As a debilitating disease with long-term consequences, stroke imposes a significant social and economic burden.1,2 Stroke is the third most common cause of death in the United States and Europe and the major cause of serious, long-term disability in adults.3 One million acute ischemic strokes are estimated to occur in Europe each year.4 Patients who have strokes require intensive inpatient and subsequent outpatient care and may develop a wide range of complications. The direct and indirect costs of stroke were estimated at US $43.3 billion (USD) in 1998.5

Until recently, stroke has been considered a disease for which little can be done at the acute stage.6 Results of the National Institutes of Health recombinant tissue-type plasminogen activator trial showed for the first time that acute ischemic stroke could be treated successfully.7 Although this is the only drug approved so far for acute ischemic stroke, many other agents are under development, and some important advances are expected in the near future.8

With the increasing pressure of the healthcare market, any pharmaceutical agent for the treatment of acute ischemic stroke has to demonstrate not only efficacy and a reasonable safety profile but also acceptable economic implications. Given the long-term consequences of stroke, it is essential to consider treatment effects on these aspects to fully understand the economic impact of a new intervention. Although long-term stroke studies are feasible in general epidemiological research, their conduct in the context of drug development is more problematic given the time and design constraints. For this information to be helpful in the setting of rational healthcare policy and thus enable appropriate care decisions by providers, insurers, and patients, results need to be available at the time of market approval. Therefore, an economic disease model is needed to fill this information gap.

The objective of this study was to develop a disease model for estimating the long-term economic impact of the treatment of acute ischemic stroke. Specifically, such a model allows identification of the cost drivers in both the short and long term and comparison of the impact in different subpopulations. The model structure was guided by 2 important principles. The model had to provide a ready link with the typical outcome measures in stroke clinical trials. Second, it was felt critical to the model credibility that the long-term projections be based as much as possible on actual data rather than expert opinion. In this article, we present the methods
and the rationale for them. Although an example using the results of two 12-week clinical trials is provided, it is not intended to address the merits of that specific drug or to provide estimates of the cost of stroke in any particular patient group or country. Rather, we hope that this example will provide sufficient understanding to enable use of this model in assessments of new agents in a defined target population.

**Subjects and Methods**

The Stroke Treatment Economic Model (STEM) consists of 3 parts. The short-term module accounts for the initial period of stroke treatment and is intended for use with typical, shorter-term clinical trial data. A long-term module extends the short-term results over the remaining lifetime of the patients. Finally, a bridge connects the short-term and lifetime modules on the basis of the functional level and location of patients at the end of the short-term period.

**Short-Term Module**

Preregistration stroke trials traditionally focus on end points related to neurological and functional impairment and mortality for a relatively short time period, generally 3 to 6 months. With a view to the development of an economic model, however, these trials provide a unique opportunity to collect information on patients’ health care after treatment. Needless to say, one should be mindful of the well-known drawbacks of collecting economic information in the context of clinical trials.9

The short-term module of STEM provides a quantitative framework for the inclusion of such short-term clinical trial data. The economic data can be in the form of detailed daily resource use accumulated by each patient during the early period after stroke, or they can reflect a less detailed level by focusing simply on a patient’s treatment or residential location. An even simpler, though less precise, implementation can be based on the length of hospital stay and discharge disposition.10 Regardless of the level of detail, the data either should reflect the mix of age, sex, stroke severity, and other such modifiers of concern to the researcher or should be analyzed for specific subgroups of interest.

Use of this module is illustrated through data from 2 randomized, double-blind, placebo-controlled phase III clinical trials of lubezulole for the treatment of acute ischemic stroke. These trials have been described in detail elsewhere.11,12 Briefly, the 2 trials were conducted in 13 countries: Australia, Austria, Belgium, Denmark, Finland, France, Germany, the Netherlands, Norway, Sweden, and the United Kingdom in one and Canada and the United States in the other. Among the 13 trial countries, the United States accounted for 44% of the patients; each of the other countries accounted for 10%. Patients with acute ischemic stroke who were ≥18 years of age were enrolled on presentation to a hospital with stroke onset of <6 hours. Of the 1446 patients enrolled in the trials, 71 did not have an ischemic stroke and no economic data were obtained for 34 patients, reducing the study population included in this analysis to 1341 patients.

The average age of the trial patients was 70.5 years (range, 19 to 96 years). There were fewer female patients (45%) who tended to be older (72.9 versus 68.5 years, \(P<0.0001\)). About 63% of patients were married or lived with a partner. Only a very small proportion of patients had medical coverage because of their disabilities. Home modifications included stairways, entrance ramps, handrails, toilets, showers, and tubs. Medical equipment included leg braces, walkers, and wheelchairs.

For inclusion in the short-term module, the proportion of trial patients in each of the 5 locations and the proportion who had died were calculated on a daily basis. Information on outpatient services, which was collected weekly, was translated into daily use by distributing the service use among those days when a patient was at home or in a retirement home. Home modifications included stairways, entrance ramps, handrails, toilets, showers, and tubs. Medical equipment included leg braces, walkers, and wheelchairs.

The second type of resource use was outpatient services used weekly by patients while they stayed in a retirement home or at home. Ten specific services were included: emergency room, doctor visits, neurologist consultations, psychiatric visits, occupational therapy, physical therapy, speech therapy, social worker visits, home nursing, and home aids. When applicable, services were further divided into 2 care settings: services provided at a patient’s place of residence and those provided at a care provider’s office. In contrast, no information on inpatient services consumed during stays in treatment locations (hospital, nursing home or rehabilitation center) was collected because research has shown that the cost of inpatient care is largely driven by the length of stay as opposed to workup procedures and salaries of physicians and therapists.13,14

The third type of resource use information provided by the trials was related to modifications of patients’ homes and equipment purchases because of their disabilities. Home modifications included stairways, entrance ramps, handrails, toilets, showers, and tubs. Medical equipment included leg braces, walkers, and wheelchairs.

For inclusion in the short-term module, the proportion of trial patients in each of the 5 locations and the proportion who had died were calculated on a daily basis. Information on outpatient services, which was collected weekly, was translated into daily use by distributing the service use among those days when a patient was at home or in a retirement home. Home modifications included stairways, entrance ramps, handrails, toilets, showers, and tubs. Medical equipment included leg braces, walkers, and wheelchairs.

The long-term module was structured with state transition models: one for strokes resulting in minor or no disability and another for major strokes. Separate models were required because the transition probabilities between states clearly depend on the functional status. There are 3 major components to such a model: the states to be considered, the transitions permitted between them, and the rates at which these transitions occur. Consistent with the principles of Markov models,20 we assumed that the rate of transition from one state to another did not depend on previous treatment patterns. Nevertheless, the transition rates were estimated separately for the first year and for all subsequent years to allow the more progressive course during the first year after stroke and the more stable course thereafter to be properly reflected. As stated, 5 locations plus mortality are considered in this model.

The dynamics of the possible transitions among these locations are...
shown in Figure 1. The probability of transferring from one location to another was based on data from 2 population-based studies. A Swedish study prospectively followed 258 stroke patients for 12 months after hospital discharge and reported their treatment or residential locations over time. That study detailed 2 levels of functional impairment at discharge: minor stroke if there was complete or nearly complete recovery and major stroke otherwise. The Oxfordshire Stroke Study has followed 675 patients for ~7 years after stroke and provided mortality rates over time.

We estimated the matrices of transition probabilities—1 matrix per severity level—by minimizing the error between the Swedish location data and Oxfordshire mortality data and the model projections for each time period subject to a number of predefined restrictions. (More information on the matrices of transition probabilities is available from the authors on request.) Given that the data were fairly consistent (ie, no outliers), we used a minimized covariance measure to estimate the error. The constraints on which transitions are allowed were placed to enable stable estimates of the probabilities given the available data. Although theoretically all transitions are possible, some are highly unlikely. For instance, transition from a location that is less treatment intensive (home, retirement home and nursing home) to one that is more treatment intensive (rehabilitation center) is unlikely unless the health status of the patient deteriorates significantly and thus requires hospitalization first. Likewise, it is unlikely that once patients have reached one of the residential states (home, retirement home, and nursing home), internal switches would occur without the patient first going to the hospital. Transition probabilities were assumed to be independent of time because the available data are insufficient to yield more detailed estimates. We used the resulting transition probability matrices to recreate the 12-month Swedish data and thereafter to project changes in patients’ residence beyond 1 year. From the second year onward, a yearly instead of monthly cycle length was used.

Bridge

The short- and long-term modules are connected via a bridge component that groups the survivors at the end of the trials according to the characteristics that drive the projections: the patient’s level of disability and place of residence. For this analysis, disability was categorized on the basis of the Barthel score at the end of the trial (but other scales can easily be used). The Barthel Index, which covers 10 activities of daily living such as dressing and eating, measures functional independence in personal care and mobility. Scoring is usually done on a 100-point scale, with a higher score indicating a greater level of independence. Barthel scores ≥75 defined a minor stroke; otherwise, the stroke was considered major. Although the current example includes only 2 severity levels, the same basic method applies when additional severity levels are considered.

Unit Costs

Although this economic model is structured and can be analyzed in terms of resource use information only if desired, unit costs are needed to generate aggregate results. In this example, unit costs from the United Kingdom were used, but those from other countries can be readily substituted, provided that caution is taken to ensure that they properly reflect the resource use components in the model. The unit costs were obtained from publications of the Personal Social Services Research Unit at the University of Kent and the Scottish National Health Service. When necessary, unit costs were supplemented by targeted surveys. All costs are reported in 1996 British pounds sterling, and the 1996 UK general inflation rate of 4.5% was used to inflate some 1995 Scottish healthcare unit costs to 1996 values. For ease of interpretation, the equivalent costs in USD based on a straight currency conversion are also provided. All costs beyond the first year were discounted at 6%/y on the basis of the recommendation of the UK Treasury at that time. The perspective of a healthcare system with comprehensive responsibility for direct medical expenses was taken in these analyses.

Analyses

STEM supports a wide variety of analyses for both cost and effectiveness. Briefly, total management costs and their accumulation over time can be estimated overall and by component, in this case, location type. Similarly, patient survival over time and the amount of time spent in the various treatment and residential locations can readily be calculated. The information can be provided incrementally and by treatment group. When used for cost-effectiveness analyses, the model allows inclusion of various effectiveness measures. A frequently used measure for such analyses is “life years gained” with or without quality adjustment. However, especially for analyses with a shorter time horizon, use of “improvement in patient functioning” as an effectiveness measure provides valuable additional information. Such improvements can be defined in terms of either absolute improvement on the Barthel Index or proportion of patients who improve from major to minor stroke during the specified time period. Finally, sensitivity analyses of any model input with respect to any output can be done.

Example

Resource Use

The structure of the short-term module permits depiction of the patient flow among various treatment and residential locations over the period of acute stroke treatment. The distribution of patients among the 5 different locations during the 12-week trials is presented in Figure 2 for all patients combined, regardless of the assigned treatment. All trial patients were admitted to the hospital on the first day of

Figure 1. Patient transitions among various locations in Markov models. Circles represent different patient locations; arrows, possible transitions among locations.

Figure 2. Distribution of trial patients among 5 locations and mortality during 12-week trials.
stroke onset. Most (70%) were discharged to various other locations over the 12-week period. The average time spent in the hospital was 26 days.

By the end of the trials, 21% of the trial patients had died. Overall, nearly half of the patients (46%) had returned home. The remaining trial patients were distributed fairly evenly among hospitals (10%), nursing homes (12%), and rehabilitation centers (11%). Among the 1062 survivors, 47% had a major disability. There was a notable difference in the distribution of patient location between the 2 functional groups: most survivors with a minor stroke (81%) returned home compared with only 30% of those with major strokes (Table 1).

**Short-Term Costs**
When the trial data and UK unit costs are applied to the short-term module, the mean cost of managing a stroke over the first 12 weeks is estimated to be about £8000. Figure 3 shows the accumulated costs per patient over the 12-week trial period and their distribution by location type. Of the £8326 (13 649 USD) average cost per patient, hospitalization accounted for 73%; rehabilitation center accounted for another 16%. The outpatient services used by patients while they stayed at home or in a retirement home consumed on average 7% of the cost, and use of a nursing home made up the remaining 4%.

Clearly, hospital costs were the driving force behind the stroke costs in the short run. This large share of total costs is attributed to the substantial amount of time the patients stayed in the hospital (about one third of the 12-week time on average) and the high unit cost of a day in the hospital (the per diem rate ranged from £165 (270 USD) for a rehabilitation ward to £1046 (1715 USD) for an intensive care ward).

A more detailed cost driver analysis is provided in Table 2, which shows the impact of each type of resource use on the short-term stroke costs. This analysis involved setting each unit cost to zero one at a time and recalculating the resulting short-term costs. Among the 5 hospital wards, general ward was the major cost component, accounting for 34% of the short-term stroke costs, and intensive care and stroke wards were the next two important components (18% and 14%, respectively).

**Long-Term Costs**
For a patient who survived to the end of the trials, the remaining lifetime costs are estimated to be about £76 000 (125 000 USD) if there remains a major impairment at 12 weeks compared with about £28 000 (46 000 USD) when there is only a minor impairment. To estimate the average lifetime costs of stroke for all patients treated initially, it is necessary to also take into account the proportion of patients who died within the first 12 weeks. Doing so, the long-term costs are predicted to be about £40 000 (66 000 USD), on average. When short-term costs are included, the total lifetime costs of managing a stroke patient increase to nearly £50 000 (82 000 USD). Thus, long-term costs account for about 80% of the total stroke costs.

Figure 4 shows the accumulated costs over 15 years and their distribution among the 5 location types. Most of the subsequent costs (88%) was accounted for by patients who went home or to a retirement home. This may seem counter-intuitive, but it can be explained by several aspects of the analysis. One explanation is that most of the patients who suffer a minor stroke, which is a substantial proportion of all surviving patients, return home. Also, although nursing homes are expensive, patients there tend to die earlier and therefore stop contributing to costs. Finally, the cost of being managed at home may have been overestimated because it was based on the resources consumed at home during the trial by patients who went home.

A similar detailed cost driver analysis as for the short-term module is provided in Table 2, illustrating the impact of each resource use on projected total costs. Institutional care is estimated to account for 26% of the total stroke costs: hospital contributes 18.4%; nursing home, 3.2%; and rehabilitation center, 4.3%.

### Table 1. Distribution of Treatment and Residential Location of Stroke Survivors by Functional Status at 12 Weeks

<table>
<thead>
<tr>
<th>Location</th>
<th>Minor Stroke</th>
<th>Major Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Hospital</td>
<td>23</td>
<td>4.1</td>
</tr>
<tr>
<td>Nursing home</td>
<td>18</td>
<td>3.2</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>56</td>
<td>9.9</td>
</tr>
<tr>
<td>Retirement home</td>
<td>9</td>
<td>1.6</td>
</tr>
<tr>
<td>Home</td>
<td>461</td>
<td>81.3</td>
</tr>
<tr>
<td>Total</td>
<td>567</td>
<td>100</td>
</tr>
</tbody>
</table>

**Figure 3.** Cumulative costs over first 12 weeks after stroke according to patient location.

**Figure 4.** Cumulative costs beyond 1 year after stroke according to patient location.
In recent years, a number of stroke models have appeared in the literature. Although these models vary considerably with regard to specifics, they share a common objective: to provide an analytical framework that allows evaluation of the lifetime consequences of various interventions in stroke, either prevention or treatment. It is noteworthy that in all cases some aspect of the natural history of stroke is used as the basis for structuring the model. Whereas one model considers a fairly broad range of events (transient ischemic attack, ischemic stroke, hemorrhagic stroke, myocardial infarction, and death), the others are restricted to recurrence of strokes and death over time. The impact of the intervention under evaluation is simulated by modifying the transition probabilities between the various health states in these models.

This approach tends to be feasible for preventive strategies, when the risk of a stroke is affected but when the subsequent course of the disease remains unchanged because the relevant parameters can usually be estimated from clinical trials or epidemiological follow-up studies. Treatments that affect stroke recovery, on the other hand, alter the subsequent transition probabilities. To the extent that these treatments improve patient functioning, eg, as documented by a shift in patient distribution among Rankin levels, transition probabilities specific to the level of stroke disability need to be defined. Although the probabilities immediately after stroke may be retrieved from clinical trials, no data are available or obtainable in a reasonable time frame to estimate the large number of conditional transition probabilities for treated patients long beyond the trial period. Consequently, researchers often convene expert panels to estimate these probabilities. It is our view that this kind of conditional data cannot be reliably estimated by expert panels, the use of which is already questionable in estimations of much less complicated rates.

Given the difficulties of using natural history as the foundation for treatment models, we selected an alternative approach, which provides a more transparent foundation for long-term stroke treatment models and strikes a better balance between precision and feasibility. We used patient location, a reflection of patient functional abilities, as the basis for projecting the long-term consequences of treatment. Both the link between functional status and patient locations and the transitions among these locations over time are based on actual data from 2 population studies.

### TABLE 2. Cost Driver Analysis Based on the UK Unit Costs

<table>
<thead>
<tr>
<th>Item</th>
<th>12-Week Costs</th>
<th></th>
<th>Total Costs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£</td>
<td>USD</td>
<td>Change, %</td>
<td>£</td>
<td>USD</td>
</tr>
<tr>
<td>Base case</td>
<td>8326</td>
<td>13 649</td>
<td>...</td>
<td>48 345</td>
<td>79 253</td>
</tr>
<tr>
<td>General ward</td>
<td>5496</td>
<td>9 010</td>
<td>−34.0</td>
<td>43 611</td>
<td>71 492</td>
</tr>
<tr>
<td>Intensive care ward</td>
<td>6866</td>
<td>11 256</td>
<td>−17.5</td>
<td>46 885</td>
<td>76 860</td>
</tr>
<tr>
<td>Stroke ward</td>
<td>7178</td>
<td>11 767</td>
<td>−13.8</td>
<td>46 708</td>
<td>76 569</td>
</tr>
<tr>
<td>Rehabilitation ward</td>
<td>7725</td>
<td>12 664</td>
<td>−7.2</td>
<td>47 275</td>
<td>77 499</td>
</tr>
<tr>
<td>Surgical ward</td>
<td>8315</td>
<td>13 631</td>
<td>−0.1</td>
<td>48 334</td>
<td>79 235</td>
</tr>
<tr>
<td>Nursing home</td>
<td>7942</td>
<td>13 020</td>
<td>−4.6</td>
<td>46 804</td>
<td>76 727</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>6978</td>
<td>11 439</td>
<td>−16.2</td>
<td>46 245</td>
<td>75 810</td>
</tr>
<tr>
<td>Home (major)</td>
<td>26 039</td>
<td>42 686</td>
<td>−46.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home (minor)</td>
<td>38 181</td>
<td>62 591</td>
<td>−21.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retirement (major)</td>
<td>45 571</td>
<td>74 706</td>
<td>−5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retirement (minor)</td>
<td>48 344</td>
<td>74 706</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total cost is recalculated after each unit cost is set to zero one at a time. The resulting change in cost compared with the baseline result is also indicated.
greater frequency of community living as opposed to institutional placement. The study conducted by Mauthe and colleagues found that selected items in the Functional Independent Measure at hospital admission can be used to predict a patient’s discharge disposition with great accuracy.

There are, however, some limitations to this modeling approach. As a consequence of the restricted data availability at the time of the model development, patient’s functional status is only classified as major and minor disability. Yet short-term stroke treatments may improve functioning even within these broad severity categories. These more subtle treatment effects would get lost in the current modeling. Further refinement of the link between disability and future location will require additional sources of data to be incorporated. Moreover, the transition probabilities in this model were based on data from only one country, and given the likely variations in resource use patterns across countries—resulting from, for instance, differences in availability of care facilities, cultural environment, and family situation—caution must be taken before these probabilities are applied elsewhere. Although the model allows time-dependent transition probabilities, the current input data were too limited to permit stable estimates as a function of time. This assumption, which may not entirely reflect clinical experience, can be relaxed as additional data sources become available. The credibility of any application of this model will also depend on the data used as input for the short-term module and bridge component.

The cost for a patient with a major impairment was estimated to be more than twice that for those with a minor impairment (£75 985 [124 564 USD] versus £27 995 [45 893 USD]). For the short term, this difference was due to the substantially longer stay in hospital; only 30% of survivors with a major stroke compared with 81% of those with minor strokes were discharged to home at the end of 12 weeks.

Results of the cost driver analysis support that a significant amount of data collection effort in a clinical trial can be safely eliminated without the loss of much precision in estimates of the economic impact of stroke treatment. Without the collection of detailed information on outpatient service use, 93% of the stroke costs during the initial stage of care can still be estimated.

Although the effective treatment of acute ischemic stroke remains a challenge, substantial advances are occurring. The need to understand and estimate the long-term economic benefits of any new acute stroke intervention can be met by the STEM.

Appendix

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References
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