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STROKE (J MESCHIA, SECTION EDITOR)

Ethics and Bias in Clinical Trial Enrollment in Stroke

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Abstract

Purpose of Review To familiarize the reader with ethical concerns and potential scientific bias in management and conduction of clinical stroke trials.

Recent Findings The goal of clinical trials in stroke is to find effective interventions for stroke prevention, acute treatment, and rehabilitation and recovery. Acute trials must be designed in the context of the time-sensitivity of revascularization therapies. Standard ethical constraints apply. However, informed consent is hindered by tight time windows for reperfusion therapy and frequent cognitive impairment in patients. These might be mitigated by using visual decision aids. Non-traditional methods of consent such as utilization of surrogates, telemedicine, and exception from informed consent are critical for successful and unbiased conduction of stroke trials. Stroke centers must have an a priori plan for deciding which trial to offer multiple-trial eligible patients. Historic non-generalizability of stroke trials due to under-enrollment of women, racial minorities, and age extremes is improving, but adequate representative recruitment and retention require up-front planning and training.

Summary Stroke trials have become less biased and more representative in the last decades, but there is still research to be done to improve ethical and unbiased recruitment and retention.

Keywords Stroke · Clinical trial · Bias · Ethics · Enrollment · Retention

Introduction

As with most complex clinical disorders, the practice of stroke care began with observational studies. However, real advancement of the science of stroke prevention, treatment, and recovery came from clinical trials [1]. There are multiple types of clinical trials, with the randomized, controlled clinical trial (RCT) widely considered the most rigorous method of determining efficacy of interventions. An RCT is a prospective study where human subjects are randomly allocated to either the intervention under study or a control intervention or placebo. The act of randomization produces groups of subjects that are comparable in the characteristics that may be reasonably expected to affect the outcome, such as sex, age, race, and presence of vascular risk factors. This allows the outcomes to be attributed to the intervention and not baseline patient differences. There are multiple types of clinical trials, and Ahn provides an excellent description of the pros and cons of each type in the context of stroke [2].

Stroke patients should first be offered proven, evidence-based therapy. However, if there is no standard care option, then providers should offer the patient enrollment in an appropriate randomized clinical trial [3]. In this way, rigorous data is generated for the benefit of future stroke patients. Trial enrollment may also benefit the enrolled stroke patient since many studies have shown that patients in clinical trials have better outcomes than patients not enrolled, regardless of the assigned randomization arm [4, 5]. This “trial effect” could be due to strict protocol adherence: a study of pre-eclampsia therapy found that if non-trial patients were also treated according to a strict clinical protocol, they had similar outcomes as enrolled patients [6]. Other authors have suggested that the trial effect may be due to superior care at tertiary centers conducting the trials or to underlying unmeasured patient factors such as co-morbidities and prior health status [7, 8].

This review is not a complete description of clinical trials but will focus on the ethical concerns and biases encountered during trial enrollment, particularly those encountered in acute stroke research. The goal of clinical trials in stroke is to find effective treatments for all three major areas of stroke care:

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primary and secondary prevention, the hyperacute and acute period, and rehabilitation and recovery. Stroke differs from many diseases, however, in that stroke is a sudden-onset and generally unpredictable disease with an extremely narrow treatment window for reperfusion therapy and a prolonged rehabilitation window. Clinical stroke trials thus must be designed in the context of the time-sensitivity of acute therapies. This time sensitivity introduces difficulties including how to ethically approach distressed families and patients with cognitive impairment and how to determine which trials to offer patients in a scientifically valid way. These are discussed in detail below.

Ethics of Stroke Trial Research

The ethical principles of clinical research were outlined in the Belmont Report in 1979 [9••] and still apply today. They include the concepts of (1) respect for persons, which holds that people should be informed of the nature of the research and free to choose whether or not to participate; (2) beneficence and non-maleficence, which is the goal to maximize possible benefits and minimize possible harms; and (3) justice, which is the idea that the burdens and benefits of research should be equitably distributed among groups of patients and is meant to prevent repeating prior abuses of disadvantaged groups such as minorities and prisoners. The principle of respect for persons is generally what guides the informed consent process, while principles of beneficence and justice generally inform study design, including recruitment.

Informed consent is well-established as a cornerstone of ethical conduction of an RCT. Informed consent is best conceived of as a process whereby potential participants are given an oral description of the study and have adequate time for all questions to be thoroughly discussed, and alternatives to be considered. The consent document is typically provided in a written form that participants and investigators both sign after the discussion. By US law, informed consent is required to include a description of the RCT objectives, methods, and procedures; the potential risks and benefits; liability in case of injury; alternatives to participation, including options for discontinuation; and investigator plans for use of private information. To give informed consent, a person must be at least 18 years old and have capacity to clearly understand the facts, implications, and future consequences of their decision.

A major barrier to providing informed consent across all diseases is low literacy and numeracy among patients. Though these difficulties can be combated by writing consent forms at a 10th grade reading level, medical jargon and research concepts are often new even to literate patients. In acute stroke, this problem is exacerbated by tight time limits and the frequent occurrence of acute cognitive impairment from the stroke [10]. Limited baseline understanding of basic concepts of clinical research also hinders obtaining informed consent. For example, the need for a placebo arm in most RCTs is particularly confusing to potential subjects. The author had a patient refuse enrollment in a stroke RCT due to the lack of a 100% guarantee of receiving the experimental drug, despite the apparent illogic of such a choice lowering the odds of experimental treatment to zero. A study of attitudes towards acute neurologic trials among patients with previous stroke or brain injury and persons at risk for traumatic brain injury found that while study participants were highly supportive of trials, they felt that placebos were unfair and unnecessary [11].

Decisional paralysis is a common occurrence when offering standard of care for patients with acute stroke, and several thought leaders in stroke have recommended visual aids for decision-making in standard of care thrombolysis to improve communication without requiring literacy or numeracy [12]. While data are still being accrued regarding the use of decision aids in the consent process for RCTs [13], a cancer study found increased recruitment, with decreased decisional confusion, and increased trial knowledge in subjects who used a visual aid [14]. Such techniques could be implemented in stroke trials.

Surrogate Consent Unfortunately, many stroke survivors have cognitive impairment, with reported prevalence rates from 20 to 80%, varying based on population, ascertainment methods, and definitions of impairment [10]. In the emergency room setting, cognitive impairment is acute and causes loss of autonomy, whether from aphasia causing a failure to make or understand speech, severe dysarthria impeding intelligible communication, neglect causing inability to grasp the gravity of the situation, or frank reduction in level of consciousness. The loss of autonomy to provide informed consent for oneself is common: across several ischemic stroke trials, including the original National Institute of Neurological Disorders and Stroke (NINDS) tPA trial, only about 30% of patients were capable of providing their own consent in the acute stroke setting [15]. It is well-established that stroke patients who are enrolled in an RCT through surrogate consent are usually older and have more severe strokes compared to patients who can provide their own consent [16]. One study found that loss of autonomy is more likely to be found in patients who are older, have left-hemispheric lesions and more severe stroke, and have higher rates of in-hospital mortality [17•]. Scientifically, it is clear that allowing surrogacy provides a more representative stroke population. And, ethically, the principle of justice requires research to benefit the widest population of patients. Thus, alternate forms of informed consent are absolutely necessary to conduct ethically sound and scientifically valid studies.

The US FDA defines the term, “legally authorized representative” (LAR) as “an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research" [18]. However, a survey by Leira found that the laws on who can act as an LAR or provide surrogate consent vary by region in the USA and across countries [19]. Additional regional variations include what constitutes loss of decision-making capacity. For example, Leira found that the National Institutes of Health (NIH) Stroke Scale score was deemed adequate to establish decisional capacity based on the language subscore by most (62%) of the co-investigators but the minority (36%) of the IRBs. Though some trial protocols specify a screening cognitive questionnaire to establish competency prior to consent [20], these have not been validated. Due to these variances, investigators should take advantage of their local IRBs to interpret local laws when designing stroke studies.

Remote Consenting over Phone and Telestroke Inter-facility transfers for acute ischemic stroke and TIA are rising, more than doubling from 2006 to 2014, with rural facilities particularly likely to transfer, at rates of 45% of patients with ischemic stroke [21]. Transfers are facilitated either via a doctor-to-doctor phone call or after a patient-to-doctor telestroke consult. This epidemiologic trend can be exploited as a unique opportunity to increase acute stroke trial enrollment while reducing time to consent and simultaneously reducing geographic bias by enrolling patients who are more likely to be from rural areas. Surrogate consent in these situations is hindered because families are often not transported with the patients, often making in-person surrogate consent impossible within a tight time window. The two main alternatives to in-person consent are to utilize phone or telestroke, but neither has been yet been broadly implemented. For example, Leira found that only 18% of surveyed international IRBs allow consent by phone [19]. Nonetheless, phone-based consent was successfully used in the large pre-hospital stroke study Field Administration of Stroke Therapy–Magnesium (FAST-MAG), dramatically reducing onset-to-enrollment times [22].

Telestroke networks are now providing acute stroke care to rural and urban areas in every state in the USA. Though some telestroke networks utilize consultants from outside the region or even country [23], it is most common in the USA for telestroke networks to employ a hub-spoke method, whereby the consultant at a larger stroke center sees a patient at a hospital within their catchment area but does not have acute stroke experts available locally. This model allows for patients to be screened for RCTs being conducted at the hub [24]. Additionally, it allows the provider to speak directly to the patient or surrogate, providing face-to-face consent, potentially including display of graphics, which likely improves communication and understanding over phone-based consent. Some trial leaders are reluctant to allow telemedicine-based consent, fearing that it is somehow inferior to in-person consent or introduces unforeseen bias. And, some trials, such as DEFUSE 3, allow phone-based consent followed by faxed signed consent, but not video-enabled consent over telestroke. However, others have embraced telemedicine consent and have seen two benefits: an increase in enrollments and a reduction in time from patient arrival at the hub to study drug initiation [17•].

Exception from Informed Consent An alternative to informed consent that is being increasingly considered in stroke trials is termed exception from informed consent (EFIC). Given the imperative to rapidly reverse ischemia and halt the subsequent ischemic cascade [25], it is ideal for stroke therapies to begin as close to stroke onset as possible, ideally in the pre-hospital setting. However, very few stroke studies have been done in the pre-hospital setting for two primary reasons. The first is that, until very recently, and even now only in rare locales, brain imaging was not available in the field, making it impossible to distinguish hemorrhagic from ischemic stroke and even stroke from stroke mimic. Thus, any investigational drug or device tested in the pre-hospital setting has to be safe for patients with intracerebral hemorrhage, infarct, and stroke mimics. Second, there may not be time in the pre-hospital phase of care for informed consent whether by the patient or a surrogate. A 2017 meta-analysis of consent methods in pre-hospital trials across multiple countries (with stroke the second most common type of disease studied, after cardiovascular disease) found that, though multiple types of consent are used internationally, in the USA, EFIC was the model of choice [26]. Authors attributed this to the clear FDA guidance in these circumstances under Title 21, Code of Federal Regulations, Section 50.24 (21 CFR 50.24) [27••]. This regulation was developed in recognition that, because of ethical concerns involved in studying subjects who cannot provide consent, much of what has become standard and accepted, medical therapy for use in emergency settings has not been evaluated by well-controlled trials that demonstrate that the treatment is either safe or effective.

According to 21 CFR 50.24, EFIC can be utilized when subjects have a life-threatening medical condition that necessitates urgent intervention for which available treatments are unproven or unsatisfactory, and who, because of their condition, cannot provide informed consent [27••]. Clarifications in 2013 state that studies of conditions with morbidity endpoints can be included as well, naming stroke specifically among appropriate diseases for EFIC utilization. The research must (a) have the prospect of direct benefit to the patient, (b) involve an investigational product that to be effective has to be administered before informed consent can be obtained, and (c) be unable to be conducted without the waiver.

There are additional responsibilities on the IRB and investigators to utilize EFIC, most notably including that investigators consult with representatives of the community in which the research will take place and from which the subjects will be drawn. Such community discussion can take several forms: using standing meetings or special meetings specifically organized to discuss the research, using local radio and/or television talk shows or interactive websites, conducting surveys, or convening focus groups. The FDA clearly lays out the required content of the consultation [27••] with the goals to provide the opportunity for discussions with, and soliciting opinions from, the representative community, including providing input into the IRB decision-making process.

Bias and Ethics of Competing Trials A unique problem encountered in stroke centers with a large trial portfolio is how to approach a patient who is eligible for multiple trials. Under the Belmont principle of respect for persons, it is considered most ethical to offer all available trials to a patient for which the patient is eligible so that the patient retains autonomy in decision-making. Indeed, this is standard practice in most research settings. However, in the setting of acute stroke, offering multiple trials to each patient is impractical, as there is insufficient time to present each trial nor provide adequate informed consent. Additionally, it can be argued that it is contrary to the Belmont principle of non-maleficence, or "do no harm," as patients and family members are under great stress during this time period trying to make decisions of standard of care that will affect possible loss of function and life. Offering more than one trial only adds to their confusion and distress. Presenting a portfolio of trials rather than one trial may delay care and reduce the effectiveness of acute stroke treatments.

The issue of how best to handle the multi-trial eligible patient is of paramount importance in StrokeNet, the national stroke trials network that was funded by the NIH starting in 2013 [28, 29]. In this network, the goal is to efficiently conduct concurrent multiple trials in the acute, preventative, and rehabilitation spheres. To study the issue of how to best approach patients in the acute period when eligible for multiple trials, the StrokeNet leadership formed a working group of experienced trialists, research coordinators, and ethicists. This group wrote a guideline in use today that requires each center to have a written policy detailing how they will offer equitable enrollment in competing trials and provides guidance for the centers as they design their approach [30]. The guideline states that (1) when timeframes permit, patients or legally authorized representatives should be presented with all trials for which the patient is eligible. This is expected to be the case for prevention and recovery trials. (2) For hyperacute and acute trials, only one trial should be offered to a patient at a time. (3) Whether (and how) research personnel disclose to patients the presence of additional, non-offered trials should be determined in advance. StrokeNet does not mandate one method over another; however, the FDA suggests that this process is best left to the informed consent discussion rather than the informed consent document [31]. (4) Acceptable methods of determining which trial to present to patients in the hyperacute-acute time period include choosing to conduct no overlapping trials at a given clinical site, randomized assignment at the time of patient presentation, and utilizing pre-specified allocation grids. Allocation grids are the most commonly used, and though the allocation grids have to be set up ahead of time, they eliminate investigator bias and limit inclusion bias.

The StrokeNet policy is meant to encourage investigators to determine the best enrollment strategies for their center, taking into account their resources and trial portfolios, so that the research team has a plan at the time of patient presentation. As Saver notes in an excellent review of the issues [32••], to do otherwise will likely introduce scientific bias, conscious or unconscious, and distort the selection of subjects. This potential selection bias is heightened if the research team offers trials based upon any of the following: clinical factors, time windows, investigator belief in efficacy, site, clinical coordinator availability, or complexity of trial. There is relatively less concern for scientific bias in offering trials based upon quota urgency, remuneration, or sponsoring agency, company, or foundation [32••].

Bias and Generalizability in Stroke Trials

Representative Study Populations Again, it is of utmost importance that stroke trial subjects be representative of the population as a whole, to increase generalizability so that study results are applicable to "real world" patients, not just a highly selected sub-population. Unfortunately, the stroke populations studied in the past have not been representative of women, minorities, and extremes of ages. For example, a study of 15 randomized placebo-controlled secondary prevention trials of statins that were published in the 1990s (and included stroke as an endpoint) found that only 23% of 31,683 patients were female [33]. Additionally, no subjects were enrolled over the age of 75 years [33]. In stroke trials specifically, women only represent 37.8% of participants, likely low even accounting for the fact that men have a higher age-specific risk of stroke [34]. However, enrollments of women are increasing. An analysis of 51 NINDS-funded phase III trials that enrolled both men and women found that women increased from 34 to 43% of the trial populations over the time periods of 1985–1994 vs 1995–2000 [34].

Under-enrollment of minorities has long been a concern, particularly since stroke incidence, mortality, and subtypes vary by race and ethnicity [35–39]. Though 80% of NINDS-funded clinical trials report some race information, 32% only dichotomize between white and non-white, 48% only report African-American race, and only 23% report Hispanic ethnicity [34]. The percentage of African-Americans in neurologic clinical trials have increased over the last 2 decades, and currently in NINDS-funded trials that report on race/ethnicity and are not single race-specific trials, African-Americans appeared to be over-represented in neurologic trials generally (14.5%) and in stroke trials specifically (22.7%) compared to the US average of 12.9% [34]. This same study found that Hispanic Americans were under-represented at only 5.8% of subjects (less than half of the US population rate of 12.5%) and that their representation has decreased over time, from 7.4% in 1985–1994 to 5.0% in 1995–2000 [34]. However, Hispanic ethnicity was only reported in 22.7% of stroke-related trial publications, and thus the true numbers are difficult to know.

Enrollment and Retention Methods Hopefully increasing attention to this issue will further improve representative trial enrollment and retention. For example, the NIH requires investigators to describe their strategy for equitable inclusion of women and minorities in the research plan and to report participant race in yearly progress reports [40]. On January 29, 2019, the NIH will begin implementing the inclusion across the lifespan policy [41], which requires the consideration of age, along with sex/gender and race/ethnicity, in applications that involve human participants. StrokeNet has a separate working group dedicated to assisting potential investigators in creating a plan for including women and minorities.

The National Initiative for Minority Involvement in Neurological Clinical Trials (NIMICT) seeks to understand investigator-level barriers to increased minority recruitment and retention in neurological trials and create evidence-based toolkits to address these challenges. NIMICT investigators interviewed clinical trial principal investigators (PIs) [42] and clinical research coordinators [43•] to determine barriers to effective minority recruitment and retention. PIs identified the leading barriers to minority recruitment as mistrust of research and medical system (46%), lack of awareness about trials (41%), and communication issues (31%), while research coordinators identified translation, literacy, family composition, patients' demographics, symptom severity, and the social legacy related to disparate racial treatment in medical research studies [44]. Though 36% of PIs said that they require cultural competency training for staff, coordinators did not identify such training as useful. Coordinators instead focused on the utility of competency assessments during hiring and careful attention to "on-boarding" training for new hires that includes how to handle the emotional difficulties of the job. A separate survey of recruiters' perspectives on barriers to recruiting Hispanics highlighted dialect differences within Spanish, culturally-appropriate non-verbal cues, contextual factors including immigration status, and, again, distrust of the medical system [45•].

The NINDS encourages and expects investigators to do as much as possible to minimize the burden of participation on both research participants and practitioners through inclusion and engagement of patients and advocacy groups early in study design [46]. Investigators are encouraged to plan staffing, resources, and budgets for active recruitment and retention initiatives, including outreach and education to enhance research awareness (especially in diverse communities), creation of toolkits, and training in gender, age, and culturally sensitive communication techniques. Investigators should consider the use of new tools such as social media and mobile health applications to enhance study efficiency, engagement, and retention. Marketing should be planned proactively and in parallel with protocol design.

Patients may drop out of long duration clinical stroke trials, such as secondary prevention and recovery trials. Low retention rates introduce scientific bias if attrition varies by factors such as demographics of race, sex, or age or clinical factors such as disease severity or coexisting risk factors. This can lead to inconclusive or invalid results particularly of subgroup analyses by race due to statistical tests being underpowered [47].

Unfortunately, reasons for drop-out [48] and retention rates by race and sex are under-reported in secondary stroke prevention trials making such bias difficult to detect. Overall low retention can also lead to premature termination of studies, wasting money and resources, and raising ethical concerns of patients who consented to help answer important scientific questions but whose individual time and risk result in no gain [46].

There has been a call to scientifically evaluate methods to improve stroke trial recruitment and retention. The top priorities for recruitment methods evaluation are short and illustrated patient information leaflets, non-written consent, reimbursement for new interventions only within a study, and monetary incentives to institutions taking part in research. Top priorities for studies of retention are involvement of patient groups, remote and central follow-up, use of mobile devices, and reminders to patients about their consent to participate [49]. Barrier-focused strategies can work. For example, FAST-MAG investigators successfully increased the percentage of Hispanics they enrolled by using a Spanish language phone line for ambulance-based consent [50]. The secondary stroke prevention STAND FIRM study found that patients who consented at home versus in-hospital had higher retention rates (93% vs 67%) and more willingness to participate [51]. The Insulin Resistance Intervention after Stroke study found that patients who lived farther from the research center were less likely to show up for in-person yearly check-ins, but distance from home-to-hospital did not affect overall study medication compliance [52].

Conclusion

In order for clinical stroke trials to reach the most patients and for their benefits to be applicable to the greatest number of populations, it is critical that stroke investigators have a solid foundation in ethical considerations and scientific bias to implement in trial design and conduction. With research now being done on trial methodology itself, we can have hope that stroke trials will continue to evolve in order to ultimately improve the lives of all stroke patients.

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Compliance with Ethical Standards

Conflict of Interest Jennifer Juhl Majersik declares that she has no conflict of interest.

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