Enrollment Yield and Reasons for Screen Failure in a Large Prehospital Stroke Trial

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Background and Purpose—The enrollment yield and reasons for screen failure in prehospital stroke trials have not been well delineated.

Methods—The Field Administration of Stroke Therapy–Magnesium (FAST-MAG) trial identified patients for enrollment using a 2 stage screening process—paramedics in person followed by physician-investigators by cell phone. Outcomes of consecutive screening calls from paramedics to enrolling physician-investigators were prospectively recorded.

Results—From 2005 to 2012, 4458 phone calls were made by paramedics to physician-investigators, an average of 1 call per vehicle every 135.7 days. A total of 1700 (38.1%) calls resulted in enrollments. The rate of enrollment of stroke mimics was 3.9%. Among the 2758 patients not enrolled, 3140 reasons for screen failure were documented. The most common reasons for nonenrollment were >2 hours from last known well (17.2%), having a prestroke condition causing disability (16.1%), and absence of a consent provider (9.5%). Novel barriers for phone informed consent specific to the prehospital setting were infrequent, but included: cell phone connection difficulties (3.2%), patient being hard of hearing (1.4%), insufficient time to complete consent (1.3%), or severely dysarthric (1.3%).

Conclusions—In this large, multicenter prehospital trial, nearly 40% of every calls from the field to physician-investigators resulted in trial enrollments. The most common reasons for nonenrollment were out of window last known well time, prestroke confounding medical condition, and absence of a consent provider.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00059332.

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Key Words: cell phones ■ clinical trial ■ informed consent ■ physician ■ stroke

In acute focal ischemic and hemorrhagic stroke, neuronal injury progresses rapidly after first onset of ischemia or hemorrhage.[1] Stroke trialists are beginning to test novel therapies in the prehospital setting, evaluating neuroprotective agents that may be administered by paramedics without requiring brain imaging and thrombolytic treatment ordered by physicians in ambulances equipped with mobile computed tomographic scanners.[2]

Many aspects of stroke trials conducted in the prehospital setting differ from traditional hospital-based trials. Enrollment yield and the reasons for screen failure may be expected to be different for prehospital than for Emergency Department acute stroke trials.

The Field Administration of Stroke Therapy–Magnesium (FAST-MAG) was the first large, prehospital pivotal stroke trial to employ physicians elicited informed consent by cell phone immediately after screening by paramedics in patients with stroke within 2 hours of symptom onset.[3] This study was undertaken to delineate the enrollment yield and reasons for nonenrollment in the FAST-MAG study.

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Methods

FAST-MAG was a pivotal, placebo-controlled, randomized clinical trial of field-initiated magnesium sulfate in acute stroke with enrollment taking place in Los Angeles and Orange Counties in the United States between January 2005 and December 2012.[3] The great preponderance (>98%) of patients in FAST-MAG were enrolled using explicit, written, informed consent procedures, with a small proportion enrolled using exception from informed consent in emergency circumstances.

The FAST-MAG trial used a 2-stage screening process for patient enrollment.[3–6] In the first step, paramedics identified potentially study eligible patients and called to the responding physician. In the second step, physician-investigators performed the final study eligibility determination, based on paramedic report and discussion with the patient or on-scene legally authorized representatives (LARs).

Initially, in addition to the modified Los Angeles Prehospital Stroke Screen, 4 inclusion criteria were developed with evaluation of all 10 study exclusion criteria left for the phone-enrolling physician-investigator.[4,5] During the course of the study, 3 revisions to the screening form were made, adding several exclusion criteria elements for paramedic performance (Table 1). Two of these revisions aimed to reduce nonenrollment calls, and exclusion of blood pressure >220 mm Hg aimed to reduce the proportion of hemorrhage patients enrolled because the study hypothesized treatment benefit in ischemia and neutral effect in hemorrhage.

For all calls from paramedics not resulting in an enrollment, physician-investigators recorded the reason for nonenrollment. Details of methods and main results of the trial have been reported previously with the final paramedic screening form and exclusion criteria.[3–6]

Results

During the 8-year study period, 4458 potential subjects were screened by enrolling physicians from paramedic phone calls. Among the 315 ambulances that participated in the trial, the median duration of active screening in the trial was 64 months (interquartile range, 24–81). Accordingly, the average ambulance made 1 screening call to an enrolling physician every 135.7 days and yielded 1 study enrollment every 355.7 days. Among these, 1700 patients (38.1%) were enrolled.

Among enrolled patients, final diagnoses of the qualifying event were cerebral ischemia in 73.3%, intracranial hemorrhage in 22.8%, and cerebrovascular disease mimic in 3.9%.

Among 2758 nonenrolled patients (61.9%), a total of 3140 reasons for nonenrollment were documented (Table 2). The most common reasons for nonenrollment were being >2 hours from last known well time (17.2%), having a preexisting condition causing disability (16.1%), and patient being not competent with no LARs on-scene to provide consent (9.5%).

Aspects of the presenting neurological deficit making the diagnosis of acute stroke insecure accounted for 29.8% of the nonenrollment reasons, including last known well time >2 hours (17.2%), rapidly improving deficit (7.6%), absence of any arm or face motor deficit (2.8%), presence of bilateral weakness (1.5%), and coma (0.7%).

Barriers to completion of prehospital phone informed consent process accounted for 20.8% of the nonenrollment reasons, including the absence of a consent provider on-scene (9.5%), patient not fluent in the English or Spanish languages (4.3%), phone connection difficulties (3.2%), patient or LARs too hard of hearing to understand physician-investigator over the phone (1.4%), etc (Table 2).

Informed nonconsent (informed decision to decline participation in the study) accounted for 6.7% of nonenrollment reasons, including declinations by patients (3.8%) and declinations by LARs (2.9%).

Changes in the screening form were not associated with a reduction, and actually associated with an increase, in the proportion of calls that were nonenrollments (P=0.009; Table 1). Before addition of initial systolic blood pressure of >220 mm Hg exclusion criteria, the rate of hemorrhage enrollment was 24.3% (190/782) and after 21.5% (197/918), (P=0.16). There was a correlation between calendar date of enrollment (by quarter) and rate of hemorrhage enrollment was 0.50 (P=0.004, Spearman test for correlation; Table I in the online-only Data Supplement).

Discussion

This study's findings highlight that the 2-stage screening method in FAST-MAG, involving paramedics and then physician-investigators, was important to assure stringent patient selection. Overall, the low rate of mimics (3.9%) entered into FAST-MAG using the 2-stage screening process contrasts favorable with the higher rates of mimics enrolled in smaller prehospital stroke trials using 1 stage, paramedic screening (7%–13%),[7–9] or less formal 2-stage processes (24%).[10] Time since onset longer than target, an exclusion criteria available to paramedics, was the most common reason for physician exclusion of patients. Enrolling physicians were able to exclude cases where there was uncertainty of onset of unfamiliarity with the strict definition of last known well time. It is possible that paramedics erred on the side of calling physicians in cases with uncertain time of onset, knowing that the trial would be more greatly set back by missing an eligible patient than by physician screening of an uncertainly eligible patient. Disability before onset of the current stroke was the second most common reason for nonenrollment, and it is a difficult variable to assess for individuals who are not experienced stroke trialists.

The enrollment yield of this prehospital study (38.1%) is similar to that (37.3%) of a recent multicenter neuroprotective trial using in-hospital recruitment,[11] but the spectrum of reasons for nonenrollment differ. First, noncompetent patients were frequently not accompanied by an LARs in the field who

Table 1. Impact of Exclusion Criteria Changes on Screen Failure and Enrollment Rate

	First Period (January 2005 to January 2007)	Second Period (February 2007 to June 2009)	Third Period (July 2009 to October 2011)	Fourth Period (November 2011 to December 2012)	*P* Value
Addition of exclusion criteria		A prisoner, homeless, on dialysis or residing in a nursing home	Initial systolic blood pressure <90 or >220 mm Hg	Dementia or Alzheimer disease and receiving chemotherapy	
Screen failure rate (%)	57.3 (351/613)	61.8 (840/1360)	61.5 (982/1596)	65.8 (585/889)	0.009

Table 2. General Enrollment Yield and Reasons of Exclusion After Central Phone Screen in FAST-MAG

	No. (%)
No. of phone calls by paramedics	4458
No. of enrollment	1700
No. of screen failure	2758
Patients with single reason	2388 (86.6)
Patients with ≥2 reasons	370 (13.4)
Reasons for exclusion	3140
Presenting neurological deficit associated with acute stroke	
Last known well >2 h	539 (17.2)
Rapid improving neurological deficit	240 (7.6)
No arm/face weakness	87 (2.8)
Bilateral arm/face weakness	46 (1.5)
Coma	22 (0.7)
Preexisting and current medical diseases or conditions	
Preexisting neurological, psychiatric, or advanced systemic condition	505 (16.1)
Systolic blood pressure <90 mm Hg or >220 mm Hg	196 (6.3)
Age <40 y	51 (1.6)
Cerebrovascular disease mimic	49 (1.5)
Recent stroke within 30 d	45 (1.4)
History of seizures	43 (1.3)
Known severe renal dysfunction (eg, creatinine >3.0)	40 (1.2)
Blood glucose <60 or > 400 mg/dL	21 (0.7)
Barrier to completion of prehospital phone informed consent	
Patients unable give informed consent and no proxy available	298 (9.5)
Patient not English or Spanish speaking	135 (4.3)
Phone connection difficulties in field	99 (3.2)
Hard of hearing	43 (1.4)
Not enough time for consent before arrival	40 (1.3)
Severe dysarthria	40 (1.3)
Informed nonconsent	
Patient competent and declined participation	119 (3.8)
Patient not competent and representative declined participation	90 (2.9)
Being transported to a nonenrolling hospital	139 (4.4)
Paramedics could not start intravenous lines	21 (0.6)
Other	232 (7.4)

FAST-MAG indicates Field Administration of Stroke Therapy–Magnesium.

could provide consent. The longer enrollment time window in Emergency Department-based trials often permits LARs to arrive or be contacted by phone. Exception from informed consent enrolling was permitted at most sites when no LARs was available, but the requirement of a person who knew the patients well and could provide a reliable prestroke medical history limited its enrollment yield. Second, cell phone connection difficulties did occur as a reason for nonenrollment in FAST-MAG, but at a low (3%) rate, indicating that incorporation of cell phone processes into enrollment mechanisms is feasible in the current cellular broadband environment. Third, noncognitive communication barriers included presbyacusis, preventing consent providers from hearing physicians over the phone, and severe dysarthria, preventing physician-investigators from understanding patients. These would usually be able to be overcome with more time to interact and the availability of nonverbal modes of complementary messaging with in person-consenting in hospital.

Because the prehospital setting might be inherently coercive, and patients and LARs in the prehospital setting are not in a position to make an unforced decision, the informed declination rate would be lower in a prehospital than a hospital-based hyperacute trial. However, the rate of declination in FAST-MAG was substantially higher (6.7% of nonenrollment reasons) than that in contemporaneous trials of in-hospital neuroprotective (1.9%) and endovascular (2.5%) acute stroke treatment.[11,12] These findings suggest that the prehospital setting and brief time window for decision-making actually somewhat influenced consent providers against rather than toward participation.

Screening form changes to reduce screen failure call were paradoxically associated with an increase, rather than decrease, in nonenrollment calls. This increase probably reflects the countervailing influences of (1) increased paramedic awareness of and enthusiasm for the trial as the study progressed, leading to call even when exclusion criteria were present just to be sure not to miss an enrollable patient, and (2) more stringent application of exclusion criteria by physician-investigator as the study progressed to enroll the most informative cohort once it was clear that study would be proceeding to completion.

Also during the course of the trial, a goal was to reduce the rate of enrollment of hemorrhagic versus patients with ischemic stroke because the study hypothesized treatment benefit in ischemia and neutral effect in hemorrhage. Exclusion of the cases with systolic blood pressure of >220 mm Hg on first measurement by paramedics was associated with a nominal decrease in hemorrhage enrollments that did not reach statistical significance. However, during the entire course of the study, a statistical significant decline in hemorrhage enrollments did occur, probably as a combined result of the screening form change and of increased enrolling-investigator stringency in assessing exclusion criteria in patients with presentations suggestive of hemorrhage.

The findings of this study will be useful to planning of future prehospital stroke trials. Studies of paramedic-delivered prehospital therapies for acute stroke should take into account that the enrollment yield from paramedic calls to off-scene enrolling physicians will be ≈40%.

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Disclosures

None.

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Supplemental Material

Enrollment Yield and Reasons for Screen Failure in a Large Prehospital Stroke Trial

Supplemental Table I. Changes in enrollment rate and proportion of patients with intracranial hemorrhage during study period

Year	Quarter	Screen Failures	Enrollments	Enrollment Rate [a]	Screen Failure Call Rate [b]	ICH Enrollments	Proportion of enrolled patients with ICH [c]	Cerebral Ischemia Enrollments	Proportion of enrolled patients with CI [d]	Mimic Enrollments	Proportion of enrolled patients with Mimic [e]
2005	01	3	4	0.571	0.429	1	0.250	3	0.750	0	0.000
	02	27	15	0.357	0.643	4	0.267	10	0.667	1	0.067
	03	16	15	0.484	0.516	2	0.133	10	0.667	3	0.200
	04	53	40	0.430	0.570	10	0.250	29	0.725	1	0.025
2006	01	73	48	0.397	0.603	9	0.188	36	0.750	3	0.063
	02	39	46	0.541	0.459	14	0.304	31	0.674	1	0.022
	03	58	39	0.402	0.598	13	0.333	22	0.564	4	0.103
	04	71	46	0.393	0.607	13	0.283	33	0.717	0	0.000
2007	01	81	63	0.438	0.563	10	0.159	50	0.794	2	0.032
	02	85	39	0.315	0.685	11	0.282	27	0.692	1	0.026
	03	94	55	0.369	0.631	11	0.200	42	0.764	2	0.036
	04	89	53	0.373	0.627	10	0.189	41	0.774	2	0.038
2008	01	81	45	0.357	0.643	12	0.267	33	0.733	0	0.000
	02	85	74	0.465	0.535	16	0.216	58	0.784	0	0.000
	03	69	49	0.415	0.585	9	0.184	39	0.796	1	0.020
	04	98	58	0.372	0.628	16	0.276	40	0.690	2	0.034

Year	Quarter	Screen Failures	Enrollments	Enrollment Rate [a]	Screen Failure Call Rate [b]	ICH Enrollments	Proportion of enrolled patients with ICH [c]	Cerebral Ischemia Enrollments	Proportion of enrolled patients with CI [d]	Mimic Enrollments	Proportion of enrolled patients with Mimic [e]
2009	01	83	49	0.371	0.629	15	0.306	32	0.653	2	0.041
	02	92	47	0.338	0.662	15	0.319	30	0.638	2	0.043
	03	88	57	0.393	0.607	13	0.228	43	0.754	1	0.018
	04	88	69	0.439	0.561	8	0.116	57	0.826	4	0.058
2010	01	86	56	0.394	0.606	14	0.250	38	0.679	4	0.071
	02	111	71	0.390	0.610	23	0.324	44	0.620	4	0.056
	03	84	65	0.436	0.564	16	0.246	45	0.692	4	0.062
	04	105	66	0.386	0.614	14	0.212	50	0.758	2	0.030
2011	01	121	61	0.335	0.665	12	0.197	46	0.754	3	0.049
	02	124	87	0.412	0.588	17	0.195	66	0.759	4	0.046
	03	129	59	0.314	0.686	17	0.288	42	0.712	0	0.000
	04	157	75	0.323	0.677	17	0.227	52	0.693	6	0.080
2012	01	146	73	0.333	0.667	11	0.151	60	0.822	2	0.027
	02	125	67	0.349	0.651	16	0.239	48	0.716	3	0.045
	03	119	59	0.331	0.669	8	0.136	50	0.847	1	0.017
	04	78	50	0.391	0.609	10	0.200	38	0.760	2	0.040

		p-value/rho
ICH Enrollments Before 27JUN2009	190/782 (24.3%)	0.1644
ICH Enrollments On or After 27JUN2009	197/918 (21.5%)	
Correlation of Enrollment Rate and Quarter	-0.4951	0.0040