Network for Clinical Stroke Trials (NeCST) for the Next Stroke Researchers in Japan

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Stroke imposes a severe burden in Asia. In Japan, stroke is the leading cause of disability requiring intensive nursing care and the fourth leading cause of death. Because the baby boomers born in the later 1940s have reached ages at which they have become susceptible to stroke, the burden is expected to increase further. Thus, research on stroke is being actively conducted in Japan. However, few Japanese researchers have been authors of multinational stroke papers.

Why NeCST?
The National Institutes of Health (NIH)–funded United States–Japan collaborative research on stroke circumstances conducted in 1962 by Prof Baker (University of Minnesota) and Prof Katsuki (Kyushu University) was likely the first multinational collaboration on stroke research in Japan. That research triggered the initiation of the Hisayama study, a well-known, population-based, prospective, cohort study. Thereafter, Japanese researchers participated in some investigator-initiated trials, including the NIH-funded international EC/IC (Extracranial–Intracranial Artery) Bypass Study. However, even in recent years, few Japanese investigators have been contributing to international investigator-initiated trials.

Several potential factors may be involved in the infrequent multicenter and multinational collaboration of Japanese investigators. As has been previously reported, repeatedly assembling the necessary personnel and infrastructure each time trials begin and their disassembly each time trials end has made for an inefficient environment for conducting trials. Furthermore, there are overwhelming shortages of study coordinators and research nurses for staff education, administration of test drugs, data management, adverse event collection, biostatistics, and other necessary tasks. Instead, Japanese physicians and nurses, who are already busy with daily clinical practice, are required to take on additional responsibilities related to clinical trials. In addition, some Japanese researchers are satisfied with participating in domestic, rather than international, consensus building; for example, some promising intravenous drugs for acute ischemic stroke, such as edaravone and argatroban, were only proven to be effective in domestic trials, and international approval was not sought. The official lower dosages for some antithrombotic and thrombolytic drugs, partly because of concerns about the high incidence of intracerebral hemorrhage in the Japanese population, are a barrier to the participation of Japanese institutes in multinational trials using globally approved dosages of drugs. Japanese researchers finally gave up their attempts to be involved in the Interventional Management of Stroke (IMS) III and Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trials because Japan’s unique official dosage of alteplase (0.6 mg/kg) was not allowed in these trials. The traditional Japanese avoidance of self-assertion may be another barrier for multinational collaboration.

The recently formed NIH StrokeNet (https://www.nih-strokenet.org/), a network of 25 regional centers across the United States that serve as the infrastructure and pipeline for NIH-funded clinical stroke studies, motivated us to overcome the barriers of multinational collaboration. The NIH StrokeNet streamlines stroke research by centralizing approval and review, lessening the time and costs of clinical trials, and assembling a comprehensive data sharing system. In Japan, a brand-new Japan Agency for Medical Research and Development (AMED) (http://www.amed.go.jp/en/), functioning as a control tower for establishing a domestic medical research environment, and our National Cerebral and Cardiovascular Center (NCVC) can establish a similar cooperative system with the NIH and core institutes of the NIH StrokeNet. The framework of the Network for Clinical Stroke Trials (NeCST) was thus first outlined in 2014.

What Is NeCST?
Our current design of the NeCST is shown. The NCVC functions as a national coordinating center and has been rapidly building the necessary infrastructure, mainly through the use of internal funding. We additionally obtained a short-term competitive grant from the AMED to strengthen the infrastructure. Several sections in the NCVC provide core functions, such as a central coordination office, data management center, and central pharmacy. A few advanced and established institutes, including Iwate Medical University (Division of Ultrahigh Field MRI, Institute for Biomedical Sciences), form central imaging laboratories. New electronic randomization and data capture systems and an imaging transfer system are prioritized tools for this fiscal year. We are also cooperating with the Japan Stroke Society in
establishing the multicenter network. We have been recruiting participating stroke institutes from among the collaborators in our recent multicenter projects, including the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) studies,7 the Thrombolysis for Acute Wake-up and Unclear-Onset Strokes With Alteplase at 0.6 mg/kg (THAWS) Trial,4 and the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-II trial.9 We assist the participating institutes in improving their human resources for trial support, strengthening the functions of their ethics committees, and joining a new nationwide registry for acute stroke patients that has evolved from the Japan Standard Stroke Registry.10

At the same time, we have actively promoted the NeCST at the NIH StrokeNet investigators’ meetings and at the meeting for the multinational trial network. The next periodic United States–Japan stroke researcher meeting will be held in Tokyo in June 2016, where collaborative trials from the NIH StrokeNet and NeCST participants will be chosen. The recent ATACH-II was a good touchstone, showing that investigator-oriented trials involving the United States and Asian countries (Japan, China, Taiwan, and Korea) were realizable, though it exposed some conflicts caused by differences in medical systems (mainly insurance systems) and ethical regulations among nations. Separate investigator-oriented trials involving the United States (NIH-funded) and Japan (AMED-funded) using essentially identical protocols, with the results combined as a meta-analysis, could resolve such insurance and ethical conflicts and make investigator-oriented multinational trials more practical.

Solidarity of Asian multinational researcher networks may still be necessary for some Asian-specific cerebrovascular disorders, including intracranial atherosclerosis and intracerebral hemorrhage.1 Since 2006, our colleagues in neighboring Korea have been managing the Clinical Research Center for Stroke project, a systematic and highly productive nationwide registry system and trial network.11 We plan to discuss Asian and global partnerships for each national network system at the 13th International Symposium on Thrombolysis, Thrombectomy, and Acute Stroke Therapy in Kobe (TTST 2016 Kobe) to be held in October 2016 (http://www2.convention.co.jp/tts2016/).

The NeCST will be a key part of the scientific and economic success of investigator-oriented trials for next-generation stroke researchers, as the acronym itself indicates. Just 3 years ago, the stroke trial network was described as an experiment;10 however, it has already proven itself as practical and indispensable for facilitating stroke research.

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None.

References

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