Acute Stroke Trial Enrollment through a Telemedicine Network: A 12-Year Experience

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Background: A major barrier to acute stroke trial enrollment is timely access to participating centers. Establishing referral relationships via telemedicine may broaden trial access. We sought to understand the utilization of telemedicine in trial enrollment at a large academic center. *Methods:* This is a single center, retrospective review of subjects consecutively enrolled into cerebrovascular trials requiring urgent consent between January 2005 and December 2016. Subjects were classified to either direct presentation to hub hospital, or transfer from spoke hospitals. We used Pearson linear correlation and a simple linear regression model to describe the relationship between annual trial enrollment rate and the number of spoke sites capable of audio-video evaluation (AVR) as a proxy for the size of the telemedicine network. We correlated the annual increase in enrollment with that of each group using parametric and nonparametric analysis. *Results:* Sixteen trials met our criteria, enrolling 299 subjects: 117 in the hub group and 182 in the spoke group. There was a direct relationship between the number of AVR-capable sites and annual trial enrollment rate ($P = <.05$). Annual increase in spoke enrollment was higher compared to hub enrollment (15.55 ± 11.30 versus 0.68 ± 1.03, $P <.0005$) and better correlated with total increase in enrollments (0.98 versus 0.94, $P <.0001$). *Conclusions:* Telemedicine networks are a major resource for trial enrollment. Expanding the use of remote enrollment could expedite the completion of acute cerebrovascular trials.

Key Words: Stroke—clinical trial—enrollment—consent—telestroke—telemedicine

Introduction

Recruitment efficiency into clinical trials of acute stroke can be hindered by delays in presentation,[1,2] particularly in patients initially evaluated at a nonenrolling spoke center. According to the American Telemedicine Association, telemedicine is the remote delivery of health care services using telecommunication.[3] It has been an effective tool delivering clinical expertise to remote populations especially for time-sensitive decisions.[4] With expanding telemedicine networks, many stroke hubs now receive a large portion of patients through referral networks from spoke hospitals. In a population-estimated study of ED visits, the rate of transfer for ischemic stroke or transient ischemic attacks increased from 8.2 per 100 ED visits in 2006 to 19.5 per 100 ED visits in 2014 (P trend <.001).[5]

Remotely obtained consent has been proposed to broaden participation and expedite trial enrollment,[6] and has not been associated with protocol deviations.[7] Its utilization can overcome hurdles previously shown to reduce enrollments,[8,9] while allowing additional lead-in preparation time for enrolling sites. We report our 12-year experience with clinical trial enrollment within an expanding telemedicine network.

Materials and Methods

We conducted a retrospective review of all subjects consecutively enrolled into cerebrovascular trials between January 2005 and December 2016 in a major health

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Table 1. *Enrollment patterns with corresponding size of telemedicine network*

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Urgent enrollment trials (n)	2	3	4	2	3	4	4	1	3	6	7	3	16
Number of remote stroke sites (n)	0	1	7	10	12	11	12	14	16	17	20	20	20
Patients enrolled (n)	7	17	24	10	8	35	27	6	17	52	53	18	274
Enrollment from hub hospital (n)	6	5	7	5	3	11	14	3	9	17	21	3	104
Enrollment from spoke hospital (n)	1	12	17	5	5	24	13	3	8	35	32	15	170
Enrollment from spoke hospital after video consultation (n)	0	0	6	4	1	4	5	3	4	13	8	2	50
Enrollment rate per trial	3.50	5.67	6.00	5.00	2.67	8.75	6.75	6.00	5.67	8.67	7.57	6.00	6.5 (mean ± 2.5)

system. Trials were eligible if consent was necessary within 2 hours of the patient's arrival to the hub hospital. Our health system consists of 3 hub hospitals and 20 spoke sites capable of conducting real-time audio-video and radiographic assessment (AVR). In addition, there are numerous out-of-system spoke sites with strong referral channels to our system. Those sites communicate with our hub via real-time telephone-based consultation but no AVR capacity. Based on the American Telemedicine Association definition, we accounted for both types of spoke sites in our telemedicine network size. We divided subjects based on mode of presentation into direct presentation to the hub, or transfer from a spoke site. All data was collected with approval of the Institutional Review Board and in compliance with the Health Insurance Portability and Accountability Act.

Consenting Process

Patients directly presenting to our hub are evaluated by the vascular neurologist and screened for trial eligibility. Eligible patients, or their legally authorized representatives (LARs), are offered enrollment by a vascular neurologist who follows standard procedures for a written, in-person consent. For patients referred from a spoke site, after the appropriate remote evaluation is conducted either by phone or video connection with physician-to-physician communication and physician-patient evaluation. If the decision is made to transfer the patient, the patient is screened for trial eligibility. Eligible patients, or their LARs, are offered enrollment remotely via phone or video communication between the teleneurologist and the patient or their LAR. A consent form is faxed to the spoke hospital. The clinical provider follows the same procedures of informed consent, with the form in the hand of the patient or the LAR, assisted by the nurse or physician at the spoke site. If the patient or LAR agrees to participate, they would sign the form and the signed form is faxed back to the hub hospital, while the original copy is transferred with the patient's records.

Statistical Analysis

We used Pearson linear correlation coefficient and simple linear regression to describe the relationship between the number of AVR-capable spoke sites and the annual trial enrollment rate. We, then, calculated the annual increase in enrollment in the total, hub and spoke groups, using first year data (2005) as a baseline as it predated the establishment of spoke health system network. Each subsequent year would be compared to the 2005 data. We compared the results using one-way ANOVA, after confirming normality using Shapiro-Wilk test. To determine whether the increase in enrollment was better correlated with hub versus spoke enrollments, we ran correlation analysis by using parametric and nonparametric correlation analyses.

Results

Sixteen trials met our criteria; 7 were related to endovascular thrombectomy, 4 to neuroprotectant therapy, 2 to endovascular perfusion augmentation, 2 to intensive medical care, and 1 to systemic thrombolysis. There were 299 subjects enrolled, 117 (39.1%) in the hub group and 182 (60.9%) in the spoke group (Table 1). AVR-capable sites initiated AV connection in 57.8% of the consults resulting in enrollment.

AVR-capable sites increased from 0 in 2005 to 20 sites in 2016. There was a direct and positive relationship between the number of AVR-capable sites and the annual trial enrollment rate ($P < .05$) (Fig 1). For each additional site, there was a 0.27-point increase in annual enrollment rate. The mean annual increase in enrollment was higher in the spoke group compared to the hub group (15.55 ± 11.30 versus 0.68 ± 1.03, $P < .0005$), and had a stronger correlation with the increase in enrollment in the spoke

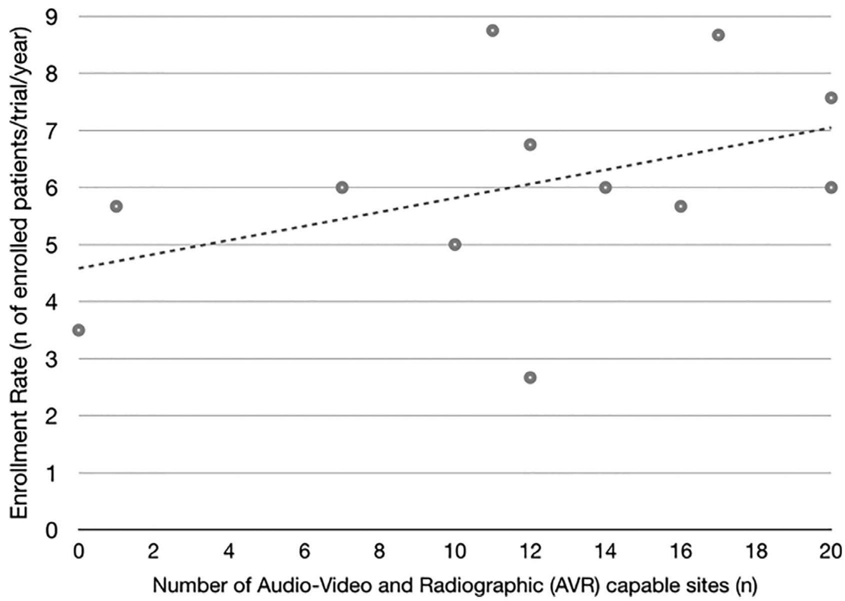

Figure 1. *Correlation between AVR-capable sites (with audio, video and radiographic connectivity) and trial enrollment rate (linear regression, Intercept 3.54, slope 0.27). Abbreviation: AVR, audio-video and radiographic assessment.*

group compared to the hub (Pearson r 0.98 versus 0.95, $P < .0001$, Hoeffding r 0.78 versus 0.60, $P < .0001$) (Fig 2).

Discussion

Our experience reveals that a majority of subjects enrolled into acute cerebrovascular studies arrived via interfacility transfer, with high utilization of AVR in equipped sites. As the network expanded, the rate of trial enrollment steadily and significantly increased.

This study expands on increasing lines of evidence that remote assessment is an important adjunct in improving the slow accrual rates of time-sensitive therapies. Prior studies have identified several recruitment challenges

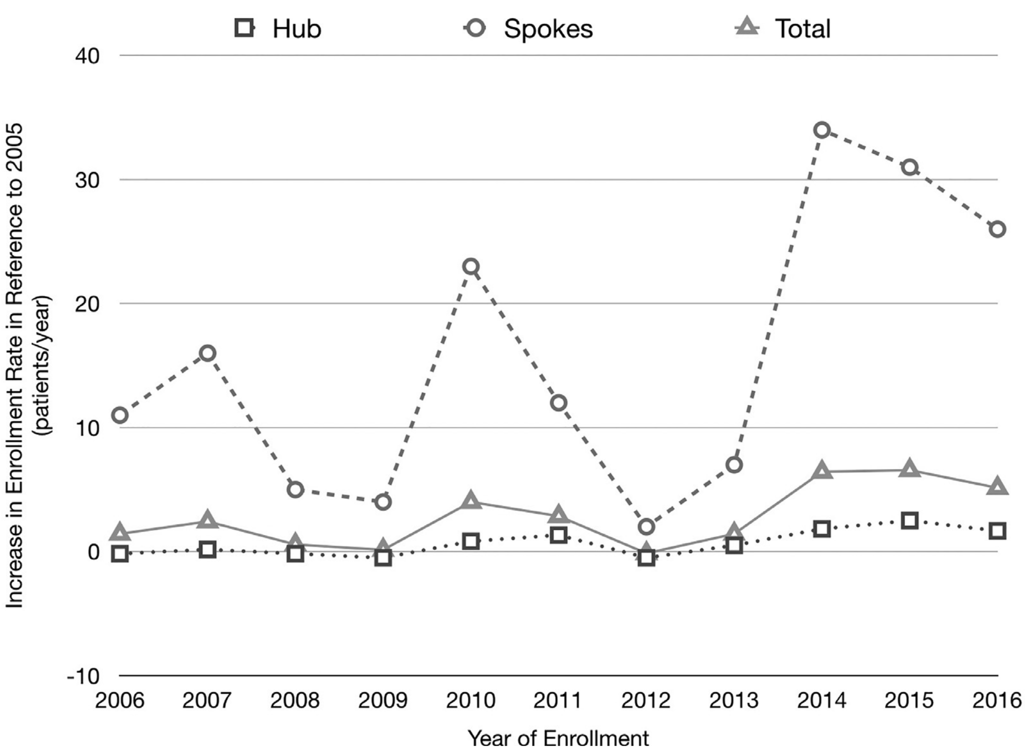

Figure 2. *Increase in enrollment rate. Enrollment rate compared to baseline data from 2005 reflect overall increase in enrollment, driven by the increase in enrollment rate from spoke sites.*

including trial access and awareness, study site organization, and stringency of enrollment criteria. The initial development of telestroke networks was prompted by a pressing need to increase IV tPA administration at facilities that lacked the necessary expertise. Within our network, we found that the use of IV tPA at spoke sites increased from 2.8% prior to the use of telemedicine in 2005 to 6.8% after starting telemedicine in 2008.[10] Similarly, we now find an increase in the availability of clinical trial participation to these remote sites. In our study, only 14% of trial enrollments in 2005 initially presented to a spoke hospital. Since the establishment of the telestroke network, more than 50% of enrollments have been recruited from spoke hospitals. We anticipate this number to grow as the network continues to grow.

Obtaining consent can be a major barrier particularly for stroke patients who may lack decision-making capacity and are often separated from LARs during transport. When in-person consent is not possible; several solutions have been adopted. Exemption from informed consent was used at Canadian and selects US sites in the ESCAPE trial, after community consultation. Such an approach is attractive, but the garnering of community consensus is time- and resource-intensive. An alternative is electronic-consent via remote technologies; a rapidly evolving entry point which is supported by the FDA and will likely be increasingly used.

Even when pre-arrival consent could not be obtained, advanced notice through the telemedicine network remains beneficial as it allows for hub-site preparedness and reduces delays of study interventions.[6]

The number of the AVR-capable sites in our network correlated with a higher trial enrollment rate. The increase in enrollment rate correlated more closely with the increase in the spoke group compared to the hub group. The role played by the likely improvement in research infrastructure at the hub hospital was not assessed or controlled for in this study, although the disproportionate increase in spoke enrollment rate suggests that larger referral networks have a significant role in faster trial conduction.

Limitations

Our study has several limitations. It represents a single health system where local conditions may not apply to other systems. For example, our IRB allows the use of remote consent for clinical trial participation but this permissibility can vary across centers. Some trials may not allow for remote consenting currently. While our findings may encourage future effort in remote consenting, they may not be immediately applicable in such circumstances. Furthermore, this is a retrospective study, which limits our ability to determine whether consenting occurred remotely or in-person. Additionally, we were unable to capture the number of fallout subjects who were ultimately not enrolled. Because our referral network outside of the health system is variable, we used the well-defined number of AVR-capable sites within the system as proxy for network size, but this underestimates the true reach of the network. Finally, there was an increase, albeit modest, in the enrollment rate from the hub. This may reflect other confounding variables not captured in our study, like the experience of researchers, trial eligibility criteria and the infrastructure of research capabilities at our facility.

Conclusions

We find a strong correlation between rate of trial enrollment and size of telemedicine network. Further expansion of telemedicine networks may be a critical step in broadening the number of patients with access to trial engagement and efficiency of study conduction.

Competing Interests

TGJ has the following disclosures: Consultant: Neuravi (steering committee -modest), Codman Neurovascular (DSMB -modest), Stryker Neurovascular (PI DAWN-unpaid), Fundacio Ictus (PI REVASCAT unpaid). Stock: Anaconda, Silk Road, Blockade Medical (modest). No other conflicts of interest or disclosures for other authors.

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