Optimizing Stroke Clinical Trial Design
Estimating the Proportion of Eligible Patients

Alexis Taylor, BA; Amanda Castle, BA; José G. Merino, MD; Amie Hsia, MD; Chelsea S. Kidwell, MD; Steven Warach, MD, PhD

Background and Purpose—Clinical trial planning and site selection require an accurate estimate of the number of eligible patients at each site. In this study, we developed a tool to calculate the proportion of patients who would meet a specific trial’s age, baseline severity, and time to treatment inclusion criteria.

Methods—From a sample of 1322 consecutive patients with acute ischemic cerebrovascular syndromes, we developed regression equations relating the proportion of patients within each range of the 3 variables. We used half the patients to develop the model and the other half to validate it by comparing predicted vs actual proportions who met the criteria for 4 current stroke trials.

Results—The predicted proportion of patients meeting inclusion criteria ranged from 6% to 28% among the different trials. The proportion of trial-eligible patients predicted from the first half of the data were within 0.4% to 1.4% of the actual proportion of eligible patients. This proportion increased logarithmically with National Institutes of Health Stroke Scale score and time from onset; lowering the baseline limits of the National Institutes of Health Stroke Scale score and extending the treatment window would have the greatest impact on the proportion of patients eligible for a stroke trial.

Conclusions—This model helps estimate the proportion of stroke patients eligible for a study based on different upper and lower limits for age, stroke severity, and time to treatment, and it may be a useful tool in clinical trial planning. (Stroke. 2010;41:2236-2238.)

Key Words: acute ischemic stroke ■ age ■ clinical trial ■ National Institutes of Health Stroke Scale ■ time factors

Clinical trial planning and site selection depend on an accurate estimate of eligible patients at each site. Overestimates may lead to slower than expected recruitment rates.1 The purpose of this study was to develop a tool to calculate the proportion of patients who would meet a specific trial’s age, baseline severity, and time to treatment inclusion criteria.

Patients and Methods
This is a retrospective analysis of data collected prospectively for quality-improvement purposes at Suburban Hospital in Bethesda, Maryland, and Washington Hospital Center in Washington, DC. This analysis includes data from all patients with acute ischemic cerebrovascular syndrome2 seen by the National Institutes of Health stroke team at both hospitals between September 30, 2000 and June 30, 2006, whose age, baseline National Institutes of Health Stroke Scale (NIHSS) score, and onset to triage time (OTT) were known. We abstracted patient data (age, NIHSS score, time last seen normal, and triage time) from the stroke team’s clinical database. For the analysis, we used the first NIHSS score recorded by the stroke team. We calculated the OTT by subtracting the time last seen normal from the triage time as documented in the emergency department log. The stroke code paging time was used as the triage time for all inpatient stroke cases. For estimating the proportion of patients presenting within a target treatment time window, we used the OTT plus 60 minutes. When the NIHSS score was missing but the hospital chart documented resolution of symptoms at the time of the evaluation, a score of 0 was given. Patients who had missing data, were younger than 18 years, or who died before hospital admission were excluded. Patient identifiers were removed before the final analyses.

Statistical Analysis
To fit the data to a regression equation, we created a cumulative frequency table that described the proportion of patients with less than or equal to nonzero values of each of the 3 variables of interest (age, NIHSS score, OTT time). We removed the outlier values (approximately the highest and lowest 2.5% of the sample for age and OTT, and the highest 2.5% for NIHSS), and fit regression curves using Data Fit 9.0.59 (Oakdale Engineering). The best-fitting curve was chosen as that which resulted in the lowest-order function that explained >99.5% of the variance and conformed to the shape of the data.

To validate the model, we divided the sample into 2 groups, A and B, randomly assigning patients into one group or the other group. Using the regression equations obtained from sample A, we calculated the probability that patients would meet the age, NIHSS, and time to treatment (estimated as OTT plus 60 minutes) criteria for 4 recently published or ongoing stroke clinical trials (DIAS-2, MR RESCUE, ROSIE, and SAINT)3–6 and compared these predicted proportions with the actual proportions of trial-eligible patients in group B. A deviation between predicted and actual of >5% was considered significant. After confirming the predictive validity of the model, we fitted regression curves for the entire sample for further use.
Several Clinical Trials

We developed a model to estimate the proportion of stroke patients who meet eligibility requirements for a combination of common clinical trial selection variables. Because in all cases the deviation between predicted and actual number of patients who met all criteria was similar (Table 2), we proceeded to create final regression equations using the entire dataset. These equations are shown in Table 3. Graphs of the cumulative frequency distribution for the actual and fitted data in group B who met these criteria were similar (Table 2).

Discussion

We developed a model to estimate the proportion of stroke patients who meet eligibility requirements for a combination of common clinical trial selection variables. With this model, it is possible to estimate the impact on recruitment rate of different cut-off points for 3 of the most influential entry criteria. Because the variables considered in this article did not correlate with each other, the simple arithmetic product of the proportions for each variable was a satisfactory predictor. This approach to estimating the proportion of patients eligible for trials could potentially accommodate additional criteria, eg, imaging features. If the additional variables correlate with the others, however, then the calculation of the proportion meeting all criteria would need to account for that.

Our study has some limitations. We excluded 256 patients from the final dataset because they were missing data, most commonly time last known well. These patients, however, would also not be eligible for acute therapies. Because of this selection bias, the model may overestimate the proportion of patients eligible for a specific clinical trial. In addition, many of our patients would have been excluded because they had a mild stroke (the median baseline NIHSS score was 3). Although our sample is large, was collected prospectively by several physicians, and combines data from 2 stroke centers serving a multi-ethnic and socioeconomically varied population in inner city and suburban settings, our results would have to be replicated with data from other stroke centers. Despite these limitations, we believe that the statistical functions describe the relationship of baseline features to the proportion of patients, although the parameters of the regression equations we defined may vary by stroke center or geographical region because of different demographic and organizational characteristics.

This model may be useful in clinical trial planning. Because the proportion of patients increased logarithmically with NIHSS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age, y</th>
<th>NIHSS Score</th>
<th>Onset to Treatment Triage, min</th>
<th>Predicted With Equation From Group A</th>
<th>Actual</th>
<th>Predicted With Equation From Entire Sample (Group A and Group B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIAS-2</td>
<td>18–85</td>
<td>8–24</td>
<td>120–480</td>
<td>6.2% (4.6%–8.2%)</td>
<td>5.4%</td>
<td>6.2% (5.0%–7.7%)</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>18–85</td>
<td>6–30</td>
<td>120–420</td>
<td>8.2% (6.2%–10.6%)</td>
<td>6.8%</td>
<td>8.2% (6.9%–9.8%)</td>
</tr>
<tr>
<td>ROSIE</td>
<td>18–80</td>
<td>0–16</td>
<td>120–1380</td>
<td>28.9% (25.5%–32.5%)</td>
<td>29.3%</td>
<td>28.5% (26.1%–31.0%)</td>
</tr>
<tr>
<td>SAINT</td>
<td>18–95</td>
<td>6–40</td>
<td>0–300</td>
<td>20.1% (17.2%–23.4%)</td>
<td>19.7%</td>
<td>22.2% (18.1%–22.5%)</td>
</tr>
</tbody>
</table>

Table 1. Demographic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample (N=1322)</th>
<th>First Group (N=651)</th>
<th>Second Group (N=671)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>71.6 (14.7)</td>
<td>71.7 (14.7)</td>
<td>71.4 (14.7)</td>
</tr>
<tr>
<td>Median NIHSS score (IQR)</td>
<td>3 (1–10)</td>
<td>3 (0–10)</td>
<td>3 (1–10)</td>
</tr>
<tr>
<td>Median OTT, min (IQR)</td>
<td>229 (75–868)</td>
<td>234 (75–862)</td>
<td>220 (75–859)</td>
</tr>
</tbody>
</table>

Group A was used to develop the model and the Group B to test it. IQR indicates interquartile range; OTT, onset to triage; SD, standard deviation.

Results

A total of 1322 patients met the inclusion criteria and their summary statistics are listed in Table 1; 651 were randomized to group A and 671 were randomized to group B. In group A, the frequency distribution for age was best fit by a Weibull function ($r^2=0.997$ and 0.997, respectively); for OTT, it was best fit by a third-order logarithmic function ($r^2=0.998$ and 0.994); and for NIHSS score, it was best fit by a first-order logarithmic function ($r^2=0.997$ and 0.997). The proportions (95% CI) of trial-eligible patients in group B predicted from group A were 6.2% (4.6%–8.2%) (Table 2), and 8.2% (6.2%–10.6%), 28.9% (25.5%–32.5%), and 20.1% (17.2%–23.4%), respectively. The actual proportions of patients within range for all 3 variables was calculated as the product of the 3 individual proportions, assuming that correlations among the 3 variables were negligible. To confirm that assumption, we calculated pair-wise correlations among the 3 variables.

We calculated the proportion of patients whose age, NIHSS score, and OTT was within a range by subtracting the proportion of patients whose values were below the lower limit. The proportion of patients within range for all 3 variables was calculated as the product of the 3 individual proportions, assuming that correlations among the 3 variables were negligible. To confirm that assumption, we calculated pair-wise correlations among the 3 variables.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Proportion (95% CI) of Patients Who Met the 3 Criteria in Group B</th>
<th>Proportion of patients less than or equal to a value for:</th>
<th>( P_{\text{All}} = P_{\text{Age}} \times P_{\text{NIHSS}} \times P_{\text{OTT}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAINT</td>
<td>6.2% (4.6%–8.2%)</td>
<td>Age: ( P_{\text{Age}} = 1 - \exp(-0.0017*1.0944) )</td>
<td>NIHSS: ( P_{\text{NIHSS}} = 0.23 + 0.22\ln(\text{NIHSS}) + 1 )</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>8.2% (6.2%–10.6%)</td>
<td>OTT: ( P_{\text{OTT}} = -0.07 + \frac{-0.15}{\ln(\text{NIHSS}) + 1} )</td>
<td></td>
</tr>
<tr>
<td>ROSIE</td>
<td>28.9% (25.5%–32.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIAS-2</td>
<td>20.1% (17.2%–23.4%)</td>
<td></td>
<td></td>
</tr>
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</table>

Table 3. Regression Equations for the Whole Sample

Regression equations for the whole sample. OTT indicates onset to triage.

Discussion

We developed a model to estimate the proportion of stroke patients who meet eligibility requirements for a combination of common clinical trial selection variables. With this model, it is possible to estimate the impact on recruitment rate of different cut-off points for 3 of the most influential entry criteria. Because the variables considered in this article did not correlate with each other, the simple arithmetic product of the proportions for each variable was a satisfactory predictor. This approach to estimating the proportion of patients eligible for trials could potentially accommodate additional criteria, eg, imaging features. If the additional variables correlate with the others, however, then the calculation of the proportion meeting all criteria would need to account for that.

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This model may be useful in clinical trial planning. Because the proportion of patients increased logarithmically with NIHSS
and time from onset (Figure), allowing the inclusion of patients with milder strokes and earlier treatment (i.e., not limiting enrollment to patients beyond the standard thrombolytic time window) will have a greater impact on the proportion of eligible patients than extending the time window or allowing older or more patients with more severe disease to enroll. The design of clinical trials strikes a balance among several important, often competing, features, including sample size, recruitment rate, years required to complete the trial, generalizability, and optimal patient selection to maximize effect size. Although lowering the minimum NIHSS requirement would exponentially increase the pool of eligible patients, these patients tend to recover spontaneously and may be less likely to demonstrate a treatment effect. Enrolling only patients outside the time window for intravenous thrombolytic therapy may be desirable when investigating the effects of a new treatment as monotherapy, but that decision would exclude the nearly 50% of otherwise eligible patients who present in time for alteplase therapy. Balancing these design factors is difficult and often depends on expert opinion. The model we developed adds a quantitative dimension to this decision-making process that has not been previously available.

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The authors thank Dr Lawrence Latour and the members of the National Institutes of Health Stroke Teams at Suburban Hospital and Washington hospital who assisted with data collection and patient care.

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Disclosure
None.

References
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背景和目的：临床试验计划和研究中心选择要求对每个研究中心符合条件的病例数进行准确估计。本研究旨在探索一种满足某种特定研究需要的患者年龄、病情严重程度和治疗时间作为纳入标准来预测入选患者比例的模型。

方法：从一组 1322 例连续性急性缺血性脑血管综合征患者中，对上述三个变量范围内的患者比例进行回归分析。其中一半患者用于新模型，另一半用于通过对实际四个卒中试验患者预测比例与实际比例的比较来验证该模型。

结果：在不同的试验中，符合纳入标准的患者预测比例为 6%-28%。根据前半年的样本数据，符合试验标准的患者预测比例为实际入选比例的 0.4%-1.4%，该比例随着美国国立卫生院卒中量表 (NIHSS) 评分增加和发病时间延长而呈对数增加。降低 NIHSS 评分基线标准和延长治疗时间窗是影响卒中试验入选患者比例的最大因素。

结论：根据年龄、卒中严重程度和治疗时间的不同可以帮助估计符合某一研究的卒中患者比例，该模型可能成为临床试验设计的有用工具。

关键词：急性缺血性卒中，年龄，临床试验，美国国立卫生院卒中量表，时间因素

(Stroke. 2010;41:2236-2238. 暨南大学附属第一医院神经内科 董大伟 译 张玉生 徐安定 校)
Stroke  October 2010

表 1 人口统计学变量结果

<table>
<thead>
<tr>
<th></th>
<th>样本总数</th>
<th>A 组</th>
<th>B 组</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=1322)</td>
<td>(N=651)</td>
<td></td>
<td>(N=671)</td>
</tr>
<tr>
<td>平均年龄, 岁 (SD)</td>
<td>71.6(14.7)</td>
<td>71.7(14.7)</td>
<td>71.4(14.7)</td>
</tr>
<tr>
<td>NIHSS 评分中位数 (IQR)</td>
<td>3(1–10)</td>
<td>3(0–10)</td>
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<td>OTT 中位数, 分 (IQR)</td>
<td>229(75–868)</td>
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</table>

A 组用于发展模型；B 组用于检验该模型。

IQR：四分位间距；OTT：发病至分诊时间；SD：标准差。

曲线。选择能解释 >99.5% 的变异并符合数据形状的最低阶功能曲线作为最佳拟合曲线。

为了验证该模型，将患者随机分为 A、B 两组。通过 A 组样本的回归方程，计算四个最近刚公布或正在进行的卒中临床试验 (DIAS-2、MR RESCUE、ROSIE 和 SAINT) [3-6] 中符合年龄、NIHSS 评分及治疗时间 (按 OTT 加上 60 分钟估计) 标准的患者比例，然后将这些预测比例值与 B 组中入选患者的实际比例值进行对比，预测值与实际值之间相差 >5% 被认为有统计学意义。在确认该模型的预测效度后，将该回归曲线应用于整个样本以进一步研究。

用低于最高限的患者比例值减去低于最低限的比例值计算出符合年龄、NIHSS 评分和 OTT 要求的患者比例。如果这三个变量之间的关联可以忽略不计，那么所有三个变量值均在可信区间的患者比例被计算为三个独立的比例值。为了验证这个假设，对这三个变量之间的配对关联性进行了计算。结果共有 1322 例患者符合纳入标准并进行统计 (见表 1)。随机地将 651 例分至 A 组，671 例分至 B 组。在 A 组，年龄频率分布最适合 Weibull 函数 (r² 分别为 0.997 和 0.997)，OTT 最符合三阶对数函数 (r² 分别为 0.998 和 0.994)，而 NIHSS 评分最符合一阶对数函数 (r² 分别为 0.997 和 0.997)。根据 A 组预测出 B 组中符合试验标准的患者比例值 (95% 可信区间 [CI]), 分别为 6.2%(4.6%-8.2%), 8.2%(6.2%-10.6%), 28.9%(25.5%-32.5%), 20.1%(17.2%-23.4%), 与 B 组中符合试验标准的患者实际比例相似 (见表 2)。因为所有符合试验标准的患者比例预测人数和实际人数偏差均小于 5%，所以将整个数据库用于建立最终的回归方程 (见表 3)。三个变量实际值和对应值的累计频率分布情况见图 1。三个变量的配对相关系数都在 0.05-0.13 之间，表明这些变量之间的相关性较差。

讨论

我们制定了一个用于估计符合普通临床试验变量选择组合条件要求的卒中患者比例的模型，利用该模型可以评价三个最重要入选标准的不同截点对患者入选率的影响。因为本文中考虑到的三个变量之间互不关联，每个变量的比例经过简单的计算都可获得令人满意的预测值。这种用于估计符合试验要求患者比例的方法极有可能被纳入附加标准，例如影像学特征。然而，如果附加变量和其它变量相关联，那么计算所有符合标准的患者比例时需对此作出说明。

我们的研究有一定的局限性。我们从最后的数据库中排除了 256 例患者，因为他们数据不完整。大部分是由于他们症状持续时间不详。这部分病人也不符合急性治疗的入选标准。由于这种选择偏倚，该模型可能会过高估计一个符合特殊临床试验的患者比例。另外，许多小卒中患者 (NIHSS 评分均值为 3) 也被我们排除在外。尽管我们的样本含量较大，且通过几个内科医师进行前瞻性收集，并且结合两个位于市内和郊区的服务多种族、多社会背景人群的卒中中心，我们的结果还必须通过其他卒中中心的数据来进一步证实。尽管有这些局限性，尽管我们定义的这个回归方程的参数可能会由于人口统计学表 2 本中心符合几个临床试验年龄、病情严重程度和治疗时间标准的患者比例

<table>
<thead>
<tr>
<th>试验</th>
<th>年龄 (岁)</th>
<th>NIHSS 评分</th>
<th>起病至治疗时间 (分钟)</th>
<th>A 组中符合 3 项标准的比例 (95% CI)</th>
<th>A、B 组合并计算预测值</th>
<th>整体样本预测值</th>
</tr>
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<tbody>
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</tr>
<tr>
<td>ROSIE</td>
<td>18–80</td>
<td>0–16</td>
<td>120–1380</td>
<td>28.9%(25.5%-32.5%)</td>
<td>29.3%</td>
<td>28.5%(26.1%-31.0%)</td>
</tr>
<tr>
<td>SAINT</td>
<td>18–95</td>
<td>6–40</td>
<td>0–300</td>
<td>20.1%(17.2%-23.4%)</td>
<td>19.7%</td>
<td>22.2%(18.1%-22.5%)</td>
</tr>
</tbody>
</table>

表 3 整体样本回归方程

年龄：PAGE = 1–exp(−0.0017*1.09*AGE)  
NIHSS：PNIHSS = 0.23+0.22*ln(NIHSS)+1  
OTT：POTT = −0.07+(−0.15)*ln(OTT)+0.07*ln(OTT)²+(−0.005)*ln(OTT)³  

为了确定患者比例在某个变量值范围内，用 PALL 目标范围最大值减去 PALL 最小值，从而计算观察变量在某一范围内的概率。
和组织上的特点等原因随着地域差异或者卒中中心不同而变化，但我们相信这个统计函数能够描述基线特征和患者比例之间的关系。

这个模型可能对临床试验设计有用。因为患者入选比例随着 NIHSS 评分增高和发病时间延长呈对数增长 (图)，允许纳入卒中中患者和接受早期治疗的患者（例如不限制纳入超过溶栓治疗时间窗的病人）与延长治疗窗或者允许纳入年长者或更多的重症患者相比，其对纳入比例的影响更大。临床试验设计要使几个重要的经常对比的特征保持平衡，包括样本大小、募集率、试验规定的完成年限、普遍性、以及理想化病人选择以便效应最大化。虽然降低纳入患者的 NIHSS 评分最低值会使合格患者量呈对数增长，但这些患者可能会因为自然恢复而难以证实治疗效果。当把一种新的治疗作为单一疗法来调查其疗效的时候，仅仅纳入超出治疗时间窗后接受静脉溶栓剂治疗的患者可能是有价值的，但是这种做法会排除接近 50% 正在进行阿替普酶治疗的合格患者。平衡这些设计因素很困难，经常是根据专家的建议而定。而我们制定的这种模型给这种决策过程增加了一种前所未有的度量尺度。

参考文献