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on behalf of the American Stroke Association, a Division of the American Heart Association
FDA Public Comments on Conduct of Emergency Research – October 11, 2006

I am speaking today on behalf of the American Heart Association (AHA), its division the American Stroke Association (ASA), and over 22.5 million AHA and ASA volunteers and supporters. The mission of the American Stroke Association (ASA) is to reduce disability and death from stroke through research, education, community programs and advocacy. We greatly appreciate this opportunity to comment on the draft Guidance regarding conduct of emergency clinical research.

My experience in acute stroke trials may be helpful to the panel's deliberations. I have been a participant in and leader of over 30 acute stroke treatment clinical trials, supported by the National Institutes of Health and by industry, including the MERCI and FAST-MAG stroke trials that employed or plan to employ waiver of explicit consent in emergency circumstances. I am currently Professor of Neurology at UCLA where I serve as Director of the UCLA Stroke Center.

Note of General Concern

Let me begin by noting that the American Stroke Association would like to express its concern that, as far as we aware, exemption from explicit consent regulations have never been employed in any trial of drug treatment for acute stroke 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 drug treatments for acute ischemic or hemorrhagic stroke. Acute stroke trials during these 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

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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 will occur only if waiver of explicit informed consent regulations are able to be more widely implemented. I will address six specific aspects of the draft Guidance document today.

Prospect of Direct Benefit – Morbidity Endpoints

First, the American Stroke Association 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 frequently produces nonfatal, but disabling, outcomes that deprive individuals of their cognitive and physical capacities. The fact that a majority of Americans rate major stroke as an outcome that is equivalent to or worse than death indicates the importance of permitting morbidity endpoints in exception from explicit informed consent trials.

Practicality – Aphasia as an Example

Secondly, the Guidance document mentions stroke patients who are comatose as an example of patients who cannot give consent. In both acute ischemic stroke and intracerebral hemorrhage, aphasia (an inability to communicate with language) is a far more common cause of noncompetency than coma. We ask that aphasia be added to the example in the document, expanding the relevant phrases from "comatose patients" to "comatose patients and aphasic patients with impaired comprehension".

Mildly Affected Patients May Be Uninformative

Thirdly, use of waiver of explicit consent mechanisms in stroke trials has been hampered by uncertainty among IRB panels regarding what factors can be considered when determining if a trial is impractical to complete using explicit informed consent procedures alone. The

American Stroke Association strongly supports the Guidance document's recognition as a salient consideration the fact that mildly affected patients who disproportionately can provide explicit consent may have much higher full recovery rates than more severely affected individuals. 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 benefit from experimental therapy.

Delay of Greater than Six Months is "Undue" for Developing New Stroke Treatments

Fourthly, we request the Guidance document clarify an additional aspect of the process of determining whether or not a study is impractical to complete using explicit consent procedures alone – how long a delay in trial completion for conditions like stroke is sufficiently "undue" that the trial is impractical. We urge FDA to make clear that, for conditions like stroke that affect a large number of individuals, produce substantial morbidity and mortality, and have few currently available treatments, a delay of six months or more in the development of a new therapy should be considered undue and justify implementation of exception from informed consent. Stroke exerts a tremendous toll on the American populace. The only proven acutely beneficial treatment, the clot-busting drug TPA, is given to only 1-4% (or less) of patients, and "cures" only 1 in 8 of these, with the result that 99.5% of acute stroke patients do not currently receive a curative therapy. New, effective therapies for acute stroke are desperately needed.

Each year about 700,000 Americans experience a new or recurrent stroke, and stroke is an contributing cause to 273,000 US deaths each year. When more than 1900 Americans each day suffer a stroke and 745 Americans each day die from stroke, a strong case can be advanced

that even one day's delay in developing a therapy for stroke 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. The American Stroke Association believes that a 6 mo 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 mos, Waiver of Explicit Consent should be permitted.

Study Designs that Offer Prospect of Direct Benefit

Fifthly, the American Stroke Association also 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 prehospital feasibility trials of drugs and devices, phase 2 signal of potential efficacy drug trials, and 510K pathway technical endpoint device trials can, in individual cases, be judged to offer a Prospect of Direct Benefit, in addition to conventional Phase 3 Trials. While definitive demonstration of benefit is not the primary overall aim of such trials, many are designed so that patients assigned to active treatment receive an intervention hypothesized to confer a direct benefit. A late phase 2 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 in all active therapy arms of such a trial have a prospect of direct benefit. Indeed, since such trials often randomize more patients to active therapy than to placebo, as opposed to the 1:1 randomization typical of phase 3 trials, such late phase 2 trials offer in some ways a greater prospect of direct benefit for the patient than phase 3 trials. Similarly, a technical endpoint device trial that evaluates a device modification intended to accomplish a technical endpoint (such as recanalization) 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 Attempts Should Not Exhaust Therapeutic Time Window

Lastly, the American Stroke Association supports the FDA's recommendation that the effect of delaying administration of a 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, including ischemic stroke, earlier treatment is more more efficacious than later within the treatment time window. 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 approach greatly increases the likelihood of study failure, as patients are disproportionately enrolled only when little salvageable tissue remains.

In conclusion, let me emphasize three key suggestions. We ask the FDA to clarify that for a common, devastating and poorly treatable condition like stroke, a delay of six months or more in trial completion is undue and should be sufficient to permit use of waiver of consent enrollment procedures; to make clear that select technical efficacy device and late phase 2 drug trials should be recognized as offering patient participants the prospect of direct benefit; and to maintain the current guidance document's recognition that avoiding disproportionate enrollment of mild patients unlikely to demonstrate a beneficial effect of treatment is an appropriate reason for approval of exception from explicit consent procedures.

Thank you for allowing the American Heart – American Stroke Association to discuss the draft Guidance on Consent in Emergency Research at this public meeting.