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Community Intervention Programs for Acute Ischemic Stroke: Assessment by Markov Model

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ABSTRACT

Stroke is a common illness with significant morbidity and mortality. Thrombolysis is the only approved therapy for ischemic stroke. Current protocols utilize a three hour time window from symptom onset for treatment eligibility. Public education campaigns regarding the symptoms of stroke have been advocated as a means to increase the treatment rates. A Markov model was constructed to simulate the experience of a population at risk for stroke. The probabilities of clinical events and health state utilities were extracted from the literature or estimated. Systematic reviews of community interventions in stroke and chest pain were performed. Base case analysis suggests that community intervention is the preferred strategy. The preference was robust in the face of multiple sensitivity analyses. A small incremental gain of 56 minutes was noted in life expectancy with a gain of 69 minutes in quality-adjusted life expectancy and 56 minutes in discounted quality-adjusted life expectancy.

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1 INTRODUCTION

1.1 Rationale

Stroke defines an acute vascular event in the brain and is a leading cause of death and disability. The next two decades are expected to see an increase in the burden of this disease in Canada and the rest of the world. Ischemic stroke is the most common type of stroke and is the consequence of decreased blood flow to a portion of the brain served by a single vessel. Thrombolytic therapy attempts to remove this impediment by administering an agent that results in the dissolution of blood clots and re-establishment of the supply of oxygen and nutrients to the affected area prior to irreversible ultra-structural changes heralding cell death. While it is the only available therapy for acute ischemic stroke, wide application has been limited due to the narrow time constraints imposed by the natural history of cerebral ischemia which results in irreversible changes within hours. Further, there is a potential to increase morbidity and mortality as the treatment can result in bleeding into the brain. Community interventions, consisting of public education campaigns intended to educate about stroke signs and symptoms, have been promoted and deployed as a means to increase utilization of thrombolysis for acute ischemic stroke by increasing the number of patients presenting within the time window for treatment. Myocardial ischemia shares similar risk factors and treatment benefits linked to a time dependent intervention. Previous experience with community interventions of this type in acute myocardial infarction, which target thrombolysis to cardiac ischemia, have shown mixed results and the potential impact of similar campaigns on acute stroke outcomes is unclear. An analysis of the impacts of community interventions for stroke is warranted prior to their widespread implementation.

1.2 Objectives

The primary objective of this work was to compare the risks and benefits of community intervention on patients with symptoms suggestive of stroke. Eligible interventions were those which targeted the general public in educational programs designed to increase rates of thrombolytic treatment by reducing delay time before presentation to a treating institution.

1.3 Thesis Overview

This project uses decision analysis to assess the impact of community interventions for stroke. Input data are derived from published and publicly-available data as well as systematic reviews of the evidence for such interventions in stroke and chest pain, which have similar requirements for prompt reporting to a treating facility after onset of symptoms. Evaluated outcomes include the range of impact on life expectancy and quality adjusted life expectancy with variation in the effectiveness of the intervention as well as variation in the effects of thrombolytic therapy across plausible ranges.

The intervention in question is complex involving a potential impact on a number of steps including symptom recognition and decision-making by individuals in an emergency situation. From an individual and societal perspective there are risks in that the intervention may increase the number of false positive stroke diagnoses subjected to a treatment, which can result in increased morbidity and mortality. At present no randomized controlled trial has provided unequivocal guidance on community interventions in acute stroke and thus the relative risks and benefits of this option are

unclear. There is unlikely to be any large trial of community interventions for stroke because randomized trials of such programmatic interventions are difficult to perform, and the intervention has already been disseminated widely.

This thesis applies decision analytic modeling to assess the impact of community intervention on acute stroke.

Decision analytic modeling provides an explicit quantitative framework to consider the impact of these interventions on all relative outcomes. Thus, while research on the effects of these interventions may have focused on surrogate outcomes such as time to presentation at a treating facility, the model can project the effect of such changes on morbidity and mortality over a long-term time horizon. Such modeling allows for measurement of outcomes with a metric which combines both quality and quantity of life-years gained for each strategy thereby providing a basis for comparison with the risks and benefits of alternative strategies vying for use of the same resources. The parameter estimates used in the model are uncertain and thus the influence of variations in the value of these parameters can be assessed by using sensitivity analyses. Finally this type of modeling allows the examination of decisions which are expected to influence policy from a societal viewpoint.

The background section describes the burden of stroke along with projections for the increase of this burden. Prior to discussing community interventions for acute stroke, the evidence for the efficacy and effectiveness of thrombolytic therapy is reviewed and

the current status of its utilization and integration into systems of acute care presented. The rationale for community interventions to increase the use of thrombolytic therapy for stroke is discussed. The methods section provides the details of the model along with the processes employed in construction and analysis. The methods and results pertaining to the systematic reviews are presented in the relevant sections. The results of the model are provided in the results section followed by a discussion.

2 BACKGROUND

Stroke has been defined as "rapidly developing clinical signs of focal or global disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than of vascular origin" (1). Mechanistically this may be disaggregated into ischemic stroke in which the primary pathology is one of occlusion of arteries carrying blood to the brain and hemorrhagic stroke which is the consequence of vessel rupture and cerebral damage due to pressure and toxic effects within the closed space of the skull. While bleeding into the space outside the brain but within the subarachnoid membrane (subarachnoid hemorrhage) is often included in the definition of stroke for the purposes of surveillance and descriptive epidemiology, its presentation and management are sufficiently unique that it will not be considered for this analysis (2). The incidence of stroke is strongly age linked (3) and the increasing median age of national populations occurring worldwide has led the World Health Organization to target this disease for surveillance with the goal of reducing associated morbidity and mortality (4). In developed countries, the burden of disease is expected to be higher due to the age structure of these populations and has led to the call for the development of

organized systems of stroke care (5). Public education, which teaches the symptoms of acute stroke and emphasizes the need to seek urgent care, has been seen as a means of increasing acute stroke treatment rates and therefore improving outcomes (6). Mass education campaigns have been devised and deployed in the absence of a comprehensive evaluation of their benefits. The current work uses systematic reviews of the literature in stroke and cardiac ischemia and a state transition Markov model to examine the potential impact of community interventions on relevant outcomes.

2.1 Stroke Epidemiology

Cerebrovascular disease is the third leading cause of death on a global basis with rates for males ranging from 340.3 per 100, 000 population in the Russian Federation to 50.5 per 100, 000 in Canada (7). Canadian rates are fortunately in the lower range for women as well with the rate of 41.7 for 100,000 population. An estimated 700,000 strokes occurred in the US in 2002 with approximately 500,000 being first events (8;9). The global burden of mortality was estimated at 4.7 million in 1995 (7).

Mortality rates for stroke declined for a number of populations in the Twentieth Century (10;11;12;13). In the US, the rate of decline was approximately 0.5% per year between 1900 and 1920 and approximately 1.5% per year from 1950 to1970 (14;15). All age groups were affected, suggesting that this was a period rather than a cohort effect. Interestingly this decrease began long before effective therapies for stroke prevention and treatment were available and thus cannot be ascribed to medical care. This trend has not continued uniformly in the latter part of the century. In Rochester, Minnesota the

incidence of stroke stabilized at approximately 150 per 100,000 population and remained so from the mid 1970's to the mid 1990's (16;17). While the initial period of this stabilization coincided with the introduction of CT scanners and thus may be explained by an increased probability of diagnosis, such an effect is less likely to explain a persistent stabilization through the next two decades. Furthermore, some populations have shown an increase in age- standardized mortality rates. Between 1960 – 64 and 1980-84 Portugal, Hungary, Bulgaria, Greece and Poland have all had an increase in these rates of between 10 % and 30% suggesting that mortality may have had a link to socio-economic status (18). This link has been documented in the UK where unskilled manual workers have a 60% higher risk of stroke than professionals along with a 50% higher age adjusted mortality rate (19).

While age-specific death rates for stroke have fallen over the last century (20;21;22), the absolute number of deaths due to cerebrovascular disease in Canada is projected to increase by 15% between 1995 and 2016 (7). The number of such deaths is now, and is expected to be in the future, greater for women than men (7). The projected increase in absolute numbers in the US is from approx 700,000 in 2002 to 1,136,000 in 2025 (9).

Both the pending increase in stroke mortality and the gender differences may be explained by the strong relationship between stroke and age. It has been over 30 years since the logarithmic relationship between stroke mortality and age was described by Kurtzke (23;24). A similar trend remains in current Canadian mortality rates (7).

Consequently, it is expected that the burden of disease will increase in absolute terms due to the increase in population median age and the alteration of the population age structure. It is possible that with increased industrialization and lifestyle changes in the less-developed parts of the world stroke will become a significant problem worldwide.

Within Canada, Newfoundland has the highest age-standardized mortality rates for stroke at approximately 60/100,000 for women and 70/100,000 for men (1997) (7). The lowest rates were approximately 40/100,000 in Quebec men and women from P.E.I. Migrants to this country have traditionally originated in Europe with more recent waves coming from China and south Asia. Stroke rates in all three populations (European, Chinese and south Asian) are similar for men (7) while Canadian women with origins in China have higher stroke rates than the other two female populations. The risk for black Americans is greater than that for white Americans with a risk-ratio of 5 for the 35-44 year age group in the greater Cincinnati/northern Kentucky study (25;26). The risk ratio is greater than one for all age groups though it approaches unity in the over 85 group. It is unclear if this risk-ratio reflects biologic or social factors or some combination thereof. In spite of the increased risks fewer blacks in the US are candidates for thrombolytic therapy (27).

The risk factors for stroke overlap significantly with those for ischemic heart disease. After age, the most important risk factor is blood pressure. The risk of stroke increases across the measured pressures for both systolic and diastolic pressure (28). For each 10mm Hg increase in systolic blood pressure or 5 mm Hg increase in diastolic

pressure the relative risk of stroke increases by a factor of 2.3 (29). Anti-hypertensive treatments result in significant reductions of risk for first and subsequent stroke (30;31;32;33). Diabetes and smoking each increase the relative risk by a factor of two (34;35;36;37;38). Hyper-homocysteinemia is an emerging risk factor with a relative risk of five to seven between the highest and lowest quartiles of serum homocysteine concentration (39). Atrial fibrillation likewise carries a relative risk of five for stroke. The link to serum cholesterol is somewhat more complex for stroke than for coronary artery disease. Observational studies do not show an increased risk with elevated cholesterol levels (40). Low cholesterol may result in an increased risk of hemorrhagic stroke (40). In spite of this a major therapeutic trial of lipid lowering therapy has demonstrated a beneficial effect on ischemic stroke incidence without an increase in hemorrhagic stroke (41).

2.2 Stroke Costs

Stroke currently consumes significant resources through health care costs and disability. Twenty-eight percent of total stroke incidence occurs in individuals under the age of 65 (42). Twenty percent of all acute care beds and twenty five percent of all chronic care beds are occupied by stroke patients (43). The acute cost per stroke in Ontario was estimated at 27,500 dollars in 1996. The absolute number of hospitalizations for stroke has been increasing for the past 20 years with a projected increase in hospitalizations of 10 to 15% between 1996 and 2016 (7). Hospitalization makes up 87% of the total direct cost of stroke care which was estimated in 1996 at 2.8 billion dollars by the Heart and Stroke Foundation of Canada (7). However, this cost does not include costs

related to either short- or long-term disability. Such costs may be considerable as, for example in ischemic stroke, only 25% of people make a full recovery (44). More recent costs are available for the U.S. where the projected 2004 cost is $ 53.6 billion (8).

Stroke has a significant impact on the quality of life. In a study of 118 consecutive stroke patients examined one year after stroke, a mean decline of 40% in the SF-36 subscales was noted compared to reference values (45). A similar reduction was noted in Sickness Impact Profile (SIP) scores. Sixty-seven percent of patients were depressed.

The Canadian Study of Health and Aging (CSHA-2) examined the association between well being and self reported stroke status in community dwelling seniors. Those reporting stroke had significant difficulties with activities of daily living and were twice as likely to require assistance with bathing and meal preparation. Survivors of stroke were three times as likely to require assistance with walking. Their sense of well being was less than that of seniors without stroke on all dimensions of the Ryff measure of psychological well-being other than autonomy and purpose in life (46).

Given the trends observed in stroke over the last 3 decades and the associated costs, stroke is and will remain for the foreseeable future a significant problem for Canada and other societies.

2.3 Community Education Programs in Acute Stroke

The rates of TPA treatment for acute stroke are low: 6% in Canada (47) and 2% in the US (48). Both the narrow eligibility criteria and the perception that protocol violations increase complications contribute to the overall low rates (49). The most significant limiting criterion is time since onset of symptoms. Englestein and colleagues retrospectively examined the records of patients admitted to a New York hospital with a diagnosis of stroke for the presence of exclusion criteria for TPA (50). Of 201 patients identified by ICD-9 codes, 94% were excluded based solely on time of presentation to the ER (50). Reports from other centers have documented rates of exclusion by delay time criteria of 44% (51) with speculation that differences arise due to variations in public awareness of symptoms in different communities (50). In Calgary 1,168 patients with ischemic stroke were prospectively identified and evaluated for reasons for exclusion for TPA therapy. Of these, 73.1% presented beyond three hours after symptom onset and thus could not be considered for treatment (52). This was the most common reason for exclusion from treatment.

The Chain of Recovery Writing Group has identified a sequence of events which must take place in order to access time dependent therapies in emergency situations (53). By analogy with processes successfully deployed for cardiac arrest, acute MI and trauma the chain consists of:

1) Identification of symptoms by patient or bystander
2) Activation of the Emergency Medical System (EMS)
3) Alerting treating centre

4) Diagnosis and treatment

Initiation of this entire sequence of events is contingent upon the correct identification of symptoms along with the appreciation of their gravity. In contrast to major trauma the seriousness of stroke symptoms may not be obvious (53).

Gaps have been identified in the public knowledge of stroke symptoms. A population-based random-digit telephone survey was conducted in the Cincinnati region (54). While 70% of 2173 respondents correctly identified at least one symptom of stroke, groups at highest risk of stroke including people over 75 years of age, men and blacks were the least knowledgeable. In a national US phone survey of 750 adults over age 50, 42% could not identify limb numbness or weakness as stroke symptoms (6). Forty percent of respondents were unaware that stroke occurs in the brain. Of patients with stroke, 39% were unable to identify any symptoms of stroke. This proportion was worse for those over the age of 65 than for those under 65 (47% vs. 28%, $p = 0.016$), paradoxically those at greater risk were less knowledgeable.

Williams interviewed consecutive admitted stroke patients within 72 hours of stroke onset regarding knowledge of and attitude to stroke symptoms (55). While 38% of 67 individuals purported to know stroke symptoms, only 25% correctly interpreted their symptoms as being due to stroke. Eighty-six per cent of those arriving after 3 hours felt that the symptoms were not serious. Interestingly patients with prior stroke were more likely to ascribe their symptoms to stroke (46% vs. 16% $p=0.03$) but were no likelier to

seek early attention (19% vs. 39% p=.35). Ambulance transport was independently associated with early arrival (OR 5.55, 95% CI 1.37 to 22.6).

Wein reported the individual activating the EMS in 429 validated admitted strokes as part of the TLL Temple Foundation Stroke Project (56). Of these, 38% (n = 163) arrived by ambulance. Of these cases the person activating the system was: self, 4.3%; family member, 60.1%; paid caregiver, 18.4%; and coworker or other, 12.9%. It was concluded that educational efforts directed exclusively at patients themselves were likely to be of low yield and wider educational efforts were required.

Consequently a number of proposals have been made for public education to increase knowledge of stroke symptoms (6;57;58;59). Such community interventions are expected to decrease delay time and consequently to improve the thrombolysis treatment rates. Several concerns about this approach remain. First, the experience in acute MI raises concern about the effectiveness of media campaigns for public education in a similar disease state (60). Second, knowledge may not translate into action. Patients involved in the Asymptomatic Carotid Atherosclerosis Study (61) received targeted education on the warning signs of stroke. In spite of these efforts in a group motivated enough to participate in the study, only 40% of all first events were reported within three days of occurrence (61). Participants in an advertised stroke-screening program were assessed before and after completion of a detailed evaluation of individual risk factors and counseling on risk factors and symptoms (62). After three months, 77% could name warning signs versus 59% prior to the intervention; however 73% reported no change in

life style in spite of an individualized, written plan of action provided at the screening. Finally the symptoms transmitted to the public in education campaigns are non-specific (63). Proper identification and immediate action by the public may therefore result in an increase of non-strokes reporting to the emergency room and thus have no impact on outcomes.

Given these concerns an analysis of the impact of community intervention programs on stroke outcomes is required. For the purposes of this thesis all programs targeting the general public will be considered.

2.4 Role of Thrombolysis in Stroke

Stroke due to vascular occlusion (ischemic stroke) comprises approximately 80% of all strokes (64). The mechanisms of occlusion are varied but have in common the deposition of platelets and fibrin. Fibrin is a protein which is deposited in strands enmeshing red blood cells and platelets alike. Plasminogen is released from the vascular endothelium and converted to plasmin by plasminogen activator and plays a role in regulating the duration and propagation of clots within the body. The human gene can be spliced into bacteria to allow large scale production of tissue plasminogen activator and harvested in commercially viable quantities. Genentech received FDA approval for its use in the coronary circulation in 1987 with subsequent use in acute occlusions of the coronary arteries.

Prior to the publication of the NINDS trial of intravenous (IV) recombinant tissue plasminogen activator (rtPA) delivered within three hours of stroke onset (65), no acute

therapy had been shown to modify the outcome of ischemic stroke in human trials. Two potential interventions for acute ischemic stroke therapy were 1) Re-establishing blood flow prior to cell death, and 2) limiting irreversible damage in ischemic brain. Efforts had been mainly directed at reducing neuronal metabolism (66;67), neuroprotection (68), and antioxidation (69). While the sequence of molecular events which led from energy failure through membrane depolarization, cytotoxin release, calcium influx with subsequent activation of destructive enzymes had been well worked out (70), attempts to influence the process in humans had been ineffective (71;72). Preclinical work on rodent models of these interventions had been highly successful, suggesting a profound disconnection between animal models of stroke and the human syndrome studied in clinical trials. Several reasons have been suggested for this failure to translate laboratory results into clinical outcomes. Animal models have focused on short time periods of drug administration and outcome evaluation with a focus on anatomic measurements (volume of infarct) rather than functional goals (72). While consideration of such trials has not stopped (73;74), the results suggest a need for a renewal of efforts on reversing vascular occlusion prior to the development of irreversible cellular damage. Thrombolysis enjoys a prominence in acute stroke due to this critical role of reestablishing perfusion in the face of repeated failure of other strategies. It is the only medical treatment approved for acute ischemic stroke in Canada and the US. The stroke community in North America has embraced this treatment for acute stroke (5;57;75;76). However, the evidence supporting this treatment rests on substantially fewer trials and numbers of patients than that accumulated for cardiac ischemia.

2.4.1 Thrombolysis trials in stroke

The Cochrane systematic review includes 16 randomized double-blind trials of thrombolytic therapy in acute stroke comprising 5727 patients (77). Overall, thrombolytic therapy administered up to six hours after the onset of symptoms resulted in less death and dependency (OR treatment vs. placebo 0.84, 95%, CI 0.75 to 0.95). This occurred in spite of an apparent excess of death in the first 10 days (OR treatment vs. placebo 1.81, 95 % CI 1.46 to 2.24). Heterogeneity was noted between trials and may have been due to drug, dose timing or route of administration or other factors. Trials of intravenous TPA comprised 50% of the total in both numbers of trials and patients. Analysis of these trials showed greater efficacy for death or dependency (OR treatment vs. placebo 0.80, 95% CI 0.69 to 0.93) and less hazard (death within 10 days) (OR treatment vs. placebo 1.24, 95% CI 0.85 to 1.81). For patients treated within three hours, therapy was also more effective and safer than for the group treated within 6 hours: death or dependency OR 0.6 treatment vs. placebo 6, 95% CI 0.53 to 0.83; death OR treatment vs. placebo 1.13, 95% CI 0.86 to 1.41. Only intravenous TPA administered within three hours of stroke onset has received widespread acceptance within North America and more recently Europe. The treatment received FDA approval in 1996 with HPB approval following on a conditional basis in 1999.

Subsequent guidelines suggested that tPA should be used within three hours of stroke onset (78). Similar recommendations followed in Canada from the Canadian Stroke Consortium (79) with the recommendation that use be limited to sites with personnel with experience in acute stroke care. Post-marketing surveillance mandated by

HPB and maintained by the CASES database (80) demonstrated a treatment rate in Canada of 6% of all stroke (47). Variability was noted in treatment rates between sites. There are currently nine designated stroke centers in the Province of Ontario with rates of thrombolysis ranging from 2.9% to 20.6% for the period July to December, 2002 (81).

2.4.2 The NINDS trial

The NINDS (National Institutes of Neurologic Disorders and Stroke) trial published in 1995 was the pivotal evidence leading to regulatory approval of TPA in North America (65). Clinical protocols currently used for thrombolysis use trial criteria regarding patient selection and blood pressure management (appendix 1). This trial has received much attention and has been reanalyzed independently on at least two separate occasions (82;83).

The trial examined the impact of TPA versus placebo on mortality and disability in acute ischemic stroke. Two open-label dose escalation studies suggested the need for a short time window and a dose of less than 0.95 mg per kg TPA to minimize the risk of hemorrhage. The study was carried out in two parts with Part 1 (n = 291) focused on 24-hour outcomes and Part 2 (n = 333) on outcomes at three months. Both parts measured an outcome at three months on four scales: Barthel Index, Modified Rankin scale, Glasgow Outcomes scale and NIHSS (National Institutes of Health) scale. The results of the two parts were combined as the protocols were identical and the results of part 1 were not known when part 2 was completed. They were subsequently stratified according to time since onset of symptoms.

Patients were randomized if they had a diagnosis of ischemic stroke with a clearly defined onset, could be treated within 180 minutes of onset and had a blood pressure less than 185/110. Patients were excluded if a CT scan demonstrated hemorrhage, subjects had rapidly improving symptoms or they met clinical criteria suggesting increased risk for bleeding. The study was double-blinded with randomization carried out centrally by means of a permuted block design. Outcome assessments were made by blinded, certified examiners. All analyses were based on the intention to treat. The primary hypothesis was tested with a global statistic derived from a general linear model. The point estimate for the relative risk of improvement at 24 hours did not reach the pre-specified level of significance (1.2, 95% CI 1.0 - 1.4). At three months the global OR for a favorable outcome was 1.7 (95%, CI 1.2 - 2.6). While symptomatic intracranial hemorrhage was more likely to occur with the TPA treatment 6.4% versus 0.6% in the placebo group, P = <0.001, mortality at three months was 17% in the TPA group and 21% in the placebo group (P = 0.30). Adjustment for covariates (aspirin use, weight, age, time to treatment and clinical centers) increased the global odds ratio to 2.0 (95% CI 1.3 - 3.1).

Intravenous TPA was approved for the treatment of ischemic stroke within the first three hours of onset based on this trial. Concern was expressed that the trial results would not translate well into clinical practice due to the very short therapeutic window as well as the lack of optimal radiological and clinical expertise (84). Indeed, the provisional approval from HPB mandated prospective follow-up of characteristics and

outcomes of TPA usage for acute stroke in Canada (80).

2.4.3 American Post Marketing Experience

The largest published post marketing cohort was the Standard Treatment with Alteplase to Reverse Stroke (STARS) study (85). This group of 389 had baseline characteristics similar to NINDS with comparable outcomes. The symptomatic intracranial hemorrhage rate was 3.3% with 35% of treated patients having minimal or no disability at one month.

A report from Cleveland was initially worrisome in showing high rates of complications; in particular the symptomatic intracranial hemorrhage rate was 20% - more than double that seen in the NINDS trial and far higher than the NINDS placebo hemorrhage rate of 0.6% (86). The authors noted a protocol violation rate (most frequently time criteria) of greater than 50% and subsequently instituted a quality improvement program in participating institutions, following which the experience was reevaluated (87). Significant improvement was noted with a symptomatic intracranial hemorrhage rate of 6.4% in the face of a protocol deviation rate of 19.1%.

2.4.4 Canadian Post Marketing Experience

TPA received provisional approval in Canada on February 16, 1999 (80). As a condition of approval, a prospective cohort of patients treated with tPA was mandated (Canadian Activase for Stroke Effectiveness Study, (CASES) (47). The resulting dataset assembled from 25 academic and 35 community sites contains 1,135 patients and is the largest such group yet assembled (47). This prospective cohort was collected between

February 17, 1999 and June 30, 2001. Outcome data was assessed at 90 days with central reading of the initial and 24-hour scan to ensure an unbiased estimate of the hemorrhage rate. Eighty-four percent of all cases treated in the country were included, based on a comprehensive survey of all Canadian hospitals with CT scanners and an on site audit of four randomly-selected centers. Neither the rate of excellent functional recovery (mRS 0, 1, 2) or the rate of intracranial hemorrhage differed significantly from that observed in the NINDS trial (38.6% and 4.5% respectively) (47). A protocol violation rate of 13.8% was noted with the majority being time violations (i.e. treatment over three hours). The distribution of clinical outcomes, including rates of hemorrhage, for those with protocol violations did not differ significantly from the group as a whole. Such outcomes have been reflected in several other observational studies (47).

2.4.5 Emergency Physicians Position on Thrombolysis for Stroke

The Canadian Association of Emergency Physicians (CAEP) has raised a cautionary note on the widespread use of this therapy, largely based on a concern that poor outcome results from use in non-expert hands. The CAEP policy statement on thrombolysis in stroke suggests that therapy be limited to formal research protocols or in monitored practice and argues that further evidence be sought prior to widespread application (84).

2.4.6 Integration of Thrombolytic Therapy into Current Practice

Thrombolysis for acute stroke has received widespread, though not universal support. It is a complex intervention making intensive use of resources and personnel

with a narrow therapeutic window. Current clinical protocols (appendix 1) limit use to a window 3 hours from symptom onset. The Heart and Stroke Foundation of Canada and Brain Attack Coalition in the United States advocate for multilevel system changes to increase the number of patients eligible and receiving treatment (88;89). Such advocacy has influenced public policy.

In May 1997, the HSFO proposed a creation of a coordinated system of stroke care for the province of Ontario. In 1998, a pilot program for regional coordination of care was launched at four sites. This was shared by the HSFO and a joint stroke strategy working group was established in partnership with the Ministry of Health and Long Term Care (90). In 2000, based on the results of the initial experience, the Ministry of Health funded a coordinated province-wide stroke strategy. Over the next three years, a total of 9 regional stroke centers were designated. The development of integrated acute care was seen as a key role of these centers.

The process of delivering acute stroke therapy involves a pre-hospital phase and an emergency room phase. The latter requires a rapid, intense and at times, parallel application of clinical, radiological and biochemical analysis of the potential candidate (Appendix 1). These evaluations serve to interpret compliance with eligibility criteria, thereby maximizing the probability of outcomes which parallel those of the NINDS results. The main determinant of eligibility is time since onset (49;52). Further, within the eligible group, regression analysis suggests that earlier treatment is associated with better outcome (52). Attention has therefore, been focused on the pre-hospital phase.

Shortening delay time in this phase requires recognition of symptoms, a decision to seek care and transportation to a facility capable of delivering care. Multiple mass media strategies were evaluated by the Heart and Stroke Foundation of Ontario (63). A positive effect was noted in the ability to name two or more warning signs of stroke after the mass media campaign and therefore, a subsequent television campaign was launched in Ontario in October 2003. It is not clear, however, that such an education strategy increases the number of potentially treatable patients nor that it improves outcomes. Further, such an intervention runs a risk of increased number of non-stroke patients presenting to emergency rooms. Evaluation and treatment of such patients might be expected to increase resource utilization and possibly worsen outcomes by exposing individuals to the risk of treatment who do not have any possibility of benefit.

The Ontario Stroke Strategy has initiated a province-wide program to train paramedics in stroke diagnosis by means of a clinical scale designed for pre-hospital personnel (91). The presumption being that outcomes will improve if paramedics have this added certainty. In spite of the effort involved in creating the instrument and training EMS providers, this remains an untested hypothesis. Detailed evaluation of this portion of the strategy falls beyond the scope of this analysis and will not be evaluated in detail.

2.5 Relevance of Acute Cardiac Care to Acute Ischemic Stroke

A number of similarities exist between acute stroke and acute myocardial ischemia. Ischemic heart disease is the leading cause of death in Canada and other industrialized countries (92). Myocardial death under ischemic conditions is a time

dependent phenomenon requiring a series of biochemical events and is not simultaneous with the onset of ischemia (93). As is the case in stroke, this time dependence provides an opportunity for therapeutic intervention and early treatment of myocardial infarction has been shown to decrease infarct size and reduce mortality (94;95). Rapid access to emergency treatment requires prompt identification of symptoms by patients or bystanders and presentation to an appropriate facility. Reperfusion of ischemic tissue can then be achieved through thrombolysis or angioplasty with the effectiveness of therapy being contingent speed of delivery (94;95;96). Patient delay in seeking care in North America is several hours and likely contributes to lower than expected outcomes from the application of available procedures (96). Prompt and appropriate application of such resource intensive procedures might be expected to improve outcomes. Increased awareness of symptoms and need for urgency amongst patients might result in reduced delay and increase rates of thrombolytic treatment. As acute myocardial infarction is the presenting symptom of ischemic heart disease in a substantial percentage of patients, a campaign aimed at unselected members of the community would be expected to reach the greatest members of people expected to benefit. Previous experience with community interventions in this target disorder spans two decades, far longer than the experience in acute stroke. Therefore this literature will be systematically reviewed to assist in providing an effect estimate for the model.

2.6 Decision Analytic Modeling

Decision analytic modeling is helpful in evaluating and making explicit the process and consequences of decisions in complex systems. In common, these systems

share the requirements that choices be made in the face of uncertainty while considering the impacts on multiple possible outcomes. The outcomes themselves may have multiple evaluations based on the viewpoint assumed by the decision maker, the relative importance of each outcome and the population under consideration. Multiple variables, each associated with some degree of uncertainty may contribute to the relationship between the decision and ultimate consequences. By allowing variability in the input parameters, sensitivity analysis and probabilistic determinations of potential outcomes can be produced. One and two-way sensitivity analyses provide insight into the effect of parameters on the optimal strategy. In particular parameter values which impact the optimal decision can be ascertained. However, it is clear that each variable within the model has some degree of uncertainty associated with its estimate. A Monte Carlo simulation permits multi-way sensitivity analysis (see 4.6 Model analysis).

The model may then be used to predict the impact of an intervention on population health measures, costs or the optimal choice for society, an individual practitioner or patient. The necessity of explicitly defining health states, outcomes, transitions and their respective values helps to resolve the reasons for differences between decision makers by making clear the reasons for such differences (97).

Modeling is not independent of nor a substitute for clinical trials. Such trials are critical in providing estimates of efficacy and harm resulting from therapeutic interventions along with defining relevant health states. Trials generally consider one intervention at a time and assess the impact on a limited number of outcomes. Health care

involves multiple interventions applied serially or in parallel and having a number of potential impacts. As the number, complexity and costs of possible interventions rise so does the potential contribution of this type of modeling.

Clinical trials provide estimates of transition probabilities, intervention effectiveness and may enable the estimation of costs particularly when economic analysis is a predetermined endpoint of the trial (98). This information can then be used to predict outcomes in population and system contexts not explicitly assessed in the trial. Models may also be helpful in calculating sample sizes for trials considering multiple outputs. Hypotheses generated by modeling may provide questions for testing in trials. Potentially the relationship between models and trials becomes recursive with the results of each informing and complementing the other. For instance, decision analytic modeling could be used to estimate the impact of a given intervention over a longer time horizon than studied in a trial, on a population with an incidence of disease different that studied within a trial or to calculate benefits and costs at a societal level of interventions explicitly defined by trials. Selected hypotheses generated by the modeling may then be the subject of future trials.

2.7 Expected Value Decision Making

The expected value of a choice is defined as the sum of the values of all the consequences of that option, each value weighted by the probability that the consequence will occur (99). For the present study the output of the calculations were expressed in life expectancy, quality adjusted life years [QALY] or discounted quality adjusted life years [disc QALY]. The weighting involved preferences elicited from a relevant population for

each health state and in common with other models involving transitions between states, the time spent in each state. It is assumed that the decision with the highest expected value will be chosen.

2.8 Utilities

Utilities are preferences for health states elicited under conditions of uncertainty. As such they are subjective valuations. Choices are made between options whose outcomes are uncertain with the classical method of eliciting such choices described by Morgenstern and Von Neumann as the standard reference gamble (SG) (100). A utility is defined as a number for comparing choices with uncertain outcomes such that the choice with the higher valuation is preferred by the decision maker. In the original formulation of Von Neumann and Morgenstern this occurs when the following axioms are fulfilled (100):

- Given any two prizes in a lottery, the decision maker must be able to state which he prefers or that he is indifferent between them.
- Preferences must be transitive: If A is preferred to B, and B is preferred to C, then A is preferred to C.
- If A is preferred to B, and B is preferred to C, there must be some probability (p) such that the decision maker is indifferent between B for certain or a gamble that results in A with a probability p and C with a probability 1-p.
- If A is preferred to B and the decision maker has a choice between two gambles in which A and B are prizes, he should prefer the gamble with the highest probability of winning A.
- All gambles that involve the same probability of winning the same prizes are equivalent, regardless of whether the prizes are won in one drawing or as the result of several simultaneous drawings.

The visual analog scan (VAS), SG and time trade-off (TTO) methods have been used to elicit preferences for health states (101).These methods may be divided into those developed from expected utility theory (SG and TTO) and psychological scaling methods (VAS) (101). The SG has been the gold standard for eliciting utilities as it is based on the axioms of expected utility theory (102). However, concern has been raised that the SG is subject to biases such as risk aversion which result in an overestimation of utilities (102). Van Osch and colleagues (103) discuss 4 biases that may affect utility measurements:

1. Utility Curvature: Utility for life years is not linear with remote years being relatively undervalued by most people. This results in a downward bias for time tradeoff measurements.
2. Probability Weighting: Probabilities are processed in a nonlinear manner with a tendency to overweight small probabilities and underweight large ones. This tends to exert an upward bias on utilities elicited by the standard gamble.
3. Loss Aversion: People tend to be more sensitive to losses than gains. The TTO method which asks for a trade off of life years (a loss) for optimal health will thus be subjected to an upward bias. The SG involves a gamble whose outcome may represent a loss and, for the risk averse, the probability of gain my need to be higher to compensate resulting in an upward bias for this method as well.
4. Scale Compatibility: More weight will be given to a characteristic which is compatible with the scale of measurement. For the TTO the scale is in years and more attention may be given to duration than health status resulting in a higher score. The SG response scale is a probability and a systematic bias

cannot be predicted for this technique.

These authors feel that the net effect of these biases is upward for the SG more difficult to predict for TTO as utility curvature and loss aversion may act in opposite direction. Gold and colleagues (101) note that the issue of choice of methods remains unsettled and while the VAS techniques appear simpler SG and TTO are more closely tied to the theoretical foundations of cost effectiveness analysis.

Utilities elicited from the general population are felt to be representative of the societal perspective. Utilities elicited from different populations may vary due to the subjective nature of the measure. Thus, for the purposes of this analysis, a systematic review of utilities elicited by multiple methods from the general public was used for the base assumptions and sensitivity analyses (104).

2.9 Markov Models

Markov models are a special form of decision analysis that are useful for situations in which an event can recur over time or those in which an individual experiences several health states in succession. In common with other types of decision analytic models, the development of this type of model requires the enumeration of health states which are mutually exclusive. Time is divided into cycles appropriate to the scenario with transitions occurring at the end of each cycle based on transition probabilities. The Markovian assumption is that the probability depends only on the health state occupied during each cycle and is independent of the previous health states traversed. The states may be temporary or absorbing (i.e. the probability of transition to another health state equals 0). At the onset of a cohort simulation, the population is distributed among health states. The model runs for a pre-specified number of cycles or

until the incremental utility falls below a given level. The expected utility for each choice is then the sum of the proportion of the population in each health state weighted by its utility over the number of cycles.

More succinctly for Markov models the expected value may be expressed as:

$$EV = \sum_{t=1}^{T} \sum_{i=1}^{n} f_{i,t} q_i$$

Where EV is the expected value, $f_{i,t}$ is the proportion of the cohort in state i by time t and q_i is a quality adjustment for state i (97). The utility of a health state was used as the quality adjustment with the well state having a utility of one and death a utility of 0.

2.10 Rewards and Discounting

The benefit (or detriment) of occupying a health state is termed a reward. Rewards are often denominated in time or money to permit comparison between models. As a principle rewards accrued in the future are less valued than those available immediately reflecting the time preference of the decision maker. The devaluation is proportional to the time until the reward is accrued. This principle of reducing rewards that are delayed is known as discounting. The rationale for discounting is relatively easy to see for costs. Money not spent today may be invested for a return or used to purchase other goods and services reflecting the opportunity cost of the money. Weinstein and Stason (105) argue that since health benefits are valued and paid for in dollars, they

should also be subjected to discounting. Failure to discount such benefits while discounting costs leads to the paradox noted by Keeler and Cretin (106). If costs are discounted while benefits are not, then the cost to benefit ratio can be improved by delaying the intervention with a theoretic zero cost after infinite delay. Discounting both costs and benefits at the same rate creates a "horizontal equity" amongst the beneficiaries of the intervention (101). Potential beneficiaries who differ only in their position in time relative to the decision maker will be treated equally.

Two general approaches have been considered for choosing an appropriate discount rate for social programs. The first is the suggestion that current market rates, particularly long term rates, conveys time preferences that are appropriate for the social rate of discount (107). It has been argued that these private market transactions reflect preferences that are distinct from those for societal outcomes and a discount rate for such outcomes must be the product of a political process (108). While there may be some merit to this approach a well-defined and accepted process to arrive at a discount rate has not been established. Much more effort has been devoted to generating a rate from market transactions. Various rates have been proposed with the US Panel on Cost-Effectiveness in Health and Medicine recommending a rate of 3% (101). The Canadian Coordinating Office for Health Technology Assessment has suggested a rate of 5% (109). As this work is undertaken in the Canadian context a discount rate of 5% was used.

3 SUMMARY AND THESIS OBJECTIVES

Stroke is common, lethal, debilitating and costly. Treatment in the acute phase is effective but available to only a small number of those with stroke, is resource intensive and potentially hazardous. Increasing the probability of treatment is beneficial on the individual level and is expected to be of benefit on the societal level. The number of potential candidates accessing acute treatment is significantly limited by the narrow time window between onset of symptoms and the initiation of treatment. It is widely believed that strategies to increase public awareness of stroke and EMS diagnosis are likely to increase the number and proportion of patients who are able to receive effective but time-dependent interventions. Prior to advocating wide implementation of pre-hospital programs in a complex system, it is important to evaluate the likelihood of success of these strategies within plausible variations of the effects of these strategies and the risks and benefits of thrombolytic treatment of acute stroke.

The primary objective of this work was to compare the risks and benefits of community intervention on patients with symptoms suggestive of stroke. Eligible interventions were those that targeted the general public with educational programs designed to increase rates of thrombolytic treatment by reducing delay time before presentation to a treating institution.

4 METHODS

The outcomes evaluated, model structure and process for the identification of input parameters is described.

4.1 Modeling Overview

In order to construct a decision analytic model all relevant health states were enumerated, assigned utilities, placed in an internally consistent structure and the relationships between different states defined by means of the probability of transitions to all possible states at the end of each cycle. Consistent with the primary objective of this project, a societal viewpoint was chosen.

4.2 Model Structure

Figures 1 and 2 provide a schematic overview of the model structure with details in figures 3-8. The population begins in the 'well' state. From here an individual may develop symptoms suggestive of stroke, die of unrelated causes or remain well. Individuals developing symptoms may transport themselves to the Emergency Department (ED) or engage an ambulance (EMS). Those transported by ambulance are evaluated by paramedics as having 'stroke' or 'not stroke'.

All patients are evaluated in the emergency department and assigned a diagnosis of 'stroke' or 'not stroke' by the emergency physician. Thus two diagnostic tests are applied: the paramedic assessment and that of the emergency room. The model permits

each assessment to be true or false. These assessments were assumed to be conditionally independent.

All patients assigned a diagnosis of ischemic stroke in the emergency department (which may be true or false) may receive tPA or be untreated; in either case the individual may die, become disabled or recover. Those diagnosed as hemorrhagic stroke do not receive tPA but may recover, become disabled or die. Transient ischemic attacks by definition have zero probability of death or disability and thus recover fully. However other pathology (i.e. 'not stroke') may result in death, disability or recovery depending on the underlying diagnosis. At the beginning of the next cycle the population is distributed through states (a) through (o). As appropriate, death is defined as an absorbing state and no further transitions are permitted. Transitions from the other states are as detailed in the list of health states. The model structure is identical for the two choices with the community intervention choice differentiated by an increased probability of treatment for diagnosis of ischemic stroke and a greater probability of ambulance utilization. Assumptions made in establishing the structure are described with the appropriate health state.

The stepwise approach of Beck and Pauker to model construction (110) was followed. The health states incorporated were:

(a) Well: Transitions from this state are detailed above and in figures 1 and 4. All individuals begin in this state. They may remain well or develop symptoms. Those developing symptoms may transport themselves to the ED or engage EMS in which case

paramedics will make assign a diagnosis of stroke or not stroke. The ED assigns a diagnosis of stroke which might be ischemic or hemorrhagic. In either case the assignment may be true or false. Ischemic stroke are either treated or not with tPA with death, disability or recovery possible in either case. Those with recovery after thrombolytic treatment begin the next cycle in the state "Well post tPA". Those who recover without treatment after stroke without thrombolysis are placed in state (g) "Post-ischemic stroke". Full recovery after hemorrhage results in transition to state "Post-hemorrhagic stroke". States (i) and (j) enumerate those who have had a stroke resulting in disability.

(b) Asymptomatic post-emergency room visit: Pathology other than cerebral ischemia may lead to the initial symptoms with these individuals having different transition probabilities than those who are well. Allowed transitions are identical to those for the well state.

(c) Well post tPA: This state accounts for those who achieve complete recovery after thrombolysis. The model assumed that this population has no disability but retains a higher risk of recurrence than the well state. Individuals in this state may remain in this state develop symptoms or die of unrelated causes.

(d) Post-TIA: This state defines those who have had transient symptoms ascribable to ischemia. Transient ischemic attack (TIA) is defined as the presence of focal neurologic symptoms of presumed vascular origin lasting less than 24 hours. Individuals experiencing a TIA have a higher transition probability to stroke as well as an increased probability of death due to the use of preventative therapy. By definition there is no long-term disability associated with this state. Individuals may die, experience symptoms

or remain in this state.

(e) Post-second TIA: This model permits an individual a maximum of two TIA's. Transitions from this state are constrained to death or stroke. This constraint was applied to make the model tractable and less computationally intensive.

(f) Untreated TIA: A TIA may be unrecognized or untreated due to medication intolerance and such individuals would have a slightly increased risk of transition to stroke and lack the risks associated with long-term medication use. Allowable transitions are identical to those in the post TIA state.

(g) Post-ischemic stroke: Stroke alters transition probabilities; in particular the probability of a second event is increased. This state assumes complete recovery with no disability as compared to state (i). Individuals may remain in this state, have a recurrent stroke, or die of other causes which include fatal bleeding from antiplatelet therapy used for prevention. A simplifying assumption is made in that recurrent ischemic strokes are not treated with thrombolytic therapy and all second strokes are fatal (the states 2d Post Isch stroke and 2d Post Hem stroke transition directly to death).

(h) Post-hemorrhagic stroke: As for (g) these individuals have no associated disability. They may remain in this state, have a second stroke, or die of unrelated causes. Antiplatelet therapy is not utilized after hemorrhagic stroke and thus the risk of death does not include an additional factor due to therapy risks. As noted for the Post-ischemic stroke state a simplifying assumption is made that all second strokes are fatal. The state Post ICH due to TPA has transitions identical to the post ischemic stroke state.

(i) Disabled after ischemic stroke: This state comprises those individuals who have had an ischemic stroke with residual disability. The utility of this state is reduced as

compared to the state represented by (g). Transitions are identical to those in (g).

(j) Disabled after hemorrhagic stroke: As above this state compromises those who have disabilities subsequent to hemorrhage and a consequent reduction in the utility. Transitions are identical to those in (h).

(k) Disabled due to other pathology: Other pathology may lead to the initial emergency room visit and carry with it some probability of disability. The range of possible pathologies is broad and includes metabolic and neurologic conditions (111). A summary estimate of the probability of this occurrence and the utility was not available and therefore was estimated.

(l) Dead of unrelated causes. This represents the probability of dying due to causes other than those enumerated specifically in this model. A table of age specific death rates was used to calculate the transition probability.

(m) Dead post-TPA: TPA may result in fatal hemorrhage or fail to improve outcome in a large stroke. This state comprises all those who are treated but died.

(n) Dead of hemorrhagic stroke.

(o) Dead of ischemic stroke.

The model compares community intervention with no intervention. The structure obeys the principles of symmetry and linkage as suggested by Detsky (112). The subtree for each option contains the same initial states, thus preventing an imbalance between options in terms of risks and benefits. Further, the subtrees are linked by use of algebraic expressions and definitions for probabilities at the origin of the tree. The subtree containing the intervention redefines relevant variables to reflect the probabilities

impacted by the intervention. Alterations of definitions for subtrees in this manner are defined as temporary bindings. Such bindings do not affect variables which apply equally to both subtrees and are defined at the root node.

Decision analysis was performed by using DATA PRO software (TreeAge Software Inc., Williamstown, Massachusetts) and Excel Software (Microsoft Inc. Redmond, Washington).

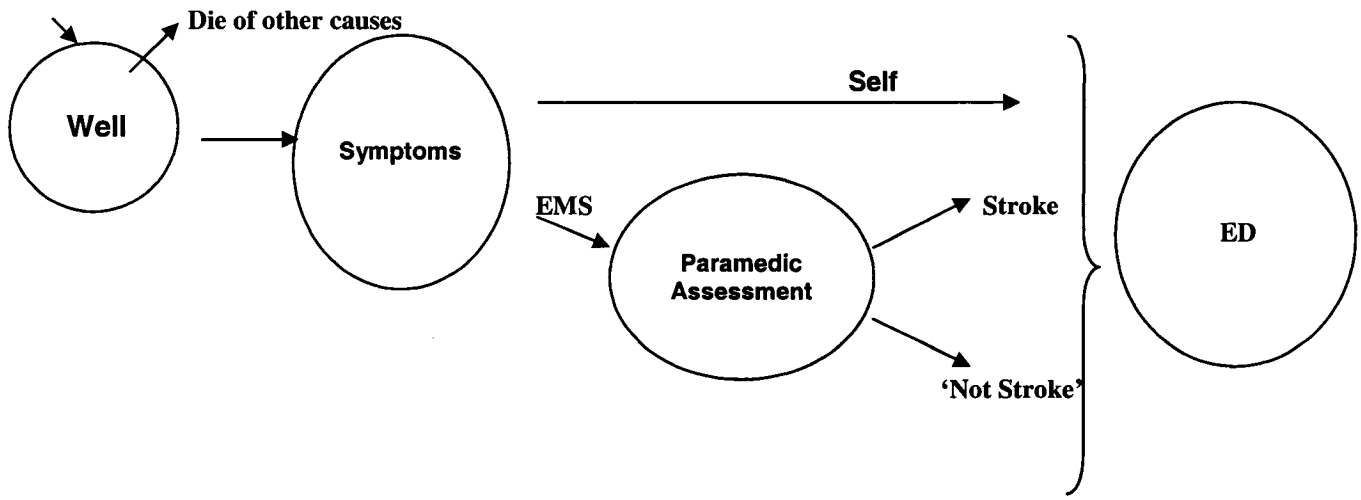

Figure 1 **Model Structure through arrival in the Emergency Department (ED)**
The assigned diagnoses of stroke and not stroke may be true or false thus the model allows for thrombolytic treatment of false positive diagnoses and denial of treatment to false negatives.

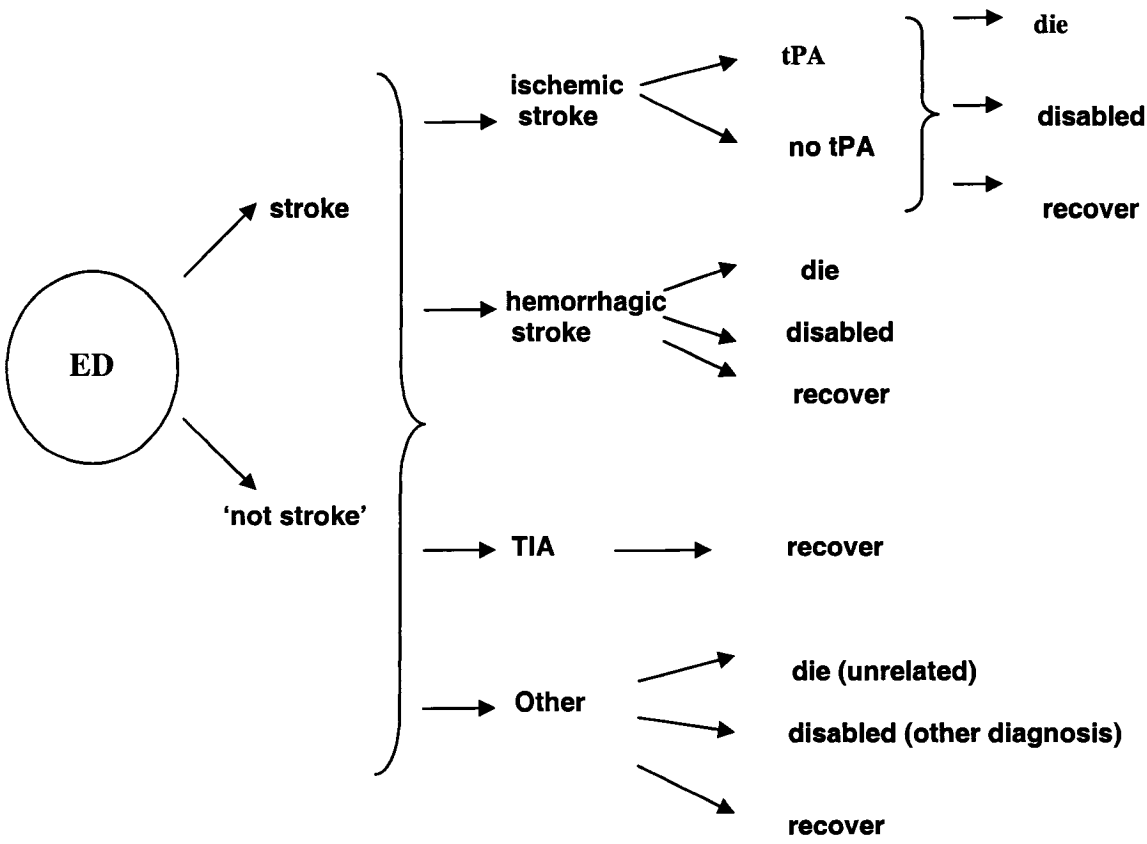

Figure 2 **Model Structure post ED arrival.**

Diagnoses other than TIA may die, become disabled or recover. TIA is defined as symptoms with complete recovery in 24 hours (113) and thus death and disability states do not follow this branch.

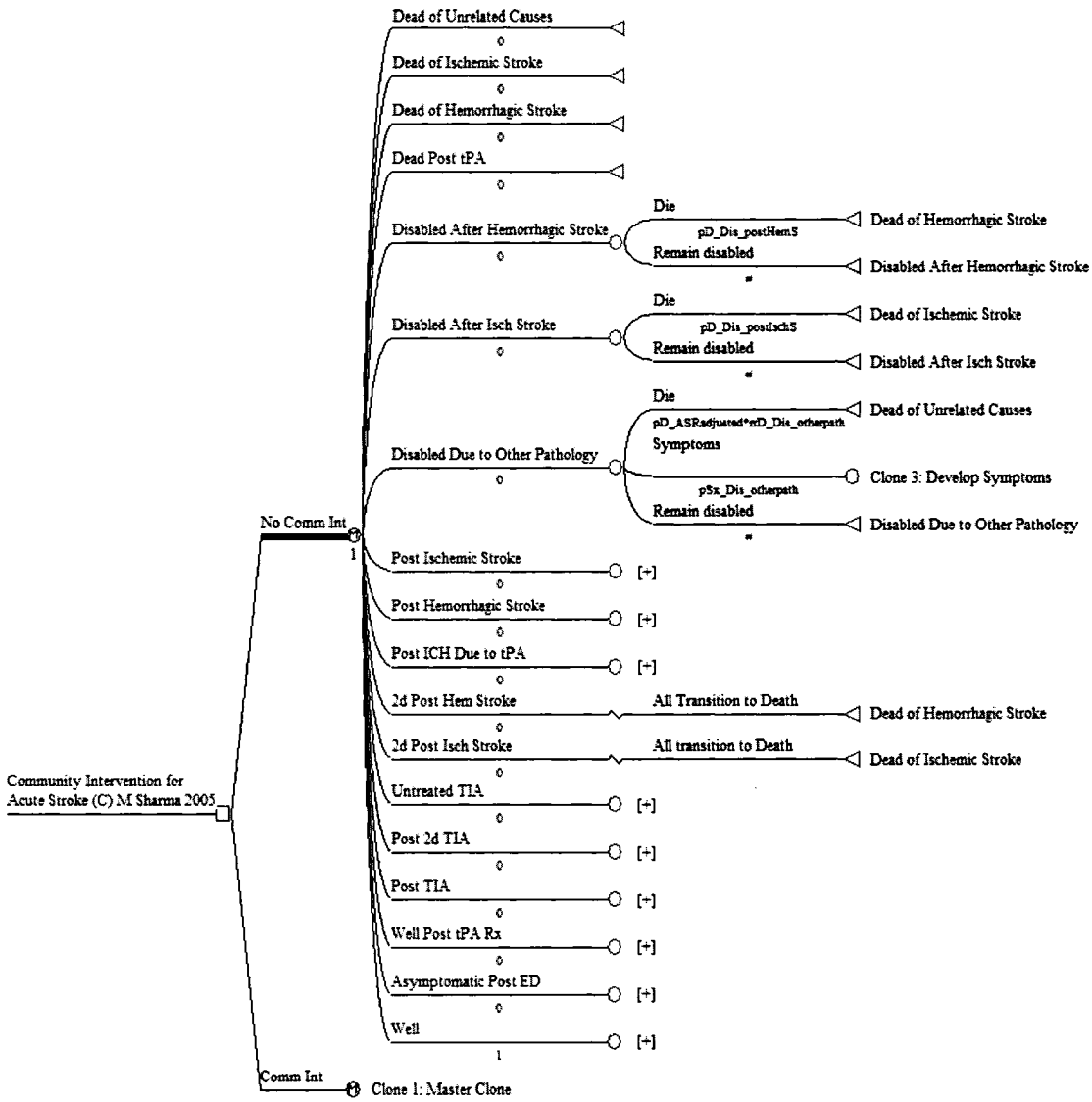

Figure 3 **Model structure from node No Comm Int**
The model compares Community Intervention against no intervention. The health states described in the text are depicted as they occur in the tree structure. The structure is identical both limbs. Also shown are the transitions from the disabled states.

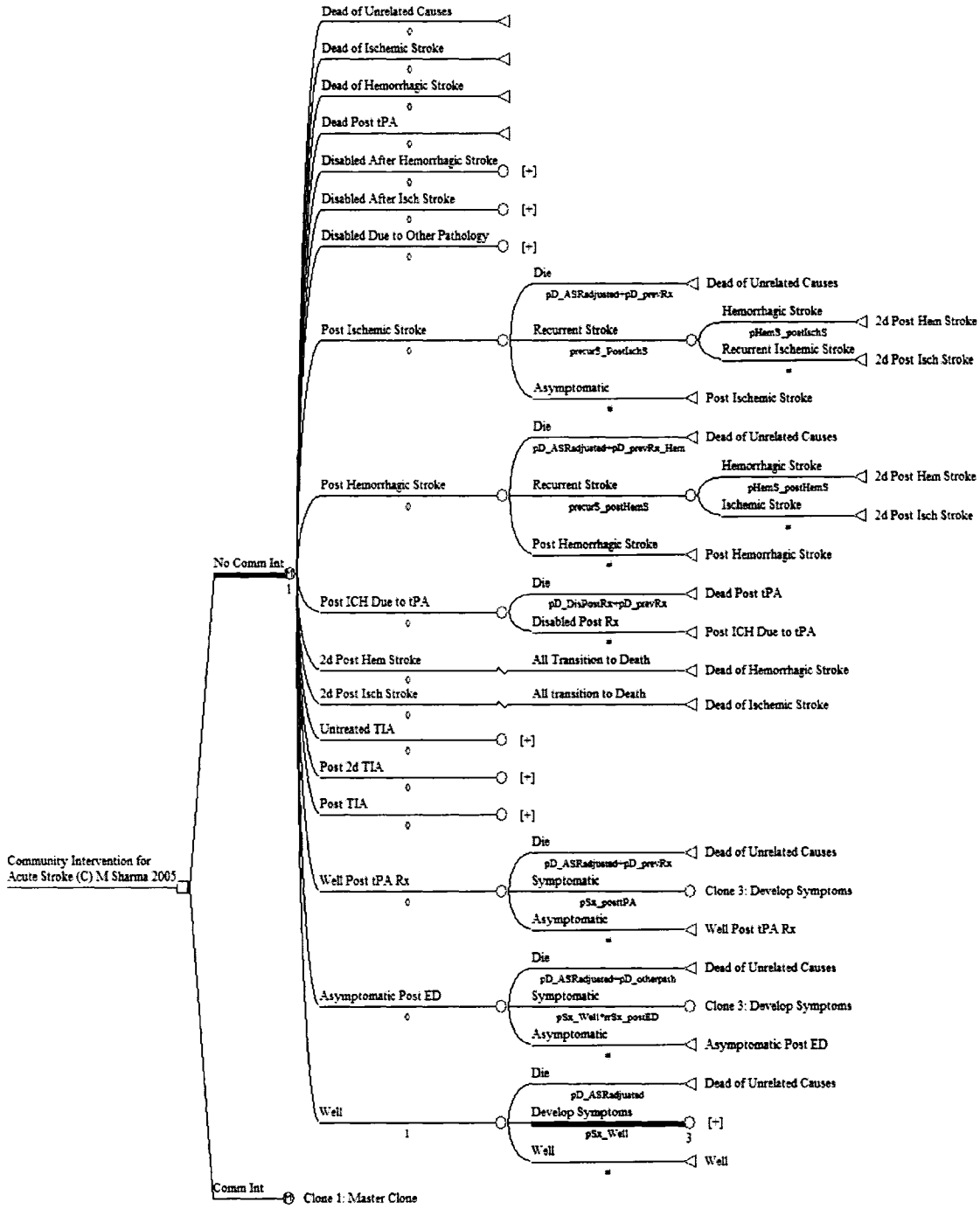

Figure 4 **Model Structure from the Well State**
The population begins in the Well state with possible transitions as shown. Transitions from asymptomatic and post-stroke states with no disability are also shown.

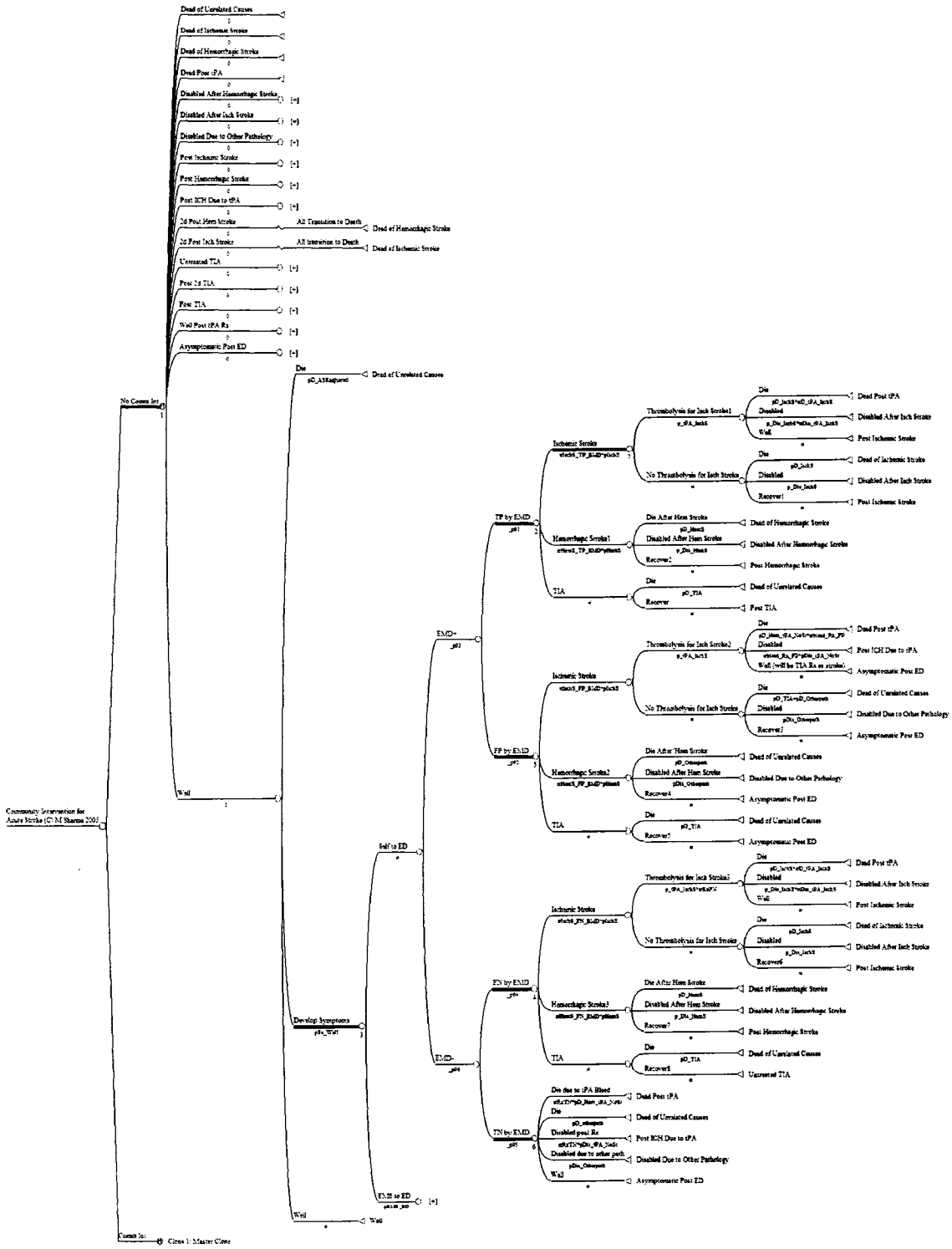

Figure 5 **Transitions from the Develop Symptoms node and Self to ED nodes**

The following 2 figures provide expanded views of the structure beyond the Self to ED node.

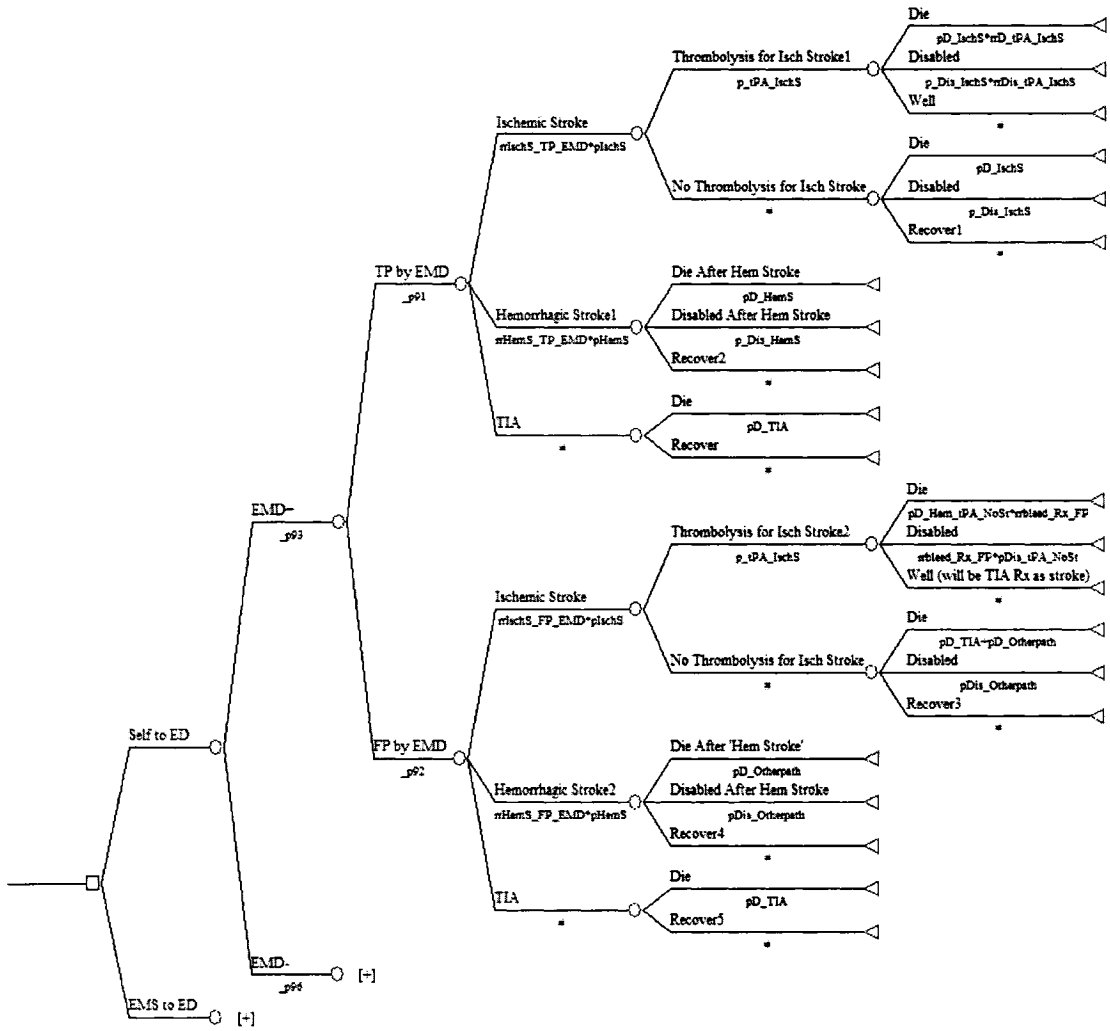

Figure 6 **Transitions from the EMD + node**

Expanded view of the structure and transitions of the EMD+ node which represents a positive diagnosis in the ED. The diagnosis may be a true positive (TP by EMD) or a false positive (FP by EMD).

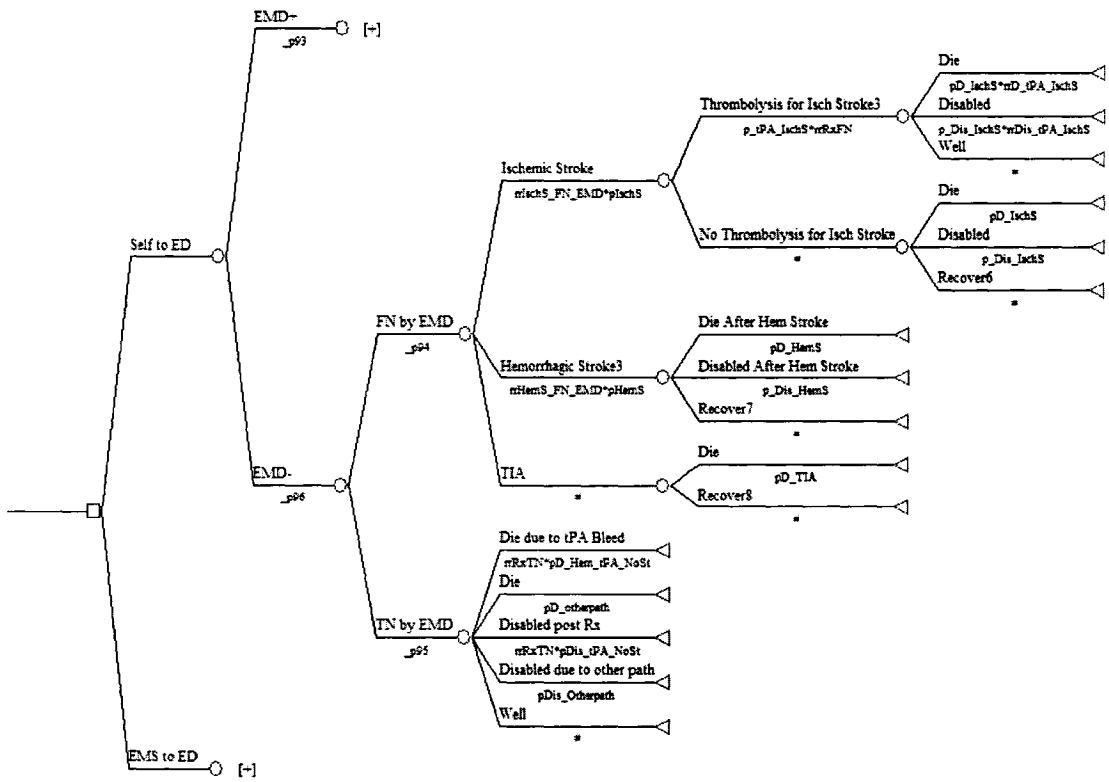

Figure 7 **Transitions from the EMD- Node**

The Node EMD- represents a negative diagnosis in the ED. The diagnosis can be a true negative (TN by EMD) or a false negative (FN by EMD).

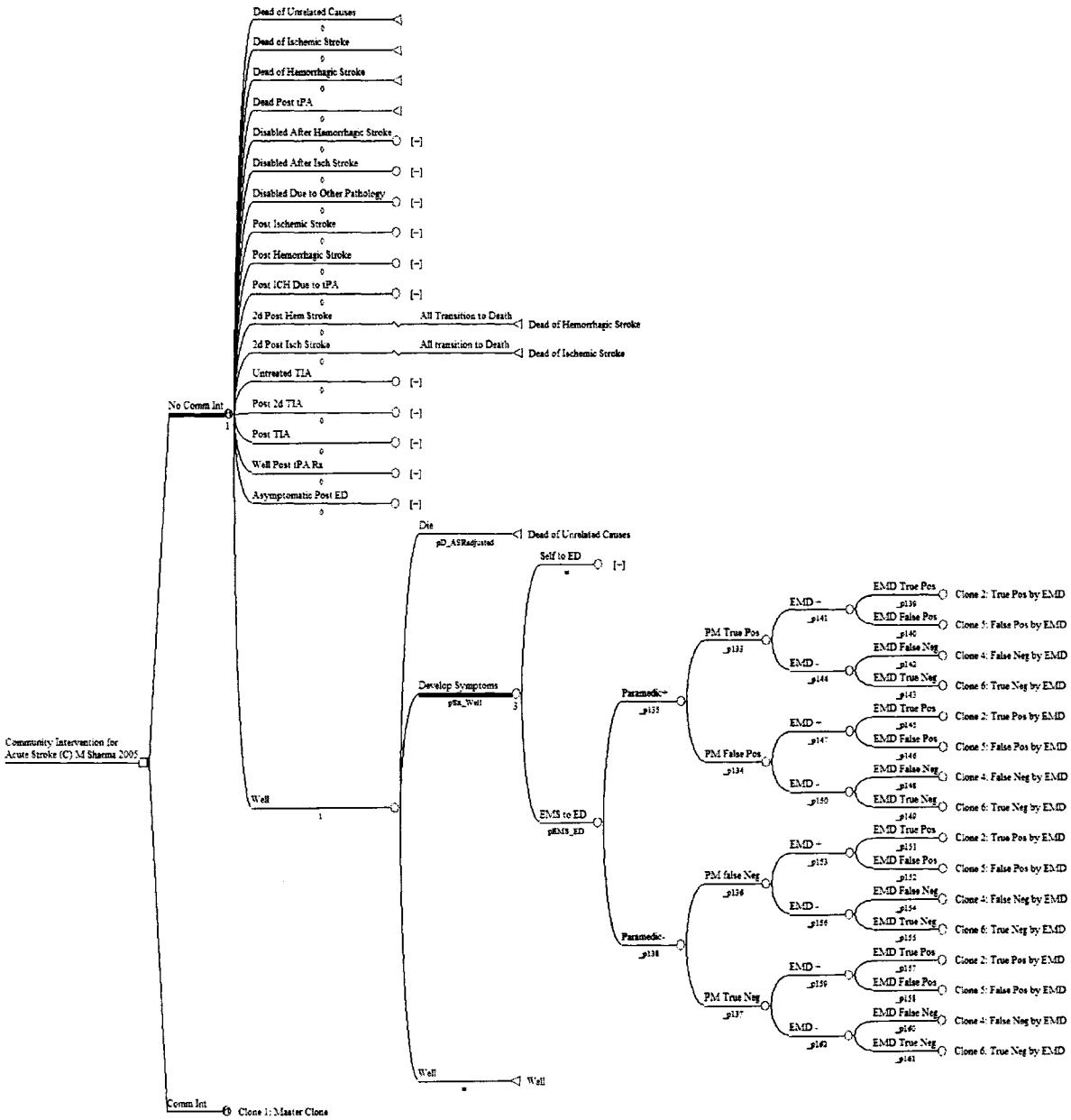

Figure 8 **Structure from the EMS to ED Node**

The EMS to ED node involves ambulance transport and paramedic assessment of the diagnosis. The paramedic diagnosis may be positive (true or false) or negative (true or false). Bayes revision was used to calculate probabilities following paramedic and ED assessment. The subsequent structure is identical to the Self to ED structure after ED diagnosis.

4.3 Model Features

As noted, the standard assumption in Markov models is that transition probabilities depend only on the state occupied. This is clearly not the case in healthcare as such probabilities may depend on demographic data or previous history. Mortality is strongly linked to age and thus a table of age-specific mortality rates (114) is used to calculate unrelated mortality. For each cycle, age is calculated and the appropriate mortality retrieved from the table for definition at the root node.

Permitting transitions at the end of the cycle equates to the counting of membership in each cycle at the beginning of the cycle. This has the effect of overestimating survival as transitions may actually occur at any point within the cycle. To correct for this, the rewards accrued in the first cycle are set at half the value of those for each subsequent cycle. This has the effect of simulating transitions at the midpoint of each cycle and is termed the half-cycle correction (99).

The medical literature reports occurrences over varying time frames as rates. Modeling requires a conversion of these rates to probabilities. This is done by means of the following relationship (115):

$$\text{Probability} = 1\text{-}e^{\text{-rate*time}}$$

Where time = Duration of rate period/ Duration of probability period

This model uses a cycle length of 1 month. This is consistent with the time frame

in which events occur in the stroke population as well as the scale at which data can be retrieved from the literature. Consistent with the intent, a societal perspective is assumed.

4.4 Input Data

Model input data including transition probabilities and utilities were collected from the literature using Medline searches. The sources and ranges used are detailed in table 1. For each parameter the period from 1966 to Dec 2003 was searched. Where available; systematic reviews were selected for abstraction of parameter estimates.

Bibliographies of all selected papers were reviewed for additional sources. Systematic reviews were conducted of community interventions in stroke and chest pain and are detailed below in section 5.

Published data were supplemented as required by the Registry of the Canadian Stroke Network (RCSN). This registry was established by the Canadian Stroke Network in 2001. It is currently operating at 9 Canadian stroke centers. Each site has a nurse investigator who prospectively collects emergency room data regarding TIA and stroke. Outcome data and process data are likewise collected for hospitalized patients. The Ministry of Health of Ontario has compiled this data for program evaluation. Access was made through Alexis Dishaw of the Priority Programs Branch of the Ministry of Health, Toronto, Ontario.

4.5 Outcomes

Three outcomes were considered in this model: life years, quality adjusted life years, and discounted quality adjusted life years.

Discounting has become standard in decision analysis. Use of the same discount rate in analyses permits comparison between analyses and lost time. The model utilized a discounted rate of 5% as recommended by published guidelines CCOHTA (109,109)

4.6 Model Analysis

Each parameter has an associated uncertainty (i.e. variation due to sampling and measurement error) and variability (ie heterogeneity based on differences between members of the population). Sensitivity analyses were used to assess variability while probabilistic Monte Carlo simulation assessed uncertainty.

One-way sensitivity analyses were performed for each model parameter over the range of values shown in table 1. The range was the 95% confidence interval of empirical variables and a reasonable range based on expert input for estimated variables. For each analysis, the remaining parameters were held constant at their expected values.

Two-way sensitivity analyses require the calculation of expected values in the tree when two parameters are simultaneously varied over their respective ranges. The preferred choice is that which has the highest expected value. Results are plotted on a surface with each axis representing one of the varied parameters. The resulting surface

then reflects the range of these parameters in which each choice is preferred.

Each parameter estimate has a degree of uncertainty associated with its value. The uncertainty is reflected by assigning a probability distribution around the expected value. Monte Carlo simulation permits an assessment of uncertainty by performing simulations through the model with parameter choices made from the prespecified distribution for each parameter. The results are presented as a frequency distribution of expected values. This permits an assessment of the uncertainty around the expected value of each option. Simulations of this type are computationally very intensive. For this model a beta distribution was assigned to probabilities, a normal distribution for utilities and a triangular distribution was used for estimated values where the underlying natural distributions of the parameters were not known (i.e. estimated parameters). Probabilities from very large cohorts (> 10,000) were taken as exact. One thousand simulations were run for each payoff. This number of simulations was consistent with the computation resources available.

4.7 Systematic Reviews of Community Interventions

4.7.1 Systematic Review of Community Interventions in Stroke

It was anticipated that the effectiveness of community interventions for patients with stroke would be a key variable. Therefore a systematic review was performed to establish a base case and range for this parameter.

A search strategy was developed with the aid of an information specialist for Medline 1966 to November 2003 and is shown in appendix 2. The strategy was adapted

for Current Contents, Dissertation Abstracts (1861 to Nov 2003), Cinahl and the Cochrane Controlled Trials Register (2nd Quarter 2003). Each database was searched separately. Two health system researchers working in the field of stroke and one media specialist working for the Heart and Stroke Foundation of Ontario were contacted to identify unpublished trials. The reference lists of all retrieved papers were examined for additional sources. All references retained were entered into Reference Manager and the duplicates removed. Hard copies of all such identified studies were obtained. One reviewer abstracted data from all eligible studies. The study design, intervention, and primary effect estimates were abstracted. Quantitative data synthesis was planned along with analysis of subgroup analysis by type of media used for the intervention.

Randomized controlled trials, controlled trials without randomization and time series analyses assessing the effectiveness of community interventions involving media or education programs whose intent was to decrease the time between symptom onset and presentation in acute stroke were valid for inclusion. Any community intervention involving media or education programs including but not limited to television, radio, newspapers, billboards, leaflets, posters, speeches or presentations was valid for inclusion. The target population for these programs was the general population thus programs aimed specifically at professionals or patients who have already had symptoms were excluded. Outcomes had to include the proportions of patients presenting within three hours and therefore potential candidates for acute thrombolysis.

4.7.2 Systematic Review of Community Interventions in Patients with Chest Pain

The use of thrombolytic therapy for myocardial infarction preceded its employment in stroke by over a decade. The results of therapy in both conditions is strongly linked to time to treatment and there exists a strong desire to decrease delay to treatment. Thus, the results of evaluations of community intervention targeted at chest pain may be of direct relevance to similar interventions in stroke.

A search strategy for Medline was developed with the aid of an information specialist and is shown in Appendix 3. Medline was searched from 1966 – October 2004. The strategy was adapted for Current Contents, Dissertation Abstracts (1861- March 2002; this database was unavailable when the search was repeated in October 2004) and the Cochrane Controlled Trials Register (2004 Issue 3), as a surrogate for hand searching. Each database was individually searched. Two investigators in the field and one content expert (cardiologist) were consulted regarding the possibility of other published or unpublished literature. The search strategy did not restrict language. Unpublished studies were specifically sought as above.

Randomized controlled trials, controlled trials without randomization and time series studies which assessed the effectiveness of community interventions in decreasing the time between symptom onset and presentation to a medical facility of adults with chest pain were eligible for inclusion. Any community intervention involving media or education programs including but not limited to television, radio, newspapers, billboards,

leaflets, posters, speeches or presentations was valid for inclusion. The target population for these programs was the general population thus programs aimed specifically at professionals or patients who have already had symptoms were excluded.

One reviewer screened titles and abstracts of studies identified in the search. Inclusion criteria were liberally applied at this stage to increase the sensitivity of the process. Any studies that fell into the uncertain category were retained for the next phase.

All references retained were entered into Reference Manager and the duplicates removed. Hard copies of all such identified studies were obtained. Two reviewers abstracted data from all eligible studies. The study design, intervention, numbers in the reference and intervention groups along with primary effect estimates were abstracted. Available data on hospital utilization, morbidity and mortality were extracted. As various study designs were included in this review a quantitative data synthesis was not possible.

5 RESULTS

5.1 Input Parameters

Input parameters for the model are summarized in table 1.A description of the parameter sources and assumptions follows the table.

Table 1 Input Data for Decision Model

Parameter	Value and Range for Sensitivity Analyses		Source
1.Additional probability of thrombolysis from intervention:	0.045	(0, 0.09)	(Systematic Reviews)
2.Probability of disability due to non-stroke pathology	0.0001	(0, 0.0002)	Estimate
3.Probability of disability due to hemorrhage with TPA in the absence of stroke	0.253	(0.20, 0.306)	(116;117)
4.Probability of dying when disabled post-treatment	0.0408	(0.0305, 0.0511)	(3)
5.Probability of death disabled post-hemorrhagic stroke	0.0408	(0.0305, 0.0511)	(3)
6.Probability of death disabled post-ischemic stroke	0.0198	(0.01, 0.03)	(3)
7.Probability of death due to hemorrhagic stroke	0.40	(0.306, 0.466)	(3)
8.Probability of death due to hemorrhage with TPA in the absence of stroke	0.47	(0.41, 0.53)	(116;117)
9.Probability of death due to ischemic stroke	0.10	(0.05, 0.20)	(3)
10.Probability of death due to non-stroke pathology	0.00015	(0.0001, 0. 001)	Estimate
11.Probability of death due to preventive treatment for ischemic stroke	3.244x10^-6,	(1.35x10^-6, 5.41x10^-6)	(118,119)
12.Probability of death due to preventive treatment for hemorrhagic stroke	3.24x10^-9	(1.35X10^-9, 5.41X10^-9)	Estimate
13.Probability of taking the ambulance service to the Emergency Department	0.45	(0.39, 0.502)	(120)
14.Probability of hemorrhagic stroke	0.134	(0.12, 0.147)	(8;81)
15.Probability of ischemic stroke	0.70	(0.65, 0.71)	(81)
16.Probability of recurrent stroke post-hemorrhagic stroke	6.9x10^-4	(3.0x10^-4, 1.0x10^-3)	(3)
17.Probability of recurrent stroke post-ischemic stroke	3.4x10^-3	(2.8x10^-3, 4.4x10^-3)	(128;129;130)
18.Prevalence of stroke	0.02	(0.01,0.04)	(120,121)
19.Probability of symptoms when disabled by non-stroke pathology (Age Specific)	3.62x10^-5	(2.7x10^-5, 1.64x10^-4)	(3)
20.Probability of symptoms post-TIA	4.6x10^-2	(3.6x10^-2, 5.6x10^-2)	(128;129;130)
21.Probability of symptoms post-TPA	4.6x10^-2	(3.6x10^-2, 5.6x10^-2)	(128;129;130)
22.Probability of symptoms when well (Age Specific)	3.63x10^-5	(2.7x10^-5, 1.64x10^-4)	(3)
23.Probability of disability due to hemorrhagic stroke	0.466	(0.233, 0.699)	(81)
24.Probability of disability after ischemic stroke	0.55	(0.275, 0.825)	(81)
25.Probability of TPA for ischemic stroke	0.06	(0.029, 0.206)	(81)
26.Relative risk of bleeding when a false positive is treated	0.0095	(0.0045, 0.0145)	(116;117)
27.Relative Risk of Disability when TPA for Ischemic stroke	0.66	(0.66, 0.83)	(77)
28.Relative risk of death when disabled by another pathology	1.01	(1.0, 1.5)	Estimate
29.Relative risk of death when TPA given for ischemic stroke	0.97	(0.69, 1.36)	(77)
30.Relative risk of using the Emergency Medical System with the intervention	1.25	(1, 1.5)	(122)
31.Relative risk of a hemorrhagic stroke when false negative by the Emergency Dept	0.0001	(0.00005,0.00015)	Estimate

Table 1 Input Data for Decision Model

Parameter	Value and Range for Sensitivity Analyses		Source
32.Relative risk of hemorrhagic stroke when false positive by the Emergency Dept	0.001	(0.0005, 0.0015)	Estimate
33.Relative risk of symptoms post-emergency department	1.001	(1.0005, 1.0015)	Estimate
34.Relative risk of symptoms post-TIA untreated	1.16	(1.13,1.25)	(123124)
35.Relative risk of using TPA through arrival by ambulance	2.3	(1.15,3.45)	(81)
36.Sensitivity of Emergency Room diagnosis	0.986	(0.973,0.999)	(125)
37.Sensitivity of Paramedic diagnosis	0.59	(0.50, 0.66)	(121)
38.Specificity of Emergency Room diagnosis	0.998	(0.997,0.999)	(125)
39.Specificity of Paramedic diagnosis	0.88	(0.80,0.96)	(121)
40.Start age	38	(30,60)	(126)
41.Transient disutility disabled by ischemic stroke	-1	(-0.5,-1.5)	Estimate
42.Transient disutility disabled by other pathology	-0.4455	(-0.2,-2.0)	Estimate
43.Transient disutility disabled by hemorrhagic stroke	-1	(-0.5,-1.5)	Estimate
44.Transient disutility due to hemorrhagic stroke with no residual disability	-0.5	(-0.25,1.0)	Estimate
45.Transient disutility due to ischemic stroke with no residual disability	-0.5	(-0.25,-1.0)	Estimate
46.Transient disutility due to other pathology with no residual disability	-0.0329	(-0.15,-0.6)	Estimate
47.Transient disutility due to TIA	-0.0329	(-0.15,-0.06)	Estimate
48.Transient disutility due to ER visit	-0.0329	(-0.15,-0.06)	Estimate
49.Utility for disability from hemorrhage stroke	0.433	(0.30,0.54)	(104)
50.Utility for disability from ischemic stroke	0.433	(0.30,0.54)	(104)
51.Utility for disability due to other pathology	0.55	(0.50,0.70)	(127)
52.Utility for disabling hemorrhage caused by TPA	0.433	(0.30,0.54)	(104)

Description of Model Inputs

The model inputs are enumerated below with an explanation of the source of the inputs and location(s) within the model. Inputs are sequenced as in table 1. Comments are provided regarding assumptions made in arriving at the values and possible biases on the parameter value.

1. Additional probability of treatment with intervention: AddRx_commint occurs at the node Commint. This input is the additional probability of receiving thrombolytic treatment for a diagnosis of ischemic stroke in the emergency room following community intervention. The probability of treatment in the intervention branch is defined as the baseline plus this additional probability. There is insufficient data in the stroke literature to define a relationship between the pre and post intervention probabilities. This estimate was the mean of the estimates from the 2 systematic reviews. The stroke review yielded an estimate of 0.09 while the chest pain review an estimate of 0. This is a conservative estimate as, for example, The Ottawa Hospital reports a treatment probability of 0.21 for the period September 2004 to March 2005 over a probability of 0.02 in 2002 (81). This improvement was achieved with a multilevel approach that included professional education and reorganization of the ER and a new treatment protocol. As these interventions were not the target intervention, these data were not used to generate the estimate for this parameter. The current mean in Ontario is 0.1, achieved by using a set of interventions similar to the Ottawa Hospital. Thus the treatment probabilities used in the model fall within a plausible range.

2. Probability of disability due to non-stroke pathology: p_Dis_Otherpath occurs at the nodes Disabled by other path in the true negative ED diagnosis arm, Disabled and

Disabled After Hem Stroke in the false positive ED diagnosis arm. This represents the probability of permanent disability due to conditions other than stroke which have similar symptoms and thus might be mistaken for stroke. A published source was not identified and expert opinion was sought from 3 neurologists who see the bulk of the referrals for a patients presenting with symptoms suggestive of stroke from the ER at The Ottawa Hospital. It was their opinion that such disability would be the result of conditions rarely mistaken for stroke such as neoplasms and multiple sclerosis while the bulk of the referrals represented benign or treatable conditions such as migraine aura, carpal tunnel syndrome, benign positional vertigo or transient global amnesia. Thus the estimate was felt to be low. A formal consensus process was not followed for this estimate. The input occurs in the model for all true negative and false positive diagnoses of stroke. It was accepted by all experts that the distribution of disabling conditions was similar for each group. This estimate could be improved by obtaining a sample of cases, preferably from multiple centers to avoid biases based on local practice patterns and calculating an estimate based on the relative proportion of each diagnosis weighted by the likelihood of causing disability.

3. Probability of disability due to hemorrhage with TPA in the absence of stroke: pDis_tPA_NoSt occurs in the model in the branch representing TPA treatment after false positive stroke diagnosis at the node Disabled following Thrombolysis for Isch Stroke2. It is shown in the true negative and false negative subtrees but the relative risk of treatment in these subtrees is zero (rrRxTN and rrRxFN are zero).Two sources were identified describing the occurrence of stroke in groups treated for myocardial ischemia with TPA. Gore et al (117) reported on the complications of thrombolytic therapy in the GUSTO trial. Approximately 10,000 patients were treated with TPA in this trial in the

setting of MI. As patient and site selection may influence the outcomes of clinical trials a second estimate was obtained from a registry of over 71,000 patients treated in the US at over 1484 centers (116).This was the estimate used. It was assumed that the risk and outcome of hemorrhage in this population was the same as that in the population with a false positive diagnosis of stroke. The study was from a population with symptomatic vascular disease which is expected to have a higher mean age and greater probability of hyperglycemia than a population composed of alternate diagnoses listed above. Both age and hyperglycemia were identified in the CASES (47) as independent risk factors for treatment related hemorrhage and thus may result in a slight overestimate of the risk.

4. Probability of dying when disabled post-treatment: (pD_DisPostRx) This parameter is the probability of dying when disabled due to a hemorrhage post TPA treatment. It occurs in the model at the node Post ICH due to TPA. No published source for this parameter was identified and it was assumed that this probability was identical to the probability of death for survivors of a hemorrhage not associated to treatment. A Canadian estimate was sought in the published literature and unpublished data from the Heart and Stroke Foundation, and the Canadian Stroke Network but no source was identified thus American data was used. Matchar and colleagues working as part of the Patient Outcomes Research Team (PORT) published estimates of the rates of death and disability in both ischemic and hemorrhagic stroke using published and unpublished data (3). The primary goal of this large project was the identification of cost effective strategies of stroke prevention. As part of the project a model was constructed of stroke care. Incidence rates along with rates of mortality and disability were required to populate the model. These rates were obtained from a systematic review of the literature, along with data obtained from The Framingham Study, Rochester/Olmstead County Epidemiologic

Project, the NASCET trial investigators, the CHS and a population based study in Milan, Italy. This supplemented a cohort assembled from a 20% random sample of Medicare enrollees (n = 265,795) admitted to hospital with a primary diagnosis of stroke in 1991 was used to estimate incidence and assemble survival data. In order to establish a cohort of incident strokes patients were removed if there was a claim for stroke during the years 1987-1990. Patients might not be admitted to hospital if the stroke is felt to be mild, if hospitalization is felt to be unhelpful in the clinical context or refused by the patient. Data from the Rochester stroke registry were used to calculate the ratio of hospitalized to non-hospitalized strokes. This ratio was then used to adjust the incidence estimate for the sample as a whole. It was assumed that the mortality experience and disability rates were identical to those of the hospitalized population. Strokes which occurred during hospital admissions for other primary diagnoses were not included in this sample. It was assumed that the mortality rate for the same for disabled and nondisabled components of this population .The parameter value was taken as the probability of dying following hemorrhagic stroke. The PORT description of the natural history of stroke was used to calculate a number of transition probabilities. These estimates, while supplemented from other sources depended heavily on the Medicare database which is unlikely to be reflective of the Canadian population in respect to racial and economic status and the availability of primary health care. These factors would be expected to overestimate incidence, disability and mortality in the Canadian population. Likewise the assumption that the mortality and disability rates are the same in the hospitalized and non-hospitalized portions of the sample likely overestimates mortality and disability rates. As the Rochester Stroke Registry estimates of the ratio of non-hospitalized to hospitalized cases ranged from 11% to 21% the impact of this may be less than the consequences of population and health care system differences. Statistics Canada has been approached

regarding the feasibility of estimating stroke incidence from Canadian administrative databases. In hospital strokes are a relatively small proportion of all strokes and their absence from the PORT sample is not expected to bias the estimates significantly. The Registry of the Canadian Stroke Network (RCSN) recorded 4% of strokes onset during hospitalization between April 2004 and March 2005 (8181).

5. Probability of death disabled post-hemorrhagic stroke: (pD_Dis_postHemS) This parameter is the probability of dying when disabled following a cerebral hemorrhage. It occurs in the node labeled: Disabled After Hemorrhagic Stroke. The estimate and source are identical to input 4 discussed above. It was assumed that the mortality of the population surviving an ICH was the same as those with ICH due to TPA treatment.

6. Probability of death disabled post-ischemic stroke: (pD_Dis_postIschS) This parameter represents the probability of death following a disabling ischemic stroke. It occurs in the model in the node labeled: Disabled After Ischemic Stroke. The estimate is obtained from the PORT report discussed above.

7. Probability of death due to hemorrhagic stroke: (pD_HemS) This parameter represents the probability of dying due to an ICH during the first cycle after occurrence. It occurs in the branches labeled: Die After Hemorrhagic Stroke at the nodes labeled: Hemorrhagic Stroke1 and Hemorrhagic Stroke2. The estimate is obtained from the PORT report discussed above. This report provides the probability of death during the index hospitalization. As the model cycle length is 1 month and the current mean length of hospitalization in the Registry of the Canadian Stroke Network is 10 days (81), this is a

reasonable estimate of the transition probability to the health state Dead of Hemorrhagic Stroke.

8. Probability of death due to hemorrhage with TPA in the absence of stroke: (pD_Hem_tPA_NoSt) This represents the probability of death due to hemorrhage caused by TPA treatment in the absence of stroke in the first cycle after treatment. It occurs in the model in the false positive diagnosis arm (FP by EMD) in the branch labeled: Thrombolysis for Isch Stroke. The estimate was obtained from mortality risks for TPA treatment in acute MI (116,117) and represents the weighted mean of the estimates from these sources. These sources are described above under input 3.

9. Probability of death due to ischemic stroke: (pD_IschS) This parameter is the probability of death within the first cycle after occurrence. It occurs in the model on branches labeled: Die which follow those labeled Thrombolysis for Ischemic Stroke1, 2, 3 and in the corresponding location following the No Thrombolysis for Isch Stroke nodes. The PORT report estimate of mortality during the acute hospitalization was the source for this estimate. This source is described under parameter 3 above.

10. Probability of death due to non-stroke pathology: (pD_Otherpath) This parameter represents the risk of death within the cycle of patients presenting with stroke symptoms due to non stroke pathologies. It occurs in the false positive by EMD arm at the Die After 'Hem Stroke', and Die nodes. It also occurs in the TN by EMD branch at the Die node. No published source for this probability was identified. Thus the value was estimated using the process described for parameter 2 above.

11. Probability of death due to preventive treatment for ischemic stroke: (pD_prevRx) The mainstay of stroke prevention post TIA is antiplatelet therapy. While these agents reduce the risk of ischemic stroke they increase the risk of hemorrhagic stroke. This parameter is the cycle specific probability of death due to the use of these agents and occurs in the post TIA states of the model (Post TIA, Post 2d TIA) and the post stroke states (Post ischemic stroke, Post hemorrhagic stroke, Post ICH due to TPA). The mortality estimates for the disabled post stroke states were derived from a treated population and thus incorporated this risk. Jiang He and colleagues reported a metanalysis of the bleeding complications associated with ASA use (118). A total of 16 English language trials of antiplatelet therapy comprising 55,426 patients were included in the analysis. The estimate for fatal bleeding due to ASA was calculated assuming that the proportion of deaths was the same as that for the hemorrhagic stroke population as a whole and that other antiplatelet agents used in this population have identical risks. All patients were assumed to be treated. This assumption is consistent with the results of trials comparing ASA and the other 2 common choices for antiplatelet therapy in stroke prevention: clopidrogel and ASA+extended release dipyridamole.

12. Probability of death due to preventive treatment for hemorrhagic stroke: (pD_prevRx_Hem) Antihypertensive agents are commonly used in the prevention of hemorrhagic stroke. This cycle specific probability was applied to the post hemorrhagic stroke states with the assumption that all patients were treated. No published source was identified and the estimate was based on the opinion of 1 Medical Director of a stroke program and an internist familiar with the treatment of hypertension.

13. Probability of taking the ambulance service to the Emergency Department: (pEMS_ED). This parameter is the probability of using the EMS system to get to the ED when symptoms develop. It occurs in the model in the EMS to ED arm after the node identified as develop symptoms. Two sources were used for this parameter. Barsan et al reported the probability of ambulance usage in this population in the process of noting process changes in acute stroke care during the course of a clinical trial (122) . In addition the Ottawa Hospital records for 2004 were reviewed. The number of ED records coded for stroke by the RCSN nurse was obtained along with the mode of arrival was obtained from these records. A weighted mean was calculated from these 2 sources. This parameter may vary depending on location and time period. Measurements from other centers would be helpful in assessing the variability.

14. Probability of hemorrhagic stroke: (pHemS) This parameter represents the probability that an individual with stroke symptoms has a hemorrhagic stroke. It occurs in the model in the EMD positive and negative arms at the nodes Hemorrhagic Stroke1, 2, 3 and is modified by a relative risk estimated for each diagnostic scenario. Data from the RCSN and the American Heart Association (AHA) formed the sources for this estimate. The RCSN database is described in section 4.4 while the AHA report summarizes data compiled from 3 separate cohorts: the Greater Cincinnati Northern Kentucky Stroke Study, the Framingham Heart study and the Atherosclerosis Risk in Communities study. The probability was assumed to be the weighted mean value from these cohorts.

15. Probability of ischemic stroke: (pIschS) This parameter represents the relative risk that a stroke is ischemic. It occurs in the model following the EMD positive and negative arms at the nodes labeled Ischemic Stroke with relative risks modifying each scenario. The sources are described for 15 above.

16. Probability of recurrent stroke post-hemorrhagic stroke: (precurS_postHemS) This parameter is an estimate of the cycle specific probability of stroke in the population surviving an ICH. It occurs in the branch following the health state Post Hemorrhagic Stroke. It was assumed that this incidence as the incidence in the population included in the PORT cohort. As some etiologies for stroke hemorrhage may lead to an increased risk of subsequent hemorrhage (e.g. multiple cavernous angioma) this may represent a slight underestimate. The estimate was obtained from the PORT report described above under input 4.

17. Probability of recurrent stroke post-ischemic stroke: (P_ recurS_PostIschS) This parameter represents the probability of recurrent stroke in the population who have had a recurrent stroke. It occurs at the node Recurrent Stroke attached to the health state Post Ischemic Stroke. The value was obtained from three sources. Burn et al reported the results of the Oxfordshire Community Stroke Project (128). Six hundred seventy-five patients were enrolled in a community based stroke register and prospectively followed for 6.5 years. The Dutch TIA Study Group prospectively followed 3127 unselected patients with TIA or stroke for a mean period of 2.6 years (129). Finally the North American Symptomatic Carotid Endarterectomy Trial randomized patients into carotid surgery or medical treatment for a period of 5 years (130). The medical treatment arm provided data on 1118 patients. This cohort provided data on patients with carotid

stenosis who were not included in the Dutch TIA trial and may have been referred directly to surgery thereby missing enrollment in the registry. The rate of recurrence per year was obtained and assumed to be constant. A weighted mean value was calculated.

18. Prevalence of stroke: This parameter represents the prevalence of stroke in the population arriving in the ER. It is the pretest probability of stroke prior to paramedic or ED evaluation. The value was obtained from the Ottawa hospital records using the total number of ED visits for 2004 and the total number of visits coded as stroke(120).

19. Probability of symptoms when disabled by non-stroke pathology: (pSx_Dis_otherpath) This parameter is the probability of symptoms in the population disabled by pathology. It occurs at the node Disabled Due to Other Pathology. As noted above this group is composed of a number of diagnoses which are not expected to change their stroke risk. It was assumed that this population had the same probability of developing symptoms as the well population. The data from the PORT report provided the probability of stroke by age. In order to adjust for the possibility of stroke and nonstroke pathology the RCSN data for the Ottawa hospital for the period 2004 were used. It was assumed that given the mixture of possible nonstroke pathologies, this group would have the same proportion of nonstroke presentations as the sample. It was assumed that the proportions of TIA and nonstroke symptoms were constant by age. The model uses a table of probability by age. The table gives the value for age 60.

20. Probability of symptoms post-TIA: (pSx_postTIA) This parameter represents the probability of stroke or TIA in the group which has had a TIA. It occurs at the node Recurr Symptoms at the health state Post TIA. The Oxfordshire, NASCET and Dutch

cohorts described in input 17 above were used as sources. As the model permits TIA or stroke following this health state the probability was corrected by the by the relative proportion of TIA and nonstroke symptoms in the RCSN data described above.

21. Probability of symptoms post-TPA: (pSx_posttPA) This parameter represents the probability of stroke or TIA in the population previously successfully treated for stroke. No published source was identified for this population and it was assumed to follow the natural history of the NASCET, Dutch and Oxfordshire cohorts described above under input 17. The value was adjusted for the possibility of TIA, or nonstroke symptoms as for 20.

22. Probability of symptoms when well: (pSX_Well) This parameter is the probability of developing symptoms in the well state. Symptoms may be due to stroke TIA or nonstroke pathology. The PORT document provided the age specific incidence of stroke which was adjusted to allow for TIA and nonstroke symptoms as described in 19 above. This parameter is represented in the model as an age specific table. It was assumed that the proportion of TIA and nonstroke did not vary with age. The model uses an age specific table for this parameter.

23. Probability of disability due to hemorrhagic stroke: (p_Dis_Hems) This parameter is the probability of being disabled due to a hemorrhagic stroke. It occurs in the true positive and false negative subtrees of the model at the Hemorrhagic Stroke1 and 3 nodes. In keeping with the systematic review of stroke utilities (104) disability was defined as a Rankin score of 2-5. The RSCN data for the period 2004 were used to provide this probability. These data provide the distribution of discharge Rankin scores by stroke type.

24. Probability of disability after ischemic stroke: (p_Dis_ Isch) This parameter represents the probability of disability (Rankin 2-5) due to ischemic stroke. As for the probability of disability due to hemorrhagic stroke, the RSCN data for the period 2004 were used to provide this probability. These data provide the distribution of discharge Rankin scores by stroke type.

25. Probability of TPA for ischemic stroke: (p_tPA_IschS)This parameter represents the probability of receiving TPA when diagnosed with an ischemic stroke. It occurs in the true positive and false positive subtrees of the model at the nodes Thrombolysis for Ischemic Stroke1 and 2. It also occurs at the node Thrombolysis for Ischemic stroke3 but here it is modified by the relative risk of treating a false negative which is zero. The CASES study (47) provided this value with data collected prospectively from 60 Canadian stroke centers for the period Feb 17, 1999 to June 30, 2001. The centers included in the study were academic and non- academic and were not restricted to a particular province. A total of 1135 patients were enrolled from these centers. Based on an audit of admission records for the diagnosis of stroke a treatment probability was calculated (131). The probability used is consistent with the reported current mean probability of 0.1 reported within the Ontario stroke system. This result is the result of implementation of multilevel system changes in the province of Ontario and thus was not used as for the pre-intervention probability in the model. The CASES database represents the first 2.5 years of approval of TPA for stroke in Canada and thus is a more appropriate source of this estimate.

26. Relative risk of bleeding when a false positive is treated : (rrbleed_Rx_FP) This parameter is the probability of bleeding treating a false positive diagnosis of ischemic stroke. The parameter was estimated from the data on MI patients treated with TPA. See parameter 3 for discussion of sources.

27. Relative Risk of Disability when TPA for Ischemic stroke: (rrDis_tPA_IschS) This parameter represents the relative risk for disability when TPA is used for ischemic stroke. It occurs at the nodes labeled Disabled following The branches Thrombolysis for Ischemic Stroke 1 and 3. The Cochrane meta-analysis of thrombolysis for ischemic stroke(77) reports on 10 trials with 1338 patients treated within 3 hours of onset as specified in the treatment protocol (Appendix 1). This search strategy included the Cochrane Stroke Group trials register, Medline and Embase. In addition pharmaceutical companies and researchers were contacted for unpublished data. Journals and conference proceedings were hand searched. Eighteen trials were included in the results though not all contributed to this outcome as not all protocols treated with 3 hours of onset.

28. Relative risk of death when disabled by pathology: (rrD_Dis_otherpath)This parameter represents the relative risk of death when disabled by non-stroke pathology. It occurs at the node Die following the health state Disabled Due to Other Pathology. It is applied to the table of age specific death rates adjusted for stroke and was assumed to be age independent. No published source was identified and the estimate was obtained from 2 stroke neurologists.
29. Relative risk of death when TPA given for ischemic stroke: (rrD_tPA_IschS) This parameter represents the relative risk of death when given TPA for ischemic stroke. It

occurs at the nodes Die following Thrombolysis for Ischemic Stroke1 and 3.The Cochrane meta-analysis formed the source for this estimate see input 27 above.

30. Relative risk of using the Emergency Medical System with the intervention: (rrEMS_Commint) This parameter represents the relative risk of engaging the EMS system in the intervention arm. It occurs at the node Comm Int. The estimate was derived from 2 separate sources. The REACT trial described in section 5.2 suggested no impact of the intervention on this rate. Barsan and colleagues noted a benefit in the setting of a stroke trial. In 1994 in order to increase recruitment for the NIH TPA pilot study a public education campaign was instituted a multimedia approach was used with an emphasis on calling 911 if symptoms occurred. Percentage arrival of stroke patients by ambulance is reported. Due to the lack of a control group a causal relationship between the campaign and the improved EMS usage cannot be established. A mean value was used from these sources. It was assumed that this factor was a constant and did not vary with the baseline EMS usage.

31. Relative risk of a hemorrhagic stroke when false negative by the Emergency Physician: (rrHemS_FN_EMD) This parameter represents the relative risk of a hemorrhagic stroke when given a false negative diagnosis by the ED. It occurs at the node Hemorrhagic stroke3. No published source was identified and the estimate was obtained by the expert opinion of 2 stroke neurologists.

32. Relative risk of hemorrhagic stroke when false positive by the Emergency Physician: (rrHemS_FP_EMD) This parameter represents the relative risk of hemorrhagic stroke when a false positive diagnosis of stroke has been made. It occurs at the node

Hemorrhagic Stroke2. No published source was identified and the estimate is derived from the opinion of 2 stroke neurologists.

33. Relative risk of symptoms post-emergency department: (rrSx_postED) This parameter represents the relative risk of developing symptoms in the population that has been discharged from the ER with a diagnosis other than stroke. No published source was identified and the estimate is based on the opinion of 2 stroke neurologists.

34. Relative risk of symptoms post-TIA untreated: (rrSx_postTIA_untreated)This parameter represents the risk of symptom in the population post-TIA which has not received prophylactic medication. It occurs following the health state Untreated TIA at the node Develop Symptoms. The antithrombotic trialists collaboration is a cumulative meta-analysis for antithrombotic therapy in vascular disease (123). The group recently reported the results of the the effect of antiplatelet agents on decreasing recurrence in patients with previous TIA/stroke. A total of 21 trials with 18,271 patients were included. The pooled recurrence rate for the control groups was used and adjusted for TIA and non-stroke symptoms with the proportions from the RSCN dataset as described above.

35. Sensitivity of Emergency Department diagnosis: (sens_EMD) This parameter is the sensitivity of the diagnosis of stroke in the ED. It is used to calculate the post-test probability of stroke at the nodes EMD+, EMD- and the respective TP, TN,FP,FN nodes using Bayes revision. Kothari and colleagues (91) examined the diagnosis of stroke in an urban hospital with a stroke intervention program. The records of 446 consecutive patients for the period May 1992 to June 1993were examined and the final admitting diagnosis of the emergency department compared to the discharge diagnosis after

assessment by a neurologist or neurosurgeon. The ED process of diagnosis in this paper involves discussion with neurology housestaff or neurologists. This process is identical to that used in the Ontario system. Further no significant changes have been made to diagnostic testing for stroke since the period of this study.

36. Sensitivity of Paramedic diagnosis: (sens_PM) This represents the sensitivity of paramedic diagnosis of stroke. It is used to calculate the post-test probability of stroke at the node PM+, PM- and the respective TP, TN, FP, FN nodes using Bayes revision. Kothari and colleagues reported on the accuracy of prehospital diagnosis of stroke through a retrospective review of EMS records for the period Jan 1986 to Oct 1990. Of 4413 records 96 were felt to be TIA or stroke by the EMS staff. Of these 86 were available for study and the diagnoses was compared to that made in the ED or in the patient discharge summary. The authors note that this was prior to the institution of a standard for prehospital diagnosis of stroke in keeping with the primary intent of the model to evaluate community level interventions.

37. Specificity of Emergency Room diagnosis: (spec_EMD) This parameter represents the specificity of stroke diagnosis in the ED. The source and use in the model are discussed under parameter 35.

38. Specificity of Paramedic diagnosis: (spec_PM) This is the specificity of the diagnosis of stroke by EMS staff. For source and description of use in the model see parameter 36.

39. Start age: The mean age of the Canadian population. Obtained from statistics Canada (126)

40. Transient disutility disabled by ischemic stroke: This represents the period of hospitalization for disabling ischemic stroke. The value and range were provided for ischemic stroke as a whole RCSN (81) but were not available by level of disability as represented by the Rankin Score. The opinion of 2 stroke neurologists was sought to provide estimates of length of stay for stroke with disability. A description of the registry is provided in section 4.4.

41. Transient disutility disabled by other pathology: This represents the period of hospitalization for diagnoses presenting to the ED with symptoms similar to stroke which are disabling. A published source was not identified. The value and range are obtained from the expert opinion of 2 stroke neurologists at the Ottawa hospital.

42. Transient disutility disabled by hemorrhagic stroke: This parameter is the period of hospitalization for disabling hemorrhagic stroke. The procedure outlined for parameter 40 was followed.

43. Transient disutility due to hemorrhagic stroke with no residual disability: This is the period of hospitalization for hemorrhagic stroke without disability. The procedure outlined for parameter 40 was followed.

44. Transient disutility due to ischemic stroke with no residual disability: Represents the period of hospitalization for ischemic stroke without disability. The procedure outlined for 40 was followed.

45. Transient disutility due to other pathology with no residual disability: This represents the period of hospitalization for nondisabling conditions with symptoms similar to stroke. The procedure for parameter 40 was followed.

46. Transient disutility due to TIA: This represents the period spent in the ED and ancillary tests for a visit due to TIA. The majority of patients leaving the ED with this diagnosis will be referred for a CT scan of the head, carotid Doppler and echocardiogram and follow up visit. The mean length of stay in the ED itself, prior to the tests, is 6 hours (RCSN (81)). To this was added an estimate of the time required to do the ancillary procedures based on the opinion of a Stroke Prevention Clinic nurse coordinator and the Medical director of a regional stroke program.

47. Transient disutility due to ER visit: This represents the time spent in the ED for diagnoses other than stroke. The estimate was obtained from the opinion of 1 Ed physician and 1 nurse.

48. Utility for disability from hemorrhagic stroke: Utilities for stroke states with disability were obtained from a published systematic review of the literature (104). Post and colleagues include 23 studies from a search of MEDLINE, Web of Science, and the Cochrane Library, reference lists and request for unpublished studies from experts. Of these 11 studies comprising 611 patients reported utility values from individuals who had not had a stroke. A weighted mean was calculated from these studies for the base case estimates. The utility scores were provided, in the review, dichotomized by the Rankin score (minor stroke = 2,3; major stroke = 4,5). The utility for the group as a

whole was the sum of the values for the 2 disability levels weighted by their relative proportion in the hemorrhagic stroke cohort in the RCSN (81).

49. Utility for disability from ischemic stroke: These Utilities were calculated from the values provided in the systematic review of Post and colleagues descried for parameter 48. For Ischemic stroke the utility was the sum of the disability levels weighted by the relative proportion in the ischemic stroke subgroup of the RCSN (81).

50. Utility for disability due to other pathology: As discussed above most pathologies presenting to the ED with symptoms similar to stroke were felt to have a nondisabling course. Three stroke neurologists were consulted as to the most common condition to result in disability that might present with stroke symptoms. Multiple sclerosis was felt to be the most common such condition. Fisk and colleagues (127) provided utilities from 187 individuals. The mean value was used for this estimate. A better estimate could be derived by enumerating all possible diagnoses in the population with potential stroke symptoms, obtaining their relative frequencies, probability for causing disability and eliciting utility values for each such health state. The limitation of this value to MS is not expected to bias the results of this model as this population is small and treated identically with respect to the utility in both branches.

51. Utility for disabling hemorrhage caused by TPA: The utility for this state was assumed to be identical for the utility of hemorrhagic stroke. See input 48.

5.2 Results: Systematic Review of Community interventions in Stroke

The literature search yielded 134 references. One individual carried out screening. One hundred references were excluded as they did not concern stroke, employ the interventions

defined, or were reviews, comments or letters. 34 studies were retrieved for examination. Of these 11 were reviews, comments or opinions, 18 employed no intervention or did not employ the intervention of interest. One did not have an outcome measure, leaving four for further consideration (56;132;133;134). No randomized controlled trials were identified and thus the preplanned quantitative data analysis and subgroup analysis was not carried out.

None of these four studies considered community intervention in isolation but rather as part of a multilevel intervention. The outcomes reported did not consider the elements individually thus the effect of community intervention could not be separated from other portions of the interventions. Three reports (56;132;133) were of a single project; the TLL Temple Foundation Stroke Project. This was a before and after study of a Texas community with a similar nearby community acting as a concurrent control. The intervention consisted of multimedia community education along with physician and ER staff education and modification of the ER processes. The intervention group had an increase of 5.7% in treatment rates of patients with stroke over a baseline rate of 1.38 % (133). The increase in the treatment rate occurred in spite of an absence of effect on the delay time between symptoms and presentation. The authors noted that treating physicians felt the patient or family prompted consideration of thrombolysis based on knowledge of treatment availability and thus the educational intervention had an impact. No significant change was noted in the comparison community over the same time period. This project contributes to the base case estimate for treatment effects secondary to the intervention.

Lattimore and colleagues reported the experience of establishing an acute stroke program at a Maryland hospital (134). The community education program associated with this effort consisted of multiple onsite programs with screening efforts, lectures and engagement of local

media that were coupled with an intense reorganization of ER protocols and designation of an acute stroke response time. Delay time prior to the intervention was not reported but an increase in the treated proportion from 1.5% prior to the intervention to 10.5% during the two years subsequent was noted. No comment was made regarding the relative contributions of the elements of the intervention to the observed outcome. Thus the relative contribution of the educational effort cannot be separated from the overall effect. The point estimate for intervention effect from this report contributes to the maximum estimate of the intervention effect.

Given the paucity of data in stroke and the similarity to the acute treatment of suspected myocardial infarction, further estimates were sought in the field of cardiac ischemia.

5.3 Systematic Review of Community Interventions in Chest Pain

The search of all databases resulted in 171 references whose abstracts were screened using the inclusion/exclusion criteria. One hundred sixty five were excluded as they were not original studies, did not measure delay time or had no control population and thus were not one of the pre-specified study types. Two reviewers who were not masked to study source performed the screening and further data abstraction. Eight articles were retrieved for inclusion in the review. Contacting two authorities in this field, along with one clinical cardiologist resulted in no further articles.

Of the eight studies that met criteria for inclusion in the review only one was a randomized controlled trial (60). The others were before and after studies, in which the control group represents the same population prior to the intervention (135;136;137;138;139). Due to the different study designs the results could not be combined quantitatively to provide a pooled effect measure. A summary of the included studies is provided in Table 2.

INTERVENTION	STUDY	LOCATION	PUBLICAT-ION DATE	SAMPLE SIZE	OUTCOME
Radio & TV	Mitic (135)	Canada	1984	101 baseline 41 intervention	1. Decreased mean delay in men 2. Increased in women
Radio, TV, Newspaper	Ho (136)	US	1989	401 baseline 489 intervention	No change in delay time
Baseline Radio, TV for all + mailing of one of 3 brochures	Meischke (137)	US	1997	5447 patients	No change over baseline of electronic media campaign
Radio, TV, Newspaper, Posters, Public Lecture	Moses (138)	US	1991	500 baseline 668 first year intervention 625 second year intervention	No change in mean delay time over baseline
Radio, Posters, Leaflet	Herlitz (139)	Sweden	1992	3308 baseline 1511 intervention	Significant improvement in median delay of 1.15 hours
Radio, Television, Newspapers, Lectures, Leaflets, Posters	Bett (140)	Australia	1993	576 Baseline 253 Post intervention	No change in medial delay time
Radio, Television, Newspapers	Gaspoz (141)	Switzerland	1996	1140 baseline 1335 post intervention	significant decrease in median delay from 180 min to 155
Radio, TV, Newspaper, Direct Mail, Brochures, Posters, Movie-on-Screen Announcements, Health Fairs	Luepker (60)	US	2000	5051 baseline 20364 intervention	No significant difference between delay time trend

Table 2 Community Interventions in Chest Pain – Summary of Studies

The REACT trial was a randomized controlled trial of the efficacy of community intervention on delay time employing cluster randomization of twenty US cities into matched control and intervention pairs (60). The design of the intervention was complex and involved expects in health behavior and epidemiology. The process of intervention design and its theoretical framework is extensively described in a companion publication (142). Emergency

Room staffs in study hospitals were trained in standardized questioning of patients regarding the nature and onset of acute symptoms. Matched pairs of cities were comparable in age distribution, education level, ethnic distribution, median income and baseline median delay time from symptom onset to presentation. Delay times were log transformed to obtain a more normal distribution. The trend of delay time was calculated by linear regression of log delay against calendar time adjusted for the patient level covariates: age, sex and past history of coronary artery disease. The trends were then compared pairwise with the matched communities. Delay times were available for 73% of the population of interest. A baseline period of four months was compared to the intervention period of eighteen months. The study had an 80% power to detect an end of trial difference of 30 minutes between intervention and control groups. During the study period mean delay time dropped by about 10 minutes in both the reference and intervention groups. The primary outcome response which was the slope difference (%/yr) between intervention and reference groups was 2.3% (95% CI -5.5 to 10.8). The intervention was consequently interpreted by the study investigators as being ineffective.

The earliest study (135) was carried out at a single hospital serving a population of 300,000 in Eastern Canada. Delay times on patients with chest pain presenting to the emergency room were collected during a four week period from patient charts followed by an eight week radio and television campaign. Times were collected again for a one-week period three months following the campaign. The mean delay times were noted to drop for men from 92.2 hours to 35.1 hours while that for women increased from 62.1 hours to 165.7 hours between pre-intervention and three months post intervention. No statistical tests were performed on this result and a standard deviation and overall mean delay time was not given. A x^2 test on the proportion presenting within two hours was significant at the 0.05 level favoring the intervention.

Ho et al (136) employed a six-week combined print and electronic media campaign in King County, Washington and measured delay time 4.5 months before and 4.5 months after the interventions. Patient delay was reported in two-hour intervals as identified from hospital records. No differences were noted pre and post intervention in the proportion of patients presenting in each two hour time window from 0 to > 6 hours. The proportion of patients with a history of myocardial infarction (MI) or angina and the proportion in which MI was confirmed declined in the post message period raising the possibility that the interventions resulted in an increase in the proportion of untreatable patients reporting to the emergency room. This has the potential to increase costs for each treatable case.

Meischke (137) examined the effect of a seven-week radio and TV campaign combined with randomized mailings of three different types of brochures targeted to households over fifty. An informational brochure provided facts about acute MI in a neutral tone. The social appeal brochure encouraged decision-making responsibility among the family, while the emotional brochure was designed to reduce fear and embarrassment that could delay appropriate assistance seeking. Six brochures were mailed out at two-month intervals. A control group received no brochures. Events identified in the coronary care unit registry were linked through addresses on the mailing list. Data was abstracted from the hospital record and delay time data was available for 69% of events. A post-hoc power calculation demonstrated a power of 70% to detect a 30-minute change between each intervention group and the control group. The data was normalized by a log-log transformation. No differences were noted between any of the intervention or control groups. The secondary outcome measure of proportion of patients calling 911 was also unaffected by the intervention.

Moses (138) employed a two-year campaign that employed multiple media: radio, TV, newspaper, brochure, posters, and public speaking. Baseline data was collected for one year prior to the interventions from a nine-month retrospective chart review and a three-month prospective collection. Emergency Room records were reviewed every two weeks for the two years of the intervention. Mean delay time did not change significantly for either the first or second year of the intervention.

Herlitz (139) initiated a campaign in 1982 in Goteberg Sweden that employed radio, posters and leaflets. This campaign lasted one year and was the only one that used radio but not television messaging during the critical three-week intensive phase. Baseline data was collected from emergency room records for 21 months prior to the intervention and thirteen months after its initiation. Data describing patients with suspected MI were presented as median and inter-quartile interval. A statistically significant decrease was noted with a baseline median time of 4.0 (1.3 – 12.0) hours and intervention median of 2.45 (1.2 – 6.5).

Bett (140) evaluated the effect of Australia's Heart Week Campaign on delay times for patients admitted to 22 coronary care units in 1989. An intensive educational campaign employed radio, television, newspapers, community and professional education supplemented with leaflets and posters focused on the prevention of death by decreasing delay time were presented nationally. Three surveys were conducted by CCU nurses focused on delay time. The first was in 1988 with the second and third immediately preceding and following the campaign. Median delay time did not differ among the three groups. Also median delay time in the post intervention survey was not influenced by knowledge of the campaign. The study did not measure the impact on EMS or hospital utilization. The power to detect a difference was limited

by the small sample sizes in the targeted groups (335, 221 and 253 for surveys 1 to 3 respectively) and variability introduced by using different CCU's for each survey.

Gaspoz (141) examined a 12-month campaign in Geneva Switzerland. Multiple media outlets were used as detailed in Table 1 for the program that began in October 1992. Data was prospectively collected by research nurses from patients, families and records for the 12 months preceding the campaign and the 12 months during it. Patients evaluated during the intervention were older, more likely to be hypertensive, have a past history of angina and less likely to have atypical chest pain. During the first three months of the campaign mean delay time was decreased by 113 minutes with no change in the median time suggesting a primary effect on outliers. Each three-month interval subsequent to the first and the intervention period demonstrated reduction in median delay time. Overall median time decreased 25 minutes ($p<0.002$) during the intervention period. Emergency room visits were significantly increased throughout the period (26 per week versus 22.2 per week at the baseline $p<0.005$).

For both stroke and chest pain the electronic literature search was complemented with a request to authorities in the field for additional, particularly unpublished studies, (e.g. abstracts, conference proceedings or internal documents). No additional studies were identified. Only one trial randomized with regard to the intervention of primary interest was available thus a meaningful funnel plot of randomized controlled trials could not be generated to assess for the possibility of publication bias

Multiply used subjects bias occurs when the same research subjects are the topic of more than one publication. It was avoided by excluding publications that arose from the same subjects. The electronic search, particularly of Medline was not limited by language to reduce language

bias. It is expected that randomized controlled trials of this type would be carried out in industrialized countries with higher rates of atherosclerotic heart disease and comprehensive health care systems (North America, Europe and Japan). Medline contains references from all three geographic areas and it is unlikely that a large randomized controlled trial of the type under consideration would be missed by the search strategy employed.

The results of community interventions in chest pain are mixed. Variation is noted on the primary treatment effect which is reported so as to preclude a simple summary statistic. There is insufficient data to comment on specific media interventions though all studies but one employed television. As the results of the largest study and single RCT show no benefit the current model included the possibility that the intervention results in no impact on treatment delay and consequently does not improve treatment rates.

5.4 Base Case Analysis

Roll back analysis of the Markov model provides the expected value for the cohort. Table 3 provides the expected values of the three payoffs (life expectancy, quality adjusted life expectancy and discounted quality adjusted life expectancy).

Payoff	No intervention	Intervention
LE	370.7805	370.7818
QALE	370.7586	370.7603
Disc QALE	168.1743	168.1747

Table 3 Markov Roll Back Analysis

The life expectancy of the no intervention group was 69 years with community intervention resulting in life expectancy gain of 0.0013 months. Community intervention remained the dominant strategy for the other two pay-offs: quality adjusted life years and discounted quality adjusted life years.

The results of the Monte Carlo simulations are provided for each payoff in the next 3 tables.

Summary Statistic	No Intervention	Intervention
Mean	370.7889	370.7901
Standard Deviation	0.2370	0.2370
Minimum	370.1674	370.1690
2.5% ile	370.2744	370.2752
Median	371.8182	371.8191
97.5%ile	371.1182	371.1195
Maximum	371.1588	371.1600

Table 4 Results of Monte Carlo Simulation for Life Expectancy (1000 trials)

Summary Statistic	No Intervention	Intervention
Mean	370.7749	370.7765
Standard Deviation	0.2380	0.2381
Minimum	370.1142	370.1146
2.5% ile	370.2668	370.2683
Median	371.8166	371.8179
97.5%ile	371.0490	371.1067
Maximum	371.1350	371.1378

Table 5 Results of Monte Carlo Simulation for QALE (1000 Trials)

Summary Statistic	No Intervention	Intervention
Mean	168.1752	168.1757
Standard Deviation	0.03797	0.03798
Minimum	168.0716	168.07200
2.5% ile	168.0927	168.0929
Median	168.1815	168.1820
97.5%ile	168.2269	168.2272
Maximum	168.2331	168.2333

Table 6 Results of Monte Carlo Simulation for Discounted QALE (1000 Trials)

The intervention is the preferred choice in all trials though the incremental gain in all 3 payoffs is small. While a standard deviation is provided the shape of the distribution is neither unimodal nor symmetric and the percentiles may be a better reflection of the uncertainty.

5.5 One-way Sensitivity Analyses

The two arms of the decision analytic model are identical apart from the probability of receiving TPA when diagnosed with an ischemic stroke and the probability of using EMS in the event of symptoms. The benefit of thrombolysis is dependent on the reduction in disability with the major detriment being an increase in the probability of intracranial hemorrhage. Treatment is contingent upon a positive diagnosis of stroke with potential for benefit with a true positive diagnosis and harm for a false positive. In order to assess whether the results are robust, one-way sensitivity analyses were performed for the model parameters over a range of plausible values as shown in Table 1. The optimal choice remained community intervention for all parameter ranges suggesting that the result is robust. Specific variables of interest are shown in figures 3 to 8 for Payoff 1. Table 7 gives numerical results for the sensitivity analysis for quality adjusted life expectancy. The preferred decision remains community intervention in all cases but the incremental benefit varies. In particular, the benefit is contingent on the intervention resulting in an increased probability of thrombolysis.

Parameter	Value	Community Int (mos)	No Community Int (mos)	Incremental Benefit to QALE (mins)
Additional probability of thrombolysis from intervention	0	370.759	370.759	12.509
	0.09	370.761	370.759	124.455
Relative risk of using the Emergency Medical System with the intervention	1	370.760	370.759	56.287
	1.5	370.761	370.759	88.390
Relative risk of death when TPA given for ischemic stroke	0.69	370.761	370.759	77.890
	1.36	370.760	370.758	66.539
Relative Risk of Disability when TPA for Ischemic stroke	0.66	370.760	370.759	72.356
	0.83	370.759	370.758	61.637
Sensitivity of Emergency Room diagnosis	0.973	370.761	370.759	71.381
	0.999	370.759	370.758	73.296
Specificity of Emergency Room diagnosis	0.997	370.760	370.759	72.179
	0.999	370.760	370.759	72.497

Table 7 Results of One Way Sensitivity Analyses

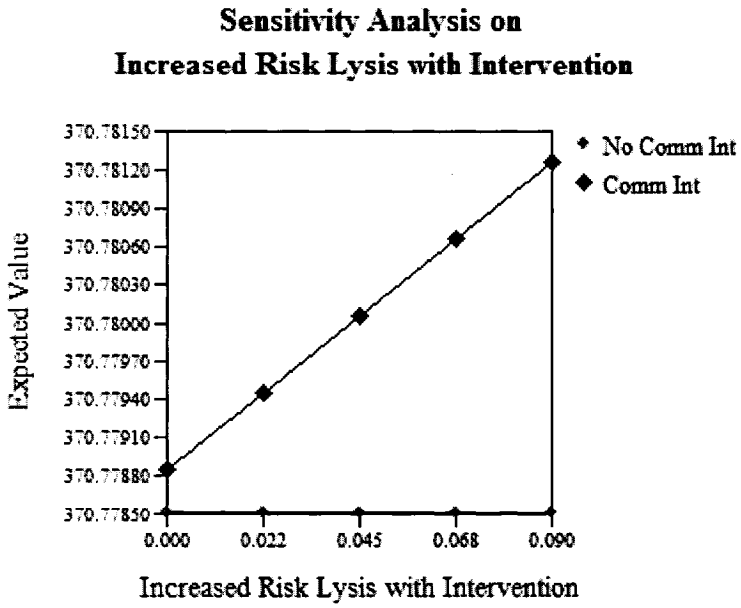

Figure 9– Sensitivity analysis on the additional probability of thrombolytic therapy

All values of this variable across this range favor community intervention. The difference in the

expected values at a value of 0 for increased risk lysis is due to the greater probability of ambulance use and subsequent treatment in the intervention arm. As expected the benefit of the intervention increases as treatment probability increases.

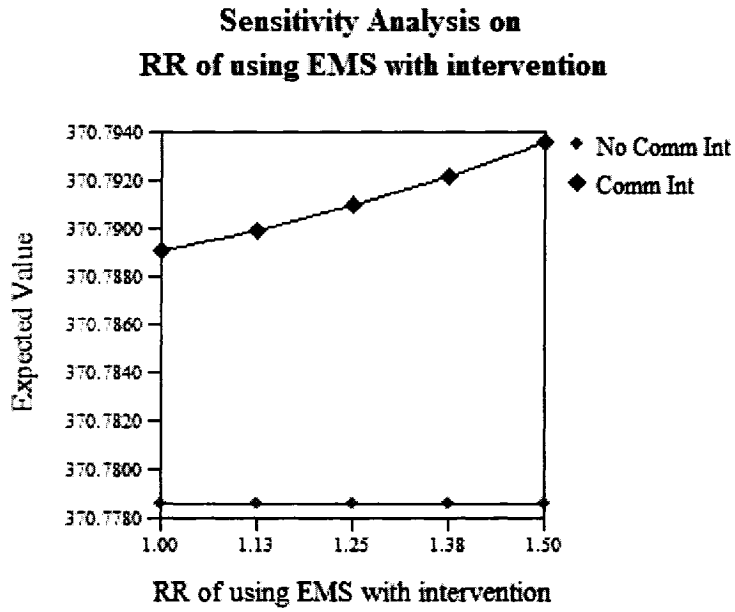

Figure 10 Sensitivity analysis on the relative risk of using an ambulance

As the probability of using an ambulance increases and conversely the probability of self-transport decreases, the incremental benefit of the intervention increases. As ambulance transport is associated with an increased probability of treatment this is the expected outcome.

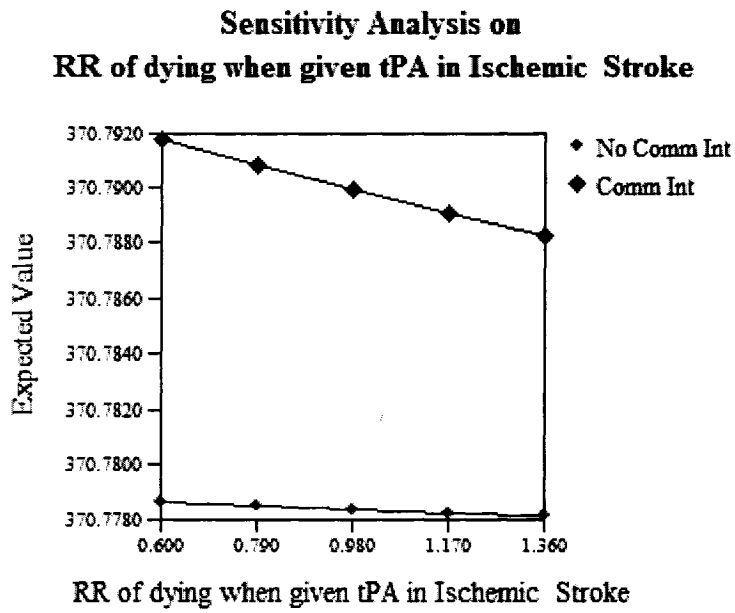

Figure 11 Sensitivity Analysis on the RR of Dying when treated with TPA

Community intervention remains the dominant strategy throughout the range with decreasing relative benefit as the risk increases. The magnitude of the decrease is greater for the intervention group due to the greater probability of treatment in this arm of the model.

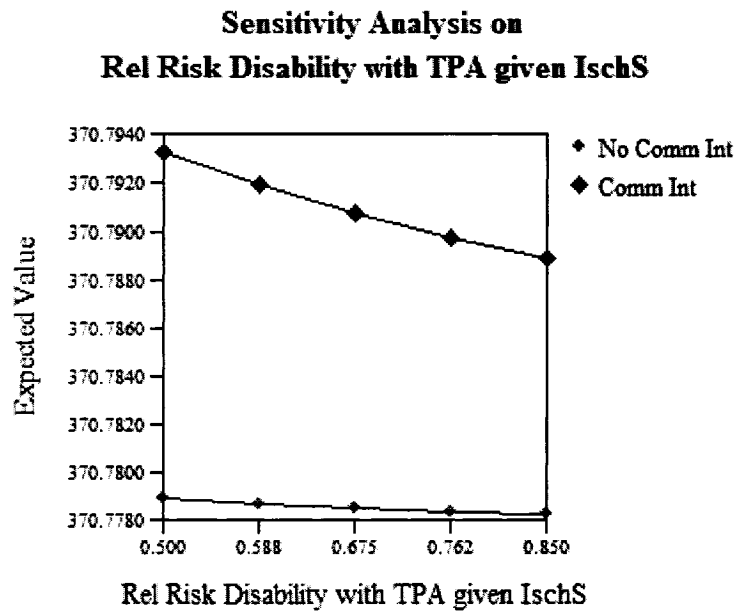

Figure 12 Sensitivity analysis of the relative risk of disability when treated with tPA.

The expected value drops as the risk of disability increases. Once again the decrease is greater in the intervention arm in which there is a greater probability of treatment.

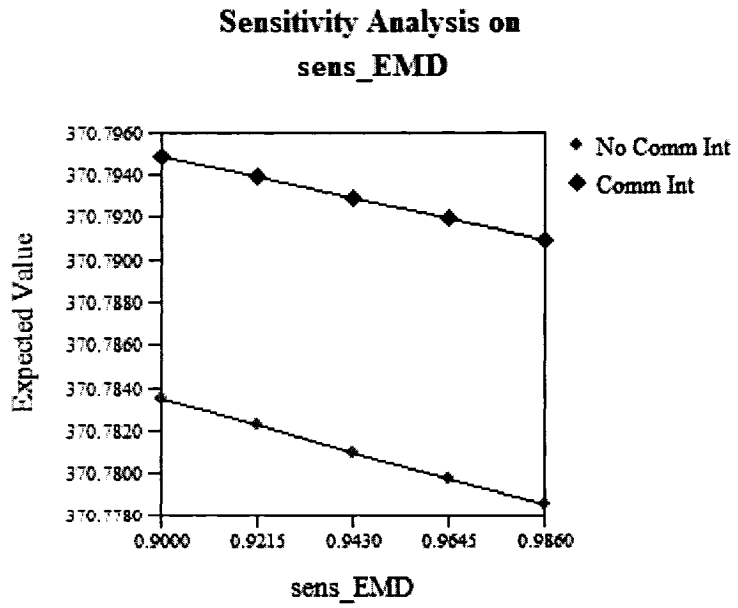

Figure 13 Sensitivity analysis of the sensitivity of ED diagnosis.

The expected value drops as the sensitivity increases but there is no reversal of the choice for

community intervention. Increased sensitivity increases the probability of a false positive diagnosis and thus is associated with a lower expected value.

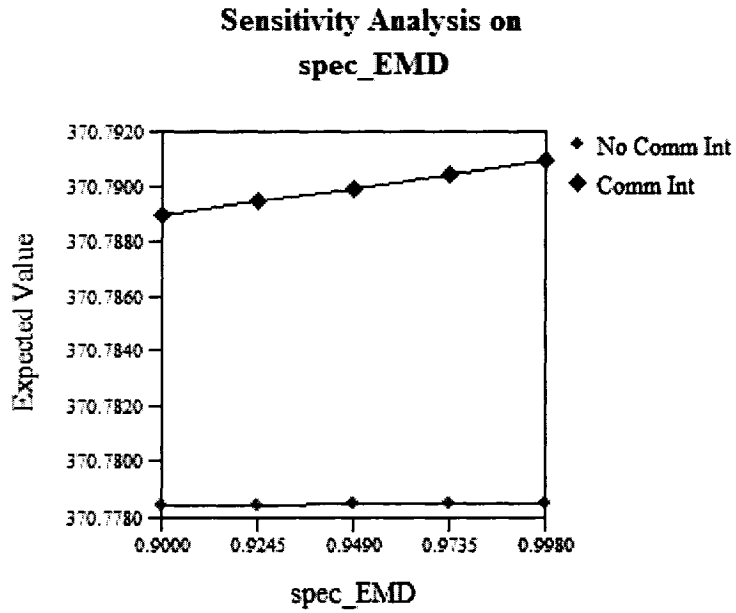

Figure 14 Sensitivity Analysis on Specificity of ED diagnosis.

Increasing the specificity decreases the probability of a false positive and improves the expected value.

5.6 Two-way Sensitivity Analysis

A two-way sensitivity analysis was performed on the relative risk of disability and death accompanying the use of TPA for acute ischemic stroke. Community intervention remains the preferred choice across any combination of values for the relative risk of death or disability when given TPA. Likewise two way sensitivity analyses of the relative risks of death and disability when treated , and EMD sensitivity and specificity with treatment favored intervention.

6 DISCUSSION

The effects of community interventions for stroke on time-dependent therapies are unclear in the literature. The published experience in stroke is limited with a more extensive record in cardiac ischemia though the results here are mixed. The results of this analysis demonstrate that community intervention remains the preferred strategy across a wide range of plausible parameter variations albeit with a small incremental benefit to population life expectancy, QALY's and discounted QALY's.

The base case assumption of a 4.5 % increase in treatment rates and a 25 % increase in ambulance utilization with the intervention resulted in improved life expectancy that was insensitive in the estimates of thrombolysis treatment effectiveness. Intervention was still the preferred choice when the least attractive measures of tPA effectiveness were assumed (relative risk of disabilities 0.85 and relative risk of death 1.360). This was the result of a smaller proportion of the population being at risk for death than for disability and low utilities ascribed to health states with stroke disability. No difference in outcome occurred between the intervention and no intervention arm on the additional treatment rate with the intervention was zero.

Concerns that the risks of treatment would worsen outcomes were not realized on the assumptions of a sensitivity and specificity of ER diagnosis of 98.6 % and 99.8 %, respectively and disease prevalence of 0.02. Varying disease prevalence from 0.002 to 0.04 (i.e. from 1/10 of that observed to double observed rates) likewise did not alter the preferred strategy. Low disease prevalence simulates centers which have smaller numbers of stroke patients within the population. Sensitivity and specificity of ER diagnosis were assumed to remain unchanged across this range of prevalence.

The model output was not sensitive to variations in the sensitivity and specificity of paramedic diagnosis under the assumption of independence between paramedic and ER diagnosis. Implicit in this model was the additional assumption that paramedics had no other intervention to offer. No data was available to test whether a presumption of stroke by the paramedic influenced his/her behavior. Plausible scenarios include an added effort to decrease transport time or alteration in the interaction with ER personnel so as to increase the probability of treatment. Ambulance transport in general is associated with an increased probability of treatment (56), a factor that was included in the model for all ambulance transports.

The preferred decision is not sensitive to parameter values and a cost-benefit analysis would be helpful in judging the relative merits to specific populations. The impact of this intervention depends on its ability to increase treatment rates either through decreasing delayed time to intervention, increasing ambulance utilization rates or altering the interaction between patients and healthcare staff in such a way to increase the likelihood of treatment. Implementation programs should ensure an impact on these specific factors. The magnitude of benefit is sensitive to the probability of thrombolysis. Programs which do not increase this probability over baseline rates are not expected to be effective.

There are at least two ways in which to judge interventions with marginal gains and life expectancy. The first is to compare the absolute gains across different strategies. It has been suggested (143) that gains in life expectancy similar to those observed in significant clinical trials (approximately 2 months) are significant and should be considered. This approach, however, does not consider the cost associated with competing options. In an atmosphere of strained and limited resources, the latter approach has considerable merit. Further work is required to accurately assess the incremental cost-effectiveness of these strategies.

Multi-level system interventions such as those envisaged by the Ontario Stroke Strategy are complex and resource-intensive in execution and evaluation. Previous modeling has restricted itself to cost benefit analysis of thrombolytic therapy (144) with a potential impact of comprehensive improvements in medical care on costs (90). This modeling has not considered the effect of community interventions on outcomes. To the best of our knowledge the current model is unique in explicitly delineating the pre-hospital phase of acute stroke care and focusing on the potential impact of community interventions. The model can be adapted in the future to consider the impact of other pre-hospital interventions. For example a trial to test the efficacy of intravenous magnesium delivered prior to hospital arrival has completed the pilot phase (145) .

The model offers the benefit of explicit assumptions of both parameter and structure so their reasons for the conclusions are clear. Sensitivity analyses demonstrate that the choice of preferred strategy does not change across plausible ranges of parameter variation. Most input parameters are derived from published sources with sensitivity analyses around assumptions.

As with any such works a number of limitations exist. This model was limited to treatment strategy based on the NINDS trial i.e. the use of intravenous tPA within three hours symptom onset with patient selection criteria conforming to trial parameters. The modeled system assumed immediate availably of clinical, radiological and laboratory resources to make an eligibility decision. The results are not applicable to centers lacking these resources nor those employing strategies such as intra-arterial thrombolysis, patient selection by MRI criteria, use of agents other than tPA or expansion of the time-window beyond three hours. Transport to a single destination was assumed and a choice between a centre delivering treatment and one that did not was not permitted. It is possible that outcomes would have been influenced by paramedic training in a system with more than one treatment destination.

Several assumptions were made in order to make the model tractable and remain within available computational resources. The effects of community intervention were assumed to be constant with time. This may not be the case as the impact of some community interventions may be greater immediately after their introduction and lessen with time (141). The probabilities of death and disability due to stroke were assumed to be independent of age when both these risks do depend on age (3). Sensitivity analyses across the risk ranges for death and disability in stroke did not alter the outcome.

The secondary prevention of stroke undertaken in those with TIA was considerably simplified. Prevention currently entails consideration of carotid endarterectomy, anti-thrombotic therapy, selection of agents for dyslipidemia, diabetes and lifestyle interventions (146;147;148;149). Each intervention carries risks and benefits contingent upon the characteristics of the individual. The model assumed the benefits and risks associated with the use of daily ASA for secondary prevention and does not include the risks and benefits associated with other preventive strategies. This assumption was consistent with the primary intent of the model, which was to examine the impact of community level interventions.

Simplifying assumptions were also made regarding the natural history of patients post TIA, stroke and those with symptoms due to other causes. A maximum of two TIA's was permitted with those having a second stroke transitioning to death. Symptoms mimicking stroke or TIA might conceivably arise from migraine, multiple sclerosis, cerebral neoplasms, infections or other space occupying lesions. In the absence of data concerning the natural history of this group as a whole simplifying assumptions were made regarding subsequent death and disability. No impact on model outcome was noted by sensitivity analyses on these parameters.

Apart from the estimates of intervention effectiveness and stroke utilities, the values for the input parameters were not the result of systematic reviews. It is possible that biases exist in some of these estimates. Phase 1 of the Canadian stroke network registry was used to obtain some parameters (81). Explicit consent from patients or caregivers was a requirement for participation in this registry (150). Patients who died or left hospital early were less likely to be included. This results in an under representation of mild and severe strokes in this population and reduces generalizability.

One source of uncertainty in decision analytic modeling is structural uncertainty. The output of a model depends upon its structure and other models structure may give outputs that are invariants with the current model. This form of uncertainty can not be resolved until other models are designed and outputs compared.

The most significant limitation of this project was the inability to separate the effects of community intervention from the impact of other system changes. While community interventions are unlikely to be planned in isolation, the wide reach of mass media educational efforts raises the possibility of exposing populations in areas where the system has not been adapted to deliver therapy effectively. Such populations are unlikely to benefit.

The concurrent systematic review on community interventions in chest pain demonstrated a range of effects. There may be several reasons for the heterogeneity of these outcomes.

Before and after studies cannot control for trends occurring in the population at large. Thus changes in the outcome variable due to the secular trends may be mistakenly ascribed to the intervention in question. This effect is clearly seen in the REACT trial(60) where delay times

decreased indistinguishably in both intervention and reference populations over the course of the study. The studies (135;151), which were felt to demonstrate a decrease in delay time coincident with the intervention, cannot exclude this explanation for the observed effect. One of these (135) demonstrated a benefit only in the male segment of the study population.

The positive studies (126;151) are distinguished in other ways from the indeterminate studies. Both were done in early to mid 1980's (Mitic 1982, Herlitz 1987), when the frequency of use of thrombolytic therapy for cardiac ischemia was lower. Consequently part of the benefit ascribed to the intervention may be secondary to an increased appreciation of the possibility of treatment amongst the general public through mechanisms separate from the intervention. Also both of these studies have relatively higher baseline delay times when compared to the latest study (60) : median baseline Mitic 12.0 hr; Herlitz 4.0 hr; versus REACT 2.3 hour. It is possible that delay times shorter that those in the earlier studies are due to factors, which are unresponsive to community interventions. For instance some level of denial may be present even in people who have been well educated to the appropriate course of action. Finally, the population of the late 1990's may well be so saturated with media messages on health that the response is cynicism and indifference precluding a positive effect. The third positive study (141) has significant differences between baseline and intervention populations, which may explain the results.

Only one randomized controlled trial was identified in this topic area. Studies of this type are, by the very nature of the intervention, large and expensive. Large studies, even when negative, tend to be published (152). As publication bias promotes the publication of studies with statistically significant results (153) it is unlikely that the conclusion of this review is affected by publication bias.

In spite of the limited quality of the data and the mixed results observed education programs continue to be advocated. The American Heart Association has endorsed the *Act in Time to Heart Attack Signs* campaign which targets physicians and the public in an effort to increase utilization of the EMS system for patients with symptoms. While the motivation is commendable our data suggest that further work is required to identify strategies which result in improved outcomes and the associated costs of such campaigns.

To summarize, the before and after trials have flaws which may invalidate their conclusions and the positive trials may apply to a less media savvy and medically knowledgeable population than that which exists today.

The REACT trial (60) is methodologically superior to the others by virtue of the randomization process that reduces potential biases by compensating for secular trends and unknown confounders. The intervention was sophisticated, intense and lengthy. Data collection was prospective with precision of delay time measurement enhanced by applying standard training and protocols to the emergency room staff that interview patients. Reliance on medical records in which the method of information collection is variable would be expected to result in less precision. The confidence intervals of the outcome measures were enhanced by the size of this study.

Thus the best available data suggests that delay time is not significantly reduced by community intervention. It would be worthwhile to reproduce the REACT trial in a country with universal healthcare, as payment issues are a potential confounding factor in the decision to seek potentially expensive medical treatment. Further research in this area should employ contemporary control groups and standardized interviewing for obtaining delay times.

Behavioral theories other than those considered in the REACT trial intervention should be explored. Reporting of median time or percentage within the treatment window is preferable to mean time, which is strongly influenced by outliers.

7 NEXT STEPS

Experience with community interventions is mixed. Further work is needed to identify the characteristics of successful campaigns. Any such efforts must have measures of behavior change as the principle outcome measures. A trial of community intervention targeted at strokes necessary to identify the impact of disease outcomes in patient behavior. Any such campaign can be expected to increase utilization of EMS and ER facilities and consequently have resource implications. A cost-effectiveness analysis is needed to place these interventions into context with other interventions, which might be implemented. The relative positioning of such interventions is a significant issue in stroke care. For instance, stroke units have demonstrated an approximately 22% reduction in the odds of death or dependency at one year with much wider applicability than thrombolysis, but have not yet been widely implemented in North America.

In this regard the BURST study is currently underway to collect current Canadian costs associated with stroke (see Appendix 4). This will be the first detailed national study of stroke costs. The resource utilization instruments are provided in the appendix. In addition a diary will be used to prospectively collect detailed utilization and indirect costs on a subset of patients. Costs will be added to the model a probabilistic Monte Carlo simulation performed. The results of the analysis will be presented as a scatter plot of incremental benefit (in QALY's) versus incremental costs. The incremental cost-effectiveness ratio is represented by the slope of incremental costs to incremental effects.

8 CONCLUSIONS

At present only a minority of potential candidates for thrombolytic therapy for acute stroke meet the stringent time criteria. Mass media community interventions have been promoted as a means of increasing treatment rates. A systematic review of the literature in chest pain suggests mixed results while a similar review in stroke is limited by the absence of trials of community interventions. The available reports in stroke suggest that when such interventions have been undertaken in the context of multilevel changes in acute stroke care, increases in treatment rates occur. Decision analytic modeling of community intervention programs in the context of a system capable of providing thrombolysis demonstrates benefits from a societal prospective. The effects on life expectancy are robust in the face of multiple parameter variations. These benefits however remain small and the available evidence does not permit a separation of the effects of community programs from other concurrent changes. Further research is necessary regarding the elements distinguishing a successful program as well as the relative benefits and cost benefits of such programs when compared to prevention and stroke unit care. Each of the latter two programs has a potential for much wider application than acute treatment with thrombolysis.

9 APPENDICES

Appendix 1 The Ottawa Hospital Acute Stroke Protocol

Table of Contents

(* - corresponding document pages)

Steps for Acute Stroke Code

Step 1	**Pre-hospital**	▪ Paramedic patch into ER department **(Important: Bring in witness, instruct them to come in immediately or stay near a telephone where a physician can reach them)** ▪ Alerts Nurse that patient is a possible "Stroke Code"
Step 2	**Emergency Department**	Triage Nurse (for ambulatory patients) ▪ Assesses patient
		Primary Nurse ▪ Alerts Emergency Physician of possible "Stroke Code ▪ Completes baseline nursing neuro exam and GCS ▪ Establishes time, including source and contact information ▪ Assesses for history of renal failure and most recent serum creatinine (**check OACIS**) ▪ Call for old chart (general campus only) ▪ Ensures blood work is done "Code Emerg" ▪ Labels CT scan requisition "Stroke Code CT Scan – possible tPA candidate"
Step 3	**Emergency Physician**	▪ Initiates "Stroke Code" **(exclude those with minimal or resolving deficits or NIHSS < 4)** ▪ Activation of Stroke Code results in notification Acute Stroke Team STAT by telecommunications: Stroke Physician, Neuroradiologists, CT Technologist, Lab and Transportation Worker ▪ Completes and signs preprinted order sheet in this package; "Initial evaluation of stroke patient for possible thrombolysis" ▪ Arranges immediate transfer to CT scanner
Step 4	**Stroke Physician**	▪ Confirms ischemic stroke ▪ Determines eligibility for IV or IA thrombolysis/angioplasty ▪ If not eligible, completes section re: reason for exclusion

IV tPA **0 – 3 hours onset of stroke**	**IA thrombolysis/angioplasty** **3 – 6 hours onset of stroke** **(see note, next page)**
▪ Stroke Physician completes and signs informed consent for IV tPA ▪ Acute Stroke Checklist for IV tPA ▪ ASPECTS scoring sheet ▪ NIH Stroke Scale ▪ Orders for thrombolysis with IV tPA ▪ Post tPA administration physician order sheet	▪ Neuroradiologist or stroke physician completes and signs Intra-arterial consent form ▪ Acute Stroke Checklist for IA tPA ▪ ASPECTS scoring sheet ▪ NIH Stroke Scale ▪ Post tPA administration physician order sheet

Target: Time from arrival of stroke patient in ER to the start of IV tPA infusion is 60 minutes

The principle of rapid recanalization of occluded vessels in the setting of acute stroke is now well established. IV tPA within 3 hours of onset is the current standard of care based on the pivotal NINDS trial and related meta analyses. It is clear, however, that this treatment reaches only a small percentage of patients and is probably less successful at recanalization of large proximal occlusions. At present for patients outside the 3 hour window (3 – 6 hours) with such occlusions TOH has the technical expertise to offer intra-arterial treatment which combines mechanical clot disruption by means of balloon angioplasty and chemical lysis. While trial support for this protocol does not yet exist it should be considered for eligible patients on a case by case basis. Decisions must be made by the stroke physician in concert with the involved neuroradiologist. The risks, alternatives and potential benefits of this treatment must be discussed with the patient and/or relative. An Intra-arterial treatment for Acute Stroke consent form developed provincially for use at regional stroke centres is included in this package. Also included is a generic consent form for those physicians comfortable with obtaining a general consent for recanalization. The Regional Stroke Centre will maintain a database of hyperacute stroke outcomes for quality control purposes with morbidity and mortality analysis for significant adverse outcomes. Patient safety is a major focus when developing and implementing new treatment modalities.

Consider IA treatment for:

1. Large vessel occlusion on CT angiogram
   AND (one or more of the following)
   - 3 – 6 hours post onset
   - anti coagulated
   - thrombolysis already administered (e.g. stroke post MI)
   - ineligible for systemic thrombolysis due to bleeding risk

2. Basilar artery ischemia may be amenable to treatment outside the 6 hour window. Further research is required to better define an appropriate time period. Cases in which clinical and imaging criteria suggest the potential for benefit with low risk may be considered outside this window with due concern exercised in selection of patients and treatment modalities.

Nurse's Evaluation of the Acute Stroke Patient -4-

Triage evaluation will determine if a stroke is probable and the timing and progression of the stroke.

1. Determine the time of onset of stroke symptoms

Documentation of the exact time of stroke onset is critically important. The stroke onset time is the time of onset of symptoms noted by a reliable patient or witness.

Questions to consider asking are:

- If the patient collapsed, was the fall witnessed?
- If not, at what time was the patient found?
- When was the patient last witnessed to be neurologically normal?
- If the patient awoke with the stroke deficit, at what time did he go to bed?
- Did he awake during the night without any neurological deficits?
- If the patient awakes or is found with stroke symptoms, the stroke onset is considered to be the time the patient was last seen to be neurologically normal

2. Primary nurse alerts ER physician of possible "Stroke Code" patient.

3. Glascow coma scale score is obtained.

Glascow Coma Scale Score	**Eyes open**	**Spontaneously** *already open with blinking (normal)*	**4**
		to speech *To speech – not necessarily to a request for eye opening*	**3**
		to pain *stimulus should not be applied to the face*	**2**
		None	**1**
	Best Verbal Motor Response	**Orientated** *Knows name, age, etc.*	**5**
		Confused *Still answers questions*	**4**
		Inappropriate *Speech is either exclamatory or random but recognizable words are produced*	**3**
		in comprehensible *Grunts or groans but do not confuse with respiratory obstruction*	**2**
		None	**1**
	Best Motor Response	**obey commands** *Moves limb to command*	**6**
		localizes pain *Changing location of the pain stimulus causes purposeful motion toward the stimulus*	**5**
		withdrawal to pain *pulls away from stimulus*	**4**
		flexion to pain *Decorticate posturing*	**3**
		extension to pain *Decerebrate posturing*	**2**
		None	**1**

4. Motor Function

Test arm strength	Ask the patient to hold arms straight out with palms up in front of chest assessing: ▪ Cannot raise arm, minimal movement = severe weakness ▪ Drifts down to bed before 10 seconds = moderate weakness ▪ Drifts downwards = mild weakness
Test leg strength	Test each leg separately: ▪ Cannot raise leg, minimal movement = severe weakness ▪ Drifts down to bed before 5 seconds = severe weakness ▪ Drifts downwards = mild weakness

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Département de l'Urgence

INTRA VENOUS tPA FOR ACUTE STROKE CHECKLIST
FEUILLE DE VÉRIFICATION POUR INTRA VEINEUSE tPA AIGUE

To be completed by Stroke Physician-À être remplie par le médecin de

HISTORY (exclusion criteria)	YES	NO
Onset of symptoms >3 hrs	☐	☐
Minor deficits (e.g. ataxia, pure sensory, dysarthria alone, mild motor)? NIHSS <4	☐	☐
Stroke or head injury in previous 3 months?	☐	☐
History of intracranial hemorrhage with ongoing risk of reoccurrence?	☐	☐
Major surgery or serious trauma in previous 2 weeks?	☐	☐
GI or GU bleeding in previous 3 weeks?	☐	☐
Pregnant?	☐	☐
Symptoms suggestive of SAH, even with normal CT?	☐	☐
History of bleeding diathesis?	☐	☐
MI within 3 weeks?	☐	☐
Recent pericarditis in last 3 months?	☐	☐
Possibility of migraine, post-ictal, tumor, MS?	☐	☐

EXAMINATION AND INVESTIGATIONS

CT shows evidence of hemorrhage (even small petechiae)?	☐	☐
(CT must be repeated if more than 45 minutes old)		
Prolonged PTT or INR >1.7?	☐	☐
Blood glucose <3 mmol/L?	☐	☐
Platelets <100,000/mm^3?	☐	☐
BP >185/110 in spite of treatment?	☐	☐

If any of the above are answered YES, patient is EXCLUDED from t-PA treatment

Patient is t-PA candidate	☐	☐
Enter reason why patient was not a candidate for tPA if not already indicated above:		
Informed consent form (part of stroke package) signed	☐	☐

Relative exclusions that increase the risk of hemorrhage

If yes to below items, exclusion is decided on an individual basis.	☐	☐
Arterial puncture at noncompressible site in previous 7 days?	☐	☐
LP in previous 7 days?	☐	☐
Liver failure?	☐	☐
Blood glucose > 22 mmol/L?	☐	☐
CT shows significant edema or mass effect?	☐	☐
CT shows tumor, AVM, aneurysm?	☐	☐

Date:	Time-Heure:	Physician's-Médecin printed-imprimé:	Signature:

N-Noted T-Transcribed to MAR O-Ordered Req-Requisition

EMG 17 A (02/2004) 1 - CHART-DOSSIER 2 - PHARMACY-PHARMACIE

NIH Stroke Scale – refer to PDF file ⇒EMG 21 (01/2004)

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e. repeated requests to patient to make a special effort).

1a. Level of consciousness : The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal, trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert, keenly, responsive 1 = Not alert, but arousable by stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped) 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not 'help' the patient with verbal or non-verbal cues.	0 = answers both questions correctly 1 = answers one question correctly 2 = answers neither question correctly	_____
1c. LOC commands: the patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e. Follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated	0 = normal 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present. 2 = Forced deviation, or total	

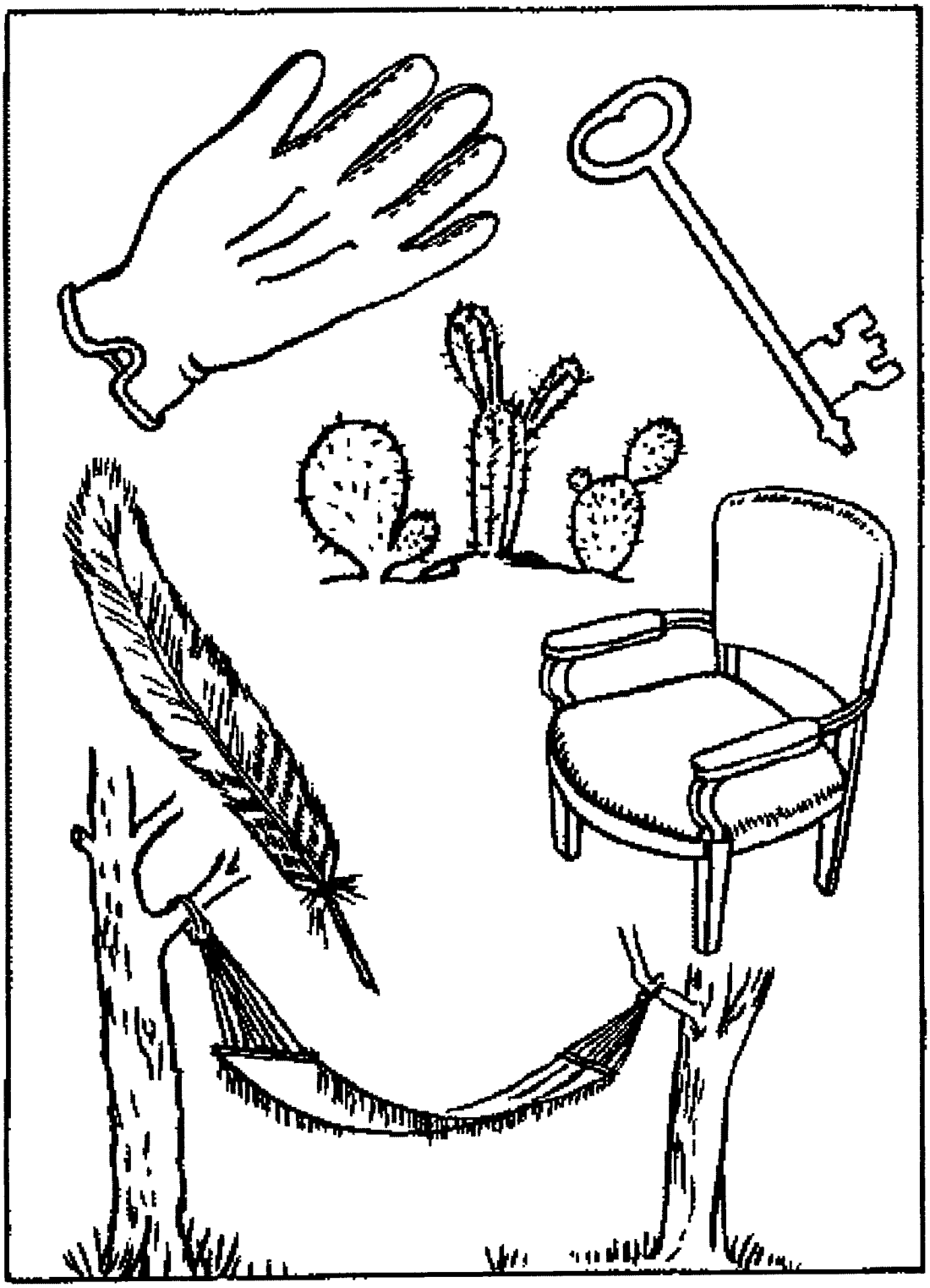
peripheral nerve paresis (CN 111, 1V, V1) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy	gaze paresis not overcome by the oculocephalic maneuver.	_____
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threats as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause score 3. Double simultaneous stimulation is performed at this point. If there is extinction patient receives a 1 and the results are used to answer question 11.	0 = No visual loss 1 = Partial hemianopia 2 = complete hemianopia 3 = bilateral hemianopia (blind including cortical blindness)	_____
4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible..	0 = normal symmetrical movement 1 = minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = partial paralysis (total or near total paralysis of lower face) 3 = complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	_____
5 & 6. Motor arm and leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be 9 and the examiner must clearly write the explanation for scoring as a 9.	0 = no drift, limb holds 90 (or 45) degrees for full 10 seconds 1 = drift, limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = no effort against gravity, limb falls. 4 = no movement 9 = Amputation, joint fusion explain: _____ 5a = Left arm 5b = right arm	5a____ 5b____

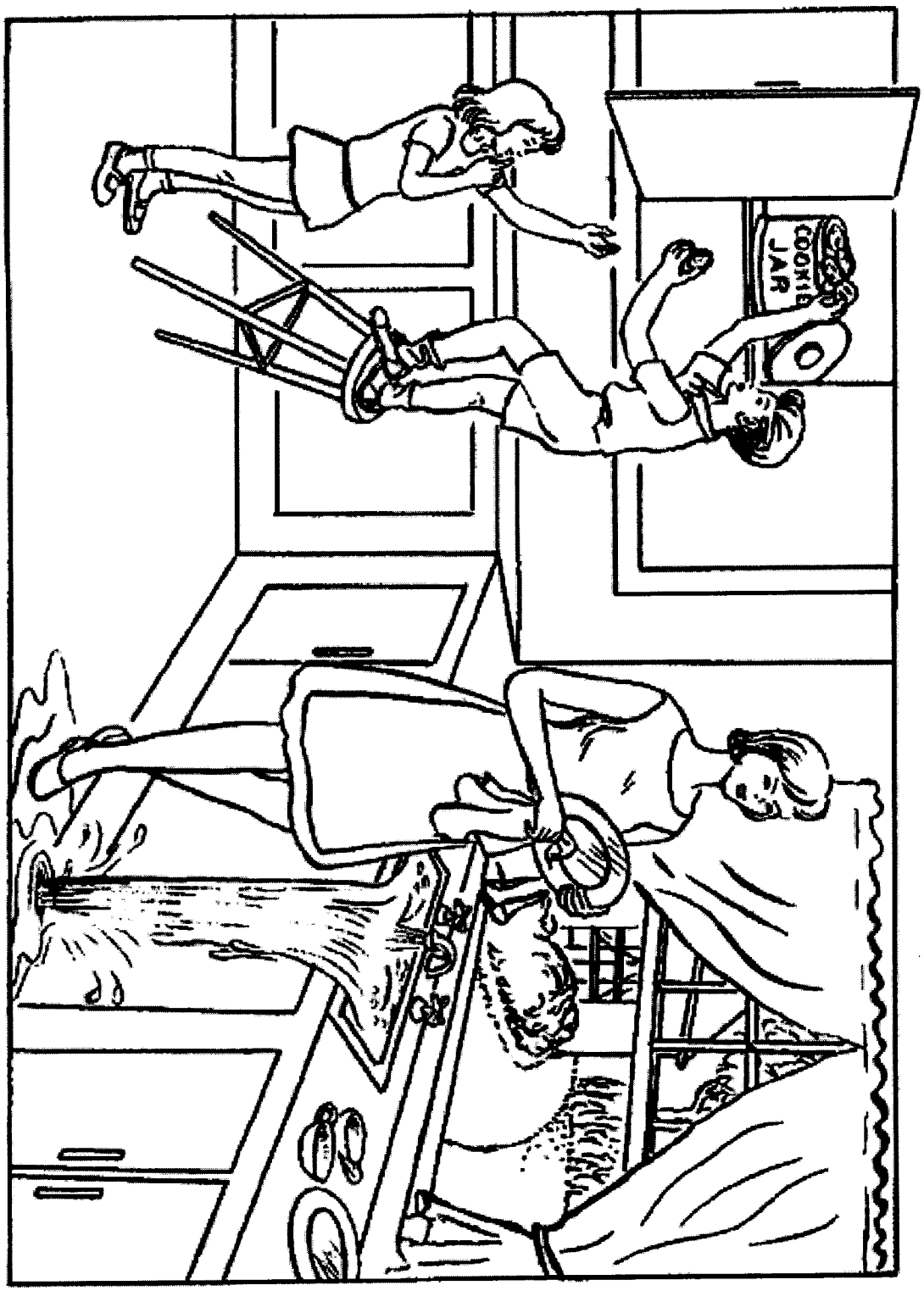
	0 = no drift, leg holds 30 degrees position for full 5 seconds 1 = drift, leg falls by the end of the 5 second period but does not hit bed 2 = some effort against gravity, leg falls to bed by 5 seconds, but has some effort against gravity. 3 = no effort against gravity, leg falls to bed immediately 4 = no movement 9 = amputation, joint fusion: explain :_____ 6a = left leg 6b = right leg	6a_____ 6b_____
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored 9, and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.	0 = absent 1 = present in one limb 2 = present in two limbs If present, is ataxia in: **Right arm** 1 = yes 2 = no 9 = amputation or joint fusion, explain _____ **Left arm** 1 = yes 2 = no 9 = amputation or joint fusion, explain _____ **Right leg** 1 = yes 2 = no 9 = amputation or joint fusion, explain. _____ **Left leg** 1 = yes 2 = no 9 = amputation or joint fusion, explain _____	_____ _____ _____ _____ _____
8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs face and trunk) as needed to accurately check for hemisensory loss. A score of 2, severe or total, should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. Patients in coma (item 1a = 3) are arbitrarily given a 2 on this item.	0 = normal, no sensory loss 1 = mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched. 2 = severe to total sensory loss; patient is not aware of being touched in the face, arm and leg	_____
9. Best Languages: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of	0 = no aphasia, normal 1 = mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however,	

the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a = 3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.	makes conversation about provided material difficult or impossible. For example in conversation about provided materials examiner can identify picture or naming card from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression: great need for inference, questioning and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patent is intubated or has other physical barrier to producing speech, may the item be scored "9", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.	0 = Normal 1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. 9 = Intubated or other physical barrier, explain_____	_____
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = no abnormality 1 = visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.	_____

Additional Item, not a part of the NIH Stroke Scale score

A. Distal Motor Function: The patient's hand is held up at the forearm by the examiner and patient is asked to extend his/her fingers as much as possible. If the patient can't or doesn't extend the fingers, the examiner places the fingers in full extension and observes for any flexion movement for 5 seconds. The patient's first attempts only are graded. Repetition of the instructions or of the testing is prohibited.	0 = Normal (no flexion after 5 seconds) 1 = At least some extension after 5 seconds, but not fully extended. Any movement of the fingers which is not a command is not scored. 2 = No voluntary extension after 5 seconds. Movements of the fingers at another time are not scored. a) Left Arm b) Right Arm	 _____ _____





You know how

Down to earth

I got home from work

Near the table in the dining room

They heard him speak on the radio last night

MAMA

TIP-TOP

FIFTY-FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

The Ottawa Hospital | L'Hôpital d'Ottawa
Department of Emergency

❑ Civic
❑ General

❑ CONSENT FOR t-PA ADMINISTRATION

You have experienced a stroke. It is also called a brain infarction or an ischemic stroke. The kind of stroke you have had is caused by a blood clot that is blocking the blood supply to your brain. The blood clot may cause permanent damage to your brain.

Your physician is prepared to give you a medication called t-PA. This medication can minimize the damage and increase chance of recovering by dissolving the clot. A full recovery can also happen. This drug is given through a vein over a one-hour period of time.

With t-PA, there is an increased chance you will improve (approximately a 31 percent chance). A full recovery can also occur.

There is some risk with this medication. There is a small chance it can cause bleeding in the brain or other parts of the body. Patients with strokes may die as a result of this treatment.

This drug, if given intravenously, needs to be started within three hours from the time your stroke symptoms began.

WITH YOUR SIGNATURE, YOU ARE INDICATING THAT YOU FULLY UNDERSTAND THIS TREATMENT, THE POSSIBLE BENEFITS AND RISKS AND THAT YOU AGREE TO RECEIVE THE DRUG t-PA.

❑ CONSENT FOR INTRA-ARTERIAL THROMBOLYSIS/ANGIOPLASTY FOR ACUTE ISCHEMIC STROKE

I, _____, hereby consent to undergo the following investigation and treatment to be performed by the radiologist, Dr. _____.

I understand that I have had a stroke caused by a blood clot in my brain.

I understand that a special test called a cerebral angiogram may be able to show where the clot is located within my brain.
I understand that if the blood clot is seen, it is possible to administer medication through an artery directly into the blood clot or to open the blood clot through the use of a balloon, and that this treatment may increase my chances of recovery from this severe stroke by dissolving the clot.
I understand that these procedures have not been approved by Health Canada.
The benefits and risks of this treatment have been discussed with me; I have had an opportunity to ask my neurologist,

Dr. _____, questions, and these have been answered to my satisfaction.

WITH YOUR SIGNATURE, YOU ARE INDICATING THAT YOU FULLY UNDERSTAND THIS TREATMENT, THE POSSIBLE BENEFITS AND RISKS AND THAT YOU AGREE TO RECEIVE THE DRUG t-PA.

Patient	Signature (Patient, significant other or representative)
If you are not the patient, please print your name and your relationship to the patient, below	
Printed name	Relationship
Signature (Witness)	Date

CON 23 (02/2004) CHART

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PHYSICIAN'S ORDERS
ORDONNANCES MÉDICALES
Emergency-Urgence

Medication Allergies/Reactions	Substances or Food Allergies/Reactions
☐ none known-aucune connue	☐ none known-aucune connue

Weight-Poids: _____ kg

INITIAL EVALUATION OF STROKE PATIENTS FOR POSSIBLE THROMBOLYSIS
ÉVALUATION INITIALE DES PATIENTS D'UN AVC PRÉSENTANT LA POSSIBILITÉ D'UNE THROMBOLYSE

NON-MEDICATION-SANS MÉDICAMENTS	Time Heure	INIT
Record time of stroke onset: hours		
Source:		
Contact info:		
Activate "Stroke Code"		
Acute Stroke Team notified STAT (includes		
☐ Stroke Physician, ☐ Neuroradiologist,		
☐ CT Technician, ☐ Transportation Worker		
Initiate "Stroke" CT of head		
Label requisition		
"Possible t-PA candidate"		
STAT blood (send "Code Emerg") for:		
a) CBC with platelet count		
b) PTT, INR, fibrinogen		
c) Lytes, creatinine, glucose		
d) Type and screen		
Glucoscan		
Pregnancy test (urine) for females in child bearing		
age (<50)		
STAT 12-lead EKG		
Weigh patient on scale **if possible.**		
record. _____kg. (not lbs)		
Baseline vital signs including neuro VS and GCS;		
then BP q 15 minutes		
Oxygen to maintain O_2 saturation > 92 %		
Nurse to escort patient to CT scan/angio suite		

I.V. & MEDICATION-SOLUTÉ & MÉDICAMENTS (Meds, dose-posologie, frequency-fréquence, route-voie)	Time Heure	INIT
No Heparin, Warfarin, Aggrenox, Ticlopidine, Clopidogrel or ASA (Aspirin) for first 24 hours if thrombolysis used.		
Saline lock x 2, one in each arm if possible • # 18 gauge needles preferred		
Acetaminophen (Tylenol) 650 mg po/pr q 4 h prn for fever >38° C degrees Dimenhydrinate (Gravol) 25-50 mg IV q 4h prn for nausea or vomiting		
If systolic BP> 185 mmHg **or** diastolic BP >105 for 2 or more readings taken 10 minutes apart see **Acute Stroke Protocol** P.30 for hypertension management.		
Orders:		

Date:	Time-Heure:	Physician's-Médecin printed-imprimé:	Signature:
Date (noted-notée):	Time-Heure:	Processed by-Traitée par:	Signature (Nurse-Infirmière):

N-Noted T-Transcribed to MAR O-Ordered Req-Requisition

SPO 91 (02/2004) 1 - CHART-DOSSIER 2 - PHARMACY-PHARMACIE

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PHYSICIAN'S ORDERS
ORDONNANCES MÉDICALES
Emergency-Urgence

Medication Allergies/Reactions	Substances or Food Allergies/Reactions
☐ none known-aucune connue	☐ none known-aucune connue

Weight-Poids: _____ kg

POST INTRAVENOUS tPA-POST tPA INTRAVEINEUX

NON-MEDICATION-SANS MÉDICAMENTS	Time Heure	INIT
Vital signs q 15 min x 1 hr, then q 30 min x 2 hrs, then q 1 h x 4 hrs then q 2h x 8 hrs, then q 4h x 24 hrs.		
Neuro signs and GCS q 15 minutes x 1 hr, then q 30 minutes x 2 hours, then q1h x 4 hours then q2h x 8 hours, then q4h x 24 hours		
Call MD STAT if evidence of bleeding or neurological deterioration or vital signs outside the following parameters: a. Systolic BP >180 or <110. b. Diastolic BP >105 or <60. c. Pulse <50. d. Respirations >24. e. Decline in neurological status, worsening of stroke signs		
Oxygen to maintain O2 saturation > 92%		
Bedrest for 24 hours		
NPO except necessary medication for 12 hours then reassess		
CT scan of head 24 hours post tPA		
Cardiac monitoring		
Avoid venipunctures for the first 12 hours unless absolutely necessary then reassess		
Do not use non-compressible sites such as the subclavian and internal jugular vein for 24 hours		
Use femoral and brachial sites for central line placement if needed for 24 hours		
Avoid nasogastric tubes and bladder catheterization if possible for 24 hours		
Avoid IM injections for 24 hours		

I.V. & MEDICATION-SOLUTÉ & MÉDICAMENTS (Meds, dose-posologie, frequency-fréquence, route-voie)	Time Heure	INIT
IV fluid (type and rate)		
Tylenol (Acetaminophen) 650 mg po/pr q 4h prn for fever >38° C degrees		
Dimenhydrinate (Gravol) 25-50 mg IV q 4h prn for nausea or vomiting		
No Heparin, Warfarin, ASA, Aggrenox, Ticlopidine, Clopidogrel or other antiplatelet agents for 24 hours.		
Medication:		

Date:	Time-Heure:	Physician's-Médecin printed-imprimé:	Signature:
Date (noted-notée):	Time-Heure:	Processed by-Traitée par:	Signature (Nurse-Infirmière):

N-Noted T-Transcribed to MAR O-Ordered Req-Requisition

SPO 93 (03/2004) 1 - CHART-DOSSIER 2 - PHARMACY-PHARMACIE

Bleeding complications of thrombolysis and management of complications

tPA acts by converting plasminogen to plasmin. Plasmin cleaves fibrin to produce clot lysis. tPA persists within a clot for several hours, although its half-life in the circulation is 30-45 minutes. Cryoprecipitate and Amicar (aminocaproic acid) may be indicated. Discuss the management with the Hematologist on-call

Bleeding complications may be classified as:

- **Intracranial**
- **Extracranial (from other body sites)**

Intracranial Bleeding

Deterioration in neurological status during or after thrombolytic treatment

All patients receiving thrombolytic therapy must be monitored for intracranial bleeding. The infusion of tPA must be immediately stopped if there is any deterioration in neurological status.

The BP is monitored q15 minutes

A repeat head CT to rule out a bleeding complication must be done immediately.

Patients with intracranial bleeds should have Neurosurgical consultation

If suspected intracerebral hemorrhage:

- **Stop thrombolytic immediately**
- **Stat non-contrast CT of head**
- **Neurosurgery consultation**
- **Hematology consultation**
- Draw STAT blood work: CBC, INR, PTT, fibrinogen level, thrombin time, type and cross

Hematology recommendations:

1. No need to do the crossmatch and put products on hold prior to TPA (costly and can be

done STAT in 10-15 minutes if bleeding is suspected) but a type and screen is essential for rapid issuing of products if necessary, also do a PTT, INR, fibrinogen prior to TPA.

2. If bleeding is suspected, do a STAT CBC, INR, PTT, thrombin time, and fibrinogen (d-dimer not likely to be helpful as often positive in patients over 60 with no illness and in acute CVA)

3. If bleeding occurs, then administer 10 units cryoprecipitate to raise the fibrinogen to above 2.0g/L and recheck q2 hours and repeat PRN according to the level (maintain fribrinogen above 2.0g/L).

4. If the INR or PTT are elevated, administer 4 U FFP and repeat INR, PTT in 2 hours

5. If the bleeding time is prolonged after correction of fibrinogen, and PTT, INR (hard to get this test after hours and on weekends), administer 5 u platelets.

6. If any heparin has been given, administer protamine 1.0mg per 100 units heparin given in the previous 4 hours (if low molecular weight heparin has been given, give 20mg and call thrombosis MD for advice re protamine infusion (use 1mg per hour for the next 24 hours and follow the anti Xa level). A prolonged TT will help identify heparin effect.

7. Give RBC as needed – check ionized calcium level

8. Check an ionized calcium after the initial cryo and particularly RBC as they all contain EDTA which chelates the calcium. Calcium is needed for coagulation (major cofactor), thus if low, no clot is formed even if all factors are present in adequate quantities.

9. Consult hematology/thrombosis

Extracranial Bleeding

Venous and arterial punctures, central lines

No venipunctures for the first 12 hours unless absolutely necessary. Avoid skin punctures if possible for 24 hours. Do not use non-compressible sites such as the subclavian and internal jugular veins. The femoral and brachial sites are acceptable for central line placement if needed.

Nasogastric tubes and bladder catheterization are also best avoided if possible for 24 hours

Minor superficial bleeding
Patients may bleed from small cuts of the skin, or the gums, usually in those with poor dentition. Apply local pressure i.e. puncture wounds, IV sites, scratches, etc. Avoid IM injections.

Gastrointestinal bleeding
The incidence of this type of bleeding is low (7%). Severe hemorrhages are uncommon.

Genitourinary bleeding
The incidence of this type of bleeding is also low.

The tPA infusion must be stopped if an extracranial bleeding complication develops that cannot be controlled.

Nausea and Vomiting:

The stroke itself, tPA, reperfusion or analgesics may induce this side effect. Gravol IV is recommended

Preparation for tPA (Activase) infusion – 100 mg vials

- Package contains 100 mg vial of tPA (Activase)
- 1-100ml vial of sterile H20
- A double-sided sterile transfer device

1. Insert one end of transfer device into the vial containing the diluent. Holding the tPA vial upside down, insert the other end of the transfer device into the center of the stopper. tPA should not be used if a vacuum is not present when mixing.
2. Insert the vials. The diluent should flow freely into the tPA vial
3. Gently swirl vial to dissolve contents. DO NOT SHAKE VIAL.
4. Inspect the solution. Remove the empty vial and transfer device. The tPA is ready for infusion. Label the vial tPA 1 mg/ml. If foaming occurs, allow the vials to sit undisturbed until the foam subsides; the drug will remain active. Note: vial may be stored at room temperature for 24 hours.
5. Prime the IV tubing with tPA and hang.
6. Set up the Colleague pump for the tPA infusion. Do not use infusion filters. Do not mix tPA with any other medication
7. Set the bolus dose as per the infusion chart to run over 1 minute (based on body weight)
8. Set the continuous infusion dose to run over 1 hour. Note: Do not exceed maximum total dose of 90 mg.
9. Start the infusion.
10. When the continuous infusion dose is complete disconnect the IV tubing and leave the saline lock in place to maintain peripheral IV access for 24 hours.

NOTE: Use tPA within eight hours once it is mixed. However, it may be stored in the refrigerator for up to 24 hours.

INFUSION ALARMS MUST BE SET!

Strict attention to the infusion rate is essential.

Managing Hypertension in Patients Receiving tPA in Acute Ischemic Stroke

If Systolic BP > 185 mmHG **or** DBP > 105 mmHG for 2 or more readings taken 10 minutes apart give:

- IV Labetolol 10 mg over 1 – 2 minutes. The dose may be repeated or doubled every 10 to 20 minutes up to a total of 150 mg.
- **If response** is not satisfactory or DPB >140 mmHG then infuse sodium nitroprusside 0.5 – 1.0 ug/kg/min.
  Arterial BP monitoring is best.

  If Labetolol or nitroprusside cannot be used give Enalapril 1.25 mg IV q6h

Management of Angioedema with Use of tPA for Ischemic Stroke

Angioedema has been reported in 1.3% (8 of 596; 95% CI 0.6-2.6%) of patients treated with IV tPA therapy for acute stroke. It has been associated with previous angiotensin converting enzyme (ACE) inhibitor therapy and with a past history of angioedema reactions. The reaction has been observed approximately 45-90 minutes after the tPA infusion was started. Patients reported dysphagia and inspection of the tongue revealed hemilingual (ipsilateral to the side of the hemiplegia) tongue swelling. Progression to the entire tongue and oropharynx may occur.

Risk Assessment

- Inquire if patient has ever experienced angioedema in past.
- Take **ACE inhibitor** history. The following is a list of currently marketed ACE inhibitors to facilitate in their identification:

Benazepril (Lotensin®)	Lisinopril (Zestril®)
Captopril (Capoten®, generic brands)	Perindopril (Coversyl®)
Cilazapril (Inhibace®)	Quinapril (Accupril®)
Enalapril (Vasotec®)	Ramipril (Altace®)
Fosinopril (Monopril®)	Trandolapril (Mavik®)

- **Angiotensin II (ATII) receptor antagonists** have been implicated in the angioedema reaction. **Currently marketed ATII antagonists include:**

Candesartan (Atacand™)	Epoprosartan (Teveten™)
Irbesartan (Avapro™)	Telmisartan (Micardis™)
Valsartan (Diovan™)	Losartan (Cozaar™)

- **Note: Combination diuretic and ACE inhibitor or ATII formulations are also currently marketed and should be noted.**

Monitoring Parameters

- Observe for facial, tongue, and/or pharyngeal angioedema 30 minutes, 45 minutes, 60 minutes and 75 minutes after initiation of IV tPA infusion and periodically for 24 hours afterwards
- Continuous O_2 monitoring during tPA IV infusion and for 24 hours afterward

Management

Treat angioedema aggressively with the following agents until resolution:

- Diphenhydramine (Benadryl) 50 mg IV Q4H
- Ranitidine 50 mg IV Q8H
- If severe, consider Hydrocortisone 100 mg IV or Methylprednisolone 80 mg IV Q8H
- Avoid use of epinephrine due to possibility of increasing risk of intracerebral hemorrhage secondary to sudden rise in blood pressure

INFORMATION FOR PATIENTS AND FAMILIES ABOUT T-PA® (TISSUE PLASMINOGEN ACTIVATOR) FOR STROKE

WHAT IS A STROKE?

A stroke is an injury to a part of the brain. It happens when there are problems with the blood flow to the brain. It may be caused by a clot blocking the blood flow or by a break in the blood vessels to your brain. Without enough blood some of the brain tissue will die. If you have had a stroke, you may be offered a treatment to try to fix the problem with blood flow to your brain.

WHAT IS t-PA®?

t-PA® is a medication that is given to you through an IV (a small tube put into your vein). T-PA® breaks up the clot and allows the blood supply to return to the brain.

CAN ALL STROKE PATIENTS GET t-PA®?

No, not everyone who has had a stroke can have t-PA®. Your doctor will decide if t-PA® is the right treatment for you or your family member. For t-PA® to work, it can only be given within the first three hours of the stroke. There are many things that help the doctor decide if t-PA® is the right treatment for you, so you will be asked many questions and have a number of tests done when you first come into the hospital. A CAT scan (x-ray of the head) will be one of the tests done as soon as possible.

WHAT ARE THE BENEFITS OF T-PA®?

Some patients will get better with t-PA®. Patients receiving t-PA® have a 30% better chance of returning to normal or near normal function within 3 months after a stroke. T-PA® must be given within 3 hours of the start of the stroke to have this benefit.

WHAT ARE THE RISKS OF t-PA®?

If you are treated with t-PA® there is a higher risk (6/100 patients) of bleeding into the brain. If you do bleed into the brain after t-PA® is given, it may cause your stroke symptoms to get worse or result in death. Overall, there is no increase in the risk of death with this treatment.

If you choose not to have treatment with t-PA®, your care will not be affected. You will still receive appropriate care for a stroke. If you have any questions about t-PA® or other treatment for stroke, please talk to your doctor or any member of your health care team.

Feb 04, The Ottawa Hospital

INFORMATION POUR LES PERSONNES AYANT SUBI UN ACCIDENT VASCULAIRE CÉRÉBRAL ET LEURS FAMILLES CONCERNANT LE t-PA^{MD} (ACTIVEUR TISSULAIRE DU PLASMINOGÈNE)

QU'EST-CE QU'UN ACCIDENT VASCULAIRE CÉRÉBRAL (AVC)?

Il s'agit de dommages causés à une partie du cerveau. Un AVC se produit lorsque la circulation sanguine au cerveau est interrompue. Ce problème peut être entraîné par un caillot de sang ou par la rupture d'un vaisseau sanguin. L'insuffisance de la circulation sanguine cause la mort de certaines cellules cérébrales. Si vous avez subi un AVC, il se peut qu'un traitement visant à tenter de rétablir la circulation sanguine de votre cerveau vous soit offert.

QU'EST-CE QUE LE t-PA^{MD}?

Le t-PA^{MD} est un médicament qui est administré par intraveineuse (un petit tube inséré dans une veine). Le t-PA^{MD} dissout le caillot sanguin et rétablit la circulation sanguine au cerveau.

EST-CE QUE TOUS LES PATIENTS PEUVENT BÉNÉFICIER DU t-PA^{MD}?

Non. Votre médecin décidera si le t-PA^{MD} est le traitement qui vous convient. Pour être efficace, le t-PA^{MD} doit être administré au cours des trois premières heures suivant l'AVC. Différents facteurs permettront au médecin de décider si le t-PA^{MD} vous convient. Vous devrez donc répondre à de nombreuses questions et subir plusieurs tests dès votre arrivée à l'hôpital. Un examen tomodensitométrique (une radiographie de la tête) sera parmi les tests qui devront être effectués aussitôt que possible.

QUELS SONT LES AVANTAGES DU t-PA^{MD}?

Certains patients se rétabliront grâce au t-PA^{MD}. Les personnes auxquelles le t-PA^{MD} a été administré ont 30 % plus de chance de recouvrer leurs fonctions normales ou quasi normales dans les 3 mois suivant l'AVC. Pour être efficace, le T-PA^{MD} doit être administré dans les 3 heures suivant le début de l'ACV.

QUELS EN SONT LES RISQUES?

Si vous êtes traité au t-PA^{MD}, le risque de saignement au cerveau est plus élevé (6 patients sur 100). Si un saignement au cerveau se produit après l'administration du t-PA^{MD}, les symptômes de l'ACV peuvent empirer ou entraîner le décès. En général, il n'y a aucune augmentation du risque de décès associé au traitement.

La décision de ne pas être traité au t-PA^{MD} n'affectera en rien la qualité des soins qui vous seront dispensés. Vous recevrez des soins appropriés au traitement d'un AVC. Pour toute question concernant le t-PA^{MD} ou le traitement d'un AVC, veuillez vous adresser à votre médecin ou à un membre de votre équipe de soins de santé.

Février 2004, L'Hôpital d'Ottawa

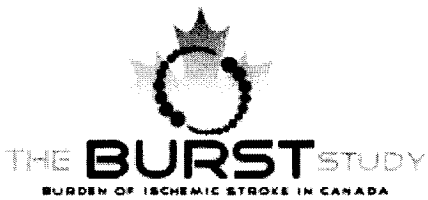
Appendix 2 - Search strategy for community interventions in ischemic stroke

1 Patient Education/
2 Health Education/
3 Community Health Services/
4 Community Health Nursing/
5 Community Networks/
6 (community education adj2 (program$ or intervention$ or outreach)).mp. [mp=ti, ab, rw, sh]
7 (community education and program$).tw.
8 (community education and outreach$).tw.
9 (community and intervention$).tw.
10 (access adj2 (EMS or emergency medical service$)).mp.
11 Health Promotion/
12 (educat$ adj2 public).tw.
13 ((educat$ or teach$) adj2 public).tw.
14 ((TV or television or advertis$ or print or media) and (campaign or program$)).tw.
15 Cerebrovascular Accident/
16 exp Cerebrovascular Disorders/
17 (stroke adj2 symptom$).tw.
18 stroke$.tw.
19 (acute adj2 stroke).tw.
20 time factors/
21 time/
22 delay time.tw.
23 (report$ adj2 (delay or urgency)).tw.
24 exp Emergency Service, Hospital/
25 or/1-13
26 or/15-19
27 or/20-24
28 and/25-27

Appendix 3 - Search strategy for community interventions in chest pain

1 exp myocardial infarct/
2 cardiac ischemia.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3 chest pain.tw.
4 or/1-3
5 health education.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
6 radio.tw.
7 television.tw.
8 newspaper$.tw.
9 public service announcements.tw.
10 poster$.tw.
11 brochure$.tw.
12 direct mail$.tw.
13 pamphlet$.tw.
14 speech$.tw.
15 presentation$.tw.
16 or/5-15
17 exp emergency treatment/
18 emergency medical service.tw.
19 emergency room.tw.
20 (ambulance or transport$).tw.
21 (hour$ treatment or hour$ therap$).tw.
22 or/17-21
23 4 and 16 and 22

APPENDIX 4 The BURST Study



January 16, 2006
Re: Dr. Sharma as co-investigator for the Burden of Ischemic stroke (BURST)

To whom it may concern:

This letter acknowledges that Dr. Sharma is a co-investigator of the Burden of Ischemic Stroke (BURST) in Canada study.

The BURST study will determine resource utilization and direct and indirect costs of managing ischemic stroke in the first six-months post stroke from a health system perspective. The primary analysis will provide an overall estimate of cost per ischemic stroke patient.

Dr. Sharma collaborated on the study concept, writing the study protocol and design of the measurement instruments. Dr. Sharma was responsible for study site recruitment as well as participant motivation. Dr. Sharma was also involved in site training and overall clinical presentations on the importance of this study.

Yours sincerely,

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THE METHODOLOGY BEHIND A PROSPECTIVE STUDY OF THE ECONOMIC *BUR*DEN OF ISCHEMIC *ST*ROKE ("BURST") IN CANADA

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2 SUNNYBROOK & WOMEN'S COLLEGE HEALTH SCIENCES CENTRE (TORONTO, CANADA)
3 UNIVERSITY OF TORONTO (TORONTO, CANADA)
4 OTTAWA HOSPITAL – GENERAL CAMPUS (OTTAWA, CANADA)
5 ASTRAZENECA CANADA (MISSISSAUGA, CANADA)

OBJECTIVES: To present the steps involved in launching the first national, prospective study determining the resource utilization and costs of treating ischemic stroke in the first six-months that includes post-acute components such as rehabilitation, outpatient stroke (prevention) care, community care and indirect costs. **METHODS**: From 2004-2005, discussions and meetings took place to finalize the methodology. The final decision was made to conduct an observational study with a convenience sample of 200 ischemic stroke patients recruited in a consecutive manner by ten stroke centres. Ethics approvals will be obtained and a minimum of one neurologist and one study coordinator per centre will be participating in order to identify, approach, obtain informed consent, and interview eligible patients. The assignment of unique four-digit study identifier numbers will ensure confidentiality. Three sets of questionnaires will be completed as well as two daily diaries. Data collected using the questionnaires will be entered electronically via a secure study website. A pilot study (n=6) will be conducted in Ottawa in July 2005. **RESULTS**: Stroke centres in Ottawa, Toronto, Calgary, Montreal, Quebec City, Edmonton, Vancouver, Halifax, Saint John and Thunder Bay will be recruiting 20 eligible ischemic stroke patients into this study. Inclusion criteria such as age, language, neuroimaging evidence and non-interventional clinical trial involvement have been defined in order for the study to be launched on September 26, 2005. The questionnaires consist of the patient's clinical and drug histories, stroke severity, disability and resource utilization as well as level of depression and utility. **CONCLUSIONS**: The BURST study will be the first Canadian study that will determine the resource utilization and costs of not only treating ischemic stroke in an acute setting, but also post-acute with the involvement of both tertiary-based and community-based stroke centres. The economic data collected will be critical for future stroke care funding systems.

Health Outcomes & PharmacoEconomics

HOPE Research Centre

PROTOCOL FOR THE ECONOMIC *BURDEN* OF ISCHEMIC *STROKE* *(The "BURST" Prospective Study)*

VERSION 16
DATE: MARCH 30, 2005

(FYI: This is an update from the study protocol #15 dated 25 February 2005)

Lead Investigation Team:
HOPE Research Centre (Contact: Ms. Soo Jin Seung)

Overall Study Background

The HOPE Research Centre is conducting a 2-phase study of stroke in Canada:

Phase I will identify and quantify approximate stroke costs and healthcare resource utilization from a provincial (Ontario) perspective within a one-year timeframe using aggregate information obtained from various databases as well as expert opinion and institutional program budgets. Costs and resource utilization will be stratified by stroke disability (Rankin score) and atrial fibrillation co-morbidity, if possible.

Phase II ("BURST") will consist of collecting prospective health information to represent post-acute stroke care once a patient is discharged from the hospital. Patient questionnaires will be completed at different time points to provide an accurate valuation/burden of stroke care in Canada. As well, the data collected from Phase II can validate the aggregate information obtained during Phase I. The results from this burden of stroke study (based on disability and atrial fibrillation co-morbidity, if possible) may be used in economic evaluations of stroke prevention therapies impacting acute and post-acute stroke care.

I. Study Synopsis and Importance of Study (BURST)

The BURST study will be a national burden of stroke study focusing on the post-acute stroke care components based on questionnaires completed by stroke patients or their caregiver after hospital discharge.

The conduct of this type of study is needed because clinical management of stroke in Canada (e.g. Ontario's Stroke Strategy) has shifted from inpatient hospital care to outside institutions such as rehabilitation facilities and home care. And the goal of establishing the Registry of the Canadian Stroke Network in 2001 was to measure, monitor and improve stroke care in the country with clinical results just now being published in the peer-reviewed literature. There remains a paucity of Canadian economic stroke studies with detailed and patient-level data still lacking and this type of data is critical for future stroke care planning.

II. Background

Based on 2002 statistics, the Heart & Stroke Foundation of Canada estimates that there are between 40,000 – 50,000 strokes annually in Canada and about 300,000 individuals who are living with the effects of stroke.[1] Of every 100 people hospitalized for stroke, 50% will be discharged home, 20% will die before leaving the hospital, 15% will require long-term care and 10% will enter an inpatient rehabilitation program.[1]

In terms of the economic impact of stroke, $2.7 billion a year is the figure most often quoted for stroke costing the Canadian economy (in 1993)[2] and for Ontario alone, it was estimated that the total cost of stroke was $857 million (in 1994-1995).[3] For first-ever stroke admissions in one Toronto hospital, it was estimated that the average cost per patient was $27,500 for acute stroke care for a total of $8 million over 2 years.[4]

III. Study Objectives

The objective of the prospective study is to determine the resource utilization and associated costs of treating ischemic stroke in the first six-months with emphasis on collecting prospective data for the post-acute stroke care components namely:

1) *Outpatient stroke centre care*
2) *Outpatient stroke rehabilitation care*
3) *Community (home) care*
4) *Indirect costs related to changes in patient's employment and out-of-pocket costs (i.e. purchase of medical equipment aids)*

As well, these costs will be stratified by stroke disability as indicated by Rankin scores when discharged from the initial hospitalization and atrial fibrillation co-morbidity, if possible.

IV. Methodology Specific to Participating Stroke Centres

a. Research Ethics Board (REB) Applications

REB applications will need to be completed since prospective post-acute stroke data will be collected from stroke centres across Canada. Although the lead investigation team (HOPE Research Centre) will be responsible for completing the ethics applications and paying fees, each of the on-site investigation teams at the stroke centres will need to obtain all required signatures for the ethics application as well as meeting any other requirements that can only be met by the on-site investigation team (i.e. attendance at the REB meeting). The HOPE Research Centre realizes

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[1] Heart and Stroke Foundation of Canada. General Info – Stroke Statistics (Sept 3, 2002). Ottawa: accessed June 11, 2004. http://ww1.heartandstroke.ca/Page.asp?PageID=33&ArticleID=428&Src=stroke&From=SubCategory#statistics

[2] Moore RS, Mao Y, Zhang J, Clarke K. Economic Burden of Illness in Canada, 1993. Ottawa: Health Canada, Laboratory Centre for Disease Control. Published 1997.

[3] Chan B and Hayes B. Cost of Stroke in Ontario, 1994/95. CMAJ 1998: 159 (Suppl 6); S2-8.

[4] Smurawska LT, Alexandrov AV, Bladin CF, Norris JW. Cost of Acute Stroke Care in Toronto, Canada. Stroke 1994: 25; 1628-1631.

that certain centres may require the on-site neurologist to be listed as the principal investigator (PI) in order for the REB submission to be accepted.

b. *Data Being Collected*

- The participating neurologist will be responsible for securing the total annual operating budget and annual patient load.
- Each on-site investigation team will be collecting resource utilization from their recruited study population via patient records and interviews.

c. *Study Eligibility*

A convenience sample of **200 ischemic stroke patients** will be recruited into the study in a consecutive manner by the participating stroke centres. Patients are eligible to participate in this study based on the following criteria:

1. *An adult over 18 years of age.*
2. *Fluent in English or French (dependent of language ability of on-site coordinator).*
3. *Patient and/or caregiver cognitively competent to complete questionnaires.*
4. *Evidence from neuroimaging study (CT or MRI scan) that patient's index stroke was an ischemic stroke (hemorrhagic stroke and TIA patients will be excluded).*
5. *The index stroke was the patient's first stroke. A patient is still eligible if they have had a previous TIA.*
6. *The patient is not participating in any research study that requires him/her to attend additional appointments with healthcare professionals or any other deviations from typical stroke care.*
7. *The patient has no major co-morbidities (e.g. cancer, dementia, multiple sclerosis) that could impact the resource utilization of stroke care. Patients with trial fibrillation, diabetes, hypertension, etc. are still eligible.*
8. *Rankin score at hospital discharge or clinic referral is available in the patient's chart.*

d. *Pilot Study*

Once REB approval and patient informed consent have been obtained, a pilot study to evaluate the instruments will be conducted with The Ottawa Hospital (General Campus) before the official start of the BURST study.

e. *Study Instruments (Questionnaires)*

There will be a total of **THREE** questionnaires that the patient or caregiver will need to complete *prospectively:*

Baseline questionnaire	Mandatory	• Demographics • Co-morbidities • Acute care data	Stroke patient/caregiver	Prior to hospital discharge. Possibility that this may be completed at first stroke centre visit.

3-month questionnaire	Mandatory	• Post-acute care costs • Indirect costs	Stroke patient/caregiver	• Stroke centre visit • Telephone
6-month questionnaire	Mandatory	• Post-acute care costs • Indirect costs	Stroke patient/caregiver	• Stroke centre visit • Telephone

f. Study Instrument (Diary) for Subset of Stroke Patients

Each of the participating stroke centres will ask all recruited patients about their participation in completing a weekly diary for the first 4-weeks after hospital discharge and 4-weeks after completing their 6-month questionnaire. Approximately 20-30 patients (10-15%) of the total study population are anticipated (2-3 per stroke centre).

Weekly diary x 4 weeks (after hospital discharge)	• Post-acute care costs • Indirect costs	Stroke patient/caregiver	Patient to mail back to stroke centre.
Weekly diary x 4 weeks (after 6-months)	• Post-acute care costs • Indirect costs	Stroke patient/caregiver	Patient to mail back to stroke centre.

g. Online Data Entry

- A BURST study website under development that can be accessed by all study investigators with their unique login and password.
- Each participating stroke centre will be able to access only their data.
- The HOPE Research Centre will act as the website administrator and will be able to access and monitor data from all stroke centres.
- Each stroke centre will login and enter patient profiles during recruitment. Each patient profile will be assigned a unique study number.
- The 3-month and 6-month questionnaires to be completed by the nurse coordinators directly on the website.

h. Participating Stroke Centres

Ten stroke centres across Canada will be participating in this study that includes **The Ottawa Hospital (General Campus)** who have been invaluable during the initial stages of this study and continue to provide important information relating to protocol development and stroke treatment practices. Another academic regional stroke centre participating in this study is **Sunnybrook & Women's College Health Sciences Centre (Toronto).**

The following stroke centres have expressed their interest in participating in this study:

- **Victoria, BC (non-academic)**
- **Vancouver, BC**
- **Edmonton, AB**
- **Calgary, AB**
- **Montreal, QC**
- **Quebec City, QC**
- **Halifax, NS**
- **St. John, NB (non-academic)**

The lead investigation team acknowledges the limitations of recruiting only academic stroke centres in an urban setting (e.g. inability to generalize results to non-academic and community-based stroke centres), but these recruited facilities are already conducting research specific to stroke and more importantly, will already have the requisite research/nursing staff to be able to coordinate this study.

i. Recruitment Targets of Stroke Centres

PATIENTS: For this patient cohort, no formal sample calculation was performed. A convenience sample of **200 ischemic stroke patients** was determined based on discussions with the Ottawa study group or 20 patients per stroke centre. Assuming a 50% successful recruitment rate, each of the 10 stroke centres will need to approach at least 40 hospitalized ischemic stroke patients, excluding those with TIA. This is to account for recruited patients dropping out, being lost to follow-up or suffering from a subsequent stroke event.

ATRIAL FIBRILLATION CO-MORBIDITY: Based on unpublished Phase-2 data from the Registry of the Canadian Stroke Network, an estimated 10% of ischemic stroke patients have an atrial fibrillation co-morbidity. This variable will be closely monitored by the stroke centres during the recruitment period.

RECRUITING AND CONTACTING STUDY PATIENTS: It will be the responsibility of the on-site study investigation teams to recruit and contact study patients regarding the completion of the questionnaires.

- Prior to hospital discharge, the on-site study coordinator will approach the patient (or caregiver) about their participation in this study and obtain signed consent.
- The baseline questionnaire will be completed prior to hospital discharge with the on-site study coordinator.
- Prior to hospital discharge, the on-site study coordinator will review with the patient how the 3-month and 6-month questionnaires will be completed (via telephone or at stroke clinic visit).
- Telephone interviews will be arranged for those study patients who are not followed-up in the outpatient stroke clinic in order to complete the 3-month and 6-month questionnaires.
- For study patients who are followed-up in the outpatient stroke clinic, the 3-month and 6-month questionnaires will be completed at the closest appointment scheduled.

CONSENT FORM: Standardized consent forms for all study patients at all stroke centres will be signed.

PARKING REIMBURSEMENT: Stroke patients participating in this study will be offered reimbursement for their parking should they complete and submit completed questionnaires while in clinic (maximum of $800 per stroke centre).

COMMUNICATION WITH HOPE RESEARCH CENTRE: Monthly teleconferences with all the stroke clinics and the HOPE Research Centre are scheduled in order to provide updates on patient recruitment and discuss about any study difficulties as well as monitor the distribution of Rankin scores and atrial fibrillation co-morbidity.

j. Stroke Centre Data Collection Steps

The table outlines the involvement of the on-site study investigator with the stroke patients or caregivers to ensure that all three questionnaires will be completed:

Patient recruitment, written patient consent, baseline questionnaire	Prior to hospital discharge	On-site coordinator	On-site coordinator discusses study with patient, obtains written patient consent and baseline questionnaire is completed.
3-month questionnaire	90 days from recruitment	On-site coordinator	Patient/caregiver completes questionnaire while visiting stroke clinic or on the telephone with the on-site coordinator.
6-month questionnaire	180 days from recruitment	On-site coordinator	Patient/caregiver completes questionnaire while visiting stroke clinic or on the telephone with the on-site coordinator.

The on-site investigator will also need to make reminder telephone calls to the 2-3 patients who agree to complete the 4-week diaries:

Weekly diary x 4 wks	Prior to hospital discharge	On-site coordinator	Prior to hospital discharge, on-site coordinator gives 4-week diary for patient to take home.
Telephone reminder #1	2-weeks after recruitment	On-site coordinator	On-site coordinator contacts patient to ask if diary is being completed.
Telephone reminder #2	4-weeks after recruitment	On-site coordinator	On-site coordinator contacts patient to ask if diary has been completed and if so, mail/bring to stroke clinic.
Weekly diary x 4 wks	After 180 days from recruitment	On-site coordinator	On-site coordinator gives 4-week diary for patient to take home.

(after 6-months)			
Telephone reminder #3	2-weeks after 180 days from recruitment	On-site coordinator	On-site coordinator contacts patient to ask if diary is being completed.
Telephone reminder #4	4-weeks after 180 days from recruitment	On-site coordinator	On-site coordinator contacts patient to ask if diary has been completed and if so, mail/bring to stroke clinic.

k. Data Storage, Shipment, Management, Analysis and Reporting

STORAGE

All study documentation will be stored and secured in locked filing cabinets by the on-site coordinator.

SHIPMENT

All study documentation will be shipped back to the HOPE Research Centre for quality assurance and then data entry/management.

ANALYSES

- All analyses will be conducted by the HOPE Research Centre.
- The questionnaires will ask patients about their demographics, stroke severity (Rankin scores), co-morbidities, resource utilization due to stroke and stroke costs.
- Descriptive statistics (means, standard deviation, ranges) will be used for the demographic, resource utilization and cost data.
- Sub-analyses involving Rankin scores and atrial fibrillation co-morbidity will involve the use of statistical software such as Excel or SPSS to conduct quantitative analyses in order to determine significance (i.e. chi-square test).

FINAL REPORT

It will be the responsibility of the lead investigation team (HOPE Research Centre) to present the final results of the study to the sponsor after circulating a draft version to the on-site investigation teams for their comments.

V. Confidentiality

The local study investigation team will also be part of the primary care team for the ischemic stroke patient cohort. Therefore, the initial approach of patients regarding their participation in this study will be made by a member of their primary care team. After a patient has been successfully recruited into the study and has signed the consent form, he/she will be assigned a unique study identifier that will be used throughout the entire study duration and included in all relevant documentation. All study documentation will remain with the local stroke centres (stored in a locked filing cabinet). And the HOPE Research Centre will access and analyze the aggregate data from the study website.

VI. Risk of Harm and Benefits if Participating in Study

There is no risk of harm (e.g. adverse drug reactions) to patients since this is a non-interventional, prospective study using questionnaires. There are no direct benefits to patients since this is a non-treatment study. However, the results of this study will be of assistance to the scientific community in compiling costing and resource utilization data about stroke care in Canada. Patients can choose to discontinue their participation any time during the study without any affect to their standard of stroke care.

VII. Indemnification, Liability and Termination Clauses for BURST Study

These clauses to be handled by the legal departments of Sunnybrook & Women's College Health Sciences Centre (on behalf of HOPE Research Centre) and the individual stroke centres.

VIII. Tentative Study Timelines

The following table outlines a tentative timeline for conducting the BURST study. However, the REB application process, and most importantly, successful patient recruitment are factors that could affect these timelines.

March 2005	Study teleconference with participating neurologists Study protocol and study tools circulated	HOPE/Stroke centres HOPE/Stroke centres
April –May 2005	Study teleconference with participating research nurses/coordinators Receive feedback about study documentation Finalize all study documentation Translation of study documentation	HOPE/Stroke centres Stroke centres HOPE HOPE
May– June 2005	Signing of study agreements Submit Ottawa REB submission	HOPE/Stroke centres HOPE/Ottawa
July – August 2005	Pilot study in Ottawa Fine-tuning of study tools	HOPE/Ottawa HOPE
Sept – Nov 2005 **(3-MONTHS OF RECRUITMENT)**	Patient recruitment begins Written patient consent obtained Baseline questionnaire completed + shipped to HOPE	Stroke centres
October – Dec 2005	First 4-week diaries completed + shipped to HOPE	Stroke centres
Dec 2005 – Feb 2006	3-month questionnaires completed + shipped to HOPE	Stroke centres
March – May 2006	6-month questionnaires completed + shipped to HOPE	Stroke centres

January 2006	Interim analysis conducted and draft report circulated CAPT abstract submitted for 2006 conference	HOPE
June 2006	Second 4-weeks diaries after study completed + shipped to HOPE	HOPE
July – August 2006	Complete analysis conducted	HOPE
September 2006	Draft report circulated for comments	HOPE/Stroke centres
October 2006	Comments received	HOPE/Stroke centres
November 2006	Final report; manuscript/publication submitted to peer-reviewed journal	

IX. Reports

- Interim study report
- Final study report

X. Publications After The Final Study Report

- The HOPE Research Centre has full-rights to publish all study findings.
- Authorship of abstracts, oral presentations and peer-reviewed articles will be based on the criteria for authorship according to the International Committee of Medical Journal Editors (ICMJE).

XI. Study Investigators (currently in order of expressing interest in study participation)

LEAD INVESTIGATION TEAM – HOPE RESEARCH CENTRE (TORONTO):

- Dr. Nicole Mittmann – Executive Director and Principal Investigator (PI)
- Ms. Soo Jin Seung – Study Coordinator

CLINICAL INVESTIGATORS #1 – OTTAWA HOSPTIAL GENERAL CAMPUS (OTTAWA):

- Dr. Mike Sharma – Neurologist
- Ms. Andrea Fisher – Advanced Practice Nurse
- Ms. Donna Cousineau – Stroke Prevention Nurse Specialist

CLINICAL INVESTIGATORS #2 – SUNNYBROOK & WOMEN'S (TORONTO)

- Dr. David Gladstone – Director of Inpatient Stroke Services

CLINICAL INVESTIGATORS #3 – FOOTHILLS MEDICAL CENTRE (CALGARY)

- Dr. Michael Hill – Director of Stroke Unit
- Ms. Marie McClelland, RN – Clinical Trial Nurse Coordinator

CLINICAL INVESTIGATORS #4 – MONTREAL GENERAL HOSPITAL (MONTREAL)

- Dr. Robert Cote – Director of Neurology
- Ms. Anne-Marie Fontaine – Study Coordinator

CLINICAL INVESTIGATORS #5 – HOPITAL DE L'ENFANT-JESUS (QUEBEC CITY)

- Dr. Ariane Mackey

CLINICAL INVESTIGATORS #6 – University of Alberta Hospital (Edmonton)

- Dr. Ashfaq Shuaib – Director, Stroke Program
- Dr. Abdul M. Nasser – Research Coordinator, Stroke Research Unit

CLINICAL INVESTIGATORS #7 – Vancouver General Hospital (Vancouver)

- Dr. Phil Teal – Director, Stroke Program
- Ms. Tracy Steele - Clinical Research Coordinator

CLINICAL INVESTIGATORS #8 – Queen Elizabeth II Health Sciences Centre (Halifax)

- Dr. Stephen Phillips – Director, Acute Stroke Program
- Dr. Gordon Gubitz
- Ms. Shannon Nearing

Stroke centres from Victoria, BC (non-academic) and St. John, NB (non-academic) may be added as the other clinical investigation teams.

XII. Funding for Stroke Centres

- As previously mentioned, each of the 10 stroke centres will need to successfully recruit 20 ischemic stroke patients and complete all three questionnaires as well as 2-3 of these patients to also complete the diaries.
- It is assumed that at each stroke clinic, 40 patients will be initially recruited, 20 patients will complete all the questionnaires and 2-3 patients will complete the diaries.
- The amount of $500 CDN per patient has been determined for each successfully recruited patients at each recruited stroke centre **($10,000 maximum).**
- There are separate budgets for operational expenses, ethics submission and patient parking reimbursement for the stroke centres.

$500 PER SUCCESSFULLY COMPLETED PATIENT = 20 PATIENTS X $500 = $10,000
OPERATIONAL EXPENSES PER STROKE CLINIC =$2,000 ETHICS SUBMISSION = $3,000 PATIENT PARKING = $800
TOTAL PER STROKE CENTRE =$15,800

XIII. Principal Investigator

Nicole Mittmann holds a faculty position as an Assistant Professor at the University of Toronto in the Department of Pharmacology. She is also a Scientist at Sunnybrook and Women's College Health Sciences Centre in the Division of Clinical Pharmacology. Nicole is a member of the Pharmacy and Therapeutics Committee at Sunnybrook and Women's College Health Sciences Centre. This position allows her to evaluate economic issues from a hospital perspective. Nicole is currently the Executive Director at Health Outcomes and Pharmacoeconomics (HOPE) Research Centre. In her capacity at HOPE, Nicole is responsible for designing and managing health economics and outcomes research projects from the government, hospital and pharmaceutical industry perspectives. In her academic capacity, Nicole has a proven track record of publications, abstracts and awards at both graduate student and scientist level. She has conducted and collaborated on notable research in the areas of meta-analysis, economic evaluations, outcomes research and utility assessments. Research methodologies include the examination of large databases, economic methodologies and decision analysis. Clinical areas of interest include cardiology, trauma, infectious disease, oncology and health policy.

Nicole has received a number of awards, including New Investigator Award from the National Institutes of Health (NIH) and National Institutes of Mental Health (NIMH) (1997), the Presidential Trainee Award from the American Association of Clinical Pharmacology and Therapeutics (1997), the New Investigator Award from the International Society for Pharmacoeconomics and Outcomes Research (2000), Best Poster Presentation at the Canadian Association for Population Therapeutics (2003) and Best Poster Finalist at the International Society of Pharmacoeconomics and Outcomes Research (2004). Most recently, Nicole has received a Canadian Institutes of Health Research (CIHR) grant for the study entitled "Economic evaluation of direct medical and non medical costs associated with a severe acute respiratory syndrome (SARS) outbreak".

Peer Reviewed Publications (chronological)

1. **Mittmann N**, Knowles SR, Gomez M, Fish J, Cartotto R, Shear NH. Evaluation of the extent of serious adverse drug reactions: the case of toxic epidermal necrolysis. *Drug Safety* 2004; 27 (7): 477-487.
2. **Mittmann N**, Knowles SR, Seung SJ, Cornish W, Oh PI, Paton T. Marijuana and the medical community. *Canadian Society of Hospital Pharmacists* 2004; 57 (3): 165-172.
3. **Mittmann N**, Oh PI, Walker SE, Bartle WR. Warfarin in the secondary prevention of atrial fibrillation: Impact of bioavailability on costs and outcomes. *PharmacoEconomics* 2004; 22 (10): 671-683.

4. Mydlarski PR, **Mittmann N**, Shear N. Intravenous immunoglobulin: use in dermatology. Skin Therapy Letters 2004;9(5):1-6.
5. Oh PI, Cohen EA, **Mittmann N**, Seung SJ. The economics of adjunctive therapies in coronary angioplasty: drugs, devices or both? *Canadian Journal of Clinical Pharmacology* (in press-Summer 2004)
6. Schortt R, Gomez M, **Mittmann N**, Cartotto R. Intravenous Immunoglobulin (IVIG) does not improve outcome in patients with toxic epidermal necrolysis. Journal Burn Care Rehabilitation 2004;25:246-255.
7. Cornish P, **Mittmann N**, Gomez M, Cartotto RC, Fish JS. Cost of medications in patients admitted to a burn center. *American Journal of Clinical Dermatology* 2003;4(12):861-7.
8. Lanctot KL, **Mittmann N**, Bradley-Kennedy C, Oh PI. Drug evaluation of meloxicam in an Ontario drug benefit eligible population. *Arthritis Trends* 2003;15 (Suppl C): 20-29.
9. Iskedjian M, Einarson TR, MacKeigan LD, Shear NH, Addis A, **Mittmann N**, Ilersich AL. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: Evidence from a meta-analysis. *Clinical Therapeutics* 2002; 24(2):302-316.
10. **Mittmann N**, Jivraj F, Wong A, Yoon A. Meta-analysis of oral fluoroquinolones in the treatment of community-acquired pneumonia and acute exacerbations of chronic bronchitis. *Canadian Journal of Infectious Diseases* 2002; 13 (5): 293-300.
11. Liu BA, Knowles S, **Mittmann N**, Einarson TR, Shear NH. Reporting fatal adverse drug reactions. *Canadian Journal of Clinical Pharmacology* 2001; 8(2): 84-88.
12. **Mittmann N**, Chan D, Trakas K, Risebrough N. Health utility attributes for chronic conditions. *Disease Management & Health Outcomes* 2001; 9(1): 11-21.
13. Oh PI, Lanctôt KL, **Mittmann N**, Iskedjian M, Addis A, Einarson TR. Cost-utility of risperidone compared with standard conventional antipyshcotics in chronic schizophrenia. *Journal of Medical Economics* 2001; 4:137-156.
14. Tavadia SMB, Mydlarski PR, Reis MD, **Mittmann N**, Pinkerton PH, Shear NH, Sauder DN. Screening for azathioprine toxicity-a pharmacoeconomic study based on a target case. *Journal of American Academy of Dermatology* 2000; 42: 628-632

Non-Peer Reviewed Publications

1. Craven C, Raynard W, **Mittmann N**, Hassouna M. The Hard Truth: an overview of erectile dysfunction for men with spinal cord injuries. Toronto Rehabilitation Institute, 2003.

Published Peer Reviewed Abstracts

1. **Mittmann N**, Seung SJ, Brown A, Coyle D, Brophy J, Title L, Cohen E. Economic evaluation of drug eluting stents. *Canadian Cardiovascular Congress* October 2004 (accepted).
2. **Mittmann N**, Craven BC, MacMillian RDH, Hassouna M, Lanctot KL, Gordon M, Tarride JE. Health preference evaluation of erectile dysfunction in spinal cord injury patients and their partners. *Canadian Association for Population Therapeutics* June 2004 (presented).

3. **Mittmann N**, Seung SJ, Brown A, Cohen E. Economic evaluation of glycoprotein inhibitors *Canadian Association for Population Therapeutics* June 2004 (presented).
4. Brown A, **Mittmann N**, Seung SJ, Noorani H, Mensinkai S. A cost-effectiveness adjunct in percutaenous coronary intervention (PCI) with stenting. *Heath Technology Assessment International* May 2004 (presented).
5. Brown A, **Mittmann N**, Seung SJ, Noorani H, Mensinkai S. Cost-effectiveness of glycoprotein 2B3A inhibitors as adjuncts in percutaneous coronary intervention (PCI) with stenting. *Canadian Association for Health Services and Policy Research* May 2004 (presented).
6. **Mittmann N**, Seung SJ, Brown A, Cohen E. Economic evaluation of glycoprotein inhibitors in diabetic patients. International Society of Pharmacoeconomics and Outcomes Research (ISPOR) May 2004 (accepted).
7. Craven BC, **Mittmann N**, Gordon M, Breton MC. The Cost Utility of Viagra for Treatment of Erectile Dysfunction in Men After Spinal Cord Injury. *Journal of Spinal Cord Medicine*, 2002; 25 (1): S44b.
8. Liu B, Anderson G, Rothwell D, **Mittmann N**, Herrmann N, Mamdani M. The risk of hip fracture associated with the use of antidepressant and other psychotropic medication in a cohort study of Ontario seniors: preliminary results. *Canadian Journal of Clinical Pharmacology* 2003; 10(1): 50.
9. **Mittmann N**, Craven C, Gordon M, MacMillian R, Hassouna M, Lanctôt KL, Tarride JE. Cost-utility of Viagra treatment of erectile dysfunction in men after spinal cord injury. *Canadian Journal of Clinical Pharmacology* 2003; 10(1): 50.
10. Lanctôt KL, Moosa S, **Mittmann N**, Bradley-Kennedy C, Oh PI. Drug use evaluation of meloxicam in an Ontario Drug Benefit (ODB) eligible population. Canadian Association for Population Therapeutics April 2002 (presented).
11. Craven C, **Mittmann N**, Raynard W, Kaiser A, Gordon M. Cost-utility of Viagra treatment of erectile dysfunction in men after spinal cord injury. American Spinal Injury Association (accepted).
12. Craven C, **Mittmann N**, Raynard W, Kaiser A, Gordon M. The "Hard Truth" an information resource for men with spinal cord injury and erectile dysfunction. American Spinal Injury Association (accepted).
13. **Mittmann N**, Bartle W, Walker SE, Oh PI. Economic analysis of warfarin in outpatients with atrial fibrillation: Innovator versus generic. Value in Health. 2000:3(2); 50.

Scientific Presentations

1. Evaluation of the extent of under-reporting of Toxic Epidermal Necrolysis in Canada, Boston, Massachusetts. American Burn Association (April 2001).

2. Evaluation of the extent of under-reporting of Toxic Epidermal Necrolysis in Canada, Toronto, Ontario. Drug Information Association (February 2001).

The Ottawa Hospital | L'Hôpital d'Ottawa

INFORMATION SHEET AND CONSENT FORM
The Economic Burden of Ischemic Stroke in Canada

On-site Study Coordinator should complete the following:

Today's date (D/M/Y): _____

Study Identifier #: _____
Ottawa = 01-001, 01-002, 01-003, etc.

Gender of study participant: ○ Male
○ Female

Date of birth (D/M/Y): _____

INFORMATION SHEET AND CONSENT FORM
The Economic Burden of Ischemic Stroke in Canada

1) BACKGROUND OF STUDY

This is a new research study that will be recruiting first-time ischemic stroke patients. Based on 2002 statistics, the Heart & Stroke Foundation of Canada estimates that there are between 40,000 – 50,000 strokes annually in Canada and about 300,000 individuals who are living with the effects of stroke.

2) PURPOSE AND DESIGN

You or your caregiver are being asked to participate in a new research study to identify and measure resources used while receiving treatment for ischemic stroke.

Participants or their caregiver will be asked to complete three questionnaires and two diaries that will record the resources used because of the participant's stroke.

Ten stroke centres across Canada are participating in this study for a total of 200 study volunteers to be recruited so each stroke centre will recruit approximately 20 ischemic stroke patients.

3) STUDY PROCEDURES

You or your caregiver will be approached by the on-site study coordinator to participate in this study because:

- You recently had your first ischemic stroke
- You or your care giver are fluent in either English or French
- You are able to complete three questionnaires with the on-site study coordinator, or are able to do so through your caregiver
- You are able to communicate with the on-site study coordinator, or are able to do so through your caregiver
- You are <u>not</u> enrolled in a clinical trial involving procedures outside of standard stroke care

- If you agree to participate in this study:
  - You or your caregiver will be asked to sign the consent form.

  - There will be three questionnaires. The on-site study coordinator will complete the FIRST questionnaire with you and/or your caregiver prior to your hospital discharge.

  - Once you are discharged from the hospital, the on-site study coordinator will arrange for the other two questionnaires to be completed; one after 3-months have passed and another after 6-months have passed.

  - The 3-month and 6-month questionnaires can be completed with the on-site study coordinator over the telephone or at the stroke centre.

  - There will be two diaries to complete; one after you are discharged from the hospital and another after you finish the 6-month questionnaire. Completed diaries can be dropped off at the stroke centre or mailed back in the pre-stamped packages.

  - The caregiver may complete all questionnaires and diaries on behalf of the patient.

Each questionnaire will take approximately 45 minutes to complete. Each diary will consist of a daily check list and will take approximately 5 minutes to complete.

The questionnaires and diaries will record the resources you have used because of your stroke. You may skip any questions in the questionnaire or diary that you or your caregiver do not wish to answer.

The questionnaires will be completed with the on-site study coordinator at the stroke centre or over the telephone while the diaries will be completed at home.

The questionnaires and diaries relate to your stroke follow-up care which is the time period for this research study.

4) DESCRIPTION OF TESTS

There are no additional tests associated with this research study.

5) LENGTH OF STUDY

The study will start at the end of 2005/beginning of 2006 and each study participant will only participate for seven months.

6) POSSIBLE SIDE EFFECTS AND/OR RISKS

There are no side effects and/or risks associated with this research study.

7) BENEFITS OF THE STUDY

There are no direct benefits associated with this study. Your participation will allow people to learn more about the resources and costs of stroke care in Canada that could result in improved stroke services in the future.

8) ALTERNATIVE TREATMENTS AVAILABLE

Since there is no drug treatment associated with this study, there are no alternative treatments.

9) WITHDRAWAL FROM THE STUDY

Your participation in this study is entirely voluntary. You may withdraw from the study at any time without any impact to the care you are receiving or will receive in the future. If you choose to withdraw, you may also ask that any information you have provided be withdrawn from the study as well.

10) STUDY EXPENSES

If you or your caregiver return to the stroke centre to complete the questionnaire, the on-site study coordinator can provide you with reimbursement for the cost of hospital parking or taxi fare.

11) CONFIDENTIALITY

All results of the study will be kept confidential. Representatives of Hope Research Center, Sunnybrook and Women's College, Health Science Centre or government regulators such as Health Canada, as well as by representatives of the Ottawa Hospital Research Ethics Board, may review your relevant records, under the supervision of Dr. Sharma for audit purposes.

You will not be identifiable in any publications or presentations resulting from this study. All information which leaves the hospital will be coded and you will not be identifiable by name. No records bearing you or your caregiver's name will leave the Ottawa Hospital.

VOLUNTARY PARTICIPATION

Participation in this study is entirely voluntary. You or your caregiver are under no obligation to participate. If you choose to participate, you may withdraw from this study at any time and do not have to give a reason for your decision. The care you currently receive at the Ottawa Hospital, General Campus will not be affected by your decisions, nor will it affect your future care.

12) QUESTIONS ABOUT THE STUDY

If you or your caregiver have any questions regarding this study or need more information about the study, you can address them to the study investigators responsible for the study, Dr. Michael Sharma at 737-8798 ext. 78798 or with the on-site study coordinators Ms. Andrea Fisher or Ms. Donna Cousineau.

Andrea Fisher	613-737-7777 ext. 74735	afisher@ottawahospital.on.ca
Donna Cousineau	613-737-8899 ext. 74518	dcousineau@ottawahospital.on.ca

If you or your caregiver have any questions about your rights as a research subject, you can contact the Chairperson of the Ottawa Hospital Research Ethics Board at (613) 798-5555, extension 14902.

CONSENT FORM

I have read this Patient Information Sheet (or have had this document read to me), and have had an opportunity to ask my study doctor or research nurse any questions I had about the study.

My questions and/or concerns have been answered to my satisfaction and I agree to participate in this study. If I decide at a later stage in the study that I would like to withdraw my consent, I may do so at any time.

A copy of the Information Sheet and Consent Form will be provided to me should I want to review the information at a later date, if I need to contact someone about the study or my participation in the study, or simply for my records.

_____

Participant's Name (Please Print)

_____ _____

Participant Signature Date (Day/Month/Year)

If applicable:

_____

Caregiver's Name (Please Print)

_____ _____

Caregiver's Signature Date (Day/Month/Year)

_____

On-site Study Coordinator (Please Print)

_____ _____

Signature Date (Day/Month/Year)

The BURST Study
BASELINE QUESTIONNAIRE
ENGLISH version

A) CLINICAL HISTORY:

Today's date (D/M/Y): [Appears as "date of completion" on website]	_____
Study Identifier #:	_____
Demographics of study participant:	GENDER O Male O Female
Who will be completing questionnaires: [Check only one]	O Participant O Caregiver O Combination of participant and caregiver
Living arrangement **PRIOR** to stroke: [Check only one]	O Alone at home O With other(s) at home O With other(s) at another person's home O Hospital facility O Rehabilitation facility O Long-term care facility O Other: _____
Date of stroke (D/M/Y):	_____
T-PA administered: [Check only one]	O No O Yes (IV)

	O Yes (IA) O Yes (IV+IA)
Co-morbidities: [Check all that apply]	O Angina O Atrial fibrillation O COPD O Diabetes O Hyperlipidemia O Hypertension O TIA – When (M/Y):_____ O None
Mode of transport to emergency: [Check all that apply]	O Ambulance O Transfer from other facility O Walk-in O Did not go to emergency
Hospitalization location: [Check all that apply]	O ICU O Step-down unit O Ward
Discharge destination (if known): [Check only one]	O Long-term care O Inpatient acute rehabilitation O Slow stream rehabilitation O Home with outpatient rehabilitation O Home with stroke clinic follow-up or other outpatient therapies O Other: _____

The BURST Study
BASELINE QUESTIONNAIRE
ENGLISH version

B) DRUG HISTORY

Antihypertensive therapy-classes:

[Check all that apply]

- O No medication
- O Accupril (quinapril)
- O Accuretic (quinapril/hydrochlorothiazide)
- O Adalat XL/PA (nifedipine XL)
- O Aldactazide (hydrochlorothiazide/spironolactone)
- O Aldomet (methyldopa)
- O Aldoril (methyldopa/hydrochlorothiazide)
- O Altace (ramipril)
- O Atacand (candesartan)
- O Atacand Plus (candesartan/hydrochlorothiazide)
- O Avalide (irbesartan/hydrochlorothiazide)
- O Avapro (irbesartan)
- O Betaloc OR Lopresor (metoprolol)
- O Blocadren (timolol)
- O Capoten OR Captril (captopril)
- O Cardizem OR Tiazec (diltiazem)
- O Cardura (doxazosin)
- O Corgard (nadolol)
- O Coronex OR Isordil (isosorbide dinitrate)
- O Coversyl (perindopril)
- O Coversyl Plus or Preterax (perindopril/indapamide)
- O Cozaar (losartan)
- O Diovan (valsaratan)
- O Diovan-HCT (valsaratan/hydrochlorothiazide)
- O Dyazide (hydrochlorothiazide/triamterene)
- O Edecrin (ethacrynic acid)
- O HydroDiuril (hydrochlorothiazide)
- O Hygroton (chlorthalidone)
- O Hytrin (terazosin)
- O Hyzaar (losartan/hydrochlorothiazide)
- O Imdur (isosorbide mononitrate)
- O Inderal (propranolol)
- O Inhibace (cilazapril)
- O Inhibace Plus (cilazapril/hydrochlorothiazide)

	O Isoptin OR Chronovera (verapamil) O Lasix (furosemide) O Lotensin (benazepril) O Lozide (indapamide) O Mavik (trandolapril) O Micardis (telmisartan) O Micardis Plus (telmisartan/hydrochlorothiazide) O Midamor (amiloride) O Minipress (prazosin) O Moduret (amiloride/hydrochlorothiazide) O Monitan OR Rhotral OR Sectral (acebutolol) O Monocor (bisoprolol) O Monopril (fosinopril) O Nitrol (nitroglycerin) O Norvasc (amlodipine) O Plendil OR Renedil (felodipine) O Prinivil OR Zestril (lisinopril) O Prinzide OR Zestoretic (lisinopril/hydrochlorothiazide) O Tenoretic (atenolol/chlorthalidone) O Tenormin (atenolol) O Teveten (eprosartan) O Teveten Plus (eprosartan/hydrochlorothiazide) O Timolide (timolol/hydrochlorothiazide) O Trandate (labetalol) O Trasicor (oxprenolol) O Vaseretic (enalapril/hydrochlorothiazide) O Vasotec (enalapril) O Viskazide (pindolol/hydrochlorothiazide) O Visken (pindolol) O Zaroxolyn (metolazone)

The BURST Study
BASELINE QUESTIONNAIRE
ENGLISH version

Anticoagulation/antiplatelet therapies: [Check all that apply]	O No medication O Aggrenox (dipyridamole/ASA) O Aspirin (ASA) O Coumadin (warfarin) O Hepalean (heparin) O Plavix (clopidogrel) O Sintrom (nicoumalone)
Low molecular weight heparin therapies: [Check all that apply]	O No medication O Arixtra (fondaparinux sodium) O Fragmin (dalteparin sodium) O Fraxiparine (nadroparin calcium) O Innohep (tinzaparin sodium) O Lovenox (enoxaparin)
Antihyperglycemic therapies: [Check all that apply]	O No medication O Actos (pioglitazone) O Amaryl (glimepiride) O Avandia (rosiglitazone) O Chloropropamide O DiaBeta (glyburide) O Diamicron (glicazide) O Gluconorm (repaglindine) O Glucophage (metformin) O Humalog OR Humulin (insulin) O Orinase (tolbutamide) O Prandase (acarbose) O Starlix (nateglinide)
	O No medication

Antihyperlipidemic therapies-classes: [Check all that apply]	O Bezalip (bezafibrate) O Colestid (colestipol) O Crestor (rosuvastatin) O Ezetrol (ezetimibe) O Lescol (fluvastatin) O Lipidil (fenofibrate) O Lipitor (atorvastatin) O Mevacor (lovastatin) O Niacin (nicotinic acid) O Pravachol (pravastatin) O Questran (cholestyramine) O Zocor (simvastatin)

The BURST Study
BASELINE QUESTIONNAIRE
ENGLISH version

C) NIH STROKE SCALE

Instructions: Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the subject does, not what the clinician thinks they can do. Answers should be recorded while administering the exam and work quickly. Except where indicated, the subject should not be coached (i.e., repeated requests to subject to make a special effort).

1a. Level of Consciousness (LOC): The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the subject makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.	_____
1b. LOC Questions: The subject is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous subjects who do not comprehend the questions will score 2. Subjects unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the subject with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	_____
1c. LOC Commands: The subject is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the subject does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Subjects with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the subject has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a subject has an isolated peripheral nerve paresis (CN III, IV or VI) score	0 = Normal 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present.	_____

a 1. Gaze is testable in all aphasic subjects. Subjects with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the subject from side to side will occasionally clarify the presence of a partial gaze palsy.	2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.	
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Subject must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If subject is blind from any cause score 3. Double simultaneous stimulation is performed at this point. If there is extinction subject receives a 1 and the results are used to answer question 11.	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness)	_____
4. Facial Palsy: Ask, or use pantomime to encourage the subject to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending subject. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.	0 = Normal symmetrical movement 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (total or near total paralysis of lower face) 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	_____
5A. Motor Left Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic subject is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "NA" and the examiner must clearly write the explanation for scoring as a "NA".	0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift, Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity, limb falls. 4 = No movement 9 = Amputation, joint fusion explain:	_____
5B. Motor Right Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic subject is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "NA" and the examiner must clearly write the explanation for scoring as a "NA".	0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement 9 = Amputation, joint fusion explain:	_____

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6A. Motor Left Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic subject is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "NA" and the examiner must clearly write the explanation for scoring as a "NA".	0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement 9 = Amputation, joint fusion explain:	____
6B. Motor Right Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic subject is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "NA" and the examiner must clearly write the explanation for scoring as a "NA".	0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement 9 = Amputation, joint fusion explain:	____
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the subject who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "NA", and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.	0 = Absent 1 = Present in one limb 2 = Present in two limbs 9 = amputation or joint fusion, explain	____
8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic subject. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic subjects will therefore probably score 1 or 0. The subject with brain stem stroke who has bilateral loss of sensation is scored 2. If the subject does not respond and is quadriplegic score 2. Subjects in coma (item 1a=3) are arbitrarily given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild to moderate sensory loss; subject feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but subject is aware he/she is being touched. 2 = Severe to total sensory loss; subject is not aware of being touched in the face, arm, and leg.	____

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9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The subject is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the subject to identify objects placed in the hand, repeat, and produce speech. The intubated subject should be asked to write. The subject in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the subject with stupor or limited cooperation but a score of 3 should be used only if the subject is mute and follows no one step commands.	0 = No aphasia, normal 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example in conversation about provided materials examiner can identify picture or naming card from subject's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from subject response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	_____
10. Dysarthria: If subject is thought to be normal an adequate sample of speech must be obtained by asking subject to read or repeat words from the attached list. If the subject has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the subject is intubated or has other physical barrier to producing speech, may the item be scored "NA", and the examiner must clearly write an explanation for not scoring. Do not tell the subject why he/she is being tested.	0 = Normal 1 = Mild to moderate; subject slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe; subject's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. 9 = Intubated or other physical barrier, explain	_____
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the subject has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the subject has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.	_____

TOTAL (0-42): ____

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D) MODIFIED RANKIN SCALE (MRS)

Instructions: The Modified Rankin Scale (MRS) describes grades of disability after a stroke (grade 5 denotes severe disability, bedridden; and grade 0 denotes no symptoms at all). **Please check ONLY ONE box.**

✓	SCORE	DESCRIPTION
☐	0	No symptoms at all
☐	1	No significant disability despite symptoms; able to carry out all usual duties and activities
☐	2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
☐	3	Moderate disability; requiring some help, but able to walk without assistance
☐	4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
☐	5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention

TOTAL (0-5): ☐

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E) BARTHEL INDEX (BI)

Instructions: The Barthel Index (BI) is a disability scale for stroke patients. For each item, rate the study participant's ability using the definitions provided below and the best available evidence (participant, caregiver or direct observation). The maximum score is 100 indicating fully independent in physical functioning; the lowest score 0 for a fully dependent bedridden state. Rate the study participant's performance over the previous 24-48 hours except where longer periods are specified. **Please check ONLY ONE box for each question.**

1. FEEDING		0	Unable	Totally dependent
		5	With help	Cutting, spreading butter, but feed self
		10	Independent	Can eat normal food provided by others but not cut up
2. BATHING		0	Dependent	
		5	Independent	Can get in and out unsupervised and wash self. In shower – independent if unsupervised/unaided
3. GROOMING (personal care)		0	With help	
		5	Independent	Washes face, does hair, brushes teeth, shaves (implements provided by helper)
4. DRESSING		0	Dependent	
		5	With help	Needs help with buttons, zippers, etc. but can do about half unaided
		10	Independent	Can select and put on clothes (including buttons, laces, etc.)
5. BOWEL CONTROL		0	Incontinent	
		5	Occasional accident	Once a week or less often
		10	Continent	
6. BLADDER CONTROL		0	Incontinent	Or catheterized and unable to manage catheter
		5	Occasional accident	Less than once a day (24 hours)
		10	Continent	For over 7 days; if catheterized, can manage catheter alone

7. TOILET USE		0	Dependent	N/A
		5	With help	Can wipe self plus can do some of the other tasks required of independent person
		10	Independent	Can reach toilet/commode, undress sufficiently, wipe self, dress and leave

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8. CHAIR/BED TRANSFER		0	Unable	No sitting balance, cannot sit, requires two people to lift
		5	Major help	Can sit, requires one strong/skilled or two normal people to lift
		10	Minor help	One person can lift easily or needs supervision for safety
		15	Independent	N/A
9. MOBILITY		0	Immobile	N/A
		5	Wheelchair independent	Can negotiate corners/doors unaided
		10	Walks with help	One untrained person providing physical help supervision or moral support
		15	Independent	Can walk 50m or around house. May use any aid e.g. stick, except rolling walker
For participants who have not tested their ability to walk up and down stairs in their home, rating should be based on the rating of the mobility item.				
10. STAIRS		0	Unable	N/A
		5	With help	Verbal or physical help or carrying aid
		10	Independent	Up and down, carrying any walking aid

TOTAL (0-100): ☐

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F) HEALTH UTILITIES INDEX MARK 3 (HUI3)

Instructions: The Health Utilities Index (HUI) is a system for measuring health status, health-related quality of life, and producing utility scores. **Please check ONLY ONE box for each question.**

1	During the past 4 weeks, have you been able to see well enough to read ordinary newsprint *without* glasses or contact lenses?	☐ **Yes → Go to #4** ☐ **No** ☐ **Don't Know** ☐ **Refused**
2	Have you been able to see well enough to read ordinary newsprint *with* glasses or contact lenses?	☐ **Yes → Go to #4** ☐ **No** ☐ **Don't know/ Didn't wear glasses or contact lenses** ☐ **Refused**
3	During the past 4 weeks, have you been able to see at all?	☐ **Yes** ☐ **No → Go to #6** ☐ **Don't know** ☐ **Refused**
4	During the past 4 weeks, have you been able to see well enough to recognize a friend on the other side of the street *without* glasses or contact lenses?	☐ **Yes → Go to #6** ☐ **No** ☐ **Don't know** ☐ **Refused**
5	Have you been able to see well enough to recognize a friend on the other side of the street with at least glasses or contact lenses?	☐ **Yes** ☐ **No** ☐ **Don't know/ Didn't wear glasses or contact lenses** ☐ **Refused**
6	During the past 4 weeks, have you been able to hear what is said in a group	☐ **Yes → Go to #11** ☐ **No** ☐ **Don't know**

	conversation with at least three other people *without* a hearing aid?	☐ **Refused**
7	Have you been able to hear what is said in a group conversation with at least three other people *with* a hearing aid?	☐ **Yes → Go to #9** ☐ **No** ☐ **Don't know/ Didn't wear a hearing aid** ☐ **Refused**
8	During the past 4 weeks, have you been able to hear at all?	☐ **Yes** ☐ **No → Go to #11** ☐ **Don't know** ☐ **Refused**
9	During the past 4 weeks, have you been able to hear what is said in a conversation with one other person in a quiet room *without* a hearing aid?	☐ **Yes → Go to #11** ☐ **No** ☐ **Don't know** ☐ **Refused**
10	Have you been able to hear what is said in a conversation with one other person in a quiet room *with* a hearing aid?	☐ **Yes** ☐ **No** ☐ **Don't know/ Didn't wear a hearing aid** ☐ **Refused**
11	During the past 4 weeks, have you been able to understand *completely* when speaking your own language with people who do not know you?	☐ **Yes → Go to #16** ☐ **No** ☐ **Don't know** ☐ **Refused**
12	Have you been able to be understood *partially* when speaking with people who do not know you?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
13	During the past 4 weeks, have you been able to be understood *completely* when speaking with people who you know well?	☐ **Yes → Go to #16** ☐ **No** ☐ **Don't know** ☐ **Refused**
14	Have you been able to be	☐ **Yes → Go to #16**

	understood *partially* when speaking with people who know you well?	☐ **No** ☐ **Don't know** ☐ **Refused**
15	During the past 4 weeks, have you been able to speak at all?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
16	During the past 4 weeks, have you been able to bend, lift, jump and run *without difficulty* and *without help or equipment* of any kind?	☐ **Yes → Go to #24** ☐ **No** ☐ **Don't know** ☐ **Refused**
17	Have you been able to walk around the neighbourhood *without difficulty* and *without help or equipment* of any kind?	☐ **Yes → Go to #24** ☐ **No** ☐ **Don't know** ☐ **Refused**
18	Have you been able to walk around the neighbourhood *with difficulty* but *without help or equipment* of any kind?	☐ **Yes → Go to #24** ☐ **No** ☐ **Don't know** ☐ **Refused**
19	During the past 4 weeks, have you been able to walk at all?	☐ **Yes** ☐ **No → Go to #22** ☐ **Don't know** ☐ **Refused**
20	Have you needed mechanical support, such as braces or a cane or crutches, to be able to walk around the neighbourhood?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
21	Have you needed the help of another person to walk?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
22	Have you needed a wheelchair to get around the neighbourhood?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
23	Have you needed the help of	☐ **Yes**

	another person to get around in the wheelchair?	☐ **No** ☐ **Don't know** ☐ **Refused**
24	During the past 4 weeks, have you had the *full use* of both hands and ten fingers?	☐ **Yes → Go to #28** ☐ **No** ☐ **Don't know** ☐ **Refused**
25	Have you needed the help of another person because of limitations in the use of your hands or fingers?	☐ **Yes** ☐ **No → Go to #27** ☐ **Don't know** ☐ **Refused**
26	Have you needed the help of another person with some tasks, most tasks, or all tasks?	☐ **Some tasks** ☐ **Most tasks** ☐ **All tasks** ☐ **Don't know** ☐ **Refused**
27	Have you needed special equipment, for example special tools to help with dressing or eating, because of limitations in the use of your hands and fingers?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
28	During the past 4 weeks, have you been able to eat, bathe, dress and use the toilet without difficulty?	☐ **Yes → Go to #31** ☐ **No** ☐ **Don't know** ☐ **Refused**
29	Have you needed the help of another person to eat, bathe, dress or use the toilet?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
30	Have you needed special equipment or tools to eat, bathe, dress or use the toilet?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**

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31	During the past 4 weeks, have you been feeling happy or unhappy?	☐ **Happy** ☐ **Unhappy → Go to #33** ☐ **Don't know** ☐ **Refused**
32	Would you describe yourself as having felt: a) happy and interested in life, or b) somewhat happy?	☐ **a → Go to #34** ☐ **b → Go to #34** ☐ **Don't know** ☐ **Refused**
33	Would you describe yourself as having felt: a) somewhat unhappy b) very unhappy c) so unhappy that life is not worthwhile	☐ **a** ☐ **b** ☐ **c** ☐ **Don't know** ☐ **Refused**
34	During the past 4 weeks, did you ever feel fretful, angry, irritable, anxious or depressed?	☐ **Yes** ☐ **No → Go to #37** ☐ **Don't know** ☐ **Refused**
35	How often did you feel fretful, angry, irritable, anxious or depressed: Rarely, occasionally, often, or almost always?	☐ **Rarely** ☐ **Occasionally** ☐ **Often** ☐ **Almost always** ☐ **Don't know** ☐ **Refused**
36	During the past 4 weeks did you feel *extremely* fretful, angry, irritable, anxious or depressed; to the point of needing professional help?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
37	How would you describe your ability to remember things, during the past 4 weeks: a) able to remember most	☐ **a** ☐ **b** ☐ **c** ☐ **d** ☐ **Don't know**

	things b) somewhat forgetful c) very forgetful d) unable to remember anything at all	☐ **Refused**
38	How would you describe your ability to think and solve day to day problems, during the past 4 weeks: a) able to think clearly and solve problems b) had a little difficulty c) had some difficulty d) had a great deal of difficulty e) unable to think or solve problems	☐ **a** ☐ **b** ☐ **c** ☐ **d** ☐ **e** ☐ **Don't know** ☐ **Refused**
39	Have you had any trouble with pain or discomfort, during the past 4 weeks?	☐ **Yes** ☐ **No → Go to #41** ☐ **Don't know** ☐ **Refused**
40	How many of your activities, during the past 4 weeks, were limited by pain or discomfort: none, a few, some, most, all?	☐ **None** ☐ **A few** ☐ **Some** ☐ **Most** ☐ **All** ☐ **Don't know** ☐ **Refused**
41	Overall, how would you rate your health during the past 4 weeks? a) excellent b) very good c) good d) fair e) poor	☐ **a** ☐ **b** ☐ **c** ☐ **d** ☐ **e** ☐ **Don't know** ☐ **Refused**

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G) HAMILTON DEPRESSION (HAM-D) RATING SCALE

Instructions: To rate the severity of depression in patients, administer this questionnaire. The higher the score, the more severe the depression. **Please check ONLY ONE box for each question.**

1. ARE YOU IN A **DEPRESSED MOOD?**		0	Absent
		1	Depressed mood indicated only on questioning
		2	Depressed mood spontaneously reported verbally
		3	Depressed mood stated non-verbally (facial expression, posture)
		4	Participant reports depressed mood as only state in both spontaneous verbal and non-verbal communication
2. DO YOU HAVE **FEELINGS OF GUILT?**		0	Absent
		1	Self reproach, feels he/she has let people down
		2	Ideas of guilt or rumination over past errors or sinful deeds
		3	Present illness is a punishment; delusions of guilt
		4	Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3. DO YOU HAVE THOUGHTS OF **SUICIDE?**		0	Absent
		1	Feels life is not worth living
		2	Wishes he/she were dead or any thoughts of possible death to self
		3	Suicidal ideas or gesture
		4	Attempts at suicide (any serious attempt rates as 4)
4. DO YOU HAVE **INSOMNIA** DURING THE **EARLY** PART OF YOUR SLEEP?		0	No difficulty falling asleep
		1	Complains of occasional difficulty falling asleep (more than ½ hour)
		2	Complains of nightly difficulty falling asleep
5. DO YOU HAVE **INSOMNIA** DURING THE **MIDDLE** PART OF YOUR SLEEP?		0	No difficulty
		1	Patient complains of being restless and disturbed during the night
		2	Walking during the night, any getting out of bed rates as 2 (except for purposes of voiding)

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6. DO YOU HAVE **INSOMNIA** DURING THE **LATE** PART OF YOUR SLEEP?		0	No difficulty
		1	Waking in early hours of the morning but goes back to sleep
		2	Unable to fall asleep again if he/she gets out of bed

7. WHAT IS THE LEVEL OF YOUR **WORK AND ACTIVITIES?**		0	No difficulty
		1	Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
		2	Loss of interest in activity; hobbies or work, either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities)
		3	Decrease in actual time spent in activities or decrease in productivity
		4	Stopped working because of present illness
8. WHAT IS YOUR **PSYCHOMOTOR** FUNCTION?		0	Normal speech and thought
		1	Slight retardation at interview
		2	Obvious retardation at interview
		3	Interview difficult
		4	Complete stupor
9. WHAT IS THE LEVEL OF YOUR **AGITATION?**		0	None
		1	Fidgetiness
		2	Playing with hands, hair, etc.
		3	Moving about, can't sit still
		4	Hand wringing, nail biting, hair-pulling, biting of lips
10. PSYCHOLOGICALLY, WHAT IS YOUR LEVEL OF **ANXIETY?**		0	No difficulty
		1	Subjective tension and irritability
		2	Worrying about minor matters
		3	Apprehensive attitude apparent in face or speech
		4	Fears expressed without questioning
11. PHYSICALLY (indigestion, stomach		0	Absent
		1	Mild

cramps, diarrhea, hyperventilation, sweating, etc.) WHAT IS YOUR LEVEL OF **ANXIETY?**		2	Moderate
		3	Severe
		4	Incapacitating
12. WHAT IS THE LEVEL OF YOUR **GASTROINTESTINAL SYMPTOMS?**		0	None
		1	Loss of appetite but eating without encouragement from others; food intake about normal
		2	Difficulty eating without urging from others; marked reduction of appetite and food intake
13. WHAT IS THE LEVEL OF YOUR **GENERAL SYMPTOMS?**		0	None
		1	Heaviness in limbs, back or head Backaches, headache, muscle aches. Loss of energy and fatigability
		2	Any clear-cut symptom rates as 2
If study participant is uncomfortable in discussing sexuality, there is option of skipping question 14			
14. WHAT IS THE LEVEL OF YOUR **SEXUAL DYSFUNCTION?**		0	Absent
		1	Mild
		2	Severe
		NA	Skipped question
15. WHAT IS THE LEVEL OF YOUR **HYPOCHONDRIASIS?**		0	Not present
		1	Self-absorption (bodily)
		2	Preoccupation with health
		3	Frequent complaints, requests for help, etc.
		4	Hypochondriacal delusions
16. HAS THERE BEEN **LOSS OF WEIGHT?**		0	No weight loss
		1	Probably weight loss associated with present illness
		2	Definite (according to patient) weight loss
17. WHAT IS THE LEVEL OF YOUR **INSIGHT?**		0	Acknowledges being depressed and ill
		1	Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
		2	Denies being ill at all

TOTAL (0-52): ☐

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H) SUPPLEMENTARY QUESTIONS

Dear Study Participant:

Thank you for agreeing to participate in this study that will identify and measure the resources new stroke patients use during their 6-months of follow-up care. You will be given a total of 3 questionnaires to complete. The information collected will be used for research purposes only.

Today, you are being asked to complete Baseline Questionnaire. We would appreciate it if you answered all of the questions. However, you do not need to answer any question you do not wish to answer. The answers provided will not affect your medical care.

Thank you again.

I. STUDY PARTICIPANT INFORMATION

1) What is the highest level of education you have completed? Check only one.

- ☐ No degree, certificate or diploma
- ☐ High school graduation certificate
- ☐ Trades or certificate diploma
- ☐ College certificate or diploma
- ☐ University certificate or diploma below bachelor level
- ☐ Bachelor's degree
- ☐ University certificate or diploma above bachelor level
- ☐ Professional degree (medical, law, dentistry, etc.)
- ☐ Master's degree
- ☐ Doctorate

2) Prior to your stroke, your EMPLOYMENT was (check only one):

- ☐ Working full-time for pay, including self-employment
- ☐ Working part-time for pay, including self-employment
- ☐ On sick leave from full-time or part-time work
- ☐ On disability leave from full-time or part-time work
- ☐ Unemployed
- ☐ Retired
- ☐ Homemaker

3) In the YEAR prior to your stroke, approximately how many times did you visit your family doctor?

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4) Prior to your stroke, what was your level of mobility? Check only one.

☐ Able to walk without difficulty, and without walking equipment

☐ Able to walk with difficulty, but did not require walking equipment or the help of another person

☐ Able to walk with walking equipment, but without the help of another person

☐ Able to walk only short distances with walking equipment, and required a wheelchair to get around the neighbourhood

☐ Unable to walk alone, even with walking equipment, but able to walk short distances with the help of another person, and required a wheelchair to get around the neighbourhood

☐ Could not walk at all

5) Please rate your GENERAL HEALTH **prior** to your stroke based on the scale below and select only one score.

0 1 2 3 4 5 6 7 8 9 10

Poor health Normal
Fit and healthy

6) Please rate your GENERAL HEALTH **after** your stroke based on the scale below and select only one score.

0 1 2 3 4 5 6 7 8 9 10

Poor health Normal
Fit and healthy

II. AFTER HOSPITAL DISCHARGE

7) Regarding HEALTH RELATED CHANGES after your stroke, check all that have been discussed:

☐ No discussion

☐ Stop or decrease smoking/nicotine consumption

☐ Stop or decrease alcohol consumption

☐ Stop or decrease caffeine consumption

☐ Start new medication(s)

☐ Start exercising/increase activity level

☐ Change in diet/weight loss

☐ Decrease activity level (housecleaning, cooking, etc.)

☐ Fatigue

☐ No health related changes needed

8) Regarding MOBILITY AID(S) after your stroke, check all that have been discussed for you to use:

☐ No discussion

☐ Wheelchair

☐ Walker

☐ Cane

☐ Orthopedic shoes

☐ Foot/leg brace

☐ No mobility aids needed

9) Regarding CHANGES IN YOUR PLACE OF RESIDENCE after your stroke, check all that have been discussed:

☐ No discussion

☐ Move to a more appropriate residence

☐ Wheelchair ramp constructed

☐ Emergency medical alarm installed

☐ Stair lift installed

☐ Bedroom location moved (e.g. main floor)

☐ Shower chair installed in bathtub

☐ Handrails installed throughout your home

☐ Rugs taped down or removed

☐ Furniture repositioned

☐ Lowering the height of where things are stored (e.g. bar for hanging clothes)

☐ Changing door/dresser handles

☐ No changes to residence needed

III. CAREGIVER INFORMATION

10) Who will likely be your primary UNPAID CAREGIVER after your stroke? *[An unpaid caregiver is a person who does **not** receive pay to provide care. If you have multiple primary unpaid caregivers, for example your spouse and child both care for you, #1 is your primary caregiver, #2 is your secondary caregiver, etc.]*

CAREGIVER #1

☐ No caregiver #1

☐ Spouse

☐ Child

☐ Parent

☐ Sibling

☐ Family relative

☐ Friend

☐ Neighbour

☐ Volunteer

☐ Other: _____

CAREGIVER #2

☐ No caregiver #2

☐ Spouse

☐ Child

☐ Parent

☐ Sibling

☐ Family relative

☐ Friend

☐ Neighbour

☐ Volunteer

☐ Other: _____

CAREGIVER #3

☐ No caregiver #3

☐ Spouse

☐ Child

☐ Parent

☐ Sibling

☐ Family relative

☐ Friend

☐ Neighbour

☐ Volunteer

☐ Other: _____

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11) Will your UNPAID CAREGIVER(S) likely have to change their number of hours worked after your stroke?

CAREGIVER #1
- ☐ No caregiver #1
- ☐ No change
- ☐ Hours decreased
- ☐ Leave of absence
- ☐ Quit job
- ☐ Don't know
- ☐ Not applicable (unpaid caregiver never worked)

CAREGIVER #2
- ☐ No caregiver #2
- ☐ No change
- ☐ Hours decreased
- ☐ Leave of absence
- ☐ Quit job
- ☐ Don't know
- ☐ Not applicable (unpaid caregiver never worked)

CAREGIVER #3
- ☐ No caregiver #3
- ☐ No change
- ☐ Hours decreased
- ☐ Leave of absence
- ☐ Quit job
- ☐ Don't know
- ☐ Not applicable (unpaid caregiver never worked)

BURST STUDY DIARY #1

As a participant in this study, we would like you to complete TWO diaries (one after hospital discharge and the second after completing the 6-month questionnaire) related to the different resources used in your stroke care. Each diary has a reporting period of 30-days and you will receive reminder phone calls about your diaries.

THE DIARY:
- Each diary page represents one day.

INSTRUCTIONS:
- There are SEVEN resource categories: doctor, wait time, facility, health professional, testing, services and stroke related items.
- Each day, please check (✓) all the boxes next to the resources that were involved with your stroke care.
- To clarify, stroke related items include purchases such as mobility aids, new clothing/shoes, home renovations and hospital parking fees because of your stroke.

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WHEN YOU ARE FINISHED:

- Please bring your completed diary the next time you see your on-site study coordinator.
- Or use the return envelope to mail the completed diary back to your on-site study coordinator.

Your completion of diary #1 is greatly appreciated. Thank you.

* * * * * * * * * *

Congratulations! The Baseline Questionnaire of the BURST Study has now been completed.

Please enter date that this questionnaire was completed (D/M/Y): _____

Contact number for patient: _____

The on-site nurse/study coordinator should now note when the 3-month questionnaire will need to be completed by this study subject (D/M/Y): _____

If applicable, check with the stroke clinic booking staff when your next visit will occur.

Please remember to bring an updated list of your MEDICATIONS in order to complete the 3-Month Questionnaire.

The BURST Study
3-MONTH QUESTIONNAIRE
ENGLISH version

A) CLINICAL HISTORY:

Today's date (D/M/Y): _____

[Appears as "date of completion" on website]

Study Identifier #: _____

Diary #1 completed and returned:
[Check only one]
- O No
- O Yes

Who will be completing questionnaires:
(should be consistent with baseline questionnaire)
[Check only one]
- O Participant
- O Caregiver
- O Combination of participant and caregiver

Co-morbidities:
[Check all that apply]
- O Angina
- O Atrial fibrillation
- O COPD
- O Diabetes
- O Hyperlipidemia
- O Hypertension
- O TIA – When (M/Y):_____
- O None

Length of hospital stay for index stroke (days): _____

- O Long-term care

Discharge destination after index stroke hospitalization: [Check only one]	○ Inpatient acute rehabilitation ○ Slow stream rehabilitation ○ Home with outpatient rehabilitation ○ Home with stroke clinic follow-up or other outpatient therapies ○ Other: _____
If **LONG-TERM CARE**, what is or was **WAIT TIME** to enter the facility from the time of index stroke: [Check only one]	○ Number of days: _____ ○ Still waiting ○ No long-term care placement
Subsequent stroke or TIA: [Check only one]	○ No ○ Yes stroke – When (M/Y):_____ ○ Yes TIA – When (M/Y):_____
Subsequent hospitalizations: (if none, enter "0")	Length of stay #1 (days): _____ Dx: _____ Length of stay #2 (days): _____ Dx: _____ Length of stay #3 (days): _____ Dx: _____ Length of stay #4 (days): _____ Dx: _____ Length of stay #5 (days): _____ Dx: _____

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B) DRUG HISTORY:

Antihypertensive therapy-classes:

[Check all that apply]

- O No medication
- O Accupril (quinapril)
- O Accuretic (quinapril/hydrochlorothiazide)
- O Adalat XL/PA (nifedipine XL)
- O Aldactazide (hydrochlorothiazide/spironolactone)
- O Aldomet (methyldopa)
- O Aldoril (methyldopa/hydrochlorothiazide)
- O Altace (ramipril)
- O Atacand (candesartan)
- O Atacand Plus (candesartan/hydrochlorothiazide)
- O Avalide (irbesartan/hydrochlorothiazide)
- O Avapro (irbesartan)
- O Betaloc OR Lopresor (metoprolol)
- O Blocadren (timolol)
- O Capoten OR Captril (captopril)
- O Cardizem OR Tiazec (diltiazem)
- O Cardura (doxazosin)
- O Corgard (nadolol)
- O Coronex OR Isordil (isosorbide dinitrate)
- O Coversyl (perindopril)
- O Coversyl Plus or Preterax (perindopril/indapamide)
- O Cozaar (losartan)
- O Diovan (valsaratan)
- O Diovan-HCT (valsaratan/hydrochlorothiazide)
- O Dyazide (hydrochlorothiazide/triamterene)
- O Edecrin (ethacrynic acid)
- O HydroDiuril (hydrochlorothiazide)
- O Hygroton (chlorthalidone)
- O Hytrin (terazosin)
- O Hyzaar (losartan/hydrochlorothiazide)
- O Imdur (isosorbide mononitrate)
- O Inderal (propranolol)
- O Inhibace (cilazapril)
- O Inhibace Plus (cilazapril/hydrochlorothiazide)
- O Isoptin OR Chronovera (verapamil)

- O Lasix (furosemide)
- O Lotensin (benazepril)
- O Lozide (indapamide)
- O Mavik (trandolapril)
- O Micardis (telmisartan)
- O Micardis Plus (telmisartan/hydrochlorothiazide)
- O Midamor (amiloride)
- O Minipress (prazosin)
- O Moduret (amiloride/hydrochlorothiazide)
- O Monitan OR Rhotral OR Sectral (acebutolol)
- O Monocor (bisoprolol)
- O Monopril (fosinopril)
- O Nitrol (nitroglycerin)
- O Norvasc (amlodipine)
- O Plendil OR Renedil (felodipine)
- O Prinivil OR Zestril (lisinopril)
- O Prinzide OR Zestoretic (lisinopril/hydrochlorothiazide)
- O Tenoretic (atenolol/chlorthalidone)
- O Tenormin (atenolol)
- O Teveten (eprosartan)
- O Teveten Plus (eprosartan/hydrochlorothiazide)
- O Timolide (timolol/hydrochlorothiazide)
- O Trandate (labetalol)
- O Trasicor (oxprenolol)
- O Vaseretic (enalapril/hydrochlorothiazide)
- O Vasotec (enalapril)
- O Viskazide (pindolol/hydrochlorothiazide)
- O Visken (pindolol)
- O Zaroxolyn (metolazone)

Anticoagulation/antiplatelet therapies:

[Check all that apply]

- O No medication
- O Aggrenox (dipyridamole/ASA)
- O Aspirin (ASA)
- O Coumadin (warfarin)
- O Hepalean (heparin)
- O Plavix (clopidogrel)
- O Sintrom (nicoumalone)

Low molecular weight heparin therapies:

[Check all that apply]

- O No medication
- O Arixtra (fondaparinux sodium)
- O Fragmin (dalteparin sodium)
- O Fraxiparine (nadroparin calcium)
- O Innohep (tinzaparin sodium)
- O Lovenox (enoxaparin)

Antihyperglycemic therapies:

[Check all that apply]

- O No medication
- O Actos (pioglitazone)
- O Amaryl (glimepiride)
- O Avandia (rosiglitazone)
- O Chloropropamide
- O DiaBeta (glyburide)
- O Diamicron (glicazide)
- O Gluconorm (repaglindine)
- O Glucophage (metformin)
- O Humalog OR Humulin (insulin)
- O Orinase (tolbutamide)
- O Prandase (acarbose)
- O Starlix (nateglinide)

Antihyperlipidemic therapies-classes:

[Check all that apply]

- O No medication
- O Bezalip (bezafibrate)
- O Colestid (colestipol)
- O Crestor (rosuvastatin)
- O Ezetrol (ezetimibe)
- O Lescol (fluvastatin)
- O Lipidil (fenofibrate)
- O Lipitor (atorvastatin)
- O Mevacor (lovastatin)
- O Niacin (nicotinic acid)
- O Pravachol (pravastatin)
- O Questran (cholestyramine)
- O Zocor (simvastatin)

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C) MODIFIED RANKIN SCALE

Instructions: The Modified Rankin Scale (MRS) describes grades of disability after a stroke (grade 5 denotes severe disability, bedridden; and grade 0 denotes no symptoms at all). **Please check ONLY ONE box.**

✓	SCORE	DESCRIPTION
☐	0	No symptoms at all
☐	1	No significant disability despite symptoms; able to carry out all usual duties and activities
☐	2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
☐	3	Moderate disability; requiring some help, but able to walk without assistance
☐	4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
☐	5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention

TOTAL (0-5): ☐

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D) BARTHEL INDEX

Instructions: The Barthel Index (BI) is a disability scale for stroke patients. For each item, rate your/his/her level of ability using the definitions provided below and the best available evidence (patient, friends/relatives, nurse and/or direct observation). The maximum score is 100 indicating fully independent in physical functioning; the lowest score 0 for a fully dependent bedridden state. Rate your/his/her performance over the previous 24-48 hours except where longer periods are specified. Please check **ONLY ONE** box for each question.

1. FEEDING		0	Unable	Totally dependent
		5	With help	Cutting, spreading butter, but feed self
		10	Independent	Can eat normal food provided by others but not cut up
2. BATHING		0	Dependent	
		5	Independent	Can get in and out unsupervised and wash self. In shower – independent if unsupervised/unaided
3. GROOMING (personal care)		0	With help	
		5	Independent	Washes face, does hair, brushes teeth, shaves (implements provided by helper)
4. DRESSING		0	Dependent	
		5	With help	Needs help with buttons, zippers, etc. but can do about half unaided
		10	Independent	Can select and put on clothes (including buttons, laces, etc.)
5. BOWEL CONTROL		0	Incontinent	
		5	Occasional accident	Once a week or less often
		10	Continent	
6. BLADDER CONTROL		0	Incontinent	Or catheterized and unable to manage catheter
		5	Occasional accident	Less than once a day (24 hours)
		10	Continent	For over 7 days; if catheterized, can manage catheter alone
7. TOILET		0	Dependent	N/A

USE		5	With help	Can wipe self plus can do some of the other tasks required of independent person
		10	Independent	Can reach toilet/commode, undress sufficiently, wipe self, dress and leave
8. CHAIR/BED TRANSFER		0	Unable	No sitting balance, cannot sit, requires two people to lift
		5	Major help	Can sit, requires one strong/skilled or two normal people to lift
		10	Minor help	One person can lift easily or needs supervision for safety
		15	Independent	N/A
9. MOBILITY		0	Immobile	N/A
		5	Wheelchair independent	Can negotiate corners/doors unaided
		10	Walks with help	One untrained person providing physical help supervision or moral support
		15	Independent	Can walk 50m or around house. May use any aid (e.g. stick), except rolling walker
For participants who have not tested their ability to walk up and down stairs in their home, rating should be based on the rating of the mobility item.				
10. STAIRS		0	Unable	N/A
		5	With help	Verbal or physical help or carrying aid
		10	Independent	Up and down, carrying any walking aid

TOTAL (0-100): ☐

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E) HEALTH UTILITIES INDEX MARK 3 (HUI3)

Instructions: The Health Utilities Index (HUI) is a system for measuring health status, health-related quality of life, and producing utility scores. **Please check ONLY ONE box for each question.**

1	During the past 4 weeks, have you been able to see well enough to read ordinary newsprint *without* glasses or contact lenses?	☐ **Yes → Go to #4** ☐ **No** ☐ **Don't Know** ☐ **Refused**
2	Have you been able to see well enough to read ordinary newsprint *with* glasses or contact lenses?	☐ **Yes → Go to #4** ☐ **No** ☐ **Don't know/ Didn't wear glasses or contact lenses** ☐ **Refused**
3	During the past 4 weeks, have you been able to see at all?	☐ **Yes** ☐ **No → Go to #6** ☐ **Don't know** ☐ **Refused**
4	During the past 4 weeks, have you been able to see well enough to recognize a friend on the other side of the street *without* glasses or contact lenses?	☐ **Yes → Go to #6** ☐ **No** ☐ **Don't know** ☐ **Refused**
5	Have you been able to see well enough to recognize a friend on the other side of the street with at least glasses or contact lenses?	☐ **Yes** ☐ **No** ☐ **Don't know/ Didn't wear glasses or contact lenses** ☐ **Refused**
6	During the past 4 weeks, have you been able to hear what is said in a group	☐ **Yes → Go to #11** ☐ **No** ☐ **Don't know**

	conversation with at least three other people *without* a hearing aid?	☐ **Refused**
7	Have you been able to hear what is said in a group conversation with at least three other people *with* a hearing aid?	☐ **Yes → Go to #9** ☐ **No** ☐ **Don't know/ Didn't wear a hearing aid** ☐ **Refused**
8	During the past 4 weeks, have you been able to hear at all?	☐ **Yes** ☐ **No → Go to #11** ☐ **Don't know** ☐ **Refused**
9	During the past 4 weeks, have you been able to hear what is said in a conversation with one other person in a quiet room *without* a hearing aid?	☐ **Yes → Go to #11** ☐ **No** ☐ **Don't know** ☐ **Refused**
10	Have you been able to hear what is said in a conversation with one other person in a quiet room *with* a hearing aid?	☐ **Yes** ☐ **No** ☐ **Don't know/ Didn't wear a hearing aid** ☐ **Refused**
11	During the past 4 weeks, have you been able to understand *completely* when speaking your own language with people who do not know you?	☐ **Yes → Go to #16** ☐ **No** ☐ **Don't know** ☐ **Refused**
12	Have you been able to be understood *partially* when speaking with people who do not know you?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
13	During the past 4 weeks, have you been able to be understood *completely* when speaking with people who you know well?	☐ **Yes → Go to #16** ☐ **No** ☐ **Don't know** ☐ **Refused**
14	Have you been able to be understood *partially* when speaking with people who	☐ **Yes → Go to #16** ☐ **No** ☐ **Don't know**

	know you well?	☐ **Refused**
15	During the past 4 weeks, have you been able to speak at all?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
16	During the past 4 weeks, have you been able to bend, lift, jump and run *without difficulty* and *without help or equipment* of any kind?	☐ **Yes → Go to #24** ☐ **No** ☐ **Don't know** ☐ **Refused**
17	Have you been able to walk around the neighbourhood *without difficulty* and *without help or equipment* of any kind?	☐ **Yes → Go to #24** ☐ **No** ☐ **Don't know** ☐ **Refused**
18	Have you been able to walk around the neighbourhood *with difficulty* but *without help or equipment* of any kind?	☐ **Yes → Go to #24** ☐ **No** ☐ **Don't know** ☐ **Refused**
19	During the past 4 weeks, have you been able to walk at all?	☐ **Yes** ☐ **No → Go to #22** ☐ **Don't know** ☐ **Refused**
20	Have you needed mechanical support, such as braces or a cane or crutches, to be able to walk around the neighbourhood?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
21	Have you needed the help of another person to walk?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
22	Have you needed a wheelchair to get around the neighbourhood?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**

23	Have you needed the help of another person to get around in the wheelchair?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
24	During the past 4 weeks, have you had the *full use* of both hands and ten fingers?	☐ **Yes → Go to #28** ☐ **No** ☐ **Don't know** ☐ **Refused**
25	Have you needed the help of another person because of limitations in the use of your hands or fingers?	☐ **Yes** ☐ **No → Go to #27** ☐ **Don't know** ☐ **Refused**
26	Have you needed the help of another person with some tasks, most tasks, or all tasks?	☐ **Some tasks** ☐ **Most tasks** ☐ **All tasks** ☐ **Don't know** ☐ **Refused**
27	Have you needed special equipment, for example special tools to help with dressing or eating, because of limitations in the use of your hands and fingers?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
28	During the past 4 weeks, have you been able to eat, bathe, dress and use the toilet without difficulty?	☐ **Yes → Go to #31** ☐ **No** ☐ **Don't know** ☐ **Refused**
29	Have you needed the help of another person to eat, bathe, dress or use the toilet?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
30	Have you needed special equipment or tools to eat, bathe, dress or use the toilet?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**

31	During the past 4 weeks, have you been feeling happy or unhappy?	☐ **Happy** ☐ **Unhappy → Go to #33** ☐ **Don't know** ☐ **Refused**
32	Would you describe yourself as having felt: a) happy and interested in life, or b) somewhat happy?	☐ **a → Go to #34** ☐ **b → Go to #34** ☐ **Don't know** ☐ **Refused**
33	Would you describe yourself as having felt: a) somewhat unhappy b) very unhappy c) so unhappy that life is not worthwhile	☐ **a** ☐ **b** ☐ **c** ☐ **Don't know** ☐ **Refused**
34	During the past 4 weeks, did you ever feel fretful, angry, irritable, anxious or depressed?	☐ **Yes** ☐ **No → Go to #37** ☐ **Don't know** ☐ **Refused**
35	How often did you feel fretful, angry, irritable, anxious or depressed: Rarely, occasionally, often, or almost always?	☐ **Rarely** ☐ **Occasionally** ☐ **Often** ☐ **Almost always** ☐ **Don't know** ☐ **Refused**
36	During the past 4 weeks did you feel *extremely* fretful, angry, irritable, anxious or depressed; to the point of needing professional help?	☐ **Yes** ☐ **No** ☐ **Don't know** ☐ **Refused**
37	How would you describe your ability to remember things, during the past 4 weeks: a) able to remember most things b) somewhat forgetful c) very forgetful d) unable to remember anything at all	☐ **a** ☐ **b** ☐ **c** ☐ **d** ☐ **Don't know** ☐ **Refused**

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38	How would you describe your ability to think and solve day to day problems, during the past 4 weeks: a) able to think clearly and solve problems b) had a little difficulty c) had some difficulty d) had a great deal of difficulty e) unable to think or solve problems	☐ **a** ☐ **b** ☐ **c** ☐ **d** ☐ **e** ☐ **Don't know** ☐ **Refused**
39	Have you had any trouble with pain or discomfort, during the past 4 weeks?	☐ **Yes** ☐ **No → Go to #41** ☐ **Don't know** ☐ **Refused**
40	How many of your activities, during the past 4 weeks, were limited by pain or discomfort: none, a few, some, most, all?	☐ **None** ☐ **A few** ☐ **Some** ☐ **Most** ☐ **All** ☐ **Don't know** ☐ **Refused**
41	Overall, how would you rate your health during the past 4 weeks? a) excellent b) very good c) good d) fair e) poor	☐ **a** ☐ **b** ☐ **c** ☐ **d** ☐ **e** ☐ **Don't know** ☐ **Refused**

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F) HAMILTON DEPRESSION (HAM-D) RATING SCALE

Instructions: To rate the severity of depression in patients, administer this questionnaire. The higher the score, the more severe the depression. **Please check ONLY ONE box for each question.**

1. ARE YOU IN A **DEPRESSED MOOD?**		0	Absent
		1	Depressed mood indicated only on questioning
		2	Depressed mood spontaneously reported verbally
		3	Depressed mood stated non-verbally (facial expression, posture)
		4	Participant reports depressed mood as only state in both spontaneous verbal and non-verbal communication
2. DO YOU HAVE **FEELINGS OF GUILT?**		0	Absent
		1	Self reproach, feels he/she has let people down
		2	Ideas of guilt or rumination over past errors or sinful deeds
		3	Present illness is a punishment; delusions of guilt
		4	Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3. DO YOU HAVE THOUGHTS OF **SUICIDE?**		0	Absent
		1	Feels life is not worth living
		2	Wishes he/she were dead or any thoughts of possible death to self
		3	Suicidal ideas or gesture
		4	Attempts at suicide (any serious attempt rates as 4)
4. DO YOU HAVE **INSOMNIA** DURING THE **EARLY** PART OF YOUR SLEEP?		0	No difficulty falling asleep
		1	Complains of occasional difficulty falling asleep (more than ½ hour)
		2	Complains of nightly difficulty falling asleep
5. DO YOU HAVE **INSOMNIA** DURING THE **MIDDLE** PART OF YOUR SLEEP?		0	No difficulty
		1	Patient complains of being restless and disturbed during the night
		2	Walking during the night, any getting out of bed rates as 2 (except for purposes of voiding)

6. DO YOU HAVE **INSOMNIA** DURING THE **LATE** PART OF YOUR SLEEP?		0	No difficulty
		1	Waking in early hours of the morning but goes back to sleep
		2	Unable to fall asleep again if he/she gets out of bed
7. WHAT IS THE LEVEL OF YOUR **WORK AND ACTIVITIES?**		0	No difficulty
		1	Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
		2	Loss of interest in activity; hobbies or work, either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities)
		3	Decrease in actual time spent in activities or decrease in productivity
		4	Stopped working because of present illness
8. WHAT IS YOUR **PSYCHOMOTOR** FUNCTION?		0	Normal speech and thought
		1	Slight retardation at interview
		2	Obvious retardation at interview
		3	Interview difficult
		4	Complete stupor
9. WHAT IS THE LEVEL OF YOUR **AGITATION?**		0	None
		1	Fidgetiness
		2	Playing with hands, hair, etc.
		3	Moving about, can't sit still
		4	Hand wringing, nail biting, hair-pulling, biting of lips
10. PSYCHOLOGICALLY, WHAT IS YOUR LEVEL OF **ANXIETY?**		0	No difficulty
		1	Subjective tension and irritability
		2	Worrying about minor matters
		3	Apprehensive attitude apparent in face or speech
		4	Fears expressed without questioning
11. PHYSICALLY (indigestion, stomach cramps, diarrhea, hyperventilation, sweating, etc.) WHAT IS YOUR LEVEL OF **ANXIETY?**		0	Absent
		1	Mild
		2	Moderate
		3	Severe
		4	Incapacitating

12. WHAT IS THE LEVEL OF YOUR **GASTROINTESTINAL SYMPTOMS?**		0	None
		1	Loss of appetite but eating without encouragement from others; food intake about normal
		2	Difficulty eating without urging from others; marked reduction of appetite and food intake

13. WHAT IS THE LEVEL OF YOUR **GENERAL SYMPTOMS?**		0	None
		1	Heaviness in limbs, back or head Backaches, headache, muscle aches. Loss of energy and fatigability
		2	Any clear-cut symptom rates as 2

If study participant is uncomfortable in discussing sexuality, there is option of skipping question 14

14. WHAT IS THE LEVEL OF YOUR **SEXUAL DYSFUNCTION?**		0	Absent
		1	Mild
		2	Severe
		NA	Skipped question
15. WHAT IS THE LEVEL OF YOUR **HYPOCHONDRIASIS?**		0	Not present
		1	Self-absorption (bodily)
		2	Preoccupation with health
		3	Frequent complaints, requests for help, etc.
		4	Hypochondriacal delusions
16. HAS THERE BEEN **LOSS OF WEIGHT?**		0	No weight loss
		1	Probably weight loss associated with present illness
		2	Definite (according to patient) weight loss
17. WHAT IS THE LEVEL OF YOUR **INSIGHT?**		0	Acknowledges being depressed and ill
		1	Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
		2	Denies being ill at all

TOTAL (0-52): ☐

The BURST Study
BASELINE QUESTIONNAIRE
ENGLISH version

G) SUPPLEMENTARY QUESTIONS

Dear Study Participant:

Thank you for agreeing to participate in this study that will identify and measure the resources new stroke patients use during their 6-months of follow-up care. You will be given a total of 3 questionnaires to complete. The information collected will be used for research purposes only.

Today, you are being asked to complete the 3-Month Questionnaire. We would appreciate it if you answered all of the questions. However, you do not need to answer any question you do not wish to answer. The answers provided will not affect your medical care.

Thank you again.

I. STUDY PARTICIPANT INFORMATION

12) **Since your stroke,** have you had to change the number of hours you work? Check only one.

- ☐ No change in hours worked
- ☐ Hours decreased (by _____ hours/week)
- ☐ No longer working due to stroke
- ☐ Anticipate return to work within 1 month
- ☐ Anticipate return to work within 1 – 3 months
- ☐ Did not work prior to stroke

13) Do you think you may have missed a promotion or pay raise at work because of your stroke? Check only one.

- ☐ No
- ☐ Yes

14) **Since your stroke,** how many CT SCANS have you had? Check only one.

- ☐ None
- ☐ One
- ☐ Two
- ☐ Three
- ☐ Four
- ☐ Five
- ☐ Other: _____

15) **Since your stroke,** how many MRIs have you had? Check only one.

- ☐ None
- ☐ One
- ☐ Two
- ☐ Three
- ☐ Four
- ☐ Five
- ☐ Other: _____

The BURST Study
3-MONTH QUESTIONNAIRE
ENGLISH version

II. POST-STROKE CARE

IIA. OUTPATIENT PHYSICIAN VISITS

16) Since the last time you completed the study questionnaire (3 months ago), how many VISITS have you had with a NEUROLOGIST? Check only one.

- ☐ None
- ☐ One
- ☐ Two
- ☐ Three
- ☐ Four
- ☐ Five
- ☐ Other: _____

17) Since the last time you completed the study questionnaire (3 months ago), how many VISITS have you had with your FAMILY DOCTOR? Check only one.

- ☐ None
- ☐ One
- ☐ Two
- ☐ Three
- ☐ Four
- ☐ Five
- ☐ Other: _____

18) Since the last time you completed the study questionnaire (3 months ago), which OTHER PROFESSIONALS have you visited and how many visits? Check all that apply. And how many visits per month?

- ☐ No professionals
- ☐ Cardiologist → # VISITS: _____
- ☐ Emergency doctor → # VISITS: _____
- ☐ Hematologist → # VISITS: _____
- ☐ Internist → # VISITS: _____
- ☐ Psychiatrist → # VISITS: _____
- ☐ Respirologist → # VISITS: _____
- ☐ Nurse Specialist → # VISITS: _____
- ☐ Surgeon → # VISITS: _____
- ☐ Other: → # VISITS: _____

The BURST Study
3-MONTH QUESTIONNAIRE
ENGLISH version

IIB. REHABILITATION

19) Did you receive REHABILITATION during your stroke hospitalization? Check only one.

- ☐ No
- ☐ Yes
- ☐ Not applicable (e.g. not hospitalized)

20) What was the first type of REHABILITATION that you received or are currently receiving? Check only one.

- ☐ None
- ☐ Inpatient rehabilitation program
- ☐ Outpatient rehabilitation program
- ☐ Outpatient physiotherapy visits
- ☐ Outpatient occupational therapy visits
- ☐ Outpatient speech therapy visits
- ☐ Other (use free text box)

21) What is or was the DURATION of this rehabilitation? Check only one.

- ☐ Not applicable (no rehabilitation received)
- ☐ Number of days entered in box below:

22) What is or was your WAIT TIME for this rehabilitation from the time of your stroke to the time you started? Check only one.

- ☐ Not applicable (no rehabilitation received)
- ☐ Number of days entered in box below:
- ☐ Still waiting

The BURST Study
3-MONTH QUESTIONNAIRE
ENGLISH version

23) What was the second type of REHABILITATION that you received or are currently receiving? Check only one.

- ☐ None
- ☐ Inpatient rehabilitation program
- ☐ Outpatient neurological rehabilitation program
- ☐ Outpatient physiotherapy visits
- ☐ Outpatient occupational therapy visits
- ☐ Outpatient speech therapy visits
- ☐ Other (use free text box)

24) What is or was the DURATION of this rehabilitation? Check only one.

- ☐ Not applicable (no rehabilitation received)
- ☐ Number of days entered in box below:

25) What is or was your WAIT TIME for this rehabilitation from the time of your stroke to the time you started? Check only one.

- ☐ Not applicable (no rehabilitation received)
- ☐ Number of days entered in box below:
- ☐ Still waiting

The BURST Study
3-MONTH QUESTIONNAIRE
ENGLISH version

26) What was your third type of REHABILITATION that you received or are currently receiving? Check only one.

- ☐ None
- ☐ Inpatient rehabilitation program
- ☐ Outpatient neurological rehabilitation program
- ☐ Outpatient physiotherapy visits
- ☐ Outpatient occupational therapy visits
- ☐ Outpatient speech therapy visits
- ☐ Other (use free text box)

27) What is or was the DURATION of this rehabilitation? Check only one.

- ☐ Not applicable (no rehabilitation received)
- ☐ Number of days entered in box below:

28) What is or was your WAIT TIME for rehabilitation from the time of your stroke to the time you started? Check only one.

- ☐ Not applicable (no rehabilitation received)
- ☐ Number of days entered in box below:
- ☐ Still waiting

The BURST Study
3-MONTH QUESTIONNAIRE
ENGLISH version

IIC. HOMECARE & ADDITIONAL CARE

29) Since the last time you completed the study questionnaire (3 months ago), what HOMECARE SERVICES are you currently receiving or have already received because of your stroke? Check all that apply.

- ☐ None
- ☐ Nursing
- ☐ Physiotherapy
- ☐ Occupational therapy
- ☐ Speech therapy
- ☐ Dietary/nutritional
- ☐ Social work
- ☐ Equipment and supplies
- ☐ Personal care
- ☐ Other (use free text box)

30) Since the last time you completed the study questionnaire (3 months ago), what ADDITIONAL STROKE CARE are you currently receiving or already received because of your stroke? Check all that apply. And how many visits per month?

- ☐ None
- ☐ Private nurse → # VISITS/month: _____
- ☐ Private physiotherapy → # VISITS/month: _____
- ☐ Private occupational therapy → # VISITS/month: _____
- ☐ Private speech therapy → # VISITS/month: _____
- ☐ Private dietary/nutritional → # VISITS/month: _____
- ☐ Private chiropractor → # VISITS/month: _____
- ☐ Private massage therapy → # VISITS/month: _____
- ☐ Private art therapy → # VISITS/month: _____
- ☐ Private water therapy → # VISITS/month: _____
- ☐ Private acupuncturist → # VISITS/month: _____
- ☐ Private counseling → # VISITS/month: _____
- ☐ Private housekeeping → # VISITS/month: _____
- ☐ Other (use free text box) → # VISITS/month: _____

The BURST Study
3-MONTH QUESTIONNAIRE
ENGLISH version

III. LIFESTYLE CHANGES

31) Since the last time you completed the questionnaire (3 months ago), what HEALTH RELATED CHANGES have you made because of your stroke? Check all that apply.

- ☐ Stop or decrease smoking/nicotine consumption
- ☐ Stop or decrease alcohol consumption
- ☐ Stop or decrease caffeine consumption
- ☐ Start new medication(s)
- ☐ Start exercising/increase activity level
- ☐ Change in diet/weight loss
- ☐ Decrease activity level (housecleaning, cooking, etc.)
- ☐ Fatigue
- ☐ No health related changes made

32) Since the last time you completed the questionnaire (3 months ago), what MOBILITY AID(S) have you purchased because of your stroke? Check all that apply.

- ☐ Wheelchair
- ☐ Walker
- ☐ Cane
- ☐ Orthopedic shoes
- ☐ Foot/leg brace
- ☐ No mobility aids needed

33) Since the last time you completed the questionnaire (3 months ago), what CHANGES IN YOUR PLACE OF RESIDENCE have taken place because of your stroke? Check all that apply.

- ☐ Move to a more appropriate residence
- ☐ Wheelchair ramp constructed
- ☐ Emergency medical alarm installed
- ☐ Stair lift installed
- ☐ Bedroom location moved (e.g. main floor)
- ☐ Shower chair installed in bathtub
- ☐ Handrails installed throughout your home
- ☐ Rugs taped down or removed
- ☐ Furniture repositioned
- ☐ Lowering the height of where things are stored (e.g. bar for hanging clothes)
- ☐ Changing door/dresser handles
- ☐ No changes to residence needed

The BURST Study
3-MONTH QUESTIONNAIRE
ENGLISH version

34) **Since your stroke,** what is your MODE OF TRANSPORTATION because of your stroke? Check the one that is most applicable.

- ☐ Car (you are the driver)
- ☐ Car (spouse/partner/caregiver or family member is the driver)
- ☐ Car (volunteer or paid worker is the driver)
- ☐ Public transportation (i.e. bus, subway)
- ☐ Taxi
- ☐ Wheel-Trans/Para-Transpo

35) **Since your stroke,** what changes have you made to your DRESSING ROUTINE because of your stroke? Check all that apply.

- ☐ New clothes/shoes with Velcro fasteners or elastic (buttons, zippers and laces replaced)
- ☐ Purchase of dressing aids, such as a button hook and dressing stick
- ☐ Assistance from spouse/partner, family member(s) or unpaid caregiver
- ☐ Assistance from volunteer
- ☐ Assistance from paid worker
- ☐ No changes to dressing routine

36) **Since your stroke,** what changes to your LEISURE ACTIVITIES have you had to undergo? Check all that apply.

- ☐ Joined stroke survivor group
- ☐ Increased knowledge about stroke (internet, books, etc.)
- ☐ Decreased opportunities to participate in sports activities (tennis, golf, etc.)
- ☐ Decreased opportunities for travel excursions
- ☐ Decreased opportunities to attend social functions and/or visit friends and family
- ☐ Decreased opportunities to attend cultural events (concerts, movies, etc.)
- ☐ No changes to leisure activities

37) **Since your stroke,** approximately what have been the TOTAL EXPENSES that you have paid for mobility aids, changes related to your health, changes in your place of residence and changes to your dressing routine? Check only one.

- ☐ $0
- ☐ $1-$99
- ☐ $100-$499
- ☐ $500-$999
- ☐ $1,000-$2,999
- ☐ $3,000-$5,999
- ☐ $6,000-$9,999
- ☐ $10,000-$19,999
- ☐ More than $20,000

The BURST Study
3-MONTH QUESTIONNAIRE
ENGLISH version

IV. UNPAID CAREGIVER INFORMATION

38) **Since your stroke,** who has been your primary UNPAID CAREGIVER? *[An unpaid caregiver is a person who does not receive pay to provide care. If you have multiple primary unpaid caregivers, for example your spouse and child both care for you, #1 is your primary caregiver, #2 is your secondary caregiver, etc.]*

CAREGIVER #1
- ☐ No caregiver #1
- ☐ Spouse
- ☐ Child
- ☐ Parent
- ☐ Sibling
- ☐ Family relative
- ☐ Friend
- ☐ Neighbour
- ☐ Volunteer
- ☐ Other: -

_____

CAREGIVER #2
- ☐ No caregiver #2
- ☐ Spouse
- ☐ Child
- ☐ Parent
- ☐ Sibling
- ☐ Family relative
- ☐ Friend
- ☐ Neighbour
- ☐ Volunteer
- ☐ Other: _____

CAREGIVER #3
- ☐ No caregiver #3
- ☐ Spouse
- ☐ Child
- ☐ Parent
- ☐ Sibling
- ☐ Family relative
- ☐ Friend
- ☐ Neighbour
- ☐ Volunteer
- ☐ Other: _____

39) **Since your stroke,** has your UNPAID CAREGIVER(S) had to change their number of hours worked?

CAREGIVER #1
- ☐ No caregiver #1
- ☐ No change
- ☐ Hours decreased
- ☐ Leave of absence
- ☐ Quit job
- ☐ Don't know
- ☐ Not applicable (unpaid caregiver never worked)

CAREGIVER #2
- ☐ No caregiver #2
- ☐ No change
- ☐ Hours decreased
- ☐ Leave of absence
- ☐ Quit job
- ☐ Don't know
- ☐ Not applicable (unpaid caregiver never worked)

CAREGIVER #3
- ☐ No caregiver #3
- ☐ No change
- ☐ Hours decreased
- ☐ Leave of absence
- ☐ Quit job
- ☐ Don't know
- ☐ Not applicable (unpaid caregiver never worked)

The BURST Study
3-MONTH QUESTIONNAIRE
ENGLISH version

40) **Since your stroke,** approximately how many hours in ONE DAY does your UNPAID CAREGIVER(S) provide you with assistance?

CAREGIVER #1	CAREGIVER #2	CAREGIVER #3
☐ No caregiver #1	☐ No caregiver #2	☐ No caregiver #3
☐ 1-3 hours	☐ 1-3 hours	☐ 1-3 hours
☐ 3-6 hours	☐ 3-6 hours	☐ 3-6 hours
☐ 6-10 hours	☐ 6-10 hours	☐ 6-10 hours
☐ 10-15 hours	☐ 10-15 hours	☐ 10-15 hours
☐ 15-24 hours	☐ 15-24 hours	☐ 15-24 hours

V. PAID CAREGIVER INFORMATION

41) **Since your stroke,** do you have a PAID CAREGIVER? Check only one.

☐ No, I don't have a paid caregiver
☐ Yes, I have a paid **visiting** caregiver
☐ Yes, I have a paid **live-in** caregiver

42) If you have a PAID CAREGIVER because of your stroke, approximately how many hours in ONE DAY does your PAID CAREGIVER provide you with assistance? Check only one.

☐ No paid caregiver
☐ 1-3 hours
☐ 3-6 hours
☐ 6-10 hours
☐ 10-15 hours
☐ 15-24 hours

* * * * * * * * * *

Congratulations! The 3-Month Questionnaire of the BURST Study has now been completed.

Please enter date that this questionnaire was completed (D/M/Y): _____

Contact number for patient: _____

The on-site nurse/study coordinator should now note when the 6-month questionnaire will need to be completed by this study subject (D/M/Y): _____

If applicable, check with the stroke clinic booking staff when your next visit will occur.

Please remember to bring an updated list of your MEDICATIONS in order to complete the 6-Month Questionnaire.

The BURST Study
6-MONTH QUESTIONNAIRE
ENGLISH version

(Identical to 3 month Questionnaire)

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