Acute stroke trials without informed consent
Toward an evidence-based ethical practice

Progress in treatment requires progress in experiment, and the treatment of acute stroke, along with many other neurologic diseases, needs more human experiments in the form of clinical trials. However, the acuity of the disease, the need for rapid intervention, and the decisional impairments in some patients present a challenge to obtaining informed consent for such trials. In addition, requiring written informed consent may select for patients who either are not able to provide it or who lack a surrogate who can do so for them. Most jurisdictions have mechanisms to allow, under certain circumstances, some types of clinical research without written informed consent. Some acute stroke trials are conducted with such waivers.

In this issue of Neurology®, Feldman et al.¹ report the results of their study of how the requirement for written informed consent affects recruitment into acute stroke trials. Their outcome measure was the number of participants enrolled per month. Their hypothesis was that trials whose informed consent methods waived the practice of written informed consent (by allowing verbal or no prospective informed consent) would have a higher recruitment rate than studies that required usual written informed consent.

Using well-accepted methods, the authors conducted a systematic review of the literature that identified 36 acute stroke trials. Thirty-five of the 36 studies were able to provide data. Of these 35 studies, most—26—required written informed consent prior to patient randomization from either a surrogate or the patient-participant. In contrast, only 9 trials did not require written informed consent from either the patient or a surrogate. Among these 9, 2 trials had designs that precluded prerandomization consent of any kind, 1 used verbal consent, and 6 did not require prospective consent. Thus, the most common informed consent practice for acute stroke trials remains written informed consent, with the option of surrogate consent.

They found that trials that waived written informed consent (whether from the patient or surrogate) had a higher recruitment rate than did the trials that required it, but this difference did not remain after 2 outlier trials were removed. The outliers—The Pre-Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke Patients Study (PHANTOM-S)² and Hyper Acute Stroke Alarm Study (HASTA)³—were trials that tested system-level interventions such as the priority or the type of ambulance/mobile unit dispatched to care for the patient.

In our view, the exclusion of the 2 outlier studies is appropriate because they were different from the other studies in a normatively salient way: consent of any kind was not possible in those 2 studies. Thus, these studies were not relevant for evaluating the question asked by Feldman et al., namely, comparison of 2 consent practices. Such a comparison makes sense only among studies that could have employed some form of informed consent. (It is also worth noting that although the studies were divided in terms of the requirement for written informed consent—thus grouping one study with verbal consent with those with no prospective consent—verbal consent is more similar to written consent than no consent at all.)

What factors predict recruitment rate? More trial centers and countries, and the exclusion of persons too ill based on scores on the modified Rankin Scale independently were associated with greater recruitment rates. Notably, location (prehospital vs hospital) of the intervention was not a predictor when the 2 atypical studies were excluded.

This study provides evidence that there is no gain in recruitment in exchange for allowing recruitment of persons without prospective written consent. This fact, along with no difference in ability to reject the null hypothesis and no difference in primary publication impact factors, suggests that in fact there is no overall scientific gain to justify the enrollment of persons without prospective written consent.

This study also demonstrates that further research would yield important data to illuminate the practice and policy in this area, and that it would not require too much more effort. Recruitment rate is just one...
lens through which to view the effect of informed consent requirements. Others include refusal rates, the proportion of persons unable to consent, how frequently surrogate consent is used, and, if it is, who are the surrogates. Only half of the studies gathered these data, and even among those that did, the authors discovered both missing data and site-to-site variability in how these data were recorded.

In addition, in studies that used deferred consent or waived consent altogether, it is crucial to gather follow-up information on the participants’ and families’ attitudes toward the practice of deferred or waived consent. How many in fact give deferred consent? Why do some refuse? Data are also needed from those who did provide prospective consent. Given the time-sensitive and emotionally taxing context of obtaining consent, do such persons understand the core facts about the research study? Did they feel they were free to say no? Would they have preferred a more abbreviated consent that provides an overall gist of the trial with an option to opt out? The NIH has invested in StrokeNet, a network of 25 regional centers that unites over 200 hospitals to conduct clinical trials, and this taxpayer-funded network could routinely collect these and other data that describe patient and surrogate preferences for research participation.

Due to the current debates surrounding the informed consent requirements for pragmatic comparative effectiveness of clinical trials, the practice of altering or waiving traditional informed consent is a subject of much debate. The value of the Feldman et al. study thus goes well beyond the acute stroke trial context. It reminds us that ethical questions in the conduct of research need to be answered not just with normative arguments but arguments informed by data.

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**REFERENCES**