Conducting Stroke Research With an Exception From the Requirement for Informed Consent

Brian T. Bateman, BA; Philip M. Meyers, MD; H. Christian Schumacher, MD; Sundeep Mangla, MD; John Pile-Spellman, MD

Background—Obtaining viable informed consent from stroke patients for participation in clinical trials of acute stroke therapies is often problematic because of patients' neurological deficits. Furthermore, obtaining permission from surrogates is often not possible or not legally permissible.

Summary of Review—In 1996 the Food and Drug Administration and Department of Health and Human Services published regulations that allow investigators to conduct emergency research without patient consent under a narrowly defined set of circumstances. We review requirements of these regulations, paying particular attention to how they may be applied in a clinical trial of an acute stroke therapy.

Conclusions—Acute stroke researchers should consider conducting clinical trials with an exception from the informed consent requirement permitted by this law. (Stroke. 2003;34:1317-1323.)

Key Words: ethics, medical informed consent stroke

Stroke is an important cause of morbidity and mortality in the United States, representing the leading cause of adult disability and the third leading cause of death.1 It is estimated that more than 750,000 cases of new or recurrent stroke occur each year in the United States,2 with healthcare and lost productivity costs of approximately $49 billion annually.1 The current modalities available to physicians for the treatment of stroke are less than optimal. The presently accepted standard of care for acute ischemic stroke at community medical centers, intravenous tissue plasminogen activator (tPA), shows only moderate efficacy (an absolute increase in favorable outcome of only 11% at 3 months as assessed by the National Institutes of Health Stroke Scale) and is limited by a therapeutic window of only 3 hours, an ineffectiveness in treating large-vessel intracranial thrombo-occlusive disease, and an associated increased risk of symptomatic hemorrhage.3,4 The standard of care at academic medical centers, intra-arterial thrombolysis, expands the therapeutic window to 6 hours, but it too is of limited effectiveness and is associated with increased risk of symptomatic intracranial hemorrhage.5 Furthermore, while dedicated stroke units have shown effectiveness in reducing the morbidity and mortality associated with both ischemic and hemorrhagic strokes,6,7 it is clear that much work remains to be done in developing highly successful stroke treatments.

Despite the inadequacy of current therapies, reason for optimism exists. Research in neurobiology is proceeding at a breakneck pace. The mechanisms underlying brain function and dysfunction are being elucidated rapidly with the use of the tools of molecular biology, developmental biology, and neuroimaging. As more is discovered about stroke cause, damage, and rehabilitation, new and potentially more effective therapies are sure to be developed. These therapies will need to be tested in well-designed clinical trials.

A serious obstacle to conducting clinical trials with acute stroke patients is the difficulty of obtaining informed consent. Patients with acute stroke can present with dysphasia, dysarthria, a depressed level of consciousness, and/or confusion,8 making meaningful communication between the patient and the physician impossible. Additionally, it is not feasible to spend a significant amount of time contacting legally authorized representatives to obtain consent because a good outcome is dependent on intervention at the earliest possible point after stroke onset. An additional complication is that in several states, no person, family member or otherwise, may provide consent on behalf of a patient to participate in research unless that person is specifically given durable power of attorney for healthcare.9 It may often be the case, therefore, that the only realistic way to conduct the clinical trial of an acute stroke therapy is to enroll patients without their consent.

On October 2, 1996, the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS) published regulations governing the waiver of in-
formed consent for emergency research.10 These regulations set forth a narrow set of circumstances under which an institutional review board (IRB) can waive the consent requirement and specify a series of extra protections that must be in place when emergency research is performed without patient consent, including engaging in community consultation, disclosing the study design and results to the community, and establishing a Data and Safety Monitoring Board (DSMB).

The purpose of this article is to bring the current regulations to the attention of stroke researchers and to explore their application to the conduct of acute stroke research.

**Background on Adoption of New Regulations**

Before the issuance of the new FDA/DHHS guidelines, the legal regulations governing waiver of the consent requirement for emergency research were a source of great confusion and frustration to researchers and IRBs.11 Two incongruous sets of guidelines, one issued by the DHHS and one issued by the FDA, stipulated the conditions under which consent could be waived. Additionally, contained within each of these sets of guidelines were requirements that seemed to disqualify most types of clinical trials from receiving a waiver. Investigators and IRBs thus had to rely on creative interpretation of the guidelines to justify the legality of research performed without consent.12

DHHS regulations apply to all research conducted, funded, or regulated by any federal department or agency.13,14 Furthermore, most institutions that conduct federally funded research agree to adhere to DHHS regulations for all studies under a Multiple Project Assurance.14,15 The previous DHHS rules allowed the waiver of informed consent when (1) the research involved no more than minimal risk (with minimal risk defined as the probability of harm associated with daily life or a routine physical),16 (2) the waiver would not adversely affect the rights and welfare of the subjects, (3) the waiver was necessary to perform the research, and (4) the subjects would be provided with pertinent information after their participation.17

Requirements 2 through 4, although somewhat ambiguous, did not present any serious obstacles to researchers. The minimal risk standard, on the other hand, seemed to preclude investigation of all but the most trivial interventions. Recognizing how limiting the standard seemed on its face, commentators sought to provide interpretations of minimal risk that would be more consonant with emergency research. For example, Abramson et al18 argued that the regulations required a “minimal differential risk,” meaning a minimal difference between the risks associated with the standard therapy and the risks associated with the experimental therapy. Levine,19 using a different tack, argued that the minimal risk standard did not apply to research on therapeutic interventions but rather to research on the pathophysiology of an acute condition in the emergency setting. These reinterpretations aside, the minimal risk requirement created an obstacle for investigators.

The FDA regulations, which govern all research intended to support the application for FDA approval of a drug or device,14 dictated a different set of conditions under which the consent requirement may be waived. These were as follows: (1) the subject is confronted by a life-threatening situation necessitating the use of the test article, (2) informed consent cannot be obtained because of an inability to communicate with or obtain legally effective consent from the subject, (3) there is no time to obtain consent from the subject’s legally authorized representative, and (4) there is no approved treatment available that provides an equal or greater likelihood of saving the subject’s life.20

Commentators generally agreed that it was impossible to justify placebo-controlled trials under the FDA guidelines and that the guidelines applied more to a single, “compassionate” use of an experimental therapy than to clinical trials.14,19,21 Furthermore, it was argued that condition 4 is a requirement that studies of investigational therapies are, by definition, unable to meet as “the likelihood of an experimental treatment offering equal or better outcomes is unknown—if it is known to be superior, there is little reason to study it.”21

Given the complication of complying with the DHHS and FDA guidelines, many investigators sought to bypass these regulations by using “deferred consent.” This approach, first introduced in 1980 by Fost and Robertson,22 obtained wide acceptance in the emergency research community.19 In a deferred consent protocol, patients with life-threatening emergencies who were unable to give consent would be enrolled in a study and then, after a prescribed period of time, the patient, if conscious, or a legally authorized representative would be given the opportunity to consent. From 1980 to 1993, many DHHS-funded and FDA-regulated studies employed such a deferred consent mechanism.19

However, in 1993 an end was put to the practices investigators and IRBs had used to circumvent the narrow DHHS and FDA guidelines governing waived consent. The Office for Protection From Research Risks, which regulates DHHS-funded research, issued a report that stated that deferred consent was not legally equivalent to informed consent and thus did not satisfy DHHS guidelines.11,23 Furthermore, the report called for stricter interpretation of the minimal risk standard. Following the lead of the Office for Protection From Research Risks, the FDA also declared that deferred consent was not in keeping with its guidelines.11

After these announcements, it became clear that if researchers wanted to perform emergency research without patient consent, they would have to conform to the letter of the law of both the DHHS and FDA guidelines. Given the difficulties of doing this, it is little wonder that in the wake of these statements by the DHHS and FDA, emergency research virtually ceased.12

The new restrictive policies taken by the DHHS and FDA were, of course, a cause of great concern for the emergency research community. Much activism ensued, leading to consensus statements,24 conferences, articles, congressional hearings, and an FDA/National Institutes of Health public forum to discuss the issue.11 Widespread agreement was voiced that the DHHS and FDA guidelines needed to be amended to make them more permissive of emergency research.

Heeding this criticism, on September 21, 1995, the FDA proposed a new set of guidelines to govern the waiver of
informed consent for emergency research, acknowledging “growing concerns that current rules are making high quality acute care research activities difficult or impossible to carry out at a time when the need for such research is increasingly recognized.”25 Issued along with the proposal was an assurance that DHHS regulations would be amended to conform with the new guidelines, such that all federal policies would be harmonious. During the comment period that followed, the FDA received statements in support of the new guidelines from a number of medical associations, including the American Medical Association, National Stroke Association, American Heart Association, American College of Emergency Physicians, and others.10 The final FDA/DHHS rules were codified and released on October 2, 1996.

New Federal Regulations and Their Application to Stroke Research

For a study to be granted an exception from the informed consent requirement, an IRB (with the concurrence of a licensed physician unconnected with the IRB or the proposed study) must find and document that it meets all of the requirements summarized below.26

Requirement 1

Subjects must be in a life-threatening situation, and available treatments must be unproven or unsatisfactory.27 Hemorrhagic stroke is without question a life-threatening condition. Studies demonstrate 30-day case fatality rates of 41.6% to 82% for intracerebral hemorrhage and 46% to 50.1% for subarachnoid hemorrhage.28–30 While ischemic stroke is generally less lethal (30-day case fatality rates of 11.5% to 12%), it is often difficult to know in the acute setting whether a particular stroke may in fact be “life-threatening.” Additionally, strokes of all types may lead to disability that increases the risk for potentially fatal infections.

Furthermore, available treatments for stroke are clearly unsatisfactory. The principal treatments available for acute ischemic stroke, intravenous tPA and intra-arterial thrombolysis, show only moderate efficacy, have a short therapeutic window, and carry an increased risk of intracranial hemorrhage.3–5 Treatment options for hemorrhagic stroke are similarly lacking. Indeed, in the comments accompanying the publication of the Final Rules, the FDA explicitly stated that stroke was a condition intended to be covered under the new guidelines.10

Requirement 2

Obtaining informed consent is not possible because (a) the subject is not competent as a result of the medical condition, (b) there is no time to contact a legally authorized representative, and (c) there is no reasonable way to prospectively identify individuals who are likely to become eligible for the study.31

Many patients with stroke will be unable to give legally and ethically viable informed consent. Ethicists Beauchamp and Childress32 identify competence to understand and decide, and voluntariness in deciding, as preconditions to any act of informed consent. One commentator estimated the incidence of dysphasia in acute stroke to be 30% to 50%, with a similarly high rate of visuospatial difficulties.33 Such neurological deficits severely limit patients’ ability to comprehend a study and the potential risks and benefits involved, to reason regarding their participation, and to articulate their wishes. Although a substantial percentage of stroke patients will have more minor deficits and therefore, potentially, the capacity to consent, excluding dysphasic patients from a study could lead to biased results. Furthermore, the question exists as to whether consent in the setting of acute stroke can ever be truly voluntary because patients with stroke deficits are under stress, fearful, and likely to place a great deal of trust in their caregivers.34

There are currently no validated instruments for measuring the competence of acute stroke patients. Clinicians who are considering entering a patient into a trial without consent will therefore need to make a subjective assessment of a patient’s competence. It would be useful for clinicians to have a standardized instrument that would measure a patient’s capacity to consent to enrollment in a study. It is possible that such measures as the Hopkins Competency Assessment Test35 and the MacArthur Competence Assessment Tool Treatment,36 which have been used with psychiatric patients, may be useful in evaluating acute stroke patients, but this has yet to be established.

This requirement also indicates that informed consent may be waived only when the subject’s legally authorized representative is unavailable. However, exactly who qualifies as a “legally authorized representative” is not specified anywhere in the federal statutes. Investigators and IRBs are thus forced to look to state law for guidance on this point. However, the law in many states is either silent or unclear regarding who is authorized to make medical decisions on behalf of a patient who lacks capacity.9 For example, New York State Law dictates, “If the human subject be otherwise legally unable to render consent, such consent shall be subscribed to in writing by such other person as may be legally empowered to act on behalf of the human subject.”37 The only mechanism found in New York State Law for a person to be so empowered is to be specifically appointed by the patient in an advanced directive to act as a healthcare agent.38 However, the majority of stroke patients who arrive in the emergency department will not have undertaken this legal action. Ambiguity thus exists about how to identify a legally authorized representative. This is an area in which federal and state law need to provide more guidance.

Part c of this requirement insists that for a study to qualify under the guidelines, it must not be practical to prospectively identify persons likely to become eligible for the study. While the risk factors for stroke are well known, the time and expense that would be required to obtain prospective consent from all the individuals in a community who suffer from disorders such as hypertension, high serum cholesterol, and diabetes would be prohibitive.

Requirement 3

Participation in the research holds out the prospect of direct benefit to the subjects, as verified by animal studies and a risk-benefit analysis.39
What constitutes direct benefit to the subjects is a difficult question in stroke research. For example, is an intervention beneficial if it is able to save patients’ lives but leaves them with devastating neurological deficits? Or, to state the situation in reverse, what about an intervention that can potentially spare patients neurological damage but that comes with an increased risk of death (as may be the case with intravenous tPA)? These are clearly extremely difficult, existential questions. The fact that subjects may be enrolled in trials of new interventions without their consent makes these questions all the more vexing.

It is therefore imperative that investigators work to develop a concept of benefit that is consonant with the values of the community in which they are performing research. Under the new guidelines, investigators and IRBs must engage in consultations with representatives from the community from which the subjects are to be drawn (to be discussed below). These consultations may be an appropriate forum in which to discuss such issues. The challenge of developing a concept of benefit acceptable to the majority of individuals within a community will be a great one, particularly for researchers working in multicultural societies in which no single ethical framework is dominant. Indeed, there may be instances in which it is determined, in the course of community consultations, that it is impossible to reach a consensus about issues such as how to conduct a proposed trial or indications for the experimental therapy. In such circumstances, researchers and IRBs may be forced to conclude that a community is an inappropriate site for a particular trial.

This requirement also implies that the only research projects that may be conducted under these FDA/DHHS guidelines are clinical trials of potential therapies. The guidelines are not intended to permit research into the pathology of acute illnesses without patient consent. This was criticized by a commentator who argued that “such research provides the basis for subsequent therapeutic innovations.”

This requirement also insists that there be substantial evidence from preclinical testing that the proposed therapy may be effective. Such testing must be as rigorous as possible in light of the fact that subjects may receive the experimental therapy without having consented.

**Requirement 4**

The investigation could not be performed without the waiver.

The FDA/DHHS believes that it is preferable to perform research with consenting subjects. However, according to the FDA, a waiver of the consent requirement is indicated if restricting the study to subjects with the capacity to consent would bias the study or cause undue delay in the conduct of the study.

**Requirement 5**

The proposed investigational plan defines the length of the therapeutic window on the basis of scientific evidence. Within this window, the investigator must attempt to contact a legally authorized representative to ask for consent. This attempt must be documented.

Determining how much time to spend attempting to contact the legally authorized representative is a difficult question. The FDA defines the therapeutic window as “the time period, based on available scientific evidence, during which the administration of the test article might reasonably produce a demonstrable clinical effect.” But for many stroke interventions, particularly those that promote recanalization, the benefit of administration greatly diminishes over time. The stark fact of stroke pathophysiology is that “time is brain.” The longer the brain parenchyma is deprived of blood flow, the more damage it will incur. It is therefore probable that for many stroke treatments, earlier intervention will likely produce a better outcome. The FDA has recognized that this may be the case and has said that the entire therapeutic window need not be spent attempting to contact a legally authorized representative. It thus is permissible, and indeed advisable under some circumstances, to specify a very short period of time for attempting to contact a legally authorized representative.

**Requirement 6**

The IRB must approve procedures and informed consent documents to be used when consent from the subject or a legally authorized representative is feasible.

This requirement serves as a reminder that even if the study is being conducted under a waiver of the informed consent requirement, enrolling a subject without consent should only be done as a last resort, when it becomes clear that obtaining consent from the patient or a legally authorized representative will not be possible.

**Requirement 7**

There must be consultation with representatives from the communities in which the research is to be conducted and from which the subjects are to be drawn. Additionally, public disclosure must be made of the plans for the investigation, its risks, and likely benefits to communities in which the research is to be conducted and from which the subjects are to be drawn. This must be done before the initiation of the study.

In the absence of informed consent by subjects, community consultation and public disclosure processes form important elements in helping to prevent “real or imagined abuses by researchers.” For the community, consultation and disclosure create the opportunity to learn about the proposed investigation and to voice concerns. For researchers, they provide the chance to determine whether the community supports the investigation, an important factor in deciding whether it is ethical to proceed with the study. Despite their importance, the FDA/DHHS guidelines do not provide detailed instructions on what these processes are to entail. It is therefore instructive to review the detailed account of the efforts of one research team to comply with these mandates.

Santora et al describe the steps they took to satisfy the community consultation and public disclosure requirements as part of the approval process for the trial of a blood substitute for trauma patients with hemorrhagic shock. First, they reviewed their trauma registry to identify all patients from the past 3 years who would have qualified for their study. With this information they determined the communities from which the majority of their trauma patients originated. They then assembled a community council made up of...
key members of these communities that included clergy, police officers, a neighborhood council president, school principals, and a high school student. Having engaged in dialogue with this council, they then set up, with the aid of the council, a number of public meetings. The study and the meetings were extensively publicized within the communities through newspaper advertisements, radio public service announcements, and flyers distributed at local health clinics. At the public meetings, members of the research team made presentations about the study, which included the basis for the study, entry and exclusion criteria, risks and possible benefits, and the FDA/DHHS regulations governing exception for the informed consent requirement. They then answered questions. In the final phase, advertisements about the study were run in regional newspapers and on the radio, a talk radio program about the study was aired, and a 24-hour call-in hotline was established to elicit community feedback. These investigators’ efforts serve as a model of how the requirements for community consultation and public disclosure can be thoroughly and effectively satisfied.

**Requirement 8**

At the conclusion of the study, public disclosure of the study’s results and of the demographic characteristics of the subjects must be made to the community and other researchers.\(^{50}\)

Here again, newspaper advertisements, radio public service announcements, and community meetings may be appropriate methods by which to apprise the community. Furthermore, trial documents could be made available for public inspection. Transparency with regard to all aspects of study design, implementation, and results should be the central goal of all such efforts. Additionally, the results must also be brought to the attention of the research community, presumably through a publication or a presentation at a national meeting.

**Requirement 9**

An independent DSMB must be established to provide oversight of the study.\(^{51}\)

The DSMB is to be established by the sponsor of the investigation. It is to be composed of experts, including clinicians, biostatisticians, and bioethicists, who are unconnected with the project. It should review study data periodically and determine whether the study remains scientifically and ethically appropriate. This protection ensures that a trial will be halted if an intervention demonstrates a clear benefit or an unacceptable level of risk.

There is a report in the literature of this process functioning effectively. The aforementioned large clinical trial\(^{40}\) that compared the addition of aspirin cross-linked hemoglobin with standard of care for adults with traumatic hemorrhagic shock was stopped with only 112 of the 850 planned patients enrolled in the trial. The DSMB recommended suspension of the trial because of higher mortality in the group receiving the experimental treatment.\(^{52}\)

Recently, there has been a proliferation of commercial IRBs and DSMBs, some of which are only compensated on approving protocols. Although 21 Code of Federal Regulations (CFR) §50.24 does not explicitly state that such companies cannot be used for study approval and oversight, such organizations are generally poor protectors of patient safety.

**Requirement 10**

If the patient is unable to provide informed consent and a legally authorized representative is not available, the investigator must attempt to contact a family member and determine whether he or she objects to the subject’s participation. This effort must be summarized for IRB review.\(^{53}\)

The guidelines define family member to include a spouse, parents, children, brothers and sisters, spouses of brothers and sisters, and “an individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.”\(^{54}\) The guidelines do not, however, specify a hierarchy of familial authority or dictate what is to be done if family members have conflicting views about a subject’s participation or continuing participation in a study. Because family members often do not agree among themselves about a subject’s participation, the IRB should specify a precise hierarchy of familial authority that is to be adhered to in the conduct of the study.

**Requirement 11**

If the subject is enrolled without consent, there must be procedures in place to inform the subject, a legally authorized representative, or a family member of the subject’s inclusion in the clinical investigation. Additionally, the subject, a legally authorized representative, or a family member has the right to terminate the enrollment of the subject from the study at any time. If the subject dies, information about the subject’s participation in the study must be provided to a legally authorized representative or family member, if feasible.\(^{55}\)

This guideline echoes a recurrent theme of the regulations that, when at all possible, the subject, legally authorized representatives, and family members are to be given complete authority to decide about a subject’s participation in a research protocol.

**Requirement 12**

Investigators intending to conduct a study involving a waiver of the informed consent requirement must submit an Investigational New Drug application or Investigational Device Exemption to the FDA that specifies that the study may involve subjects who are unable to consent.\(^{56}\) The study may not proceed until the FDA grants written authorization.\(^{57}\)

This requirement ensures that the FDA reviews and authorizes all studies performed with a waiver of the informed consent requirement. It also reiterates the point that these guidelines only apply to research on therapeutic interventions. There is currently no mechanism in place in federal law that permits research on the pathophysiology of acute illness without consent.

**Conclusions**

The requirements of 21 CFR §50.24, although demanding, can be met by most trials of acute stroke therapies provided that investigators are willing to invest the time and money necessary to performing community consultation and public disclosure. However, investigators must also carefully con-
sider the ethical issues raised in performing research without patient consent.

Informed consent has long been considered a fundamental element in the ethical conduct of research with human subjects. Its significance has been noted in each of the major declarations and codes of medical ethics from the latter half of the 20th century, including the Nuremberg Code,58 the Declaration of Helsinki,39 and the Belmont Report.60 The new assertion of the FDA/DHHS guidelines that informed consent is not an absolute requirement for ethical research has therefore been a source of great concern for some.61 Informed consent, fundamentally rooted in the principle of autonomy or respect for persons, is intended to ensure that individuals are free to make decisions about their involvement in research that reflects their personal values and interests. However, if a patient is comatose, disoriented, or unable to communicate, it is impossible to know with certainty the patient’s wishes regarding participation in research. It is obviously not possible in such circumstances to defer to the patient’s autonomous choice. While one study suggests that it is the wish of the majority of patients to be included in trials of promising, life-saving interventions when standard therapies are unsatisfactory, even if the patients are to be enrolled without consent,62 it is impossible to predict what every individual’s desire might be in every given circumstance. IRBs and researchers will therefore have to engage in very careful ethical deliberations before deciding to proceed with a study that does not require the informed consent of all participants.

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