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*Learn and Live™***AHA-ASA Abstract of Proposed FDA Public Hearing: Conduct of Emergency Clinical Research Docket No: 2006D-0031**

The American Stroke Association (ASA), a division of the American Heart Association, has dedicated itself to reducing disability and death from stroke through research, education, community programs and advocacy. Central to these efforts is our commitment to promoting the interests of patients by ensuring that clinical research findings are translated into practice in an appropriate and timely manner. To this end, the ASA is committed to achieving a reduction in stroke and associated risk by 25 percent by 2010. Moreover, as the lead voluntary organization the AHA is viewed as the premier resource for science on stroke through our scientific conferences, journals, and the resources that the organizations makes available both to healthcare providers and the general public.

In support of this mission, the American Heart Association strongly supported the adoption in 1996 of the regulations permitting Waiver of Explicit Consent for Research in Emergency Circumstances. We are grateful to now have this opportunity to comment on the 2006 draft guidance regarding these regulations. We will direct our comments to particular aspects of the Guidance that address issues which have had a specific impact on clinical trials involving patients with acute stroke.

Note of General Concern

We are concerned that exemption from explicit consent regulations have been rarely employed in stroke trials conducted over the past 10 years. We believe it is not a coincidence that this past decade is also notable for the absence of approval of any new treatments for acute ischemic or hemorrhagic stroke. Acute stroke trials in the past ten years have enrolled only a fraction of the number of patients enrolled in acute myocardial infarction trials, and very few in the first 3 hours after onset, when treatments are most likely to exert a benefit. Strokes often render patients unable to provide explicit informed consent, making recruitment of patients affected by an acute stroke difficult. Substantial progress in acute stroke therapy is likely to occur only if waiver of explicit informed regulations are able to be more widely implemented.

Prospect of Direct Benefit

The AHA-ASA strongly supports the Guidance document's endorsement of morbidity endpoints, in addition to mortality endpoints, as appropriate outcome measures for select exception from explicit informed consent trials. Stroke can produce disabling outcomes that deprive individuals of their cognitive and physical capacities. A majority of Americans rate major stroke as an outcome that is equivalent to or worse than death.

Practicality

1. The guidance document mentions stroke patients who are comatose as an example of patients who cannot give consent. In both ischemic stroke and intracerebral hemorrhage, aphasia (an inability to communicate with language, either spoken or written) is a far more common than coma. We ask that aphasia be added to the document, expanding the salient phrases to “...(e.g., people with a stroke who are not comatose or aphasic with impaired comprehension)...” and “...(e.g. comatose patients and aphasic patients with impaired comprehension)...”

2. The AHA-ASA strongly supports the guidance document’s recognition of that subjects who are able to provide consent having better prospects for a full recovery constitutes one reason that it may not be reasonable to extrapolate results from the less ill population. This situation is common in stroke. Mildly affected patients are almost always able to provide consent, but are often uninformative when enrolled in clinical trials because they have a high frequency of good outcomes even when assigned to control therapy. Moderate and severely affected patients often cannot provide informed consent, yet they constitute the informative patients needed for clinical trials as they have the capacity to show a differential response and direct benefit from experimental therapy.

3. We request the guidance document clarify that for conditions that affect a large number of individuals, produce substantial morbidity and mortality, and have few treatments, a delay of six months in the development of a therapy would be considered undue and justify implementation of exception from informed consent. Ambiguity and uncertainty regarding how long a delay is undue has hampered use of Waiver in acute stroke trials. Stroke exerts a tremendous toll on the American populace. Of the three leading killers of Americans, heart disease, cancer, and stroke, stroke stands out as the condition for which acute therapies are utterly lacking. As TPA is given to only 1-4% (or less) of patients, and “cures” only 1 in 8 of these, 99.5% of acute stroke patients do not currently receive a curative therapy. New, effective therapies for acute stroke are desperately needed.

The American Heart Association’s 2006 Heart Disease and Stroke Statistics – 2006 Update states that each year about 700,000 Americans experience a new or recurrent stroke, and that stroke is an underlying or contributing cause of 273,000 US deaths each year. When more than 1900 Americans each day suffer a stroke, a strong case can be advanced that even one day’s delay in developing a therapy for stroke is “undue”. When 745 Americans die each day from a disease, a strong case can be advanced that even one day’s delay in developing a therapy for that disease is “undue”. It is against this tremendous daily burden of disability and death from stroke that the moral imperative to protect subjects with diminished autonomy must be balanced.

We believe that a 6 month delay threshold is an appropriate demarcation for excessive delay in developing acute stroke therapies. When failure to use Waiver of Explicit Consent will prolong evaluation of a promising stroke therapy by more than 6 months, Waiver of Explicit Consent should be permitted. During a delay of 7 months, more than 400,000 additional Americans will have a stroke and 159,000 Americans will suffer a stroke-related death. Clearly this tremendous burden of suffering and death would be unwarranted and undue.

Study Design

The AHA-ASA requests more explicit language in the guidance document recognizing that a variety of non-phase 3 trial types offer participants a prospect of direct benefit and would qualify for exception from explicit informed consent. We ask the document state that pilot trials of drugs and devices, feasibility trials of drugs and devices, phase 2 signal of potential efficacy drug trials, and FK506 pathway technical endpoint, device trials can, in individual cases, be judged to offer a Prospect of Direct Benefit, in addition to Phase 3 Trials. While definitive demonstration of benefit is not the primary aim of such trials, many are

designed so that patients assigned to active treatment receive an intervention hypothesized to confer a direct benefit. A pilot, feasibility trial of paramedic prehospital administration of drug therapy may be employing a dose of agent expected to be fully active and beneficial, working out the most efficient way to provide this agent in the field. Patients participating in such a trial have as great a prospect of direct benefit as patients participating in a phase 3 Trial. A phase 2b trial may be testing the 2 or 3 most promising dose regimens, each of which delivers drug at levels expected to be within a therapeutic range. Patients receiving active therapy in all arms of such a trial have a prospect of direct benefit. Indeed, since such trials often randomize more patients to active therapy at one of the dose tiers than to placebo, as opposed to the 1:1 randomization typical of phase 3 trials, these trials offer in some ways a greater prospect of direct benefit for the patient than phase 3 trials. A technical endpoint device trial that evaluates a device modification hypothesized to accomplish a technical endpoint (e.g. recanalization, collateral enhancement, hypothermia) more effectively than a predicate device already known from randomized trials to improve clinical outcomes offers as great a prospect of direct benefit as a phase 3 randomized controlled trial.

Contact of Family Members

1. The AHA-ASA supports the FDA's recommendation that the effect of delaying administration of the test article be taken into account when determining the portion of the therapeutic window to be devoted to seeking informed consent from a legally authorized representative or the opportunity to object from a family member. For most conditions in which effective therapy is time-limited, earlier treatment is much more efficacious than treatment late in the time window. In both acute ischemic stroke and acute myocardial infarction, recanalization therapies in the first hour after onset are much more effective than in the fourth or fifth hour. Some IRBs have considered requiring that trials wait until the very last minute of a theoretical time limit for therapy before enrolling patients under waiver of consent regulations. This is a recipe for study failure, ensuring that trials will have the least possible power to detect a promising agent's beneficial effects because patients are disproportionately enrolled only when little salvageable tissue remains.

2. An important consideration regarding the availability of legally authorized representatives (LARs) is variation in the definition of LAR in different jurisdiction. The guidance document and the exception from informed consent regulations are generally framed for circumstances in which close relatives can readily serve as LARs, making the need for waiver of explicit consent relatively uncommon. However, in several states, such as New York, the definition of a LAR is highly restrictive. In these jurisdictions, LARs are almost never available in emergency circumstances. This places extra burdens upon researchers, IRBs, and sponsors in conduct of emergency research and impairs patient access to innovative therapies in these jurisdictions. The AHA-ASA urges FDA to support a standard definition of LAR that could be adopted by jurisdictions throughout the country that would permit close family members to act as LARs, even in the absence of an advanced directive. This support would allow the exception from informed consent regulations to be implemented in the manner and situations that FDA generally intends, and allow more stroke trials to be conducted under conditions in which research subject rights are protected by family members who best know the potential participants' outlooks and wishes.