

# Developing and Implementing Future Stroke Therapies: The Potential of Telemedicine

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Stroke is a major public health concern with few positive phase III clinical trials and a shortage of stroke care expertise. Drug development likely can be enhanced by adapting new outcome measures and following guidelines generated by consensus groups. To enhance rates of drug implementation and to improve stroke care, some states are requiring that acute care hospitals obtain primary stroke center certification, and this mandate necessitates that smaller hospitals join larger ones in stroke care networks. Cutting-edge technology in the form of telemedicine is being implemented in stroke care networks to combat the lack of stroke care expertise by extending the availability of physician stroke expertise. The telemedicine network can be used to transmit real-time data from stroke care-certified community hospitals (spokes) to a tertiary center (hub). Telemedicine can be used to educate physicians in spoke hospitals about new stroke treatments. The advent and development of telemedicine has the potential to ensure that patients with stroke have a greater opportunity to receive the full range of therapeutic options currently available and those that will become available in the future. The implementation of future drug therapies through telemedicine-organized stroke networks will likely substantially influence the future of acute stroke therapy.

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Stroke is the third leading cause of death in the United States and is a major cause of disability.<sup>1,2</sup> By 1999, there were a total of 178 controlled clinical trials, which investigated 75 different treatments for acute ischemic stroke, only 1 of which was approved.<sup>3</sup> Recombinant tissue plasminogen activator (rt-PA; given within 3 hours of onset) is the only currently approved drug to treat stroke.<sup>4</sup> This narrow therapeutic window presents a serious treatment limitation because many patients have a delayed time-to-hospital presentation.<sup>5</sup> In addition, patients often are not treated with rt-PA due to exclusion criteria and difficulties in implementation.<sup>6</sup> Given the personal and societal consequences of stroke, as well as the aging of the US population that will increase its prevalence, new strategies to improve drug development and the implementation of existing and new therapies are essential to meet the growing needs of patients with stroke.

## Strategies to Improve Drug Development

Groups composed of physicians and researchers were organized to discuss and suggest recommendations regarding standards of preclinical and clinical trial development and conduct in an attempt to increase the success of novel therapeutics for stroke. The Stroke

Therapy Academic Industry Roundtable (STAIR) forum published guidelines to improve future experimental and clinical trials, as did the International Trial Subcommittee of the International Stroke Liaison Committee of the American Stroke Association.<sup>7–11</sup> In brief, the groups suggested that to improve development of novel therapeutics for acute stroke, clinical trials must incorporate new trial designs, innovative technologies, and appropriate outcome measures; expand trial populations to account for changes in the profile of those primarily affected by stroke; have an appropriate Steering Committee; and encourage a good working relationship between the sponsor and the investigators.<sup>9–11</sup>

Aside from the expert committee guidelines, other recommendations also appeared. These recommendations were targeted to increase the success rate of future trials. One proposal was to use a prognosis-based entry criterion. Only patients with a better chance of a favorable outcome, as determined by a simple prognostic model that accounts for baseline variation such as age and stroke severity, should be included in a clinical trial using this approach.<sup>12</sup> Statistical inadequacies have been a problem in prior stroke studies.<sup>13–15</sup> Trials should be powered properly, have appropriate sample

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size calculations, and be analyzed using an appropriate ordinal statistical test to improve statistical power.<sup>13-15</sup> Finally, it would be beneficial if what constitutes a minimum clinically important difference is agreed on.<sup>15</sup>

How to measure treatment effects in acute stroke therapy trials has been contentious. In past trials, a responder analysis was used by looking for little or no residual abnormality in activities of daily living on the Barthel Index, functional abnormality on the modified Rankin Scale (mRS), or neurological deficit on the National Institutes of Health Stroke Scale.<sup>3,4</sup> Looking for “cures” with these various outcome measures may not be the most effective way to assess treatment effects. Recently, it was proposed that looking for more subtle treatment effects by evaluating an improvement of one or more points on the mRS may be a more appropriate measure in acute ischemic stroke.<sup>16</sup> The benefit of rt-PA therapy in the 3-hour window was more apparent using this approach than with the responder analysis used to evaluate the National Institute of Neurological Disorders and Stroke rt-PA trial. A shift from 4 to 3 on the mRS is likely to have substantial impact on patient outcome because patients achieving a score of 3 can walk without assistance, whereas those achieving a score of 4 cannot, suggesting a much greater chance that these patients eventually will be in a nursing home.<sup>17</sup> Being at home after a stroke, as opposed to in a nursing home, has a different impact on patients, their families, and the subsequent cost of care. Similarly, a shift from 3 to 2 on the mRS is also meaningful because patients with a score of 3 have moderate deficits, whereas those with a score of 2 have only a

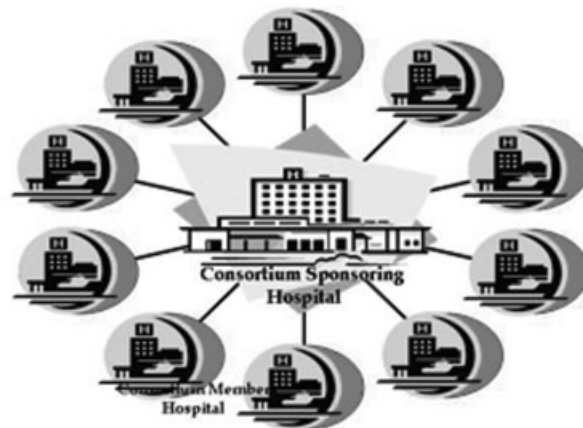
mild deficit in function. Looking for a more subtle but meaningful treatment effect as opposed to a “cure” is also more appropriate in view of how both thrombolytic and neuroprotective acute stroke therapies apparently impart their benefits. Both approaches ultimately are designed to reduce infarct size, and this should translate into improved outcome.<sup>18</sup> The reduction of mean infarct size by a relatively modest volume is unlikely to be manifested as a cure clinically, but rather as a more subtle effect that can probably be captured more effectively by looking at outcomes such as a favorable shift of one or more points on the mRS.

### Telemedicine-Directed Stroke Care

A hub and spoke model of telemedicine-directed stroke care currently is being developed and can be used to enhance the delivery of the one currently approved acute stroke therapy, rt-PA, within 3 hours of onset, as well as new treatments that are approved in the future. In this model, hospitals that do not have onsite stroke expertise (the spokes) are provided access to stroke centers (the hub) in real time (Fig). Three different methods for audiovisual interaction have been described: telephone assistance, videoconferencing with an on-call stroke team using an Internet-based or high-speed, secure, dedicated, landline system; and a combination of telephone and video methods. In the telephone-assisted method, community hospitals are provided with the hub’s emergency department stroke evaluation and order forms.<sup>19</sup> After the patient’s arrival, an emergency department physician at the spoke hospital calls the hub stroke team, who help to evaluate the patient via telephone support. In accordance with American

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## TeleStroke Hub and Spoke Model



*Fig. Telemedicine hub and spoke model.*

Stroke Association guidelines, the hub's attending physician provides counsel on the decision to potentially use rt-PA and gives other recommendations for patient management.<sup>19</sup> In the videoconferencing method, the hub hospital stroke team is called or paged when the patient presents to the spoke hospital and rapidly accesses a computer workstation or laptop computer.<sup>20</sup> Videoconferencing is established, which allows the patient, the patient's family, and the spoke and hub physicians to interact visually and audibly. Computed tomography or magnetic resonance imaging scans can be transmitted to the hub stroke center for joint viewing by the spoke's emergency department physician and the hub's stroke neurologist. With the combined approach, a telephone link between the spoke and hub centers is established initially and the patient is discussed.<sup>21</sup> For patients who are likely to be rt-PA candidates, appropriate laboratory and imaging studies are initiated rapidly, and then the videoconferencing link is established. Different telemedicine networks have taken varying approaches toward implementation, and it remains unclear whether videoconferencing is indeed superior to a strictly telephone interaction. Although without a video system, the imaging studies obtained at the spoke hospital cannot be viewed rapidly by stroke experts or radiologists to help guide a timely decision about rt-PA initiation.

A basic difference in videoconferencing systems is the use of an onsite workstation at the hub site requiring hub personnel to be constantly available onsite or a wireless system that allows the evaluating hub expert to remotely access the telemedicine system on a laptop computer.<sup>21,22</sup> Both approaches have advantages and disadvantages as outlined in the Table, together with

the merits of telephone interaction versus video conferencing. One disadvantage to video conferencing compared with a solely telephone interaction is the inherent delay in activating the system and completing the consultation. This delay can be shortened with the use of wireless Internet access to the telemedicine system by hub experts that should allow for at-home calls, avoiding onsite calls or delays in reaching the hub workstation. In one study with a hub-based workstation, the mean door to needle time was 104 minutes, and the mean onset to needle time was 135 minutes.<sup>23</sup> Whereas in another study with a hub-based workstation, the mean door to needle time was 106 minutes.<sup>20</sup> Despite these slow treatment times, telemedicine networks have enabled more patients to receive treatment with rt-PA within the 3-hour window than would have occurred without the telemedicine network.<sup>19-21</sup> In one network that linked rural hospitals to an academic center by videoconferencing, 12 patients were treated with rt-PA over a 13-month period who would not have been treated before development of the network.<sup>23</sup> Another concern is the reliability of remotely performed neurological assessments. Studies have evaluated the reliability of remote administration of the National Institutes of Health Stroke Scale and have determined that the telemedicine assessment was able to detect deficits as reliably as a neurologist performing the assessment at the patient's bedside.<sup>22,24,25</sup> It appears that overall risk for intracerebral bleeding with rt-PA use directed by remote telephone or videoconferencing is not increased compared with the risk observed in the initial rt-PA trial or in subsequent clinical use.<sup>3,26</sup> In one study, the rate of symptomatic hemorrhage was 11%, but this increased rate of symptomatic

Table. Advantages and Disadvantages of Several Reported Stroke Telemedicine Systems

Telemedicine System	Comment
Telephone network developed by Barrow Neurological Institute (Phoenix, AZ) <sup>19</sup>	Patients given infusion at outside emergency department and continued during duration of flight to hospital (average time, 30 minutes); 72% more patients treated with rt-PA when it was administered with phone support (n = 53), low hemorrhage rate
Remote Evaluation of Acute Ischemic Stroke (REACH): electronic and phone system <sup>23</sup>	Allows for timely rt-PA administration to qualified patients in small rural hospitals and rapid transfer to a stroke care center; dedicated ISDN lines allow for quicker and more consistent service but may not allow for MD response via their home computers; it is better to use the Internet
STRoke DOC Wireless/Site Independent Telemedicine System: interactive video using broad band technology <sup>22</sup>	No technical failures, Internet access with a laptop computer, excellent agreement for 67% of NIHSS items and 82% of modified NIHSS items
TeleStroke: videoconferencing system <sup>20</sup>	Six patients at a small island hospital with ischemic stroke received rt-PA after video consult; in the 2 years before the use of TeleStroke, no patients with ischemic stroke received rt-PA
Telemedic Pilot Project for Integrative Stroke Care (TEMPiS) in Bavaria: initial telephone contact, and then videoconferencing system activated <sup>21</sup>	Greater number of patients receiving systemic thrombolysis after system was implemented, but symptomatic hemorrhage rate was 11%

rt-PA = recombinant tissue plasminogen activator; ISDN = integrated services digital network; NIHSS = National Institutes of Health Stroke Scale.

hemorrhage has not been observed in the other reported telemedicine case series.<sup>19,21,23</sup> The number of patients reported so far who have been treated with rt-PA via remote interaction has been small, thus the risk for associated hemorrhage needs to be assessed in much larger patient numbers to assure that the safety is truly comparable with onsite assessment and implementation.<sup>26</sup>

### **New Strategies to Enhance Acute Stroke Care**

A recent development that will likely have a great impact on both the drug development processes for acute ischemic stroke therapies and their implementation is the requirement in some states for primary stroke center certification. Massachusetts initiated this process in 2004 through a mandate by the Department of Public Health (DPH), and several other states are now implementing similar mandates. The Massachusetts DPH mandate for stroke requires that acute care hospitals be certified as primary stroke centers to maintain their capability to admit such patients. To qualify for state DPH certification, hospitals must have the ability to provide treatment with intravenous (IV) rt-PA 24 hours a day, 7 days a week and to provide around-the-clock brain imaging necessary to implement this therapy. A written emergency department and in-hospital stroke care plan must be implemented, and appropriately trained medical and allied health personnel must be available at all times. Continuing professional and lay public educational programs must be provided, and there must be in place a centralized data collection instrument used to monitor patient characteristics and to assess individual hospital compliance with recommended guidelines for patient care. Onsite evaluations of the hospitals' ability to meet these requirements were performed during the latter part of 2004, and currently more than 70% of acute care hospitals in Massachusetts have received preliminary approval by the DPH as primary stroke centers. It is anticipated that soon it will be mandated that patients with stroke be admitted only to hospitals with such a designation.

The Massachusetts DPH primary stroke center designation process has several important implications. The approval process was relatively straightforward for large tertiary care hospitals because most of them already had many, if not all, of the required elements in place before the DPH stroke center mandate. Meeting the DPH mandate for these larger hospitals did require substantial effort but was readily achievable. For many of the smaller hospitals in the state, meeting all of the DPH requirements was difficult or not possible without outside help. Some hospitals could not guarantee that IV rt-PA could be administered all of the time because around-the-clock neurology coverage was not available, and many emergency room physicians were not comfortable with rt-PA usage in patients with

stroke without a neurologist's input. In addition, written care protocols and personnel training mechanisms were unavailable, requiring substantial efforts to provide them. Personnel to provide ongoing professional and lay education were also not available locally in many of the hospitals interested in becoming stroke centers. One obvious solution to these problems was the implementation of stroke care networks, so that expertise and material available at the large, tertiary care centers could be used at the local hospitals to meet the DPH requirements, allowing these hospitals to achieve a primary stroke center designation. The hub hospital can also benefit from participation in the network by enhancing its referral base and receiving more patients with complex cerebrovascular problems, as well as establishing closer ties with spoke hospitals that could lead to additional referrals with other complex disorders.

The organization of stroke care networks in Massachusetts has revolved around two main processes. First, the tertiary care centers agreed to share protocols for patient care and support ongoing educational efforts with the smaller hospitals so that these hospitals could adapt and use these protocols for local needs. In addition, personnel from the tertiary care centers will provide ongoing educational efforts to the local hospitals, either by onsite activities or remotely via advanced communication networks. Second, telemedicine consultative availability was organized to allow local hospitals access to specialized stroke neurology expertise whenever the need arises. Such telemedicine stroke consultations allow the local hospitals to offer IV rt-PA therapy at all times and to provide expert guidance and input to local emergency department physicians who will initiate the thrombolytic therapy in their emergency departments. Reimbursement for the spoke and hub hospitals, as well as physicians providing telemedicine services, remains a contentious issue that will need to be resolved if the obvious potential benefits to stroke patients and health care delivery systems are to be fully realized.

Having IV rt-PA at local hospitals is key, because it is abundantly clear that initiating treatment earlier in the currently approved 3-hour treatment window is associated with a higher probability for a better outcome.<sup>27</sup> Not only is local or onsite availability of IV rt-PA therapy required for DPH stroke center certification, but rapid initiation, with the help of telemedicine stroke consultations, will likely increase the percentage of patients with stroke treated earlier in the 3-hour treatment window, when it is the most effective. Not having the service available locally or onsite and requiring the transport of patients to centers equipped to provide IV rt-PA treatment would preclude many patients from potentially receiving the only currently approved acute ischemic stroke therapy, be-

cause they would not arrive in time for the treatment to be started within 3 hours of stroke onset. Nonetheless, some clinicians believe that patients should be immediately transferred to a tertiary stroke center rather than having rt-PA administered at a community or spoke hospital because of the risk for complications associated with rt-PA use, such as bleeding.<sup>3,28</sup> Another model for providing IV rt-PA therapy at smaller hospitals is to send the stroke expert into the community, as has been done in Cincinnati. This approach is not practical for most stroke care networks because of the demands on the stroke experts, and the distances in many locations would preclude the timely initiation of therapy.

The telemedicine network system could be of great value to the development and implementation of new acute stroke therapies. It can be envisioned that the hub and spoke hospitals in the network could function as an expanded unit for the identification of appropriate patients to enroll in future acute stroke therapy trials. With a therapy using relatively simple dosing that is being assessed in a trial, such as a neuroprotective drug to be administered IV, affiliated hospitals and local onsite subinvestigators could be included as enrollment sites under the guidance of the hub hospital. Potential patients for the trial could be identified locally, and then a telemedicine consultation with a stroke expert at the hub hospital should be obtained to verify that the patient can be randomized into the trial. Of course, local pharmacies and other support services will be needed onsite at the local hospital, and this will add to the complexity of trial organization. Alternatively, for more complex therapies such as intraarterial delivery of drugs or the evaluation of devices requiring special expertise for their use, patients identified locally at spoke hospitals and vetted by the hub experts can be transported to the hub hospital for inclusion in the trial. Both approaches that use the telemedicine stroke networks should expand the pool of patients available for acute stroke therapy trials and presumably enhance and shorten the time to complete the study.

The telemedicine network approach to stroke care will also likely have a substantial impact on the dissemination of future approved acute stroke therapies. The organized telemedicine network of hub and spoke hospitals will provide a readily available mechanism to make physicians aware of newly approved acute stroke treatments. Presumably, the initial focus for introducing new therapies primarily will be to educate personnel at the hub hospitals and to allow them to determine how best to use the therapies. The hub physicians can then update their colleagues at the spoke hospitals in their network by telemedicine conferences, supplemented with live educational meetings. The hub and spoke hospital physicians and administrators can also coordinate efforts to determine how to most effectively

and efficiently implement these new therapies. An approach similar to that described for trial implementation can be considered. Many new therapies can likely be initiated onsite at the spoke hospital, with guidance provided via the telemedicine system. For more complex therapies requiring special expertise not available at the spoke hospital, patients can be triaged using the telemedicine system and arrangements made for rapid transport to the hub hospital. These approaches should provide mechanisms for more rapid acceptance and implementation of newly approved therapies.

## Conclusion

The medical and health care organizational communities have a common goal: greater success in the development and implementation of current and future acute stroke therapeutics. Published recommendations for drug development will help to pave the way for greater success in this endeavor. The use of telemedicine-based stroke care networks will likely be an efficient and effective method to reach the greatest number of patients with stroke. This will enhance the overall delivery of care and maximize the use of the only currently approved therapy, rt-PA, and other treatments that will obtain subsequent approval. Indeed, with new stroke therapeutics on the horizon, it would be shortsighted not to explore the rapid development of telemedicine networks and to resolve the current limitations to more widespread implementation.

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