Translational Neurorehabilitation Research in the Third World
What Barriers to Trial Participation Can Teach Us

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Background and Purpose—Most stroke rehabilitation studies have been performed in high-income countries. The aim of this study was to identify the main barriers for patient inclusion in a research protocol performed in Brazil.

Methods—We evaluated reasons for exclusion of patients in a pilot, randomized, double-blinded clinical trial of stroke rehabilitation. Descriptive statistical analysis was performed.

Results—Only 5.6% of 571 screened patients were included. Recurrent stroke was responsible for exclusion of 45.4% of potentially eligible patients.

Conclusions—Recurrent stroke represented a big barrier to enroll patients in the protocol. External validity of rehabilitation trials will benefit from definition of study criteria according to regional characteristics of patients, including rates of recurrent stroke.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01333579.

(Stroke. 2014;45:1495-1497.)

Key Words: rehabilitation  ■ stroke

Two thirds of strokes occur in low- and middle-income countries, where stroke incidence has increased 100% in the past 4 decades.1 Disability in survivors presents escalating challenges to health care. Novel, cost-effective rehabilitation strategies are deeply needed.

Rehabilitation research has steadily grown in the past decade. Still, the vast majority of rehabilitation trials for patients with stroke have been performed in high-income Western countries.2 Difficulties in patient recruitment represent a big barrier to advances in the field, even in high-income areas.3,4 Reasons for the paucity of trials in low- and middle-income countries likely include lack of funding and skilled personnel for research, but local conditions and characteristics of patients with stroke in these areas are equally important.5 Strategies must be not only cost effective but also deliverable in the societal context. To build evidence-based rehabilitation treatments adapted to real-world conditions, it is crucial to understand differences in obstacles for inclusion of patients in stroke rehabilitation protocols across low-, middle-, and high-income countries.

Among the many gaps in knowledge that must be addressed by stroke rehabilitation research, improvement of upper limb function deserves special attention because 30% to 66% of hemiplegic patients do not gain arm function 6 months after stroke,5 and evidence-based rehabilitation strategies to improve arm and hand function are scarce.2 Because of the issues outlined above, in-depth data on patient profiles and recruitment characteristics were acquired for a proof-of-principle clinical trial on upper limb motor rehabilitation conducted in Brazil to obtain a better picture on the sources of barriers to participation in rehabilitation trials.

Methods

Study Design

We prospectively evaluated reasons for exclusion of patients in a pilot, randomized, double-blinded clinical trial performed at Hospital das Clínicas/Sao Paulo University, the largest hospital in South America with 2200 beds.6 Sao Paulo is the biggest Brazilian city, with an estimated population of 20 million in its metropolitan area. In this trial, patients with first-ever ischemic stroke were randomized for treatment with physical therapy and either low-frequency repetitive transcranial magnetic stimulation of the contralesional hemisphere or sham repetitive transcranial magnetic stimulation. Results have been published elsewhere.7

Patients admitted to the Neurology Emergency Room were screened from February 2008 to December 2011 by evaluation of medical files and interviews about their clinical conditions. Inclusion and exclusion criteria are described in the Figure. If inclusion and exclusion criteria were fulfilled, patients were contacted by phone after discharge to schedule an evaluation to recheck eligibility.

Exclusion criteria were evaluated sequentially according to the numeric order listed in the Figure. For instance, if a patient had a history...
of previous stroke, other criteria were not checked. Descriptive statistical analysis was performed. Continuous data are shown as means and SDs. Categorical data are shown as frequencies.

Results
The trial’s flowchart is shown in the Figure. The average age (±SD) of patients screened for the protocol was 61.6±15.0 years. Fifty-seven percent (n=325) of the patients were male. Twenty percent (n=114) were Afro-Brazilian, 78% (n=444) were white, and 2% (n=13) were Asian.

Complete information for screening was retrieved from 571 patients. Only 5.6% (32) of them were included.

Table 1 shows the counts/percentages of patients who did not fulfill inclusion criteria, and Table 2 shows the counts/percentages of patients who fulfilled inclusion criteria but presented exclusion criteria. A total of 124 of 273 (45.5%) patients who fulfilled inclusion criteria were excluded because of history of previous stroke.

Discussion
Almost half of the patients who fulfilled the inclusion criteria were excluded because of history of previous stroke. In Brazil, more than one third of all strokes were recurrent in a population-based study (42.6%).9 These rates are higher than those reported in high-income countries (20%–30%),10 in line with reports of greater stroke recurrence in populations that have lower socioeconomic status.11 Therefore, it is expected that recurrent strokes represent a big barrier to rehabilitation research in low- and middle-income countries if recurrent stroke is an exclusion criterion.

In contrast, in Extremity Constraint Induced Therapy Evaluation (EXCITE), a multicenter study performed in a high-income country (United States), recurrent stroke accounted for 9% of exclusions.12,13 Inclusion and exclusion criteria were not exactly the same, but were comparable between EXCITE and the present study. To the best of our knowledge, EXCITE is the only clinical trial on upper paresis rehabilitation reporting exclusion statistics that allows for comparison with our own data.

Clinical research is always faced with the conundrum of the need for methodological rigor versus the need for applicability of the intervention to the wider population. Whereas explanatory studies are designed to identify mechanisms, pragmatic trials are conducted to provide a systematic assessment of feasible interventions.14 In many third world environments, the need for clinically relevant research requires an adaptation of protocols to local needs and population characteristics.

Conclusions
Despite studies indicating that functional prognosis in patients with recurrent strokes is not necessarily worse than after first-ever stroke,10 rehabilitation trials often exclude patients with recurrent strokes. Considering that 85% of all strokes occur in low- and middle-income countries where rates of recurrence are relatively high,15 rehabilitation protocols with less exclusive criteria are deeply needed to have appropriate external validities. This approach, expected to foster development of interventions under realistic conditions, is faced with several difficulties including development of research infrastructure and funding. No matter how daring, the global burden of stroke is worthwhile the effort.
**Sources of Funding**

This study was funded by grant 2006/55504-0 from São Paulo State’s Foundation for Research Support (FAPESP). Dr Conforto received a research scholarship from the National Council for Scientific and Technologic Development (CNPq—2011–2013; 301883/2010–6). Training scholarships were granted by FAPESP (2010–2012; 2010/15660–8) and by the National Institutes of Health (2012–ongoing; grant D71TW009132-01) to S.M. Anjos.

**Disclosures**

None.

**References**

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Stroke. 2014;45:1495-1497; originally published online March 18, 2014;
doi: 10.1161/STROKEAHA.113.003572
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/5/1495

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