. Inclusion criteria for trials were studies of patients with acute ischemic stroke who would be eligible for IV

Table 1.

Demographic Characteristics of the Six Trials That Completed the Survey

	ENCHANTED	*noR-TEST 2*	*IV vs. IA tPA*	*TNKS2B*	*noR-TEST*	*TPK Derivative*
NCT identifier	NCT01422616	NCT03854500	NCT00624000	NCT00252239	NCT01949948	NCT04028518
Status of trial	Completed	Ongoing	Completed	Completed	Completed	Ongoing
Time window	2011 to 2019	2019	2008 to 2011	2015	2013 to 2017	2019
PMID of result publication	27161018	Ongoing	19277904	20185783	28780236	Ongoing
Trial location(s)	Asia, Australia, Europe, South America	Europe	North America	North America	Europe	Asia
Number of participants	3206	Ongoing	7	112	1100	Ongoing
Median NIHSS score (IQR)	8 (5-14)	Ongoing	16 (7-20)	13 (5-17)	8 (7-11)	Ongoing
Control arm median DTT (min.)	170	10	180	65	34	43
Experimental arm median DTT (min.)	170	10	240	65	32	42
Time limit imposed for informed consent	Within 20 minutes of discussion	No	Yes	No	No	No
Statement of informed consent	Yes	Ongoing	Yes	Yes	Yes	Ongoing
Statement of informed consent obtained	Yes	Ongoing	Yes	Yes	Yes	Ongoing
Statement of ethics approval	Yes	Ongoing	No	No	Yes	Ongoing

This data includes the median NIHSS score, DTT times, and information about the informed consent discussion in the published results from the trials. The term "statement of informed consent" indicates that the words "informed consent" appear in the resulting publication. "Statement of informed consent obtained" indicates that the resulting publication specifically states that informed consent was obtained. "Statement of ethics approval" indicates that the resulting publication specifically states that an ethics committee approved the trial protocol.

NCT = national clinical trial; ENCHANTED = Enhanced Control of Hypertension and Thrombolysis Stroke Study; noR-TEST 2 = Norwegian Tenecteplase Stroke Trial 2; IV vs. IA tPA = IV vs. IA tPA (Activase) in Acute Ischemic Stroke with CTA Evidence of Major Vessel Occlusion; TNKS2B = Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke; noR-TEST = Norwegian Tenecteplase Stroke Trial; TPK Derivative = A Phase II, Multicenter, Prospective Randomized, Open Blinded Endpoint Study to Evaluate Safety and Efficacy of Injection for Recombinant Human Tissue Plasminogen Kinase Derivative in Treatment of Acute Ischemic Stroke

tPA administration within 4.5 hours of symptom onset and comparison of IV tPA to an alternative treatment. Administration of tPA within 4.5 hours was selected as an inclusion criterion because this is the current recommendation for treatment of acute ischemic stroke and would allow for a more equal comparison of informed consent constraints.[19] Exclusion criteria were trials where IV tPA was combined with an alternative treatment or where an alternative treatment was compared to a placebo only. IV tPA versus an alternative treatment was targeted to specifically study the constraints that come from using an alternative therapy as its own trial arm without the possible research protocol advantages that an alternative therapy in addition to the standard of care may provide. Three authors assessed all trials independently for eligibility and subsequently collaborated to agree upon the final trials included. Of the 401 articles uploaded to Rayyan (a web-based platform used to extract articles for systematic reviews and based in Doha, Qatar)[20] for researcher review, 14 trials met inclusion and exclusion criteria (see figure 1).[21]

Study teams contacted. The corresponding author and trial coordinators listed on ClinicalTrials.gov from each of the 14 trials were emailed by our study team with a request for a copy of their participant consent form and other documents related to informed consent and to complete a survey developed as described below. The email also explained that participation was voluntary and that participants were not required to leave their contact information. Individuals receiving the survey were asked to share the survey with other members of their trial team who were knowledgeable about informed consent for the trial. The survey contained 24 questions pertaining to the informed consent process, including multiple-choice and free-response questions (see appendix 1). Forty-three representatives from the 14 trials were contacted. Six representatives from 6 studies completed the survey in its entirety;[22] one representative from 1 study partially completed the survey, and therefore results were excluded;[23] and the remaining 7 studies had no response from any representative after a third contact. In total, we included 6 survey responses representing 6 different studies.

Survey development. An anonymous online survey developed using Qualtrics (SAP software company, Utah, USA) assessed how informed consent was obtained in a population that may have challenges with standard consent due to absence of capacity in the setting of acute stroke. Survey questions included demographic questions (about the year of publication of the results, the location, the participants, and the median National Institutes of Health Stroke Scale [NIHSS] of the trial arms), multiple-choice ("Yes," "No," or "Unknown") questions regarding specific aspects of the informed consent process, and free-response questions concerning challenges trials may have faced. A draft of the survey was presented to a stroke neurologist (Lesli Skolarus), who provided specific feedback on content and format. The survey was then revised and distributed to the 43 contacts mentioned above.

Statistical analysis. Informed consent documents from each trial were analyzed for the presence or absence of a statement of informed consent (see table 1). Although there were a small number of survey respondents, we still made an effort to objectively analyze the data: if data was published on median DTT times and the survey respondents used estimates of DTT times, the published DTT times of the trials were used in the statistical analysis. Descriptive statistics were displayed for continuous variables as either mean ± standard deviation or median (interquartile range), depending upon data distributions, and as frequency (percent) for categorical variables. Nonparametric methods (including Wilcoxon rank sums and the Kruskal-Wallis test) were used to evaluate factors potentially affecting DTT time. Power analysis was performed using Monte-Carlo simulations in the R-package MK Power for each Wilcoxon rank sum test and using a chi-squared test in the MultNonParam R package for each Kruskal-Wallis test. We had 83.4% power to detect a p value of nominal significance ($p = 0.1$) on each Wilcoxon rank sum test and 80.0% power to detect a p value of nominal significance on each Kruskal-Wallis test. Statistical analyses were performed using R version 3.62 (r-project.org) and Excel. (Data that were used in this study are available on request from the corresponding author, William Meurer.)

STUDY RESULTS

All analyses presented here were performed on a small sample size of six trials. Table 1 shows the demographic characteristics of the six included trials

Table 2.
Respondents' Descriptions of Challenges Encountered with Study Protocol Development or in Obtaining Informed Consent from Patients

Challenges with study protocol development	*Challenges in obtaining informed consent*
We are allowed to include patients in the trial on the basis of their verbal consent. Written informed consent is obtained after treatment has been administered. The rationale behind this is to avoid delay of treatment because of written informed consent.	It is in some situations difficult to obtain a verbal informed consent in acute stroke patients. After the acute phase, it may also be difficult for the patients to give their written informed consent. In our study, it [h]as also been challenging to obtain written informed consent for study participation from patient/proxy if the patient suffers from a complication such as intracranial hemorrhage following treatment.
Too numerous to count. This was prior to the era of central IRBs, so each participating institution had their own IRB weighing in on the consent. While our consent was templated, each participating institution's approved consent form was reviewed by us to be sure it contained all elements required by our IRB and OHRP.	Finding proxies for aphasic patients unable to consent for themselves was sometimes challenging. If no proxy available, the patient could not be enrolled.
The study was performed strictly according to SOP for acute stroke. Information and randomized treatment were the only study specific the changes. Ethical aspects of informed consent in patients with a brain lesion, even a small one, resulted in lengthy discussions.	We informed the patient verbally, regardless of the patient's state. We did not require an oral consent from patient for the treatment. The patient (or proxy) was later asked for a written consent to use their data for research.
Whether patients given endovascular therapy will exclude them from the study.	The safety and efficacy about the study drug. More details on the outcome for the former participants.

that responded to the survey, two of which are ongoing, and four of which were ongoing between 2011 and 2017. The trials were conducted collectively in six continents, and the number of participants in each trial ranged widely from 7 to 3,206 patients. All four published trials mentioned the term "informed consent," and the researchers for two of the trials explicitly stated the involvement of an ethics committee in their published manuscript.[24]

Capacity to provide informed consent. The median NIHSS score for each completed trial was at least 8, meaning most participants experienced a moderate stroke (see table 1). Five trials allowed for consent to be obtained from a designated patient proxy if the patient was deemed to lack capacity to provide consent (see figure 2). Of those five trials, two required assent from the patient if the patient was consented by proxy; the other two trials did not require patient assent. Trials reporting direct consent of 75% to 100% of their participants were associated nonsignificantly with shorter DTT times than trials reporting direct consent of 25% to 50% of patients for both the experimental and control arms, with a trend toward significance (group = median minutes [IQR]; 75% to 100% experimental = 32 [16-48], control = 34 [17.5-50.5]; 25% to 50% experimental = 117.5 [65-170], control 117.5 [65-170]). However, one of the six trials did impose a time limit in which informed consent needed to take place (see table 1). When the stroke study team members were asked to comment on challenges that arose during study protocol development, all comments mentioned problems delineating specific exclusion or inclusion criteria (see table 2). Additionally, when asked about challenges related to obtaining consent, three out of the five comments mentioned difficulty with obtaining proxy consent.

Logistics of obtaining informed consent. All trials allowed physician-researchers to obtain informed consent in the emergency department, but no trial allowed nurses, emergency medical technicians, undergraduate students, or residents other than a neurology resident to obtain participant or surrogate consent (see figure 3). Although some trials allowed consent to take place in

the hospital and in one case it was permitted over the phone, no trial allowed for consent to be obtained in an ambulance or while at an outside hospital (a hospital at which the treatment was not administered) prior to transfer. When asked to describe the required formal training received specific to the informed consent process, study team members from only two trials mentioned specific training with regard to informed consent skills, and one trial did not require formal training specific to that trial.

Foreign language. The six trials took place in various continents, and four out of the six made translators and translated consent documents available. Interestingly, trials that offered translated consent documents had longer DTT than trials that did not offer translated documents in both the control and the experimental arms (see figure 4). Similarly, trials that offered translation services had longer DTT than trials that did not in both the control and experimental arms.

DISCUSSION

Acute stroke treatment trials face unique challenges in obtaining informed consent due to the time-sensitive nature of acute stroke treatments and a patient population with neurologic deficits. The goal of our study was to characterize the approaches and barriers to obtaining informed consent in trials comparing the effectiveness of tPA with that of alternative treatment. To our knowledge, this study is the first to investigate the experiences of international stroke trial investigators related to obtaining informed consent.[25] The results presented in this work were limited by a small sample size of respondents affiliated with six trials. However, our findings highlight the many challenges of obtaining consent for research participation in the acute setting and suggest that increasing transparency of the current informed consent process for the scientific community at large will allow for an effective characterization of traditional consent processes used and identification of areas for improvement that are needed to facilitate testing of new treatments that could improve stroke outcomes.

The informed consent process is a mechanism for patients to exercise autonomy in deciding whether to participate in a research study. Patients and their surrogates also derive value from informed consent discussions.[26] Thus, how patients participate is intrinsically an ethical factor in trials without straightforward informed consent processes, such as trials of acute stroke or other emergency treatments. Investigators surveyed from the trial called A Study of Effectiveness and Safety of Abciximab in Patients with Acute Ischemic Stroke (AbESTT II) indicated that obtaining informed consent produces unnecessary delays in time to treatment but simultaneously felt that an exemption from the ethical—and, in the U.S., regulatory—requirement for informed consent was inappropriate.[27] Thus, the implementation of an informed consent process presents a conflict between balancing patient-centric care with faster DTT times for superior outcomes, development of superior stroke therapies, and respect for patients as autonomous human beings.[28]

Trial characteristics. Six out of the 14 trials from whom respondents completed the survey were conducted at major stroke institutions in various countries, with representation from North America, Asia, Europe, Australia, and South America. Because of this variation in location, different institutional and cultural values may have influenced the methods and parameters used for obtaining informed consent, as evidenced in previous studies.[29] There have been many regulatory changes regarding the conduct of a clinical trial, and a unique challenge was that one major change concerning single IRB (sIRB) systems took place in 2015, which was in the middle of the study period for many of the U.S. trials we studied here (see table 2). Therefore, each participating U.S. trial site created their own consent form and consent protocol for approval by their institution's IRB, which decreased reproducibility of the informed consent process across trial sites. Another significant variation we identified was that the number of participants in the trials we examined for our study ranged from 7 to 3,206. It is likely that the trials with a large number of participants encountered challenges with greater frequency, but these multicenter trials may have had the motivation and resources to implement more standardized approaches at multiple locations (see table 1). Although the differences between the trials examined may be related to legal, institutional, and cultural effects, these trials overall provide evidence of the diverse landscape of informed consent and the need to study

the various approaches to characterize advantages and disadvantages of each.

Reporting the consent process. Information about how consent was obtained, consent forms, and the personnel involved across the trials we examined was highly variable and often could not be located publicly through protocol papers or within the published manuscripts. Interestingly, only half of the trials mentioned the involvement of a research ethics committee in their published results. In the design of future studies, including an ethical oversight committee to oversee abbreviated methods of informed consent—as the ongoing Alteplase Compared to Tenecteplase in Patients with Acute Ischemic Stroke: QuICR & OPTIMISE (AcT QuICR) trial does—may be a useful approach to mitigate ethical dilemmas.[30] None of the 14 trials that met inclusion criteria made a copy of the informed consent document publicly available. Even after we contacted trials for a copy of the informed consent document, only two provided forms for further examination. The absence of information highlights the need for research ethics involvement in trial design and greater transparency concerning informed consent in published manuscripts. Without additional information from survey respondents, we are limited in our ability to conduct analysis and draw conclusions across the field as a whole concerning approaches and barriers to obtaining informed consent. Without accurate characterization of these barriers, significant problems stroke researchers face may not be understood or addressed.

Capacity to consent and surrogate consent. Given that patients experiencing a stroke are a vulnerable population on the basis of the neurologic nature of the disease, understanding patients' decisional capacity to provide consent is critical in determining best practices for informed consent. In this study, three out of six trials reported obtaining consent from patients for 75% to 100% of participants, while only one trial reported obtaining consent from patients for less than 25% of participants (see figure 2). It remains important, however, to include cognitively impaired participants to determine the generalizability of the proposed interventions.[31] NIHSS scores reported indicate that most participants experienced a moderate stroke (see table 1). In the moderate NIHSS group, the ability to cognitively understand circumstances and make an informed decision varies widely.[32] This potentially discordant finding between reports that the majority of patients provided consent and had a "moderate" stroke could be due to alternative or more relaxed definitions of participant consent outside of the U.S.[33] For example, four of the six trials in this study were conducted outside of the U.S., and the practice of enrolling participants without their consent under a "deferred consent" model is common outside the U.S.[34] Deferred consent involves randomization of the patient into a study arm based on the discretion of the investigator, followed by informed consent during a later phase of clinical care, after the treatment has been administered. In that scenario, investigators may have received assent from the stroke patient and formal written consent from the legally authorized representative before the treatment was administered. Given this, some trial representatives may have interpreted the survey question in a way we had not foreseen, responding with a focus on who actually signed the consent form rather than who initially provided consent before treatment was administered (see appendix 1). This may explain why, although most patients experienced a moderate stroke, our study respondents indicated that over 75% of stroke patients provided consent on their own. Although deferred consent is one possible solution to ensure that patients receive treatment in a timely manner and are appropriately aware of therapies, patient autonomy may become an issue: the investigator cannot take away the medications or treatment already provided, even if the patient later declines to participate in the trial.

It is unclear how trials in our study determined whether patients had the decisional capacity to provide consent to participate in a trial. The literature indicates that some stroke trials have used aspects of the NIHSS to assess decisional capacity, including the sections regarding "level of consciousness," "best gaze," and "best language."[35] More research needs to be conducted about ways to best assess decisional capacity for patients with a moderate stroke scale score to determine whether examining aspects of the NIHSS is sufficient to determine decisional capacity.[36] When patients do not have decisional capacity, many stroke trials obtain consent for research participation from an authorized surrogate.[37] From an ethical perspective, there is concern as to whether surrogates are aligned with the wishes of the

patients regarding participation in research studies.[38] To address this issue, patient assent can be required in addition to proxy consent, as it was in only two of the trials in the studies we examined (see figure 2).[39] Although surrogate decision-makers must make difficult choices, the research team should still involve the patient to their fullest extent by attempting to gain their assent if they do not have decisional capacity to provide consent to enroll in a study.

Logistics of obtaining informed consent. Although communication techniques employed during the consent process between research staff and patients are vital for obtaining consent in an ethical and efficient manner, only a subset of the trials we examined indicated that a dedicated training process for obtaining consent had been in place (see table 3). All trials in our study sample relied on highly educated and experienced providers as well as dedicated research coordinators to obtain consent (see figure 3, part A). A dedicated training protocol for conducting the informed consent process can ensure a high standard of communication and create more time to discuss the trial with patients and families.[40]

In the trials studied, consent was obtained in a variety of settings; however, only one trial allowed consent to be obtained over the phone, and no trials obtained consent upon patient transfer or in an ambulance (see appendix 1). Obtaining consent over the phone in a prehospital setting has been performed in the Field Administration of Stroke Therapy—Magnesium (FAST-MAG) trial and provided more time for patients to consider consent and increased efficiency.[41] Obtaining consent before a patient arrives at the hospital is an option to consider for future trials. Another modality of consent to be considered is via a phone call: 3 out of 5 trials reported challenges obtaining consent by proxy, and some of these challenges may be mitigated by allowing for phone consent. Phone consent is important when no proxy is available within the time window due to geographic constraints.[42] However, it can be challenging to reach patient families with distressing information and to ask for a decision when they are most vulnerable.

Recent revisions to the Common Rule, which governs federally funded research in the U.S., emphasize the responsibility of study team members to deliver information with concise and simple language during the consent process.[43] Consent forms should emphasize key points for participation up front.[44] This is important because enrollment decisions in stroke trials can occur in a highly stressful environment that may increase cognitive load and diminish comprehension. One of the trials reviewed implemented a time limit in which consent had to be obtained (see table 1). This approach may be appropriate in the acute setting to indicate the time-sensitive nature of the process to research staff and to promote efficiency in the consent process. One trial made note of the decision to allow patients to provide verbal consent to initiate treatment followed by deferred written consent (see table 2). Interpersonal communication may be a more efficient means to obtain consent and may produce better understanding in comparison to the medium of paper forms.[45] Verbal consent has thus previously been proposed as a function-based approach to informed consent.[46] Shortening the consent form is another consideration to reduce complexity.[47] Overall, a more targeted consent model may be preferable on an ethical basis due to the time-sensitive nature of benefit to the patient and the potential to enhance patient understanding.[48]

FOREIGN LANGUAGE

Translators and translated consent documents may provide an avenue to greater patient diversity in stroke trials, allowing fair access to trial drugs to all people, which would fulfill the principle of justice. Trials that included patients with potential language barriers who required translators and translated consent documents demonstrated a trend toward increased DTT time, suggesting that efficiency and efficacy may be impacted where such barriers exist (figure 4). Efforts to increase the availability of rapid bedside interpretation services, such as with interpreter phones and professional translators, may help correct well-documented ethnicity-based disparities in thrombolysis.[49] Additional barriers in the consent process may also exist for patients who speak foreign languages. Patients with limited proficiency in the native language of that region may have lower health literacy, availability of surrogate decision-makers, or knowledge of concepts related to study design, such as randomization.[50] Although these additional barriers exist and slow the informed consent process, these barriers can be in part mitigated by increasing rapid translation services and education at

the bedside to ensure informed consent is achieved in a timely manner and to promote the inclusion of a more representative, diverse patient population.

LIMITATIONS

The findings from this study are limited by the small sample of trials that met inclusion criteria. Further, we did not have responses from 8 of the 14 trials that met inclusion criteria and could not locate trial protocols or procedure manuals that outlined the informed consent procedures. This lack of survey responses and publicly available information has limited our statistical analysis and the generalizability of our results to the field of stroke research as a whole. We welcome any trial investigators or staff to complete our survey at http://bit.ly/strokeconsent or by contacting the corresponding author (Meurer). Some of the trials were ongoing, and the respondents could not complete all data fields. In cases where the trial was conducted across multiple clinical sites, responses may not reflect site-specific variation in how informed consent was obtained. Trials were additionally limited to studies listed in trial registries in English, thus excluding the pool of international studies that otherwise satisfied inclusion criteria. Besides informed consent, unreported clinical factors, such as blood pressure management, may also influence the DTT times in the included trials.[51] Finally, other countries have different regulations and consent approaches that were not captured by this study. A new landscape for informed consent in the acute setting may be necessary to ensure medical care does not stagnate and that research can allow for the development of the next standard of care.

CONCLUSIONS

Time is most valuable for patients suffering from a stroke: the amount of brain function regained is directly proportional to the time it takes to administer treatment. It is critical that investigators respect this race against time. However, investigators are researching thrombolytic therapies that have the potential to improve the quality of life and provide great benefit to society. Our inability to obtain informed consent documents, protocols from published results, or survey responses from trials highlights the lack of transparency of the current informed consent process to the scientific community at large. The lack of information does not allow for effective characterization of current consent processes and makes it difficult to identify improvements in the consent processes that better facilitate the direct comparison of tPA to an alternative with potentially greater benefits. This research cannot progress unless the standards of informed consent change, but researchers must balance the value of pivotal scientific discoveries in medicine with the importance of protecting the individuals whose willing involvement can enable such progress. Therefore, we recommend a new era of informed consent in acute stroke trials with ethical oversight to develop a targeted approach to informed consent. We acknowledge that uniform standards of obtaining consent may not be applicable in all trials or scenarios, but future trials should be designed with an emphasis on communication with patients of diverse backgrounds, robust consent protocols, and transparency in the informed consent process. This new approach will pave the way for more streamlined and inclusive study of treatments in acute stroke.♦

SUPPORTING INFORMATION

Table 3, the figures, and the appendix are available in the "Supporting Information" section for the online version of this article and via *Ethics & Human Research*'s "Supporting Information" page: https://www.thehastingscenter.org/supporting-information-ehr/.

Tiffany Bellomo, MD, *is a vascular surgery resident at the Massachusetts General Hospital;* **Jennifer Fokas, MD,** *is a neurology resident at McGaw Medical Center of Northwestern University;* **Noah Tsao, BS,** *is a medical student at the University of Rochester;* **Clare Anderson, MD,** *is an internal medicine resident at Duke University Hospital;* **Christopher Becker, MD,** *is an internal medicine resident at the University of Michigan;* **Rachel Gioscia-Ryan, MD,** *is an anesthesia resident at the University of Michigan; and* **William Meurer, MD,** *is an associate professor of emergency medicine at the University of Michigan.*

ACKNOWLEDGMENTS

This research was unfunded. We wish to thank participating studies; without their assistance, this research would not have been possible. We also wish to thank James F. Burke MD, MS, for his critical editing of this manuscript and Lesli E. Skolarus, MD, for her expert review of the survey.

REFERENCES

1. World Medical Association, "World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects," *Journal of the American Medical Association* 310 (2013): doi:10.1001/jama.2013.281053.

2. Virani, S. S., et al., "Heart Disease and Stroke Statistics—2020 Update: A Report from the American Heart Association," *Circulation* 141 (2020): doi:10.1161/CIR.0000000000000757; Heidenreich, P. A., et al., "Forecasting the Impact of Heart Failure in the United States: A Policy Statement from the American Heart Association," *Circulation: Heart Failure* 6, no. 3 (2013): doi:10.1161/HHF.0b013e318291329a.

3. Powers, W. J., et al., "Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association," *Stroke* (2019): doi:10.1161/STR.0000000000000211; Palaniswami, M., and B. Yan, "Mechanical Thrombectomy Is Now the Gold Standard for Acute Ischemic Stroke: Implications for Routine Clinical Practice," *Interventional Neurology* 4, no. 1-2 (2015): doi:10.1159/000438774.

4. Saver, J. L., "Time Is Brain—Quantified," *Stroke* (2006): doi:10.1161/01.STR.0000196957.55928.ab; Saver, J. L., et al., "Time to Treatment with Intravenous Tissue Plasminogen Activator and Outcome from Acute Ischemic Stroke," *Journal of the American Medical Association* 309 (2013): doi:10.1001/jama.2013.6959; Hacke, W., et al., "Association of Outcome with Early Stroke Treatment: Pooled Analysis of ATLANTIS, ECASS, and NINDS Rt-PA Stroke Trials," *Lancet* 363 (2004): doi:10.1016/S0140-6736(04)15692-4.

5. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, "Tissue Plasminogen Activator for Acute Ischemic Stroke," *New England Journal of Medicine* 333 (1995): 1581-87.

6. Mendelson, S. J., et al., "National Practice Patterns of Obtaining Informed Consent for Stroke Thrombolysis," *Stroke* 49, no. 3 (2018): doi:10.1161/STROKEAHA.117.020474.

7. Thomalla, G., et al., "Effect of Informed Consent on Patient Characteristics in a Stroke Thrombolysis Trial," *Neurology* 89 (2017): doi:10.1212/WNL.0000000000004414.

8. Mendelson et al., "National Practice Patterns of Obtaining Informed Consent"; Janssen, P. M., et al., "Neurological Deficits in Stroke Patients That May Impede the Capacity to Provide Informed Consent for Endovascular Treatment Trials," *Journal of Stroke and Cerebrovascular Diseases* 28, no. 12 (2019): doi:10.1016/j.jstrokecerebrovasdis.2019.104447.

9. Yanagida, T., et al., "Causes of Prehospital Delay in Stroke Patients in an Urban Aging Society," *Journal of Clinical Gerontology and Geriatrics* 5, no. 3 (2014): doi:10.1016/j.jcgg.2014.02.001.

10. Wendler, D., et al., "Targeted Consent for Research on Standard of Care Interventions in the Emergency Setting," *Critical Care Medicine* (2017): doi:10.1097/CCM.0000000000002023.

11. Skolarus, L. E., et al., "Getting the GIST across Is Enough for Informed Consent for Acute Stroke Thrombolytics," *Stroke* 50 (2019): doi:10.1161/STROKEAHA.119.024653.

12. Powers et al., "Guidelines for the Early Management of Patients with Acute Ischemic Stroke."

13. Both PubMed (see https://pubmed.ncbi.nlm.nih.gov/) and ClinicalTrials.gov are made available by the U.S. National Library of Medicine.

14. See JPRN Search Portal, https://rctportal.niph.go.jp/en/.

15. Europe PMC, https://europepmc.org/.

16. EU Clinical Trials Register, https://www.clinicaltrialsregister.eu/.

17. Australian New Zealand Clinical Trials Registry, https://www.anzctr.org.au/.

18. World Health Organization, International Clinical Trials Registry Platform, search portal, apps.who.int/trialsearch/.

19. Powers et al., "Guidelines for the Early Management of Patients with Acute Ischemic Stroke."

20. Rayan, https://rayyan.qcri.org/.

21. Angde Biotech Pharmaceutical Co., "A Phase II of Injection for Recombinant Human Tissue Plasminogen Kinase Derivative in Treatment of Acute Ischemic Stroke," ClinicalTrials.gov, identifier: NCT04028518, 2019, accessed January 3, 2020; Menon, B. K., et al., "Alteplase Compared to Tenecteplase in Patients with Acute Ischemic Stroke," ClinicalTrials.gov, identifier: NCT03889249, 2019, accessed January 3, 2020; General Hospital of Shenyang Military Region, "Antiplatelet vs R-tPA for Acute Mild Ischemic Stroke," ClinicalTrials.gov, identifier: NCT03661411, 2020, accessed January 3, 2020; Tasly Biopharmaceuticals Co., "Study of rhPro-UK in Patients with Acute Ischaemic Stroke in 4.5 Hours after Stroke Onset," ClinicalTrials.gov, identifier: NCT03541668, 2020, accessed January 3, 2020; Melbourne Health, "Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance," ClinicalTrials.gov, identifier: NCT04071613, 2020, accessed January 3, 2020; Haukeland University Hospital, "The Norwegian Tenecteplase Stroke Trial 2," ClinicalTrials.gov, identifier: NCT03854500, 2019, accessed January 3, 2020; Anderson, C. S., et al., "Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke," *New England Journal of Medicine* 374 (2016): 2313-23; Campbell, B. C. V., et al., "Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke," *New England Journal of Medicine* 378 (2018): 1573-82; Ciccone, A., et al., "Endovascular Treatment for Acute Ischemic Stroke," *New England Journal of Medicine* 368 (2013): 904-13; Haley, E. C., et al., "Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke: Results of a Prematurely Terminated Randomized Clinical Trial,"

Stroke 41, no. 4 (2010): 707-11; Huang, X., et al., "Alteplase versus Tenecteplase for Thrombolysis after Ischaemic Stroke (ATTEST): A Phase 2, Randomised, Open-Label, Blinded Endpoint Study," *Lancet Neurology* 14 no. 4 (2015): 368-76; Khatri, P., et al., "Effect of Alteplase vs Aspirin on Functional Outcome for Patients with Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits: The PRISMS Randomized Clinical Trial," *Journal of the American Medical Association* 320 (2018): 156-66; Logallo, N., et al., "Tenecteplase versus Alteplase for Management of Acute Ischaemic Stroke (NOR-TEST): A Phase 3, Randomised, Open-Label, Blinded Endpoint Trial," *Lancet Neurology* 16, no. 10 (2017): 781-88; Sen, S., et al., "IV vs. IA TPA in Acute Ischemic Stroke with CT Angiographic Evidence of Major Vessel Occlusion: A Feasibility Study," *Neurocritical Care* 11, no. 1 (2009): 76-81.

22. Haley et al., "Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke"; Anderson et al., "Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke"; Sen et al., "IV vs. IA TPA in Acute Ischemic Stroke with CT Angiographic Evidence of Major Vessel Occlusion"; Logallo et al., "Tenecteplase versus Alteplase for Management of Acute Ischaemic Stroke (NOR-TEST)"; Angde Biotech Pharmaceutical Co., "A Phase II of Injection for Recombinant Human Tissue Plasminogen Kinase Derivative in Treatment of Acute Ischemic Stroke"; Haukeland University Hospital, "The Norwegian Tenecteplase Stroke Trial 2."

23. Menon et al., "Alteplase Compared to Tenecteplase in Patients with Acute Ischemic Stroke."

24. Finlay, K. A., and C. V. Fernandez, "Failure to Report and Provide Commentary on Research Ethics Board Approval and Informed Consent in Medical Journals," *Journal of Medical Ethics* 34 (2008): doi:10.1136/jme.2007.023325; Schroter, S., et al., "Reporting Ethics Committee Approval and Patient Consent by Study Design in Five General Medical Journals," *Journal of Medical Ethics* 32 (2006): doi:10.1136/jme.2005.015115.

25. Bateman, B. T., et al., "Conducting Stroke Research with an Exception from the Requirement for Informed Consent," *Stroke* 34 (2003): doi:10.1161/01.STR.0000065230.00053.B4.

26. Scicluna, V. M., et al., "Determinants of Patient and Surrogate Experiences with Acute Care Research Consent: A Key Informant Interview Study," *Journal of the American Heart Association* 8, no. 22 (2019): doi:10.1161/JAHA.119.012599; Dickert, N. W., et al., "Emergency Consent: Patients' and Surrogates' Perspectives on Consent for Clinical Trials in Acute Stroke and Myocardial Infarction," *Journal of the American Heart Association* 8, no. 2 (2019): doi:10.1161/JAHA.118.010905.

27. Leira, E. C., et al., "Lack of International Consensus on Ethical Aspects of Acute Stroke Trials," *Journal of Stroke and Cerebrovascular Diseases* 21, no. 3 (2012): doi:10.1016/j.jstrokecerebrovasdis.2010.06.008.

28. Ibid.; Saver, "Time Is Brain—Quantified."

29. Halkoaho, A., et al., "Cultural Aspects Related to Informed Consent in Health Research: A Systematic Review," *Nursing Ethics* (2016): doi:10.1177/0969733015579312.

30. Menon et al., "Alteplase Compared to Tenecteplase in Patients with Acute Ischemic Stroke"; Dewar, B., and Shamy, M. C., response to letter regarding the article "Deferral of Consent in Acute Stroke Trials: Lessons from the ESCAPE Trial," *Stroke* 50, no. 8 (2019): doi:10.1161/STROKEAHA.119.026278.

31. Tu, J. V., et al., "Impracticability of Informed Consent in the Registry of the Canadian Stroke Network," *New England Journal of Medicine* 350 (2004): doi:10.1056/NEJMsa031697.

32. Nys, G. M. S., et al., "Cognitive Disorders in Acute Stroke: Prevalence and Clinical Determinants," *Cerebrovascular Diseases* 23 (2007): doi:10.1159/000101464; Kauranen, T., et al., "The Cognitive Burden of Stroke Emerges Even with an Intact NIH Stroke Scale Score: A Cohort Study," *Journal of Neurology, Neurosurgery and Psychiatry* 85, no. 3 (2014): doi:10.1136/jnnp-2013-305585.

33. Flaherty, M. L., et al., "How Important Is Surrogate Consent for Stroke Research?," *Neurology* 71 (2008): doi:10.1212/01.wnl.0000316196.63704.f5.

34. Jansen, T. C., et al., "Deferred Consent in Emergency Intensive Care Research: What If the Patient Dies Early? Use the Data or Not?," *Intensive Care Medicine* 33 (2007): doi:10.1007/s00134-007-0580-8; Shamy, M. C. F., et al., "Deferral of Consent in Acute Stroke Trials: Lessons from the ESCAPE Trial," *Stroke* 50, no. 4 (2019): doi:10.1161/STROKEAHA.118.024096.

35. Janssen et al., "Neurological Deficits in Stroke Patients."

36. Rose, D. Z., and S. E. Kasner, "Informed Consent: The Rate-Limiting Step in Trials," *Frontiers in Neurology* (2011): doi:10.3389/fneur.2011.00065.

37. Flaherty et al., "How Important Is Surrogate Consent for Stroke Research?"

38. Bryant, J., et al., "The Accuracy of Surrogate Decision Makers: Informed Consent in Hypothetical Acute Stroke Scenarios," *BMC Emergency Medicine* 13, no. 1 (2013): doi:10.1186/1471-227X-13-18.

39. Scicluna et al., "Determinants of Patient and Surrogate Experiences."

40. Rose and Kasner, "Informed Consent"; Flory, J., and E. Emanuel, "Interventions to Improve Research Participants' Understanding in Informed Consent for Research: A Systematic Review," *Journal of the American Medical Association* (2004): doi:10.1001/jama.292.13.1593.

41. Saver, J. L., et al., "Prehospital Use of Magnesium Sulfate as Neuroprotection in Acute Stroke," *New England Journal of Medicine* 372 (2015): doi:10.1056/NEJMoa1408827.

42. Biros, M. H., et al., "Balancing Ethical Goals in Challenging Individual Participant Scenarios Occurring in a Trial Conducted with Exception from Informed Consent," *Academic Emergency Medicine* 22 (2015): doi:10.1111/acem.12602;

Dickert et al., "Emergency Consent."

43. "Federal Policy for the Protection of Human Subjects. Final Rule," *Federal Register* 82, no. 12 (January 2017): 7149–7274; Simonds, V. W., and D. Buchwald, "Too Dense and Too Detailed: Evaluation of the Health Literacy Attributes of an Informed Consent Document," *Journal of Racial and Ethnic Health Disparities* 7 (2020): doi:10.1007/s40615-019-00661-1; Schmidt, T. A., et al., "Confronting the Ethical Challenges to Informed Consent in Emergency Medicine Research," *Academic Emergency Medicine* 11 (2004): doi:10.1197/j.aem.2004.05.028.

44. "Revised Common Rule Q&As," U.S. Department of Health and Human Services, Office for Human Research Protections, 2018, https://www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/revised-common-rule-q-and-a/index.html.

45. Flory and Emanuel, "Interventions to Improve Research Participants' Understanding in Informed Consent for Research"; Falagas, M. E., et al., "Informed Consent: How Much and What Do Patients Understand?," *American Journal of Surgery* (2009): doi:10.1016/j.amjsurg.2009.02.010.

46. Feldman, W. B., et al., "Effect of Waivers of Consent on Recruitment in Acute Stroke Trials," *Neurology* 86 (2016): doi:10.1212/WNL.0000000000002587; Dickert, N. W., et al., "Reframing Consent for Clinical Research: A Function-Based Approach," *American Journal of Bioethics* 17, no. 12 (2017): doi:10.1080/15265161.2017.1388448; Dickert, N. W., et al., "Understanding Preferences regarding Consent for Pragmatic Trials in Acute Care," *Clinical Trials* 15 (2018): doi:10.1177/1740774518801007.

47. Dickert, N. W., et al., "Confronting Ethical and Regulatory Challenges of Emergency Care Research with Conscious Patients," *Annals of Emergency Medicine* 67, no. 4 (2016): doi:10.1016/j.annemergmed.2015.10.026; Scicluna et al., "Determinants of Patient and Surrogate Experiences"; Nishimura, A., et al., "Improving Understanding in the Research Informed Consent Process: A Systematic Review of 54 Interventions Tested in Randomized Control Trials," *BMC Medical Ethics* 14, no. 1 (2013): doi:10.1186/1472-6939-14-28.

48. Wendler et al., "Targeted Consent for Research on Standard of Care Interventions in the Emergency Setting."

49. Schenker, Y., et al., "The Impact of Language Barriers on Documentation of Informed Consent at a Hospital with On-Site Interpreter Services," supplement, *Journal of General Internal Medicine* 22, no. 2 (2007): doi:10.1007/s11606-007-0359-1; Mendelson, S. J., et al., "Racial Disparities in Refusal of Stroke Thrombolysis in Chicago," *Neurology* 90, no. 5 (2018): doi:10.1212/WNL.0000000000004905.

50. Krieger, J. L., et al., "Linguistic Strategies for Improving Informed Consent in Clinical Trials among Low Health Literacy Patients," *Journal of the National Cancer Institute* 109, no. 3 (2017): doi:10.1093/jnci/djw233; Nardini, C., "The Ethics of Clinical Trials," *Ecancer* 8, no. 1 (2014): doi:10.3332/ecancer.2014.387.

51. Carrera, J. F., et al., "Delay to Tissue Plasminogen Activator in Hypertensive Stroke Patients: An Analysis of Delay Duration across Agents," *Journal of Stroke and Cerebrovascular Diseases* 29, no. 2 (2020): doi:10.1016/j.jstrokecerebrovasdis.2019.104525.