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Efficiency of Enrollment in a Successful Phase II Acute Stroke Clinical Trial

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Abstract

Background—Recruitment challenges are common in acute stroke clinical trials. In a population-based study, we determined eligibility and actual enrollment for a successful, phase II acute stroke clinical trial. We hypothesized that missed opportunities for enrollment of eligible patients occurred frequently, despite the success of the trial.

Methods—In 2005, acute ischemic stroke (AIS) cases in our region were identified at all 17 local hospitals as part of an epidemiologic study. The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA (CLEAR) trial assessed the safety of this combination in AIS patients within 3 hours of symptom onset. In 2005, we determined the proportion of AIS patients who were eligible for CLEAR and the proportion that were actually enrolled.

Results—At 8 participating hospitals, 33 (2.8%) of 1175 AIS patients were eligible for CLEAR. Of 33 eligible patients, 18 (54.5%) were approached for enrollment, 4 (12.1%) refused, 1 (3.0%) was not consentable, and 13 (39.4%) were enrolled. Of the 15 not approached for enrollment in the trial, 10 were evaluated by the stroke team; 7 received rt-PA. Enrollment was not associated with night or weekend presentation.

Conclusions—Although the CLEAR trial was successful in meeting its delineated recruitment goals, our findings suggest enrollment could have been more efficient. Three out of 4 patients approached for enrollment participated in the trial. Eligible patients who were not approached and those treated with rt-PA but not enrolled represent targets for improving enrollment rates.

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Keywords

clinical trials; emergency medicine; acute stroke; thrombolysis

Introduction

Recruitment challenges are common in acute stroke clinical trials. For example, the recently published phase IIB/III trial of tenecteplase in acute ischemic stroke was terminated for slow enrollment, with available data unable to establish neither promise nor futility.[1] The UK Glucose Insulin in Stroke Trial (GIST-UK) is another recent, large acute stroke study that was terminated early due to poor recruitment.[2] GIST-UK was ultimately underpowered to determine a difference in the primary outcome measure of death at 90 days between treated and untreated patients. Given the considerable intellectual effort and monetary and logistical costs that clinical trials entail, further research is warranted to explore the efficiency of clinical trials.

Epidemiology can be used to guide clinical trial design and planning. The availability of eligible patients for a given clinical trial within the population is arguably the most important factor in trial enrollment. For instance, we have previously demonstrated that only 8% of all AIS patients within our population arrived within 3 hours of onset and met other criteria for recombinant tissue plasminogen activator (rt-PA) administration.[3] Thus, any trial with enrollment criteria that require rt-PA administration while adding restrictions on age, baseline function, time-to-treatment, etc. should anticipate a low proportion of eligible AIS patients. Further, since acute stroke trials often require early intervention, hospital arrival at night or on weekends when staffing is less available on site may contribute to poor enrollment rates.

In a population-based study, we retrospectively determined the proportion of stroke patients within the region who were eligible for a successful, phase II acute stroke clinical trial that was ongoing during calendar year 2005. We further determined how many eligible patients were in fact enrolled in the trial. We hypothesized that missed opportunities for enrollment of eligible patients occurred frequently, despite the success of the trial.

Materials and Methods

Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS)

The GCNKSS is a population-based epidemiological study of stroke in blacks and whites, specifically designed to measure temporal trends in incidence, and racial differences in incidence of stroke and stroke risk factor profiles. The GCNKSS study population is defined as the 1.3 million residents of the Greater Cincinnati/Northern Kentucky region, which includes two southern Ohio counties and three contiguous Northern Kentucky counties that border the Ohio River. Included in this area are 17 hospitals. Although residents of nearby counties also seek care at the 17 hospitals, only residents of the five study area counties were included as cases. The study period was from 1/1/2005 to 12/31/2005.

The methods of case ascertainment and data collection have been previously reported.[4] Briefly, study nurses retrospectively reviewed and abstracted the medical records of all inpatients with primary or secondary stroke-related ICD-9 discharge diagnoses (430–436) from the 17 acute-care hospitals in the study region. In addition, strokes not found by inpatient screening were ascertained by monitoring all stroke-related visits to hospital emergency departments (ED) (with the exception of Cincinnati Children's Hospital), 16 public health clinics, and 14 hospital-based outpatient clinics and family practice centers.

Cases for which stroke was listed as the primary or secondary cause of death by one of the five county coroners' offices were also included. Further monitoring was performed by examining the records of potential stroke cases in a random sample of 51 of the 832 primary care physicians' offices and 25 of the 126 nursing homes in the GCNK region. This sampling was necessary given the large number of physician offices and nursing homes in the region. Events found by out-of-hospital monitoring were crosschecked against inpatient records to prevent double counting. Patients were identified as being from the study area based on county of residence. To qualify as a GCNKSS incident case, a patient must have met the criteria for one of the five stroke categories adapted from the Classification for Cerebrovascular Diseases III.[5]

Once cases of stroke or TIA were identified, a study nurse abstracted the medical record using standardized case report forms. Study physicians reviewed every abstract and decided whether a stroke or TIA had occurred. The physicians assigned stroke subtype and mechanism to each verified case based on all available information, using definitions previously reported.[4]

The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke: the CLEAR stroke trial

The CLEAR trial was a successful multicenter, randomized, double-blind, sequential, dose-escalation and safety study of low-dose rt-PA in combination with eptifibatide versus standard-dose rt-PA alone given to patients diagnosed with acute ischemic stroke and treated within 3 hours of symptom onset.[6] Eligible patients were 18 to 80 years of age with a clinical diagnosis of acute ischemic stroke and a National Institutes of Health Stroke Scale (NIHSS) score >5. The protocol required that the study drug be initiated within 3 hours from the time the patient was last seen normal. From July 2003 to April 2007, nine US centers, including the University of Cincinnati, enrolled 94 patients.

Data were managed and analyzed using SAS® versions 8.02 and 9.1 respectively (SAS Institute, Cary NC). For this analysis, we determined population-based eligibility for CLEAR within the population at large and specifically at participating hospitals using data from the GCNKSS in 2005. Patients who had documented arrival less than 150 minutes from onset were considered eligible. We compared the population-based eligibility to actual CLEAR enrollment rates in the Greater Cincinnati region in 2005. Potential reasons for missed enrollments were examined by detailed chart review. These data are presented as raw numbers with the weighted percentages due to the sampling scheme. T-test, Wilcoxon rank sum, Chi-square and Fisher's Exact tests were used for between-group, enrolled versus not enrolled, and eligible and approached for CLEAR enrollment versus not approached for CLEAR enrollment comparisons as appropriate.

Results

In 2005, 1853 ischemic stroke patients presented to all local EDs in the GCNK region. Enrollment in CLEAR was placed on hold for a DSMB review during November, 2005 but enrollment was otherwise ongoing for the rest of the calendar year. Thus, 1697 stroke patients presented to all local EDs during CLEAR enrollment. Of these, 47 (2.6%) were eligible for enrollment in CLEAR as documented by retrospective review of the medical chart for inclusion/exclusion criteria. The most common reasons (not mutually exclusive) for ineligibility within the population were NIHSS ≤5 (n=1,124), time of arrival >150 minutes (n=1,353), age <18 or >80 (n=451), and baseline modified Rankin (mRS) >2 (n=468). CLEAR eligibility criteria are shown in Table 1.

Of the 17 hospitals in the region, 8 participated in CLEAR. A description of the hospitals is provided in Table 2. Annual ED visits and hospital admissions, and stroke-specific ED visits and hospital admissions are presented. At these participating hospitals, 33 (2.8%) of 1175 ischemic stroke patients were eligible for CLEAR enrollment. Time of ED arrival >150 minutes remained the most common reason for exclusion (n=923). Of the 33 eligible patients, 18 (54.5%) were approached for enrollment in CLEAR: 4 (12.1%) refused, 1 (3.0%) was not consentable, and 13 (39.4%) were enrolled. Neither time of day nor weekend stroke was associated with the likelihood of being approached for enrollment (Table 3).

Summary characteristics of the 15 eligible patients at participating hospitals who were not approached for enrollment in the CLEAR trial are presented in Table 4. Seven of these patients were evaluated by the stroke team in person and 3 were evaluated by the stroke team over the phone. Of these 10 patients, 7 received rt-PA (5 IV only, 1 IA only and 1 IV/IA). Of the 6 who were seen in person by the stroke team and received rt-PA, 2 had diagnostic uncertainty and 4 had no documented reason for not being enrolled in the CLEAR trial. One eligible patient was seen by the stroke team in person but did not receive rt-PA for unclear reasons. One case evaluated by the stroke team over the phone received rt-PA. Five of the eligible patients who were not approached for enrollment in CLEAR were not evaluated by the stroke team and none of these patients received rt-PA. Patients who were eligible but not enrolled in CLEAR were not enrolled in any other stroke trial.

Discussion

Of the 33 eligible patients who presented to local hospitals participating in the CLEAR trial in 2005, 39% were enrolled in the trial. Night or weekend presentation did not influence the likelihood of trial enrollment in our study. About half of the patients who were eligible for the CLEAR trial in our population were not approached for enrollment in the trial. Since 3 out of 4 approached patients agreed to participate and were enrolled in CLEAR, eligible patients who were not approached for trial participation represent missed opportunities for enrollment in the trial. To our knowledge, this is the first study to compare population-based eligibility to actual enrollment in an ongoing acute stroke trial within the same population. Our findings may have implications for the design and planning of future acute stroke clinical trials.

Overall, less than 3% of all stroke patients were eligible for enrollment in the CLEAR stroke trial within our population in 2005. Since 8% of stroke patients in our population are eligible for rt-PA administration,[3] CLEAR trial criteria eliminated over half of rt-PA eligible patients from consideration for enrollment. Trial eligibility criteria and organization of participating sites accounted for approximately 40% of the variability in recruitment efficiency in a previous report.[7] Thus, the number of potentially eligible patients within the population for a proposed trial should be considered prior to embarking on any large scale clinical trial. Elkins et al. suggest that increasing the number of participating sites may improve overall enrollment but at reduced efficiency and increased costs.[7] Thus, to increase enrollment in a given clinical trial, efforts aimed at improving the organization of participating sites may be more efficient than increasing the total number of participating sites. For instance, while 14 CLEAR-eligible patients presented to non-participating hospitals in our region, expanding the trial to these hospitals to capture those patients may be less cost-efficient than focusing efforts on the 15 patients at participating hospitals who were not approached.

We closely reviewed the records of these 15 patients for any insights into rectifiable reasons for the missed opportunities for enrollment in the CLEAR trial (Table 4). Notably, the stroke team was not activated for 5 cases and none of those patients received rt-PA despite early

hospital arrival in all cases and an NIHSS score as high as 17 in one case. For cases where the stroke team evaluated the patient in person, diagnostic uncertainty accounted for 2 missed cases but no documented reason was available in the remaining 5 cases. For cases where the stroke team was involved by phone, it is possible that an under-estimation of clinical deficits led to the decision not to administer rt-PA, and thus not enroll in the trial. All 3 of these patients had an NIHSS of 6 and one received rt-PA before arrival of the stroke team physician due to time. Overall, these findings indicate that missed opportunities for appropriate treatment of ischemic stroke persist. Involvement of the stroke team by in-person evaluation or telemedicine assessment may improve treatment and clinical trial enrollment rates.[8]

Our finding that 3 out of 4 patients who were approached for enrollment in the CLEAR trial were in fact enrolled in the trial is encouraging. On the other hand, it means that stroke clinical trial investigators may have to account for up to a 25% refusal rate in eligible patients approached for trial participation. This rate of refusal for trial participation in conjunction with low rates of eligibility within the population may have contributed to the poor recruitment rates in recent stroke clinical trials.[1,2]

The main limitation of our study is the inability to generalize our findings beyond our community. All hospitals in the GCNK region have been served by an aggressive and readily accessible stroke team predominately composed of experienced stroke physicians who have been actively engaged in conducting clinical trials at the participating hospitals for over twenty years. Thus, the enrollment rates at participating hospitals in our region may not be reflective of trial enrollment rates at other centers.

Another limitation of our study was the retrospective ascertainment of eligibility for the CLEAR trial within our population. Although chart review revealed no documented reasons for not enrolling and/or not receiving rt-PA in some cases, it is possible that legitimate reasons for exclusion from the trial and treatment were encountered at the time of care delivery. For instance, we found that 1 out of 4 patients who were approached for enrollment in the CLEAR trial refused to participate in the study. Poor documentation of refusal to participate in the trial in the medical records may explain the cases that were treated with rt-PA by the stroke team but not enrolled in the trial. Further, one eligible case received intra-arterial therapy only, suggesting that patient may not have been a candidate for systemic rt-PA and one case was seen by the stroke team in person but not treated with rt-PA (no stroke team note was available for this patient).

In summary, although the CLEAR trial was successful in meeting its delineated recruitment goals, our findings suggest enrollment could have been more efficient. We found that missed opportunities for rt-PA treatment and enrollment in the clinical trial occurred frequently. Given the high enrollment rates in patients who were approached for participation in the study, eligible patients who were not approached and those treated with rt-PA but not enrolled represent targets for improving future trial enrollment rates.

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Table 1

Ischemic Strokes Cases Meeting CLEAR Criteria During Enrollment in 2005*

Inclusion criteria	N (%)
NIH Stroke Scale score >5	573 (34.0%)
Age of 18 through 80 years	1246 (72.8%)
ED arrival within 2.5 hours of stroke onset	344 (20.0%)
Exclusion criteria	
History of stroke in the past 3 months.	68 (5.5%)
Previous intra-cranial hemorrhage, neoplasm, subarachnoid hemorrhage, or arterial venous malformation	37 (2.1%)
Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT scan is normal	0 (0%)
Hypertension at time of treatment; systolic BP > 185 or diastolic > 110 mmHg or aggressive measures to lower blood pressure to below these limits are needed.	56 (3.1%)
Recent (within 30 days) surgery or biopsy of parenchymal organ	51 (2.8%)
Prothrombin time greater than 15 or INR > 1.4	191 (13.2%)
Glucose < 50 or > 400 mg/dl, platelets <100,000 /mm3, or creatinine > 4 mg/dl	93 (5.2%)
PTT >40	94 (6.1%)
Seizure at onset of stroke	30 (1.7%)
Pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations (mRS >2)	468 (29.0%)
Current participation in another research drug treatment protocol. Patient cannot start another experimental agent until after 90 days	2 (0.1%)
High density lesion consistent with hemorrhage of any degree.	320 (17.8%)
All inclusion and no exclusion criteria	47 (2.6%)

* Data presented as raw numbers and (weighted %)

Table 2

Description of Hospitals Participating in CLEAR

Hospital	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**
Bed Number[a]	160	162	209	375	481	501	513	521
Hospital Type[b]	Non-teaching	Non-teaching	Teaching	Teaching	Teaching	Teaching	Teaching	Teaching
Annual ED Visit[a]	39,368	60,445	34,108	83,716	79,748	72,957	43,004	50,362
Annual hospital admissions[a]	8,083	7,717	12,065	25,188	27,516	31,411	24,230	27,659
Neurology on call	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Neurosurgery on call	No	No	No	Yes	Yes	Yes	Yes	Yes
Dedicated Neuro-ICU	No	No	No	No	Yes	No	No	Yes
Full-time Neurointensivist	No	No	No	No	Yes	No	No	No
Annual stroke presentations to ED (2005)[c]	109	81	125	180	157	180	173	170
Annual stroke discharges from the hospital (2005)[c]	105	75	122	173	149	172	171	168
Number of patients eligible for CLEAR (2005)[c]	3	2	3	5	5	7	1	7
Number of patients enrolled in CLEAR (2005)[c]	1	1	1	0	2	4	1	3

[a] 2007 data from the American Hospital Association

[b] A hospital with *any* residency program is designated "Teaching."

[c] 2005 data from the GCNKSS

Table 3

Comparison of Eligible Patients Approached and Not Approached for CLEAR Trial Enrollment

	Approached	Not approached	P value
N	18	15	
Age (years)	65.5 ± 9.9	61.1 ± 12.1	0.27
Race (black)	2 (11.1%)	5 (33.3%)	0.12
Gender (female)	8 (44.4%)	7 (46.7%)	0.90
NIHSS	12.5 (9, 17)	9.0 (6, 17)	0.46
Baseline mRS	1 (0, 1)	1 (0, 2)	0.56
Systolic BP (mmHg)	146 ± 21	160 ± 19	0.05
Diastolic BP (mmHg)	78 ± 15	86 ± 18	0.19
Time of day 0700–1500 1500–2300 2300–0700	7 (38.9%) 9 (50.0%) 2 (11.1%)	5 (33.3%) 6(40.0%) 4 (26.7%)	0.51
Weekend Stroke	5 (27.8%)	6 (40.0%)	0.46
IV rt-PA	18 (100%)	7 (46.7%)	0.0004
Prior stroke	2 (11.1%)	3 (20.0%)	0.64
Diabetes	6 (33.3%)	4 (26.7%)	0.68
Hypertension	10 (55.6%)	11 (73.3%)	0.29
Coronary Disease	3 (16.7%)	3 (20.0%)	1.00
Atrial fibrillation	4 (22.2%)	3 (20.0%)	1.00
Stroke Team Activation	18(100.0%)	10(66.7%)	0.013

Data presented as n(%), mean ± standard deviation or median (25^{th}, 75^{th} percentile)

Table 4

Summary Characteristics of Eligible Patients Not Approached for CLEAR Trial Enrollment

Patient No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Age (years)	51	80	46	64	80	69	45	59	58	57	48	51	62	68	79
Race	B	W	B	B	W	W	B	W	W	W	B	W	W	W	W
Gender	F	F	M	F	M	M	M	M	M	F	F	F	M	M	F
NIHSS	7	9	29	20	18	15	10	7	15	6	17	7	6	6	6
Stroke Team Activation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes[#]	Yes[#]	Yes[#]
Rt-PA Administered	Yes	Yes	Yes	Yes[*]	Yes	Yes[^]	No	No	No	No	No	No	No	No	Yes[#]
Reason for Trial Exclusion	DU	NR	NR	NR	DU	NR	NR	NST	NST	NST	NST	NST	PE	PE	PE

[*] IA only;

[^] IV/IA;

[#] By phone; DU=diagnostic uncertainty; NR=no reason; NST=no stroke team evaluation; PE=phone evaluation