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Feasibility Study to Derive a Clinical Decision Rule for the Investigation of Alert Patients Suspected of Having a Non-Traumatic Subarachnoid Haemorrhage

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Feasibility Study to Derive a Clinical Decision Rule for the Investigation of Alert Patients Suspected of Having a Non-Traumatic Subarachnoid Haemorrhage

By

Dr. Jeffrey Joseph Perry

Thesis submitted to the School of Graduate Studies and Research in partial fulfilment of the requirements for the MSc degree in Epidemiology

University of Ottawa

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ABSTRACT

***CONTEXT*:** Subarachnoid haemorrhage is a type of haemorrhagic stroke with an annual incidence of 1 per 10,000 people and accounts for 1% of emergency department visits for acute headache. The median age of onset is 50 years. The overall mortality is 50% within 6 months and 42% of survivors are left with neurological deficits. Up to 40% of patients with subarachnoid haemorrhage have had smaller unrecognized bleeds prior to a larger bleed, which subsequently has a worse prognosis. Thus, ruling out subarachnoid haemorrhage in alert patients with a headache is a priority in the emergency department. Currently, this is accomplished by using computed tomography and lumbar puncture. Computed tomography, however, misses up to 10% of subarachnoid haemorrhages and is associated with a high cost. Lumbar punctures are painful and invasive procedures. Therefore, it is important to be efficient in determining which patients to investigate for subarachnoid haemorrhage. Clinical guidelines to rule out subarachnoid haemorrhage in alert patients with headache and normal neurological examination do not currently exist. This thesis comprised of two studies: a phase 0 historical cohort study to determine current practice and a phase 1 prospective cohort study to determine the feasibility of generating a clinical decision rule to determine which alert patients with headache and normal neurological examination require investigation.

***OBJECTIVES*:** 1) Phase 0: To determine patient characteristics, association of predictor variables with subarachnoid haemorrhage, mean length of stay determined by investigation(s) performed, and an estimate of the incidence of subarachnoid haemorrhage in alert patients with headache and normal neurological examination at the Ottawa

Hospital. 2) Phase 1: To develop and pre-test standardized clinical assessments in alert patients with possible subarachnoid haemorrhage and apply these standardized clinical assessments to alert patients with possible subarachnoid haemorrhage. With these clinical assessments, determine the statistical association between the clinical findings and the diagnosis of subarachnoid haemorrhage, and develop a preliminary decision rule to determine which patients require investigation to rule out subarachnoid haemorrhage.

DESIGN: 1) Phase 0: Historical cohort study. 2) Phase 1: Prospective cohort study.

SETTING: i) Phase 0: The emergency department of the Ottawa Hospital Civic Campus 2) Phase 1: The Ottawa Hospital General and Civic Campus emergency departments. The data management and analysis was completed at the Ottawa Health Research Institute, Clinical Epidemiology Unit, Ottawa Hospital Civic Campus.

SUBJECTS: 1) Phase 0: 10-month consecutive sample of patients with headache, syncope or possible subarachnoid haemorrhage from January 1 to October 31, 2000. 2) Phase 1: 7-month consecutive sample of alert patients over 15 years of age with suspected subarachnoid haemorrhage.

DATA COLLECTION: 1) Phase 0: A structured data collection form was completed for all identified patients for historical and physical examination characteristics. 2) Phase 1: All enrolled patients had a data collection form completed prospectively by an emergency physician. If computed tomography and/or a lumbar puncture were not obtained, patients were contacted one month to ensure they had not suffered any adverse events.

DATA ANALYSIS: Data was entered into SAS and converted to SPSS for the analysis.

MAIN OUTCOME MEASURE: The primary outcome for both phases was subarachnoid

haemorrhage, which was defined by the presence of any one of the following: 1) subarachnoid blood on computed tomography, 2) the presence of xanthochromia in the cerebral spinal fluid or 3) the presence of red blood cells in the third or fourth tube of cerebral spinal fluid with an aneurysm on cerebral angiography.

RESULTS: 1) Phase 0: There were 1957 eligible patients identified. Of the 891 patients enrolled, 10 (1%) had a subarachnoid haemorrhage. The mean age of patients was 42 years and 66% were female. Computed tomography was utilized in 35% of the patients, while 9.5% underwent a lumbar puncture. Seventy seven percent of the final diagnoses were due to migraine or other benign headaches. Serious diagnoses, including subarachnoid haemorrhage, ischemic event, brain tumour, bacterial meningitis and temporal arteritis, accounted for 3% of the diagnoses. The mean time spent in the emergency department without investigation until referral or discharge was 4 hours. Patients who underwent computed tomography stayed a mean 5 hours, while patients undergoing a lumbar puncture stayed a mean 7 hours.

2) Phase 1: There were 1652 patients with a presenting complaint of headache or syncope. Of these, there were 225 eligible patients, with prospective data collected on 134 (60%). 14 (10%) of enrolled cases were positive. The mean time from onset to peak headache was 13 minutes and the severity was 8.8 on a scale from 0 (low) to 10 (high). This was reported as the worst headache of their life in 77% of subjects. Those with a subarachnoid haemorrhage were older than those with other diagnoses (57 versus 41 years; $p < 0.01$). Other significant associations (p-value < 0.05) for subarachnoid haemorrhage were: "onset during exertion", presence of the "worst headache of the patient's life", "transient loss of

consciousness", "obligated to rest with onset of pain", "complaint of neck pain", "neck stiffness with lateral rotation", "neck stiffness with flexion/extension" and the "physician's rating of patient distress". The logistic regression model included the terms: "age > 40", "transient loss of consciousness" or "obligated to rest/buckling of legs", "neck stiffness with lateral or flexion/extension" and "diastolic blood pressure > 110 mm of Hg". The recursive partitioning model included the terms "age > 45" and "neck stiffness with lateral rotation". This latter model had 100% sensitivity (95%CI: 77-100) and 57% specificity (95%CI: 47-65).

CONCLUSIONS: 1) Phase 0: The current use of computed tomography and lumbar puncture is inefficient. Potential predictor variables identified were: "time from onset of the headache to its' peak", "neck pain", the absence of a history of a "similar headache in the past", "neck stiffness" and "blood pressure".

2) Phase 1: In this prospective cohort study, almost all of the patients were investigated for possible subarachnoid haemorrhage, with only 10% having a final diagnosis of subarachnoid haemorrhage. Thus there is a need for a clinical decision rule to determine which patients require investigation to rule out subarachnoid haemorrhage. The preliminary model derived from this study, included the terms "age over 45" and "neck stiffness with lateral rotation". Although this preliminary rule has large confidence intervals, with a larger sample size, it is likely that a highly sensitive decision rule can be determined for alert patients with a headache and a normal neurological examination to determine which patients require investigation to rule out subarachnoid haemorrhage.

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CHAPTER 1: BACKGROUND AND REVIEW OF LITERATURE

Alert patients with non-traumatic headaches of sudden onset often undergo expensive and invasive procedures to rule out the presence of subarachnoid haemorrhage. Currently it is not known which patients require testing; therefore the goal of this thesis is to determine if a clinical decision rule to determine which patients require investigations is feasible.

1.1 Introduction to Non-Traumatic Subarachnoid Haemorrhage

1.1.1 Definition of Subarachnoid Haemorrhage

Subarachnoid haemorrhage is a type of haemorrhagic stroke in which blood leaks from a cerebral blood vessel into the subarachnoid space.[1]

1.1.2 Presentation of Non-Traumatic Subarachnoid Haemorrhage

The presentation of non-traumatic subarachnoid haemorrhage is variable. The majority of patients present with a history of a sudden severe headache. Often this headache is located in the occipitalnuchal region of the head.[2] Nearly half of all patients with a subarachnoid haemorrhage have a normal neurological examination, normal vital signs and the absence of neck stiffness.[3] Other presentations may include marked neurological deficits, decreased level of consciousness or syncope. At the other extreme, patients may have subtle symptoms with a less severe headache and the absence of other historical or physical findings.[2]

1.1.3 Prognosis of Non-Traumatic Subarachnoid Haemorrhage

Subarachnoid haemorrhage has a high mortality. Overall mortality is 25% after one day and 50% within six months. Of the survivors, almost half are left with permanent

neurological deficits.[4] There is a large amount of research demonstrating that alert patients without neurological deficits have a much more favourable prognosis than patients with a decreased level of consciousness or a neurological deficit. Hunt and Hess demonstrated this when they developed the current grading system (Table 1).[5]

1.1.4 Investigation for Diagnosis of Non-Traumatic Subarachnoid Haemorrhage

Subarachnoid haemorrhage is confirmed by: 1) a computed tomography with blood visible in the basal cisterns, sylvian fissures or ventricles 2) lumbar puncture with either xanthochromia (the degradation products of old red blood cells) or persistent red blood cells in cerebral spinal fluid, 3) cerebral angiography demonstrating an aneurysm, or 4) at time of autopsy.[1]

1.1.5 Treatment of Non-Traumatic Subarachnoid Haemorrhage

Subarachnoid haemorrhage is a neurosurgical emergency. If clinically indicated, patients require immediate resuscitation including: intubation, ventilation, mannitol (an osmotic diuretic to decrease the intracranial pressure) and maintenance of an adequate blood pressure. Patients may receive medications, such as, phenytoin to decrease the risk of seizures and nimodipine (a calcium channel blocker) to decrease the rate of vasospasm. Identified aneurysms are obliterated surgically if accessible, and the patient is determined to be an acceptable surgical candidate (determined by the surgeon based on previous medical conditions and extent of current problem). All patients require constant supervision in an acute care setting.[6]

1.1.6 Statement of Problem in Emergency Department

Headache is a common symptom representing up to 4.5% of presenting complaints in the emergency department.[7] The greatest concern in this patient population, is ruling out the possibility of a subarachnoid haemorrhage, which accounts for one percent of all headaches seen in the emergency department.[8] In particular, physicians try to rule out the diagnosis of subarachnoid haemorrhage in alert patients with normal neurological examinations as they are the most difficult to diagnose and are the ones that can be most helped by a prompt diagnosis.[1;9-12]

Up to 40% of patients with subarachnoid haemorrhage have a small warning bleed a short time prior to a large bleed.[13] These patients initially appear relatively well and are consequently often misdiagnosed as having a benign headache. However, once they have a subsequent large bleed their prognosis is much worse than those who are diagnosed at the time of initial presentation.[13] The main reason for a delay in referral to a neurosurgeon, as demonstrated by a large number of studies, is that the treating physician makes an incorrect initial diagnosis.[3;13-16;16-26] Early surgery has been demonstrated to decrease the mortality of patients from 65% to 40%.[6;27-29]

Despite the large number of patients who present to emergency departments with a headache, the indications for which patients to investigate are vague. This is particularly true of the cohort of alert patients who do not have any abnormal neurological findings. Currently, most authorities recommend a non-enhanced computed tomography scan of the patient's head, followed by a lumbar puncture if the computed tomography is normal. However, to which headache patients this applies is not known. In addition to the cost of

these procedures and the extra time and emergency department resources used, these procedures pose risks to the patient. With computed tomography, patients are exposed to low dose radiation (x-rays). The lumbar puncture is a painful and invasive procedure, which can cause severe headache after the procedure that can last for many days. Clinical guidelines to rule out subarachnoid haemorrhage for alert patients with a headache, which follow the "six major stages in the development and testing of a new clinical decision rule", do not currently exist.[30]

1.2 Recognition of the Need for a Decision Rule by Emergency Physicians

In a recent survey of emergency physicians, a clinical practice guideline for investigating patients presenting with an acute non-traumatic headache was the third most requested clinical guideline among North American physicians and was chosen first by their European counterparts.[31] With such a low prevalence of subarachnoid haemorrhage in the patients with an acute headache, there is a substantial amount of time and money spent on unnecessary computed tomography and unnecessary morbidity for patients who undergo a lumbar puncture.

1.3 Review of Electronic Database

A review of an electronic database of patient visits to the Ottawa Hospital Civic Campus emergency department for 1999 (Figure 1), previously done by the principal investigator, found there were 3625 patients (6.3%) who presented with either headache, syncope or possible subarachnoid haemorrhage out of 57300 total patient visits. Of these patients, 142 (3.9%) were diagnosed with subarachnoid haemorrhage. Of 1085 patients undergoing computed tomography, 7.6% were diagnosed with subarachnoid haemorrhage.

Among the patients with an acute headache referred from smaller centres for computed tomography, 10% had a subarachnoid haemorrhage. This inconsistency further highlights the need for a validated clinical decision rule to improve the quality of care and proper resource utilisation.

1.4 Pathophysiology and Epidemiology

In 80% of non-traumatic subarachnoid haemorrhage cases, blood from a ruptured cerebral arterial aneurysm is released under high pressure into the subarachnoid space. This leads to cellular damage as well as a rapid increase in intra-cranial pressure. Ten percent of subarachnoid haemorrhages are due to arteriovenous malformations and 10% are due to perimesencephalic haemorrhages (bleeding from small, low-pressure vessels). Rare causes of non-traumatic subarachnoid haemorrhage are from spinal aneurysms, tumours and spinal arteriovenous malformations.[32] About 50% of aneurysms are due to berry aneurysms (small congenital cerebral aneurysms) at the bifurcation of arteries, with the remainder due to aneurysms in other locations in the cerebral arteries.[2]

Subarachnoid haemorrhage has an annual incidence of 1 to 2.5 per 10000.[1 7;33] Women have a higher incidence than men, with an annual age adjusted incidence of 12.2 to 18.3 per 100,000 women compared to 7.2 to 10.5 for men.[12;34] Although the incidence of other forms of stroke has decreased over time, the incidence of subarachnoid haemorrhage has remained constant.[1;34] Subarachnoid haemorrhage occurs in young people, with a median age of 50 years.[24] Overall mortality is 25% in 24 hours and 50% within six months. Of the survivors, 42% are left with neurological sequelae.[4;24] Up to 40% of patients with subarachnoid haemorrhage have smaller, often unrecognized,

warning bleeds prior to a larger bleed.[16;17;19;23;35] If a patient survives the initial neurological insult, the major threats to life are rebleeding and vasospasm causing cerebral ischemia. These are best remedied by early surgery and calcium channel blocker medication.[36]

Several studies have used one-month follow-up as the time period in which a person is felt to be at increased risk following a sentinel bleed. It is believed that after one month, the aneurysm would have resealed and the patient returns to baseline risk.[37;38] However, other studies state that a six-month period is required for the risk to approach the baseline level.[21]

1.5 Methodologic Standards for Decision Rules

There has been a large amount of research done recently in the area of clinical decision rules. A clinical decision rule is defined as a decision making tool that is derived from original research and incorporates three or more variables from the history, physical examination, or simple tests.[30;39] These rules have been developed to help improve the standard of care and often to reduce the number of tests performed, without compromising the care given to patients. Given the great interest in developing such rules, there has also been research into developing methodological standards for the derivation and validation of such rules. The standards are summarized as follows:[30;39;40]

1. The **outcome** or **diagnosis** must be clearly defined prior to starting data collection for the decision rule, and the assessment of this outcome should be made in a blinded manner.

2. The clinical information to be used as **predictors** must be clearly defined and standardized and their assessment of each patient must be done prior to the knowledge of the outcome or diagnosis.
3. The **reliability or reproducibility** of the clinical information used as predictors must be clearly demonstrated.
4. The **study population must be selected without bias** and should be representative of the target population of the decision rule.
5. The **mathematical methods** used for deriving the rule must be clearly identified.
6. Clinical decision rules should be **sensible**. As such, they should have a clear purpose, be clinically relevant, be clinically valid, be concise and be easy to remember and used in the appropriate clinical application.
7. The **accuracy** of the decision rule needs to be established. This includes reporting the sensitivity and the specificity of the clinical decision rule.
8. **Prospective validation** in a new, separate patient population is an essential test of accuracy of the decision rule.
9. **Implementation** to demonstrate the true effect on patient care is the final and most conclusive test of any clinical decision rule.[5;24;27;36;41-43]

1.6 Review of Previous Studies

The previous work in the area of determining which patients with an acute headache require investigation for possible subarachnoid haemorrhage has not been successful in generating a methodologically sound clinical decision rule. Many of the

studies were too small and very few were conducted prospectively. A summary of the studies identified is listed in Table 2.

1.7 Potential Predictor Variables Identified from Literature Review

1.7.1 Features from History

Many patients with subarachnoid haemorrhage have a presenting complaint of a sudden severe headache, which is frequently described as the worst headache of the their life.[2;11] However, other presentations may be syncope or unconsciousness.[11] All patients with an altered mental status or a focal neurological deficit will be investigated for subarachnoid haemorrhage. Therefore, it is only those patients presenting in an alert state without any neurological findings on physical examination with a severe headache that pose a diagnostic challenge. Although it has been suggested that a headache alone is not enough to warrant aggressive investigations, there have been no studies to support this conclusion.[44]

Scheivink in 1989 determined from a retrospective chart review of 500 patients with aneurysmal subarachnoid haemorrhage (both patient's who were alert and those with altered levels of consciousness) found risk factors for subarachnoid haemorrhage included females over age 50 and males less than 50.[45] They found that a stressful event preceding the subarachnoid haemorrhage was more common than non-stressful events. However the events classified as non-stressful included many potentially stressful situations (housework, bathing and dressing). They also reported that 12% of their study had the onset of subarachnoid haemorrhage during sleep.[45]

Rosenorn in 1987 found the mean age of onset was 49 years, and that a provoking factor was present in 30% of cases, including intercourse in 5.5% of cases.[46] Sixteen percent had a seizure, 31% were unconscious for greater than one hour and another 26% were unconscious for less than one hour.[46]

Another study assessed the differences between benign exertional headache, sexual headaches, cough headaches and subarachnoid haemorrhage in alert patients.[47] The investigators found that 42% of this group had intra-cranial pathology but only one was a subarachnoid haemorrhage.[47] One small study suggested that posterior neck pain might be an important risk factor.[48]

Additional symptoms associated with the outcome of subarachnoid haemorrhage have been presented in reviews of this subject. Some of these symptoms are: onset during exertion, buckling of legs with onset of headache and vomiting.[11] Transient loss of consciousness is frequently found to be related to the outcome of subarachnoid haemorrhage.[11;46;49] In addition, transient neurological deficits may be reported by the patient.[19] Headaches are reported most frequently to be bilateral and located in the occipitalnuchal region of their head.[2] Caution is suggested not to discount patients who get spontaneous or medicated relief of their headache.[2;9]

There are several studies that demonstrate an increased risk of subarachnoid haemorrhage in patients whose first degree relatives have had a subarachnoid haemorrhage.[1;50-57] However, in a study which retrospectively identified patients who had suffered a fatal stroke, families were contacted to determine if they were able to identify correctly between an ischemic stroke, an intracerebral haemorrhage and a subarachnoid

haemorrhage. The families were not able to make this distinction, hence this may not be a reliable predictor.[58]

Other risk factors identified included: alcohol consumption, smoking, hypertension and oral contraceptives.[7;19-21;59-68] These variables are very prevalent among patients presenting to the emergency department and may not be clinically useful for differentiating subarachnoid haemorrhage from other headaches. Connective tissue disorders are associated with an increased risk including: Ehlers-Danlos syndrome type IV, autosomal dominant polycystic kidney disease, neurofibromatosis type I, alpha-one antitrypsin deficiency and Marfan's syndrome.[1] However, these risk factors are very rare in the general population and may not be useful to differentiate patients with subarachnoid haemorrhage in a clinical decision rule.[69-74]

1.7.2 Physical Examination Findings

The presence of neck stiffness has been frequently associated with the diagnosis of subarachnoid haemorrhage and is cited in reviews of the topic.[1;2;11] This relates to stiffness with flexion and extension of the neck. No studies have looked at lateral rotation of the neck in this population. Additional features associated with the outcome of subarachnoid haemorrhage include elevated systolic and diastolic blood pressure.[11]

An article by Kasner in 1997 and another by Garfinkle in 1992 discussed the opthalmological findings in Terson's syndrome (intraocular haemorrhage in the unconscious patient with an anterior communicating artery aneurysmal haemorrhage). They describe subhyaloid haemorrhage as being a favourable sign and intraocular blood being associated with greater mortality.[75;76] These results, although interesting, do not

occur in alert and conscious patients who are neurologically intact and would not prompt a treating physician to alter current management.

1.8 Current Investigations for Suspected Subarachnoid Haemorrhage

Currently there are no accepted standards for investigating alert patients with a severe headache and intact neurological examination. Patients with a decreased level of consciousness or an abnormal neurological examination will receive a complete work-up until the source of the neurological deficit is identified.

1.9 Use of Head Computed Tomography

1.9.1 Overview

The most commonly used modality to begin investigating patients suspected of having a subarachnoid haemorrhage is to obtain a non-enhanced computed tomography scan of the patient's head. If the computed tomography is normal, and the diagnosis of subarachnoid haemorrhage is still considered, a lumbar puncture is done if there are no contraindications.[2;77]

1.9.2 Review of Relevant Literature

Studies have demonstrated that computed tomography (including third generation plus scanners) miss up to 10% of subarachnoid haemorrhages.[4;77-79] One retrospective study demonstrated that the rate of normal scans in patients with subarachnoid haemorrhage was only 3.9% if neurological signs were present.[80] However, if they included patients without neurological signs (Hunt and Hess grades 1-2 (Table 1)), this percent increased to 8.4%.[80] A retrospective study by Sidman in 1996 found that prior to 12 hours the computed tomography scans were 100% sensitive (95% confidence interval

was 95% to 100%).[4] In other studies, computed tomography has been found to be only 90.5% to 93.1% sensitive within the first 24 hours.[79;81] This rate decreases dramatically after 24 hours with about 67% sensitivity by three days, 50% after one week and 30% at two weeks.[82] Although the absolute optimal time is not known, research suggests that, when possible, computed tomography should be done prior to 12 hours from the onset of the headache.[4]

1.9.3 Findings on Computed Tomography

The image of blood in the cerebral spinal fluid is detected by the difference in Hounsfield units (a unit for measuring tissue density), which is high for blood (56 units) compared to the normal cerebral spinal fluid (0-5 units). This is in contrast to the normal brain parenchyma, which has an attenuation of 37-41 units (grey matter).[32] Blood from a subarachnoid haemorrhage can be located in the basal cisterns, sylvian fissures, ventricles and brain parenchyma.[32] The pattern of blood on the computed tomography can determine the location of the aneurysm in 80% of cases.[32] Anterior communicating artery aneurysms are primarily in the interhemisheric fissure plus or minus the supracellar cisterns or third ventricle.[32] The middle cerebral artery aneurysms bleed into the sylvian fissures plus or minus the middle cerebral artery fissure.[32] The basilar tip aneurysms bleed centrally into the interpeduncular, chiasmatic and prepontine cisterns.[32] The posterior cerebral arteries and distal carotid aneurysms bleed laterally near the supraclinoid internal carotid artery.[32] Finally, the posterior-inferior cerebellar artery bleeds into the fourth ventricle, occasionally extending into the aqueduct and third ventricle.[32]

1.9.4 Cause of False Positive Results

There is no data reporting how frequently false positive results occur. Expert opinion suggests that it is uncommon and mainly due to over interpretation by inexperienced physicians reading the scan.[83] This may be due to calcification of the arteries in the circle of Willis or due to volume averaging by the scanner with adjacent bone structures.[83]

1.9.5 Cause of False Negative Results

Causes of false negative scans are mainly due to a long passage of time from the ictus to the time of computed tomography. As previously stated, the sensitivity decreases progressively after 12 hours following the ictus. This is explained by reabsorption of the blood and breaking down of the residual blood. A rare cause of false negative scans is patients who are profoundly anaemic in which the blood is isodence with the brain parenchyma.[84] Another possible cause would be the under-reading by emergency physicians. However this has not been well studied.

1.9.6 Sensitivity of Interpretation by Emergency Physicians

In many centres, the emergency physicians perform the initial interpretation of computed tomography scans. A study in 1998 demonstrated that emergency physicians correctly diagnosed only 67% of scans compared to 83% for both neurologists and radiologists. However, this study was aimed at assessing indications for giving thrombolytics in acute ischemic stroke rather than subarachnoid haemorrhage. Acute ischemic strokes are much more difficult to interpret than subarachnoid haemorrhage.[85]

There was no data found looking at the sensitivity of emergency physician's interpretation for subarachnoid haemorrhage.

1.9.7 Disadvantages of Performing Computed Tomography

There are many problems with performing computed tomography for all patients presenting to the emergency department with an acute headache. The most obvious is the high cost with each scan costing about $170 at the Ottawa Hospital for the cost of the equipment, technician and radiologist interpretation.[86] The charge at the Ottawa Hospital for uninsured Canadians is $450, while it is $900 for non Canadian residents.[86] Other costs include transporting patients from rural and remote areas without the required equipment to larger centres with computed tomography. This can involve air or ground transportation, paramedics, and often a physician to accompany the patient in case they deteriorate on route. Other problems include the burden on emergency department flow and the resulting increased waiting times. Minor disadvantages for the patient include the amount of time it takes to wait for a scan, the radiation exposure and anxiety for patients with claustrophobia given the small space they are confined to for the test.

1.10 Use of Lumbar Puncture

1.10.1 Overview

Lumbar puncture is used to obtain cerebral spinal fluid. The fluid is collected and examined for the cell counts (number of red blood cells, white blood cells). Another tube is centrifuged to cause all of the cells to settle at the bottom. The fluid on top, the supernatant, is examined for the presence of xanthochromia (yellow pigmented formed by

the break down of red blood cells to oxyhaemoglobin, bilirubin and methaemoglobin within the cerebral spinal fluid).

1.10.2 Review of Relevant Literature

The optimal test for the cerebral spinal fluid is uncertain. Studies have argued to test the red blood cell count of the final tube of cerebral spinal fluid and others to check the supernatant for xanthochromia. A study by Macdonald in 1988 found that the red blood cell count was more sensitive than xanthochromia.[87] Vermeulen refuted this by finding that xanthochromia by spectrophotometry was 100% sensitive in a case review of 111 patients.[88] They argued that Macdonald's study had used visual inspection of the cerebral spinal fluid supernatant and that accounted for the lack of sensitivity of the xanthochromia test. However, both of these studies were retrospective case series.

In a prospective cohort study of emergency patients presenting with the worst headache of their lives, Morgenstern found that of the 107 patients, 18 had a subarachnoid haemorrhage. They found that two patients were missed by computed tomography and both were identified by high red blood cells in the cerebral spinal fluid. There were many false positive tests for xanthochromia using spectrophotometry.[37;37] However, neither of the two patients who were diagnosed with subarachnoid haemorrhage by lumbar puncture who had normal computed tomography scans were found to have aneurysms with repeated cerebral angiograms. Hence, it is unclear if these two cases were false positives and if the cerebral spinal fluid testing added to the diagnosis of subarachnoid haemorrhage in this study.

The combined use of computed tomography and lumbar puncture (checking for both cell counts and xanthochromia) is thought to yield the highest sensitivity.[2;89-91]

1.10.3 Alternative Approaches

Cerebral spinal fluid has also been studied for D-dimers, bilirubin and ferritin. With the exception of an unblinded study with a small sample size, which claimed 100% sensitivity and specificity, the studies looking into using D-dimers did not add any information above that of the red blood cell count and the presence of xanthochromia.[92] This was also true of the studies testing for bilirubin and ferritin.[93]

One study suggested that patients with a lone acute sudden headache and a normal examination should have a lumbar puncture as the first investigation, and computed tomography if this result was positive.[94] This study was based on a mathematical model and has not been prospectively validated. The safety of doing a lumbar puncture in patients with subarachnoid haemorrhage was questioned when seven out of 55 patients deteriorated after having a lumbar puncture while being investigated for possible subarachnoid haemorrhage in 1982.[95] These patients, however, all had focal deficits and/or neck stiffness. A subsequent study found that lumbar puncture was safe after 91 patients underwent the procedure without adverse events.[96] Therefore, it is likely that this is a safe, albeit unproven technique. However, it does not address the issue of which patients to test, the time delay with this test, or the morbidity involved with this procedure.

1.10.4 Cause of False Positive Results

The main cause of red blood cells being present in the cerebral spinal fluid is a traumatic tap. This is a term which represents the presence of blood due to the spinal

needle passing through a blood vessel prior to entering the subarachnoid space causing the collection of blood (alone or mixed with cerebral spinal fluid), instead of solely the cerebral spinal fluid. Up to 25% of lumbar puncture result in a traumatic tap. Since this is fresh blood, it has been suggested that this should be negative for xanthochromia, which takes several hours to form. Many studies have tried to resolve this issue, however, none have been adequately proven to be a gold standard.[97]

Causes of false positive xanthochromia are jaundice, high cerebral spinal fluid protein, dietary hypercarotenemia, malignant melanomatosis, and oral intake of rifampin.[83]

1.10.5 Cause of False Negative Results

False negatives for red blood cell counts are mainly due to laboratory error. False negative results for xanthochromia may be made in 30-50% of the time by using visual diagnosis without spectrophotometry.[88]

1.10.6 Disadvantages of Performing Lumbar Puncture

There are many disadvantages to performing a lumbar puncture. First, most patients are very fearful of the physician inserting a needle into their back. The procedure is painful, despite the use of local anaesthetic, and often takes several attempts, even in the most skilled physicians' hands. In addition, about 6-8% of patients will suffer a severe headache after the procedure lasting for several days and possibly requiring a subsequent procedure to alleviate the pain. There is also a very small risk of introducing a pathogen into the cerebral spinal fluid resulting in meningitis.[94]

1.11 Use of Angiography

This is the gold standard for locating a cerebral aneurysm. This procedure is invasive as it requires the passage of a catheter through a patient's artery in the leg up to the cerebral arteries and injecting contrast dye. The procedure is not without risk including: cerebral infarction, renal failure, infection and hematoma at the puncture site. The mortality of this procedure is less than 1 in 1000 and the rate of permanent neurological injury is about 5 in 1000.[98]

1.12 Use of Magnetic Resonance Imaging/Magnetic Resonance Angiography

Standard magnetic resonance imaging is not used routinely for the diagnosis of subarachnoid haemorrhage. This procedure involves using magnetic fields instead of x-rays to take successive cuts of the area investigated. It is associated with a high cost, almost twice that of computed tomography, and is not widely available. It has not been shown to be significantly superior to non-enhanced computed tomography in the first three days following a headache.[83]

Magnetic resonance imaging angiography is used for detecting aneurysms after the diagnosis of subarachnoid haemorrhage is made. This involves injecting the patient's vein with contrast and taking a picture with the magnetic resonance imager. It can locate aneurysms as small as two millimetres. It is almost a risk free procedure, however, it is not as useful for surgical planning as traditional angiography.[1;99]

1.13 Rationale for Study

Non-traumatic subarachnoid haemorrhage in the alert patient presenting with a headache and without any neurological findings is a difficult but critical diagnosis to

make. These early or small bleeds have a good prognosis if diagnosed correctly and treated quickly. Currently, there are no standard criteria to determine which patient requires investigation for this serious medical problem. Indiscriminate use of computed tomography is inefficient and lumbar punctures are time consuming, invasive procedures with significant morbidity associated with them.

Emergency physicians from across North America and Europe recognize the need for a clinical decision rule. Further, the information from our initial review of our local database of emergency department patients suggests that a clinical decision rule is required.

CHAPTER 2: GOALS AND OBJECTIVES

The overall goal was to determine the feasibility of conducting a study to develop a clinical decision rule for determining which alert patients with normal neurological examinations and a chief complaint of headache require investigations to rule out subarachnoid haemorrhage. This was accomplished by two studies within the thesis. The first study, phase 0, was a historical cohort study using a chart review methodology to determine current practice and the second, phase 1, was a prospective cohort study to explore possible clinical variables and determine the feasibility of generating a clinical decision rule.

2.1 Phase 0: Baseline Status

The goal of phase 0 was to determine current practice of management for patients presenting with an acute headache.

The specific objectives of phase 0 were:

1. To describe the demographic and clinical characteristics of the patients seen in this cohort.
2. To determine the proportion of patients with subarachnoid haemorrhage who had a previous emergency department visit within the previous six-months with a symptom compatible with a sentinel bleed.
3. To assess the univariate association of the variables collected with the outcome, subarachnoid haemorrhage.
4. To determine the mean length of stay in the emergency department according to the investigations performed.

5. To determine the proportion of eligible patients who underwent computed tomography and/or lumbar puncture.

6. To determine the yield of computed tomography and lumbar puncture, i.e. number, that were positive for subarachnoid haemorrhage.

7. To determine the incidence of subarachnoid haemorrhage in the study population to provide an estimate for future prospective studies.

2.2 Phase 1: Feasibility Study for the Derivation of a Preliminary Clinical Decision Rule

The goal of the phase 1 study was to prospectively collect data for a seven-month period to evaluate the feasibility of conducting a larger study. This rule will guide the use of lumbar puncture and computed tomography for the investigation of possible subarachnoid haemorrhage.

The specific objectives for phase 1 were:

1. To develop and pre-test standardized clinical assessments in alert patients with possible subarachnoid haemorrhage.

2. To apply these standardized clinical assessments to alert patients with possible subarachnoid haemorrhage.

3. To determine the inter-observer reliability of the clinical variables.

4. To determine the statistical association between the clinical findings and the diagnosis of subarachnoid haemorrhage.

5. To use multivariate analysis to determine which variables may be useful for further study to develop a highly sensitive clinical decision rule for alert patients with possible subarachnoid haemorrhage.

6. To assess the comfort of emergency physicians in not ordering head computed tomography or performing a lumbar puncture.

7. To determine emergency physicians' accuracy in predicting subarachnoid haemorrhage without a decision rule.

CHAPTER 3: METHODS – PHASE 0

3.1 Study Design

The study design used was an historical cohort study using emergency department health records.

3.2 Study Population

This review included all cases identified by a database search of patients presenting to the Ottawa Hospital Civic Campus emergency department in the first ten months of 2000 (January 1 to October 31).

3.2.1 Inclusion Criteria

All patients 15 years of age or greater with a headache, syncope or possible subarachnoid haemorrhage who were assessed by an emergency physician, and not seen directly by a speciality service were eligible for inclusion.

3.2.2 Exclusion Criteria

A patient was excluded if they fell into one of the following categories:

1. Patient was referred from another centre with a confirmed subarachnoid haemorrhage by either computed tomography or lumbar puncture.
2. Patient had three or more visits to the emergency department in the last year for headache.
3. Patient had a recorded history of direct trauma to the head in the seven days prior to presentation.
4. The patient's headache was recorded to reach maximal intensity in greater than one hour.

5. The patient's headache was recorded to have been present continuously for greater than 14 days.
6. Patient returned for a reassessment of the same headache and had been previously investigated with computed tomography and/or lumbar puncture at the Ottawa Hospital Civic Campus emergency department.
7. Patient was recorded to have focal neurological deficits or papilledema on physical examination.
8. Patient was recorded to have a Glasgow Coma Scale of less than 15 (or estimated to from available information in the chart).

3.3 Data Collection

Data was extracted from each record of treatment, which included physician, nursing, consultant, triage, ambulance, and radiology reports. Data were first recorded on a data collection form (Appendix 1) and then entered into a computerized database using Statistical Analysis System (SAS) software. The variables collected are listed in Table 3. All variables required a yes/no/not recorded, response by the chart reviewer, unless otherwise stated.

3.4 Data Analysis

The variables were evaluated by looking for outlying data points by examining frequency reports and graphing the variables using stem and leaf plots. Questionable values were verified with the original data. Descriptive statistics including means and medians for continuous variables and percentages for dichotomous variables were generated. Univariate analysis using Fisher's exact test was used for nominal variables

and the unpaired, two-tailed t-test for continuous variables using either a pooled or separate variance estimates as appropriate. The analysis was performed with SPSS version 10.0 software.

3.5 Ethical Concerns

The study protocol received approval by the institutional ethics review board of the Ottawa Hospital (Appendix 2) prior to data collection. There were no specific ethical concerns and informed consent was not required. All personal identifiers were kept strictly confidential and stored separately from the clinical information collected.

CHAPTER 4: METHODS – PHASE 1

4.1 Study Design

The design of the feasibility study was a prospective cohort study.

4.2 Study Period

This feasibility study collected data for a seven-month period. Both sites of the Ottawa Hospital (Civic and General) commenced and terminated concurrently.

4.3 Study Centres

The study centres included the two full service emergency departments of the Ottawa Hospital, a tertiary care institution with an annual census of approximately 109 000 emergency department visits. The data management and analysis was done at the University of Ottawa, Ottawa Health Research Institute, Clinical Epidemiology Unit, Ottawa Hospital Civic Campus.

4.4 Study Population

4.4.1 Inclusion Criteria

All alert patients 15 years of age or greater, presenting to one of the participating emergency departments with a chief complaint of a non-traumatic acute headache or syncope associated with a headache were considered for enrolment. Patients referred from other centres with suspected subarachnoid haemorrhage were eligible for inclusion.

1. **"Alert"** was defined as a Glasgow Coma Scale score of 15,
2. **"Non-traumatic"** was defined as no falls or direct trauma to the head in the previous seven days,

3. **"Acute"** referred to headache reaching maximal intensity in less than one hour and the patient presenting within 14 days of the headache's onset.

4.4.2 Exclusion Criteria

Patients were excluded if they fell into one of the following categories:

1. Patient with a history of three or more recurrent headaches of the same character as the presenting headache over a period of greater than six-months.
2. Patient referred from other centres with a confirmed subarachnoid haemorrhage by either computed tomography or lumbar puncture.
3. Patient who returned for reassessment of the same headache if already investigated with computed tomography and/or a lumbar puncture.
4. Patient with papilledema.
5. Patient with new focal neurological deficits on physical examination.
6. Patient with a previous diagnosis of subarachnoid haemorrhage.
7. Patient with a previous diagnosis of a brain neoplasm.

4.5 Patient Selection

Consecutive eligible patients with possible subarachnoid haemorrhage were entered into the study if they met the inclusion/exclusion criteria, and if a designated physician assessed the patient.

4.5.1 Study Flow

When potentially eligible patients presented to one of the two emergency departments of the Ottawa Hospital, a physician's data collection sheet (Appendix 3) was attached by the registration clerk, nurse or treating physician. The treating physician

determined eligibility, completed the data collection form and ordered appropriate investigations. At a later date, the study nurse collected these forms and attached a copy of the record of treatment, imaging reports, results of lumbar puncture and any neurosurgical reports. In addition, the study nurse reviewed the logs of all patient visits at both campuses to identify any missed patients. A missed patient form was completed for all potentially missed patients (Appendix 4). In addition, she extracted information for all eligible patients from their record of treatment, which was not required of the physician such as the gender and age of the patient (Appendix 5). Patients who did not undergo both computed tomography and a lumbar puncture with normal results, had a follow up phone call form completed in one-month time (Appendix 6). The data was then extracted from all eligible patients' data collection forms and inputted into a SAS database. This information was then reviewed and edited by the principal investigator prior to analysis.

4.6 Standardized Patient Assessment

4.6.1 Patient Assessment

All patient assessments were made by staff physicians who are certified in emergency medicine by the Royal College of Physicians and Surgeons of Canada and/or the College of Family Physicians of Canada or emergency medicine residents. Rotating housestaff were permitted to initially assess eligible patients but they were requested to have staff physicians make the study assessments. Physicians were oriented to the study and the standardized assessment by means of a formal presentation. All physicians recorded their findings on the data collection sheets attached to the patient's record of treatment and did so prior to obtaining the results of any investigations ordered.

4.6.2 Quality Assurance

There was ongoing evaluation of the completeness and compliance of the data collection forms and individual physicians' performance. Feedback was given to physicians regarding any problems with their data recording and the percentage of eligible patients enrolled. Feedback was not given regarding the accuracy or the reliability of the individual variables.

4.6.3 Selection of Variables

The selection of variables was based on a comprehensive review of the literature followed by a committee meeting involving five emergency physicians. Each variable was evaluated based on both the existing literature and clinical practice to determine its' usefulness and the feasibility of assessing the variable. It was realized that the inclusion of too many variables would hinder the compliance of the assessing physicians. This list was then discussed with Dr. Howard Lesiuk, a neurosurgeon at the Ottawa Hospital, to ensure that each variable was appropriate.

4.6.4 Variables Collected

The variables collected are listed in Tables 4 and 5. Each required a yes/no response unless otherwise stated.

4.6.5 Pilot Study

The data collection sheets and patient assessment techniques were evaluated and revised after a two-week pilot period. This provided additional time for training physician assessors. Only minor modifications were required, hence all information from the initial two-week run-in was used for the subsequent analysis.

4.6.6 Interobserver Reliability

A subset of patients was assessed for the clinical variables by a second emergency physician who was blinded to the findings of the first assessor. These assessments were done on a convenience basis, i.e. when possible.

4.7 Outcome Measures

4.7.1 Primary Outcome

The primary outcome, subarachnoid haemorrhage, was defined by the presence of subarachnoid blood on computed tomography, the presence of xanthochromia in the cerebral spinal fluid either by visual inspection or spectrophotometry, or the presence of red blood cells in the third or fourth tube of cerebral spinal fluid (this third method of diagnosis must have been confirmed with cerebral angiography or magnetic resonance imaging angiography).[89]

All computed tomography results were verified by a radiologist either the same or the following day. The radiologists were blinded to the contents of the data collection forms when interpreting the films but had the normal clinical information currently provided. All computed tomography scanners used were third generation or better. Lumbar puncture were done as per current practice, with the results assessing the presence of red blood cells or xanthochromia as determined by visual comparison on white paper.[77;79]

4.7.2 Proxy Primary Outcome

With current practice, many patients with an acute headache are not investigated for subarachnoid haemorrhage or only undergo either computed tomography or lumbar

puncture. The study protocol did not alter current practice. Therefore, eligible patients who did not undergo computed tomography and/or lumbar puncture had their chart reviewed to ensure that they did not have any further visits. They were also contacted in one-month to verify that they had not suffered any subsequent adverse events. The following questions were asked with yes or no answers unless otherwise stated. If the patients had difficulty comprehending the questions, the research nurse assisted the patient to understand the meaning of the questions.

1. Do they still have a headache? If yes, they were asked to rate their headache (mild, moderate, severe);
2. Have they returned to see a physician since their initial emergency visit? If yes, they are asked to explain the nature of their repeat visit;
3. Has their headache been diagnosed differently since their initial emergency visit? If yes, they are asked to state the diagnosis;
4. Have they suffered any ill effects from their headache? If yes, they are asked to explain;
5. Have they had computed tomography of their head since they were discharged from the emergency department? If yes, they are asked where they had the computed tomography done and what was the result;
6. Have they had a lumbar puncture since they were discharged from the emergency department? If yes, they are asked where they had the lumbar puncture done and what was the result;

7. Did they require any surgical intervention (e.g. craniotomy)? If yes, they are asked to state the intervention.

4.8 Data Analysis

The variables were evaluated by looking for outlying data points by examining frequency reports and graphing the variables using stem and leaf plots. Questionable values were verified with the original data.

4.8.1 Interobserver Agreement

The interobserver agreement for each variable was measured using the kappa coefficient, which measures the proportion of potential agreement beyond chance. The 95% confidence intervals were calculated around this value.[100]

4.8.2 Univariate Analysis

Univariate analyses determined the strength of the association between each variable and the outcome variable. Those variables making clinical sense and having a p-value of less than 0.50 were used in the subsequent multivariate analysis. This p-value was used to ensure that useful variables would not be excluded simply because of the small sample size of the feasibility study. Fisher's exact test was used for nominal variables and the unpaired, two-tailed t-test for continuous variables using either a pooled or separate variance estimates as appropriate.

4.8.3 Multivariate Analysis

Models to predict which patients require testing to diagnose subarachnoid haemorrhage required multivariate analysis. Variables found to have a p-value of < 0.50 were simultaneously evaluated using two different multivariate techniques, recursive

partitioning and logistic regression. Given that this was a feasibility study we used less stringent criteria than normal (i.e. a p-value of less than 0.20). Interaction among variables was assessed and considered for incorporation into the multivariate analysis by means looking for any variables that are clinically known to interact with each other.

This analysis was performed to prepare for a subsequent derivation study, as the sample size in this feasibility study was too small to develop a stable model. Often a sample size of 10 per variable is desired in a regression analysis and this small sample size will likely create an unstable model with large standard errors.[101]

The model created, used the best combination of predictor variables for detecting the outcome measure of subarachnoid haemorrhage. The final model must be nearly 100% sensitive to be clinically acceptable. In addition, the model must make clinical sense and be easily incorporated into clinical practice.

Recursive partitioning was performed using Knowledge seeker software to determine the most significant variables for the primary outcome.[102] This procedure progressively divided the subjects using successive Chi-squared analysis for the variables collected for the outcome of subarachnoid haemorrhage until a sub-population without any cases of subarachnoid haemorrhage was found. Although a logistic regression analysis was also performed, the experience of others developing decision rules in the past has been that recursive partitioning is more suitable when the objective is to correctly classify one outcome group at the expense of the other (i.e. high sensitivity is more important than overall accuracy).[103]

4.8.4 Physicians' Judgement

Data from the questions pertaining to physicians' comfort and predictions were tabulated and presented in a descriptive format. The predicted probability was used to calculate a receiver operating characteristic (ROC) curve for determining subarachnoid haemorrhage.[104]

4.8.5 Sample Size for Feasibility Study

The feasibility study collected data for a seven-month period. No formal sample size calculation was made. We took all eligible patients at the two sites of the Ottawa Hospital who presented during the study period.

4.9 Patient Recruitment

Patient recruitment was expected to be similar to other studies with about 80% compliance. As this is a feasibility study, recruitment was terminated after the seven-month period.

4.10 Ethical Concerns

The study protocol had been reviewed and accepted by the institutional ethics review board of the Ottawa Hospital prior to commencing data collection (Appendix 7). There were no specific ethical concerns, as patients continued to be investigated as per current practice. Participants were informed that they could be contacted in one-month for an update on their status. Verbal informed consent was sought at the time of the telephone call. All personal identifiers were kept strictly confidential and stored separately from the clinical information collected.

CHAPTER 5: RESULTS- PHASE 0

5.1 Study Flow

The electronic database identified a total of 1957 patients who had presented during the study period with a complaint of headache, syncope or rule out subarachnoid haemorrhage. There were a total of 891 eligible patients entered into the study, of which, ten were positive cases of subarachnoid haemorrhage (Figure 2).

5.2 Descriptive Statistics

The 891 eligible patients were first evaluated with descriptive statistics for demographic and clinical features (Table 6). The mean age of the cohort was 41.9 years and was comprised of 66.4% females.

This cohort was studied to determine the diagnostic procedures completed, the overall disposition, and the final diagnosis made in the emergency department (Table 7). We found that 35.1% of the patients had a computed tomography scan of their head, while 9.5% underwent a lumbar puncture. The final diagnosis in the emergency department included 43.5% migraine and 33.0% other benign headaches, giving a total of 76.5% with a benign headache. Few patients had serious diagnoses: 1.1% subarachnoid haemorrhage, 1.0% an ischemic event, 0.7% a brain tumour, 0.4% bacterial meningitis and 0.3% temporal arteritis. There were no patients identified who had been seen in the previous six months who had been diagnosed with a headache or syncope who subsequently were diagnosed with subarachnoid haemorrhage.

5.3 Univariate Analysis

This cohort was divided into positive and negative cases for subarachnoid haemorrhage. The univariate results are shown in Table 8. The mean time from onset to peak was significantly less in the patients with subarachnoid haemorrhage with $p<0.01$. There was also a significant increase in the time spent in the emergency department for patients with a subarachnoid haemorrhage. The presence of neck stiffness was recorded more frequently for patients with subarachnoid haemorrhage than those in this cohort with other diagnoses.

5.4 Prevalence of Disease and Test Yields

The prevalence of subarachnoid haemorrhage in this study population was 1.1%. The percentage of patients referred to the neurosurgical service for the whole group was 2.9%. The yield of computed tomography and lumbar punctures for the diagnosis of subarachnoid haemorrhage is provided in Table 9. Only 8 out of 312 (2.6%) computed tomography scans were positive and 2 out of 85 (2.4%) lumbar punctures were positive for subarachnoid haemorrhage.

The duration of time spent by the patients in the department with and without investigations is shown in Table 10. This demonstrated that patients not undergoing testing stayed in the emergency department without referral or discharge for 3 hours 57 minutes. Patients with only computed tomography without a lumbar puncture stayed a mean of 5 hours 2 minutes. If patients had a lumbar puncture only, they stayed for an average 7 hours 6 minutes prior to referral or discharge.

CHAPTER 6: RESULTS – PHASE 1

6.1 Study Flow

A total of 1652 potentially eligible patients were identified as having either a headache or syncope as a presenting complaint. The study flow is illustrated in Figure 3. There were 225 eligible patients and data collection forms were completed for 134 patients. From the enrolled patients, there were 14 positive cases. Of the 91 eligible patients not enrolled, there were two positive cases.

6.2 Descriptive Statistics

Once the data set was verified for accuracy and completeness, all of the variables were examined by generating descriptive statistics of patient characteristics as shown in Table 11. For eligible and enrolled patients, the mean age of the entire cohort was 42.8 years with a range from 16 to 80 years. Females accounted for 61.9% of the patients enrolled. The mean time from onset to peak was 13.2 minutes and the mean severity was 8.75 on a scale from 0 to 10. This headache was reported to be the worst headache of the patient's lives in 76.9% of subjects.

The management and outcomes of the enrolled cohort are shown in Table 12. There were investigations ordered for 88.8% of the patients (computed tomography, lumbar puncture or both). Only 3.7% had a lumbar puncture without first having a computed tomography. A cerebral angiogram was performed in 12.7% of the patients. There were 13.4% of the patients admitted to hospital and 14.2% had a neurosurgical consultation. The most frequent emergency department diagnosis was migraine,

accounting for 38.1% of the cases. The total percentage of benign headaches was 73.9%. Of all enrolled patients, 10.4% were found to have suffered a subarachnoid haemorrhage.

6.3 Univariate Analysis

The univariate association of historical features with subarachnoid haemorrhage is shown in Table 13. Patients having a subarachnoid haemorrhage were significantly older than those without (56.9 versus 41.2 years; $p<0.01$). The mean duration of the headache was longer in the subarachnoid haemorrhage group (1012 minutes versus 693 minutes; $p=0.03$). Other statistically significant findings, for a p-value of 0.05, in the subarachnoid haemorrhage group were: onset during exertion, presence of the worst headache of the patient's life, transient loss of consciousness, obligated to rest with onset of pain and complaint of neck pain. For the variable "connective tissue disorder" a Fisher's exact test was not calculated as there were not any positive cases in either the with or the without subarachnoid haemorrhage groups.

Table 14 demonstrates the results of the univariate analysis for the physical examination findings. The variables found to be statistically significant for a p-value of 0.05 were: neck stiffness with lateral rotation 35.7% versus 8.6%, neck stiffness for flexion or extension 50% versus 11% and the physician's rating of patient distress (6.3 versus 2.9; $p<0.01$).

6.4 Interobserver Agreement

The kappa statistic for interobserver agreement was calculated for the three cases where interobserver information was available. We found that the kappa value was 1.0 (for the following variables: "worst headache of life", "relieved with anti-migraine

treatment", "patient complaint of neck pain" and " neck stiffness (flexion/extension)". Unfortunately, due to the low number of interobserver forms completed, it was not possible to calculate the kappa statistic for many of the variables.

6.5 Missed Eligible Patients

There were 91patients who were eligible but for whom data forms were not completed (Table 15). These patients had a mean age of 45 years and were 60.7% female. This group had computed tomography ordered in 79.8% of the patients and lumbar puncture in 40.4% of the patients. There were two positive cases of subarachnoid haemorrhage. At the time of the one-month follow-up of the missed eligible patients, no additional patients had suffered a subarachnoid haemorrhage, but one patient had died due to metastatic carcinoma of the pancreas. Two patients were lost to follow up. Patients who could not be clearly excluded by the eligibility criteria based on the notes in the patient chart were classified as being missed.

6.6 Multivariate Analysis

6.6.1 Initial Logistic Regression Model

Initially, all of the possible predictor variables were analyzed with logistic regression individually with the outcome variable, diagnosis of subarachnoid haemorrhage (Appendix 8). This standard errors were very high for the variables: "did headache awake patient from sleep", "was this the worst headache", "family history of subarachnoid haemorrhage" and "was the onset of the headache during a cough". This was due to the presence of cells with no cases for the variables. There were no cases of subarachnoid haemorrhage for the variables: "did headache awake patient from sleep", "family history

of subarachnoid haemorrhage" and the "was the onset of the headache during a cough". All of the positive cases of subarachnoid haemorrhage answered "yes" for the variable "was this the worst headache". These variables are likely important, and thus will be kept for the subsequent derivation study. However they were not used in further regression analysis due to their effect on the stability of the model based on the standard errors of the predictor variables. The standard errors were also high in the variables "sympathomimetic use" and "adult onset polycystic kidney disease". Hence, these variables were not used in the subsequent analysis and due to their low prevalence in both groups.

6.6.2 Refined Logistic Regression Models

All of the remaining variables with a p-value of less than 0.50 were offered to a model. This analysis included 17 variables plus 4 dummy variables for the ordinal variable of "position of patient in room" for a total of 20 degrees of freedom. This logistic regression analysis was conducted using a forward likelihood ratio model with a p-to enter of 0.50 and a p-to remove of 0.25 and became unstable after step 5 as demonstrated by the exceedingly high standard errors. The term "position of patient in room" was collapsed into a dichotomous variable but it was not significant and the variable was dropped from the subsequent analysis.

In an effort to decrease the degrees of freedom and improve the stability of the model, the subsequent analysis was offered combination variables for "onset with exertional activity" with "onset with sexual activity" and "transient loss of consciousness" with "obligated to rest or buckling of legs". These combinations were chosen because they are clinically similar. This analysis contained 14 variables with 13 degrees of

freedom and became unstable after the 5th step with very high standard errors. In an effort to further decrease the degrees of freedom, the two neck stiffness variables were combined and the terms for the symptoms of neck pain and occipital head pain were combined. In addition the variable photophobia was removed because it was the variable with the least significance.

In addition, the continuous variables were explored for clinically important cut points. The variables systolic blood pressure and temperature were not found to have clinically meaningful cut points and were dropped from the subsequent models. A cut point of greater than 110 mm of Hg for diastolic blood pressure was found and used. The forward regression model included the terms: patient distress, age 40, the combination term for transient loss of consciousness or buckling of legs, occipital pain, and the combination variable for onset during exertion or sexual activity (Appendix 9).

The variable "patient distress" was dropped because it is not useful in a clinical decision model given its lack of generalizability. Therefore, the model was developed again finding that the same variables remained except the terms vomiting, diastolic blood pressure of greater than 110 mm of Hg, and combination variable of stiffness of the neck with lateral rotation or stiffness of the neck with flexion/extension were added to the model.

6.6.3 Goodness-of-fit Test for Logistic Regression Models

The Hosmer and Lemeshow test for goodness-of-fit was performed. Removing the variable with the least significance (occipital pain) further refined the model. The R square value was virtually unchanged decreasing from 0.547 to 0.537. The variable for

exertional or sexual activity was the next least significant and was therefore removed. Table 16 demonstrates the Hosmer and Lemeshow test for goodness-of-fit for the models.

6.6.4 Final Logistic Regression Model

This final model included the terms: age 40, transient loss of consciousness or obligated to rest/buckling of legs, neck stiffness with lateral or flexion/extension and diastolic blood pressure of greater than 110 mm of Hg. The corresponding odds ratios with their respective 95% confidence intervals are found in Table 17. This model was chosen based on modelling and by ensuring that all clinically important variables were included and that the final model made clinical sense.

6.6.5 Interaction Terms for the Logistic Regression Model

Interaction terms were not added given the small sample size and that there were no combinations known to interact with each other based on the literature review.

6.6.6 Sensitivity and Specificity of the Logistic Regression Model

The sensitivity/specificity of the regression model was determined using probability classification cut points from 0.01 to 0.95. Table 18 lists the sensitivities and specificities for this range of cut points. Figure 4 displays the receiver operator characteristic curve (ROC) for the final logistic regression model.[104] The area under the curve was 0.90 (95%CI: 0.82, 0.98) with a standard error of 0.04.

6.7 Recursive Partitioning

Table 19 includes the possible models including their respective sensitivity and specificity. The classification and flow of patients in the recursive partitioning model are shown in Figure 5 (the remaining models are demonstrated in Appendices 10-14). Figure 6 includes the proposed final model from the feasibility study data. The model with the variables of age over 45 years and neck stiffness with lateral rotation was found to have 100% sensitivity and 57% specificity. This model was chosen both for the statistical features but also for the clinical ease of using these variables. Figure 7 shows the classification performance, the sensitivity, the specificity and the proportion of patients in this cohort that would theoretically require testing based on this rule.

6.8 Physicians' Comfort in Testing

Physicians reported being "uncomfortable" in performing a lumbar puncture without first ordering a computed tomography scan of the patient's head in 52.2% of the cases. They were only "very comfortable" in performing a lumbar puncture without computed tomography in 5.3% of the cases (Table 20). Physicians similarly reported that they were "uncomfortable" not ordering any tests in 80.2% of the cases while they were "very comfortable" not ordering tests in only 8.3% of the cases (Table 21).

6.9 Physicians' Accuracy in Predicting Subarachnoid Haemorrhage

The results of the question asking physicians to predict the likelihood that their patient has a subarachnoid haemorrhage prior to testing are shown in Table 22. This is graphically represented with a receiver operator characteristic curve (ROC) in Figure 8. The area under the curve was found to be 0.90 (95%CI, 0.80-1.0). There was one patient

who had a subarachnoid haemorrhage with a physician pre-test probability of 2% and three patients with subarachnoid haemorrhage with a physician pre-test probability of 10%. The remainder of the patients enrolled had a physician pre-test probability of 20% or greater.

CHAPTER 7: DISCUSSION

7.1 Phase 0: 10-Month Chart Review

7.1.1 Enrolment

There was approximately one positive case per month during the duration of this study at the Ottawa Hospital Civic Campus. The Civic Campus and General Campus emergency departments have an annual census of 57,000 and 52,000 patient visits respectively. As both centres are full service tertiary care emergency departments within the core of the city of Ottawa, we can probably assume that the General site would have proportionally the same incidence of subarachnoid haemorrhage as the Civic Site. As such, from this phase 0 study, we expect approximately 23 cases per year to be seen at the Ottawa Hospital's two emergency departments.

The study period was revised from the original protocol from a one-year period to 10 months. This was done because the last four months of 1999 were not entered into the electronic database from which we retrieved the list of patients to review. We also wanted the most current information without overlapping the two phases of the thesis.

Data collection was achieved for all charts except 76, which, despite repeated attempts, were not located. This is not likely to alter the results of the study as we do not believe that there is a systematic reason for these particular charts to be missing. Unfortunately it is a common occurrence for charts to be unavailable. This happens for many reasons including requests for information from the patient, clinic appointments, other research and incorrect filing.

7.1.2 Yield of Computed Tomography and Lumbar Puncture

Despite the large number of computed tomography scans ordered there was a very low yield for the diagnosis of subarachnoid haemorrhage. This clearly indicates that many computed tomography scans are ordered unnecessarily in alert patients with a normal neurological examination who present to the emergency department with a headache.

Further, it is obvious that physicians were reluctant to perform a lumbar puncture. Only a quarter of the patients underwent a lumbar puncture after normal computed tomography. This is surprising given that computed tomography is only sensitive enough to diagnose 90% of positive cases. Nevertheless, even at this reduced rate of lumbar puncture, the yield was still very small. Thus, there was inefficiency in ordering lumbar punctures for alert patients with an acute headache with a normal neurological examination beyond that found for computed tomography. This highlights the need for a clinical decision rule to help guide physicians as to which patients require investigation to rule out a subarachnoid haemorrhage.

7.1.3 Time Spent in the Emergency Department With and Without Investigation

Emergency departments across the country have often been identified as being overcrowded with long waiting times. This situation is not helped by inefficient use of time and resources for a given clinical problem. This study demonstrated that for patients without the diagnosis of subarachnoid haemorrhage, who were not investigated spent much less time in the department than those who underwent investigation. This was especially true for patients that underwent a lumbar puncture either alone or in combination with computed tomography. They spent over three hours more than patients

who did not require investigation in the department prior to discharge or referral. The patients with a diagnosis of subarachnoid haemorrhage were not included in these length of time in emergency calculations to avoid the bias associated with sicker patients getting computed tomography and/or lumbar puncture. Thus, if the efficiency of test ordering were improved, this would help free up important emergency department resources and improve patient flow. This is another reason to develop a clinical decision rule for the problem of acute headache.

7.1.4 Potentially Important Clinical Variables

The univariate analysis from this part of the study is statistically weak, as expected. This is in part due to the large amount of missing data in the patients' records of treatment for the variables collected and also because the record of treatment is often not completed until after the diagnosis of subarachnoid haemorrhage is confirmed. This introduces recall bias making the clinical features listed in textbooks appear to have a stronger association that may be true.

Nevertheless, several variables in the univariate analysis appear to be important for a future clinical decision rule to predicting subarachnoid haemorrhage. These variables include the "time from onset of the headache to the peak", the "complaint of neck pain", the "absence of a history of a similar headache in the past", the "presence of neck stiffness" and "elevated blood pressure" (both systolic and diastolic). These variables require subsequent prospective evaluation due to the potential bias of this type of study. The variables, "mean time in the department" and the number of patients undergoing "lumbar puncture" or "computed tomography", were also associated with the outcome.

However, they are not useful as predictor variables given the dependence of the outcome on these variables as determined by the definition of the outcome given in section 4.7.1.

7.1.5 Final Diagnoses

The vast majority of alert patients with normal neurological examinations had benign headaches. Migraines and other benign headaches (cluster headaches, tension, or diagnosis of headache) were by far the most frequently seen diagnoses. The number of serious headaches (tumour, bacterial meningitis, temporal arteritis and subarachnoid haemorrhage) was quite small. Thus, most patients required analgesia and not extensive investigation.

7.1.6 Comparison of Results to Previous Studies

The results of this study are consistent with other chart reviews. The retrospective chart review by Dhopesh in 1979 and Leicht in 1980 studied patients with a chief complaint of headache presenting to the emergency department.[10;105;105] They had similar baseline characteristics except Dhopesh included pediatric patients.[105] This probably accounts for the lower number of serious intracranial problems than our study. Our study found 3.6% of cases had a serious intracranial problem versus their 1.5%.[105] We limited our study to patients over the age of 15 because subarachnoid haemorrhage is very rare in children and the Ottawa Hospital sees very few patients younger than 15 years of age. The study by Leicht found that 5% of their study had serious problems.[10] They did not include pediatric patients in their study either, hence looking at the results of the two studies, the rate of serious problems has not changed appreciatively since the late 1970s when these two studies were performed.[105 10]

7.1.7 Strengths of the Study

This was a large consecutive patient cohort study of alert emergency patients with a complaint of headache associated with a normal neurological examination. We had a structured data collection form and had relatively few missing cases. We focussed on the yield of testing in this cohort and the amount of time spent in the emergency department, which has not been the focus of previous studies.

7.1.8 Limitations of the Study

The main limitation of this study was its' retrospective nature and that many of the clinical predictor variables were not recorded in the patient's record of treatment. In addition, charts were identified from an electronic database, which may have miscoded some of the headaches leading to their absence from the list. Finally, patients with less severe headaches were likely included due to missing information in the record of treatment, as we only excluded patients if their was an exclusion criteria written in the chart.

7.1.9 Conclusions Phase 0 Study

This 10-month study of alert patients with a headache and a normal neurological examination who presented to the Ottawa Hospital Civic Campus emergency department found we could expect 23 positive subarachnoid haemorrhage cases in a one-year period from the two campuses of the Ottawa Hospital. This corresponds to an annual incidence of 0.2 per 1000 patient visits. None of the positive cases had been seen in the emergency department with a complaint compatible with a sentinel bleed, hence we believe that there were not any missed cases among this cohort. Although we would not have a record if

patients presented to a different hospital, were seen here while visiting from out of town or if they had sudden death prior to arrival at the hospital.

This study found the current use of computed tomography and lumbar puncture is very inefficient with a very low yield. This resulted in large time delays in the emergency department, a place that is already chronically overcrowded.

The variables found to be potentially important predictors were, "time from onset of the headache to the peak", the "complaint of neck pain", the "absence of a history of a similar headache in the past", the "presence of neck stiffness" and "elevated blood pressure" (both systolic and diastolic).

7.2 Phase 1: Prospective 7-Month Feasibility Study

7.2.1 Enrolment

The enrolment of the study was sub-optimal because emergency departments are busy environments. It is very difficult to add to an already heavy workload in such a place. Despite this, the compliance of completed forms for eligible patients was 60%. With incentives for unit clerk/nurses/physicians to attach and complete data collection forms and more research nursing time, compliance is usually about 80%. The demographic statistics of the patients found that there were fewer cases of subarachnoid haemorrhage in the missed patient population. This was likely because if we could not clearly determine that patients did not satisfy the eligibility criteria from the information recorded on the patient's chart, then we classified them as missed. Many physicians did not record the length of time from onset to peak, or used vague terms such as "gradual" to

describe this time period. Thus by including such patients, we would have included patients who were not at risk of subarachnoid haemorrhage.

7.2.2 Potentially Important Variables Determined by Univariate Analysis

The univariate analysis demonstrated several statistically significant differences in the variables between the positive subarachnoid haemorrhage and negative groups. The variables found to be statistically significant, using a p-value of less than 0.05 were, "age", "onset during exertional activity", "duration of the headache", "worst headache in their life", "transient loss of consciousness", "buckling of legs/obligated to rest", "complaint of neck pain", "elevated blood pressure" and "neck stiffness on physical examination". These variables are frequently referred to in the literature and in emergency medicine textbooks as related to the outcome of subarachnoid haemorrhage. They are potentially important for a clinical decision rule as they are related to the outcome. Clinicians are more likely to trust them as they already associate them with the outcome of subarachnoid haemorrhage (face validity).

This large number of statistically significant variables makes it likely that the derivation of a clinical decision rule will be plausible. In addition to statistical significance each variable was assessed for clinical significance to ensure that the difference found was clinically important. Each of these variables was considered for the multivariate analysis.

The variables for "severity" and the "time from onset to peak" were not statistically significant. This is likely because the inclusion criteria only allowed patients who might have had a subarachnoid haemorrhage and excluded other less severe, slower onset headaches that peak after one hour from the onset. This differed from the previous phase

0 study, which often could not determine how long it took for the headache to reach maximal intensity from the documentation in the patient's record of treatment.

7.2.3 Logistic Regression Models

The logistic regression analysis was found to be less useful than the recursive partitioning method. Previous investigators have noted this.[39] The final logistic regression model does not have 100% sensitivity for diagnosing subarachnoid haemorrhage unless extremely small probability cut points are used, necessitating that the patient be investigated for subarachnoid haemorrhage if any of the variables is present. Clinicians are not likely to use a rule for such a serious condition if it is not nearly 100% sensitive. The logistic regression model has a much lower sensitivity than the recursive partitioning model. In addition, the model using logistic regression is not easy to use without the use of an aid to determine the specific probability for each patient.

7.2.4 Recursive Partitioning Models

The recursive partitioning analysis was found to be the superior method of generating a clinical decision rule. Several possible models were created that would identify all of the positive cases of subarachnoid haemorrhage. However, none of the final models are robust enough to form a clinical decision rule at present due to very large confidence intervals around the sensitivities and specificities. It is very encouraging, however, to find so many possible combinations to include all of the cases of subarachnoid haemorrhage. It is very likely that a highly sensitive rule can be derived given the results of this study.

In addition to being statistically significant, all of the variables included in these recursive partitioning models are clinically important. External validity will be helped by the fact that all of the proposed variables are easily defined.

7.2.5 Lateral Neck Stiffness

Neck stiffness with lateral rotation has not been previously related to the outcome of subarachnoid haemorrhage. This variable however, was significantly associated with the outcome in this study. This is important given the ease of defining lateral neck stiffness as not being able to rotate the patient's head 45 degrees in both direction. If this variable is chosen as a final predictor variable it will help with the rule's correct use as compared to the flexion and extension of the neck to determine neck stiffness which is more difficult to define. The definition used for normal flexion and extension for this study was the ability to lift their head 8 cm off the bed when supine and ability to touch their chin to their chest. There is no standard definition for either examination, but in a clinical setting, it is easier to measure 45 degrees of lateral rotation than to measure the patient lifting their head off of the bed.

7.2.6 Other Variables Considered for Further Analysis

The other physical examination variable that correlates well with the finding of subarachnoid haemorrhage is the "physician rating of patient distress" (both as a continuous variable and when dichotomised). This variable is interesting in that physicians are able to a large extent determine which patients are sicker. Although this is very interesting, this variable is not easily quantifiable and exportable to other settings or

even between physicians in the study centres. Hence it may not be of benefit for generating a clinical decision rule.

It was also interesting that there is a trend that headaches that awaken patients from sleep were not subarachnoid haemorrhages, although this difference did not reach statistical significance. This has not been previously sited as a protective factor in the literature.

7.2.7 Comparison of Results to Previous Studies

The prospective studies by Morganstern in 1998 and Linn in 1998, had similar baseline characteristics as our study.[37;106] Both of these studies looked at a similar patient populations with criteria that patients must have had an acute severe headache for enrolment.[37;106] The study by Morganstern allowed patients with focal neurological signs, whereas, the study by Linn and our own did not.[37;106] All patients enrolled in the study by Linn were referred to the emergency department after first seeing their family physician.[106] This may explain why 65 out of the 102 patients had a diagnosis of subarachnoid haemorrhage, i.e. there was referral bias present.[106] The study by Morganstern found that 20 patients out of 107 had a diagnosis of subarachnoid haemorrhage.[37] This compares with our result of 14 positive cases out of 134 enrolled patients.

7.2.8 Variables for Future Study

The variables not found to be prevalent or statistically significant will be removed from subsequent data collection for the derivation phase of this study. These variables included: "connective tissue disorders", "adult onset polycystic kidney disease", "sympathomimetic abuse", "photophobia", "family history of subarachnoid haemorrhage".

The rare conditions of "connective tissue disorders", "adult onset polycystic kidney disease" and "family history of subarachnoid haemorrhage" may be important individually but are not common enough to be useful in the derivation of a clinical decision rule. Incorporating such variables would lead to a cumbersome rule with too many variables to be clinically useful. By eliminating these variables, the data collection forms will be shorter and this will likely improve the compliance of the emergency physicians.

7.2.9 Interobserver Agreement

The interobserver agreement statistics were not of much value due to the very low number of interobserver forms completed. These statistics were calculated solely for the purpose of determining how to calculate them for future study. Although results were calculated when possible for a minority of the variables, they are unreliable due to the small numbers and the correspondingly large confidence intervals. The number of interobserver forms was low due to the difficulty of obtaining a second emergency physician assessment in a busy emergency department. In addition, for about 33% of the day there is not a second physician on duty who can complete an interobserver form.

7.2.10 Physicians' Comfort in Ordering Tests

We found that physicians were generally uncomfortable in performing a lumbar puncture without first obtaining computed tomography. Only in very few cases was the physician very comfortable with this option. This demonstrates a problem with the mathematical model of Schull in 1999, which proposed performing a lumbar puncture directly for patients with a normal neurological examination.[94] Even if this would be a

safe and effective method, it appears that clinicians at the test centres would not accept this option. Our study, however, was done at tertiary care centre with computed tomography scanners readily available 24 hours a day. In rural and remote areas there could be a greater acceptance of such care due to the lack of scanners.

In addition to the invasiveness of a lumbar puncture, patients are required to stay in the emergency department for an average of three hours longer if they underwent this test. Thus patients undergoing lumbar puncture use more emergency department time and resources. Therefore, lumbar puncture is not likely to be the preferred route of diagnosing patients if computed tomography is available. This negates the necessity of performing the lumbar puncture if the computed tomography is positive.

Physicians were also generally uncomfortable with the idea of managing this cohort of patients without any investigations and relying only on their clinical judgement. In less than 10% of cases would they be very comfortable not ordering any investigations. Given the small number of positive subarachnoid haemorrhage found in our study, it is likely that the amount of testing can be safely reduced. We believe that the level of comfort in not ordering tests would greatly increase if there were a sensitive clinical decision rule, which safely ruled out subarachnoid haemorrhage in alert patients with a headache and a normal neurological examination.

7.2.11 Strengths of the Study

This study collected data prospectively providing us with a very complete and blinded assessment prior to obtaining each patient's final diagnosis. This allowed us to eliminate recall bias and reduced the interviewer bias.

We attempted to enrol all alert patients presenting to the Ottawa Hospital with an acute headache and who were neurologically intact. We put much effort into tracking missed patients to ensure the validity of our results. We found that the patients who were eligible but not enrolled had similar demographics and outcomes as our study population thereby demonstrating that the study was reasonably free from selection bias.

We conformed to the current standards for generating clinical decision rules. We identified a clinically important outcome, which we clearly defined as the presence of subarachnoid blood on computed tomography, the presence of xanthochromia in the cerebral spinal fluid either by visual inspection or spectrophotometry, or the presence of red blood cells in the third or fourth tube of cerebral spinal fluid (this third method of diagnosis must have been confirmed with cerebral angiography or magnetic resonance imaging angiography).[89] We developed standardized clinical assessments which were completed blindly prior to investigating patients. We encouraged interobserver data collection to determine the interobserver reliability of the variables. We used an unbiased patient population by accepting all patients who presented to one of the Ottawa Hospital emergency sites during the study period who met the eligibility criteria. We also kept the variables simple and ensured that the variables made clinical sense to facilitate external validity and implementation.

7.2.12 Limitations of the Study

The main limitation of this study is that the small sample size results in confidence intervals around the sensitivity, which are too wide to conclude that the proposed model is

stable. However, given that this was designed as a feasibility study, it does appear that the generation of a clinical decision rule is feasible with continued study.

Another limitation included the low number of interobserver forms completed. The results generated by only three cases are not reliable. This needs to be greatly improved in the subsequent study. This will be achieved through information sessions for the physicians, incentives and frequent reminding from the research team. The final clinical decision rule, derived from subsequent study, must be able to demonstrate good interobserver correlation to ensure that the results are reproducible and valid.

7.2.13 Future Research

For the definitive decision rule study, the sample size will be based on the estimation of the precision of the sensitivity of the derived decision rule as well as the precision of the interobserver variability and logistic regression coefficients. The sample size has to account for the low incidence of subarachnoid haemorrhage and that many patients with headaches will be excluded by exclusion criteria

Based on the results of the phase 1 study, 120 patients with subarachnoid haemorrhage will be required to produce a decision rule with nearly 100% sensitivity (95% Confidence Interval, 97%-100%), which will be required given the high morbidity and mortality of a missed diagnosis. Without this high sensitivity physicians are unlikely to use this decision rule for fear of missing a positive case.

The derivation study will require 1150 patients to be enrolled. This number was derived from the results of phase 1. This number assumes 10.4% of patients will be positive cases and that the sensitivity and specificity will be unchanged in future patients.

With additional study sites, the study could be completed in a reasonable period of time, i.e. two years.

This study will collect fewer variables, with the omission of the variables that were not useful in the phase 1 study. We will place clear definitions of each variable on the data collection forms to help ensure reproducibility. We will expand to other sites to enable us to have faster recruitment and also assist us to achieve better external validity. A focus on obtaining more interobserver forms will be a priority for subsequent study.

In addition, a longer follow up period will be used for the derivation study. In addition to one-month follow-up, we will contact patients at 6 months for additional follow-up. This additional follow-up will be done to reflect two papers which used this time period for follow-up, although it is very rare to have an event after one month.[7;12]

7.2.14 Importance and Relevance

The results of this feasibility study indicate that an accurate and reliable clinical decision rule can likely be derived. This supports continued and expanded research in this area to obtain sufficient sample size to confidently determine which patients with an acute headache require investigation. In addition to the cost savings and improved efficiency of the emergency departments across the country, this would also decrease the morbidity associated with investigation for patients with acute headaches. As previously stated in the introduction, emergency physicians in North America and Europe have indicated the importance of a clinical decision rule to determine which patients require investigation to rule out subarachnoid haemorrhage. This study is the first step towards achieving such a rule.

7.2.15 Conclusions

There were 14 cases of subarachnoid haemorrhage among the 134 prospectively enrolled emergency department patients, with a complaint of headache and no neurological deficits. Nearly all of the patients were investigated for possible subarachnoid haemorrhage, with only 10% having a final diagnosis of subarachnoid haemorrhage. Thus, current practice is not very efficient. This would likely be improved with a clinical decision rule to determine which patients require investigation to rule out subarachnoid haemorrhage.

We found several variables that were highly related to the outcome of subarachnoid haemorrhage. These variables included: "age", "onset during exertional activity", "duration of the headache", "worst headache in their life", "transient loss of consciousness", "buckling of legs/obligated to rest" and the "complaint of neck pain", "elevated blood pressure" and "neck stiffness".

The preliminary model derived from this study, included the terms "age over 45" and "neck stiffness with lateral rotation". This preliminary rule has large confidence intervals reflecting the small sample size of this study. With a larger sample size, it is likely that a highly sensitive decision rule can be derived for alert patients with a headache and a normal neurological examination to determine which patients require investigation to rule out a subarachnoid haemorrhage.

The results of this feasibility study will simplify subsequent data collection by eliminating several variables. As in this initial feasibility study, the final model will be determined by using recursive partitioning techniques.

Table 1
Hunt and Hess Classification of Subarachnoid Haemorrhage

Category	Criteria
Grade I	Asymptomatic, or minimal headache and slight nuchal rigidity
Grade II	Moderate to severe headache, nuchal rigidity, and no neurological deficit other than cranial nerve palsy
Grade III	Drowsiness, confusion, or mild focal deficit
Grade IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances
Grade V	Deep coma, decerebrate rigidity, moribund appearance

Table 2
Review and Critical Appraisal of Current Literature for Determining High Risk Patients for the Outcome of Subarachnoid Haemorrhage with a Presenting Complaint of Headache

Author	Patient Population	Outcome/ Important Variables	Comments
Hunt and Hess 1967[5] Prospective (n=272)	Admitted with SAH*	Prognostic	Focused on outcomes and surgery, not which patients to investigate
Soderstrom 1977[91] Prospective (n=231)	Cerebrovascular disease who with LP[t]	Looks at LP[t] using spectrophotometry	Formulating a clinical decision rule was not the focus of the study
Dhopesh 1979[105;105] Chart review (n=872)	Patients with Headache at Emergency	Looks at final diagnosis	Not isolated to acute headaches Dated study, classification system has changed
Adams 1980[20] Chart review (n=182)	Admitted with SAH*	Looked at delay of diagnosis	Did not look at all patients with acute headaches
Leicht 1980[10] Chart review (n=631)	Headaches in Emergency	Looked at diagnosis	Did not look at signs or symptoms
Buruma 1981[97;97] Prospective (n=50)	25 with SAH* and 25 Traumatic Taps	Focus on differentiating traumatic tap from SAH*	Did not look at signs or symptoms
Van Gijn 1982[82] Prospective (n=100)	Admitted with SAH*	Looking at sensitivity of CT[f]	Did not look at all patients with acute headaches
Duffy 1982[95] Chart review (n=74)	Admitted with SAH*	Looks at safety of LP[t] versus CT[f]	Did not look at signs or symptoms nor all headaches
Adams 1983[81] Prospective (n=1412)	Admitted with SAH*	Sub-study looking at CT[f] yield	Did not look at all patients with acute headaches
Bonita 1985[12] Prospective (n=180)	Admitted with SAH*	Overview of epidemiology, diagnosis, management and outcome	Formulating a clinical decision rule was not the focus of the study

Tsementzis 1985[89] Prospective (n=99)	Admitted with SAH*	Compares yield of CT[f] and LP[t] for xanthochromia	Did not look at signs or symptoms nor all headaches
Patel 1986[96] Chart review (n=123)	Admitted with SAH*	Looks at LP versus CT[f]	Did not look at signs or symptoms nor all headaches
Hillman 1986[80] Chart review (n=283)	Admitted with SAH*	Focuses on methods of diagnosis (CT[f] versus LP[t])	Was not focused on clinical variables Did not state if the patient has neurological signs
Rosenorn 1987[46] Prospective (n=1076)	Admitted with SAH*	Exertional activity 30%, Intercourse 5.5%, 31% LOC[3] > 1 hour, 26% LOC[3] < 1 hour	Only enrolled only positive cases No controls
Scheivink 1988[13] Chart review (n=343)	Admitted with SAH*	Looks at causes of delayed diagnosis	Did not report the use/availability of CT[f] Suspect delays are currently shorter
MacDonald 1988[87] Chart review (n=100)	Admitted with SAH*	Looked at diagnostic modalities	Formulating a clinical decision rule was not the focus of the study
Verweij 1988[15] Prospective Case-Controlled (n=150)	30 with SAH* 20 with CVA[⊥] 100 without neurological problem	Looking for warning headache	Interviewer was not blinded Did not look at signs or symptoms
Scheivink 1989[45] Chart review (n=500)	Admitted with SAH*	Females > age 50, Males < 50, Stressful event	Events classified non-stressful included many stresses (housework/bathing)
Harling 1989[107] Prospective (n=49)	Patients admitted with sudden/severe headache	Nausea and obliged to rest with the onset of the headache	Found no need to investigate patients with a negative CT[f] and LP[t] Did not look at all patients with acute headaches
Vermeulen 1989[88] Chart review (n=111)	Admitted with SAH*	Looked at sensitivity of xanthochromia	Formulating a clinical decision rule was not the focus of the study
Ferro 1991[14] Chart review (n=112)	Admitted with SAH*	Focus on delay of diagnosis	Did not focus on clinical symptoms/signs

Linn 1994[106] Prospective (n=148)	Community based study	Looking for investigations and diagnosis	Not emergency based
Van der Wee 1995[77] Prospective (n=175)	Acute headache in emergency	Looked at diagnostic modalities	Must not have included all patients with acute headache with yield of 117 positive cases
Sved 1995[18] Chart review (n=511)	Admitted with SAH*	Looking for delays in diagnosis	Did not look at all patients with acute headaches
Sidman 1996[4] Chart review (n=140)	Admitted with SAH*	Looked at diagnostic modalities	Formulating a clinical decision rule was not the focus of the study
Jakobsson 1996[16] Prospective (n=422)	Admitted with SAH*	Determined if warning leak had occurred	Did not look at signs or symptoms
Hillman 1996[27;27] Prospective (n=49)	Admitted with Posterior Fossa Aneurysms	Focus on management	Did not look at signs or symptoms
Le Roux 1996[28] Chart review (n=159)	Aggressively Managed Patients with SAH*	Focus on management	Did not look at signs or symptoms
Sames 1996[79] Chart review (n=181)	Admitted with SAH*	Focus on sensitivity of CT[f]	Did not look at signs or symptoms
Pascual 1996[47] Case Series (n=72)	Cough, Exertional, Sexual Headaches	Looked for final diagnosis for patients with these complaints	Did not look at all patients with acute headaches Likely missed several cases due to coding
Neil-Dwyer 1997[21] Prospective (n=180)	Admitted with SAH*	Looked at delay of diagnosis	Did not look at all patients with acute headaches
Ramireq-Lassepas 1997[7] Case-Controlled (n=468)	Patients with headaches and controls	Looked for significant intracranial pathology	Too broad of a spectrum to generate a clinical decision rule
Linn 1998[49] Prospective (n=102)	Emergency Patients with Severe Sudden Headache	Seizures and temporary loss of consciousness were had associations	Did not formulate a clinical decision rule from findings

Morganstern 1998[37] Prospective (n=455)	Patients with headache at emergency	Looks at CT^{f} and LP^{ι}	Formulating a clinical decision rule was not the focus of the study

* = Subarachnoid Haemorrhage

ι = Lumbar Puncture

f = Computed Tomography

ɜ = Loss of Consciousness

⊥ = Cerebral Vascular Accident

Table 3
Phase 0: List of Variables Collected from the Record of Treatment for 10-Month Historical Cohort Study

	Variables to be Collected	
Demographics	• Age (years) • Mode of arrival (ambulance/ambulatory) • Gender (male/female) • Transfer from other emergency department • Date (y/m/d)	• Arrival time (hours) • Discharge time/Referral time (whichever is first, in hours) • Attending emergency physician (code) • Was the patient referred to neurosurgery?
Headache Characteristics	• Patient seen in emergency for either syncope or headache in the last six-months • Recorded time from onset to peak (<1hour / >or = 1 hour) • Recorded pain severity at peak intensity (0-10)	• Worst headache the patient has ever had • Similar headache in past • Previous subarachnoid haemorrhage
Associated Findings	• Decreased level of consciousness, defined as a Glasgow Coma Scale <15 • Transient loss of consciousness • Photophobia	• Family history of subarachnoid haemorrhage • Transient motor deficits • Vomited
Physical Examination	• Temperature (degrees Celsius) • Heart rate (beats per minute) • Systolic blood pressure (mm of Hg)	• Diastolic blood pressure (mm of Hg) • Neck stiffness
Investigations	• Computed tomography done • Computed tomography positive for SAH*	• Lumbar puncture done • Lumbar puncture positive for SAH*

*SAH = Subarachnoid Haemorrhage

Table 4
Phase 1: List of Historical Variables Collected by Physician or Research Nurse for Prospective Study

	Variables to be Collected	
Demographics	• Age (years) • Date of emergency visit (d/m/y) • Physician status (full-time, part-time, housestaff) • Physician (code) • Site (General/Civic)	• Gender (male/female) • Interobserver case, if yes second physician (code) • Transfer from another emergency department • Arrival by ambulance
Headache Characteristics	• Onset time to peak (seconds, minutes) • Time of onset (hours, minutes; a.m., p.m.) • Did the headache awake patient [not headache with normal waking] • If gone, what was the duration of the headache (hours) • History of similar type of headache in past • Onset during sexual activity • Onset during exertional activity [weight lifting, exercise, etc.]	• Onset during cough • Is the pain now completely gone? • Is this the worst headache the patient has ever had in their life? • Pain severity at peak intensity (0-10) [0 = no distress, 10 = very distressed] • Is the headache located only in the occipital area? • Is the headache unilateral? • Was the pain partially relieved with anti-migraine treatment? If yes, which agent(s)?
Associated Symptoms	• Transient loss of consciousness • Photophobia • Obligated to rest or buckling of legs at onset of headache	• Patient complaint of neck pain or stiffness • Vomiting • Transient motor deficits [as recalled by patient]
Past Medical History	• Sympathomimetic use [cocaine or amphetamine use up to 48 hours prior to headache] • Connective tissue disorder [e.g. Ehlers-Danlos syndrome, neurofibromatosis, Marfan's, alfa 1 anti-trypsan deficiency, etc.]	• Adult onset polycystic kidney disease • Family history of subarachnoid haemorrhage

Table 5
Phase 1: List of Physical Examination and Investigation Variables Collected by Physician or Research Nurse for Prospective Study

	Variables to be Collected	
Physical Examination	• Temperature (degrees Celsius) • Heart rate (beats per minute) • Systolic blood pressure (mm of Hg) • Diastolic blood pressure (mm of Hg) • Position of patient in room (walking, sitting, lying, lying still, lying still in dark room)	• Neck stiffness (flexion/extension) • Localizing neurological signs • Neck stiffness (lateral rotation) • Patient's distress (0-10) [0 = no distress, 10 = very distressed]
Information regarding tests ordered	• Number of hours from ictus to head computed tomography scan	• Number of hours from ictus to lumbar puncture
Investigations	• Head computed tomography scan head done, if yes (normal, abnormal) • If abnormal (subarachnoid hemorrhage, subdural hematoma, intracerebral hematoma, cerebellar hematoma, epidural hematoma, cerebral contusion, intraventricular hemorrhage, tumour [primary], tumour [metastatic], abscess, other)	• Lumbar puncture done, if yes (normal, abnormal) • If lumbar puncture abnormal (white blood cell count >5, red blood cell count [with first tube], red blood cell count [with final tube], xanthochromia, bacteria on gram stain, culture result [organism])
Physician Judgement	• Comfort in performing only lumbar puncture without a head computed tomography scan (comfortable, uncomfortable or very comfortable) • Comfort in not ordering any investigations (comfortable, uncomfortable or very comfortable)	• Probability of the patient has a subarachnoid haemorrhage (to the closest percent)

Table 6
Phase 0: Characteristics of the 891 Patients with Acute Headache or Syncope from a 10-Month Historical Cohort Study of Emergency Patients

Characteristics	Number of Patients (N=891)
Demographics	
Mean Age (SD)	41.9 (17.0)
Range	15-94
Female (%)	592 (66.4)
Arrival by Ambulance [n=792]* (%)	122 (15.4)
Transfer from Another Emergency Department (%)	52 (5.8)
Mean Length of Stay in the Emergency in Minutes (SD)	239 (148.3)
Range	17-1438
Patients Seen in Previous 6 Months for Headache or Syncope (%)	131 (14.7)
Timing of Headache	
Mean Time in Minutes from Onset to Peak [n=111]* (SD)	1.13 (5.13)
Range	1-3
Mean Pain Severity at Peak [0-10] [n=77]* (SD)	8.0 (2.4)
Range	0-10
Clinical Features	
Worst Headache of Life [n=73]* (%)	44 (60.3)
Similar Headache Quality in Past [n=270]* (%)	211 (78.1)
Previous Subarachnoid Haemorrhage [n=10]* (%)	6 (60.0)
Transient Loss of Consciousness [n=103]* (%)	42 (40.8)
Photophobia [n=402]* (%)	267 (66.4)
Patient Complaint of Neck Pain [n=181]* (%)	117 (64.5)
Vomiting [n=538]* (%)	228 (42.4)
Transient Motor Deficits [n=238]* (%)	53 (22.2)
Family History of Subarachnoid Haemorrhage [n=16]* (%)	7 (43.8)
Physical Examination Findings	
Mean Temperature in Celsius (SD)	35.9 (0.8)
Mean Heart Rate [BPM] (SD)	83.5 (16.5)
Mean Systolic Blood Pressure [mm of Hg] (SD)	136.5 (25.8)
Mean Diastolic Blood Pressure [mm of Hg] (SD)	78.3 (12.9)
Neck Stiffness [n=444]* (%)	16 (3.6)

* Data available for only some cases

Table 7

Phase 0: Management and Outcome of the 891 Patients with Acute Headache or Syncope from a 10-Month Historical Cohort Study of Emergency Patients

Outcome	Number of Patients (N=891)
Diagnostic Procedures	
Underwent Computed Tomography Scan of Head (%)	312 (35.0)
Underwent Lumbar Puncture (%)	85 (9.5)
Disposition	
Admitted to Hospital (%)	33 (3.7)
Referral to Neurosurgery (%)	26 (2.9)
Final Diagnosis	
Migraine Headache (%)	388 (43.5)
Other Benign Headache (%)	294 (33.0)
Non Central Nervous System (%)	65 (7.3)
Viral Illness (%)	35 (3.9)
Benign Syncope or Pre-syncope (%)	20 (2.2)
Anxiety (%)	11 (1.2)
Subarachnoid Haemorrhage (%)	10 (1.1)
Transient Ischemic Attack/Ischemic Stroke (%)	9 (1.0)
Trauma/Post Trauma (%)	8 (0.9)
Not Determined (%)	8 (0.9)
Tumour (%)	6 (0.7)
Hypertension (%)	6 (0.7)
Sinusitis (%)	6 (0.7)
Medication Related (%)	6 (0.7)
Vertigo (%)	5 (0.6)
Other Central Nervous System (%)	5 (0.6)
Bacterial Meningitis (%)	4 (0.4)
Temporal Arteritis (%)	3 (0.3)

Table 8

Phase 0: Univariate Correlation of Variables of the 891 Patients with Acute Headache or Syncope from a 10-Month Historical Cohort Study of Emergency Patients

	No SAH [N=881]	Positive SAH [N=10]	p-value
Demographics			
Mean Age (SD)	41.8 (17)	47.8 (10)	0.27
Female (%)	587 (66.6)	5 (50)	0.32
Timing of Headache			
Mean Time in Minutes from Onset to Peak [n=101/10]* (SD)	2.76 (0.64)	1.20 (0.63)	<0.01
Range of Time in Minutes from Onset to Peak [n=101/10]*	1-3	1-3	
Mean Pain Severity at Peak [0-10] [n=75/2]* (SD)	8.0 (2.4)	10.0 (0.0)	0.25
Range of Pain Severity at Peak [0-10] [n=75/2]*	0-10	10-10	
Mean Time in Emergency in Minutes (SD)	237 (142)	402 (411)	<0.01
Range of Time in Emergency in Minutes	17-1330	17-1438	
Clinical Features			
Worst Headache of Life [n=70/3]* (%)	41 (58.6)	3 (100)	0.27
Similar Headache Quality in Past [n=265/5]* (%)	209 (78.9)	2 (40)	0.07
Transient Loss of Consciousness [n=102/1]* (%)	42 (41)	0 (0)	1.0
Photophobia [n=399/3]* (%)	265 (66.4)	2 (66.7)	1.0
Patient Complaint of Neck Pain [n=175/6]* (%)	111 (63.4)	6 (100)	0.09
Vomiting [n=532/6]* (%)	225 (42.3)	3 (50)	0.70
Transient Motor Deficits [n=237/1]* (%)	53 (22.4)	0 (0)	1.0
Family History of Subarachnoid Haemorrhage [n=15/1]* (%)	6 (40)	1 (100)	0.44
Physical Examination Findings			
Mean Temperature in Celsius (SD)	35.9 (0.8)	35.6(0.7)	0.26
Mean Heart Rate [BPM] (SD)	84 (16.5)	77(12.0)	0.24
Mean Systolic Blood Pressure [mm of Hg] (SD)	136 (25.8)	150(18.2)	0.10
Mean Diastolic Blood Pressure [mm of Hg] (SD)	78 (12.9)	86(9.5)	0.06
Neck Stiffness [n=436/8]* (%)	12 (2.8)	4 (50)	<0.01
Diagnostic Procedures			
Computed Tomography [881/9]* (%)	303 (34.4)	9 (100)	<0.01
Lumbar Puncture [881/9]* (%)	83 (9.4)	2 (22.2)	0.21

* Data available for only some cases

Table 9

Phase 0: Test Yields for Diagnosis of Subarachnoid Haemorrhage from the 891 Patients with Acute Headache or Syncope from a 10-Month Historical Cohort Study of Emergency Patients

Test Ordered	Diagnostic Yield for SAH
Computed Tomography of Patient's Head [n= 312] (%)	8 (2.6)
Lumbar Puncture [n=85] (%)	2 (2.4)

Table 10

Phase 0: Mean Number of Minutes Spent in the Emergency Department as Determined by the Tests Ordered from the Patients with Acute Headache or Syncope from a 10-Month Historical Cohort Study of Emergency Patients Who Did Not Suffer a Subarachnoid Haemorrhage

Test Ordered	Mean Time in ED in Minutes (SD)
Without Testing [n=826]	237 (144)
With Computed Tomography [n=187]	302 (157)
With Lumbar Puncture [n=34]	426 (137)
With Computed Tomography **or** Lumbar Puncture [n=200]	311 (158)
With Computed Tomography **and** Lumbar Puncture [n=22]	424 (146)

Table 11
Phase 1: Characteristics from a 7-Month Prospective Cohort Study of 134 Emergency Patients with an Acute Headache

Characteristics	Number of Patients (N=134)
Demographics	
Mean Age (SD)	42.8 (15.7)
Range	16-80
Female (%)	83 (61.9)
Arrival by Ambulance (%)	23 (17.2)
Transfer from Another ED (%)	8 (6.0)
Interobserver Case (%)	3 (2.2)
Mean Length of Stay in Department in Minutes (SD)	311 (188)
Range	40-1140
Clinical Features	
Mean Time from Onset to Peak in Minutes (SD)	13.2 (27.2)
Range	0-60
Mean Duration of Headache in Minutes (SD)	726 (525)
Range	0-1380
Mean Pain Severity at Peak [0-10] (SD)	8.75 (1.7)
Range	2-10
Onset During Exertional Activity (%)	12 (9.0)
Onset During Sexual Activity (%)	5 (3.7)
Onset During Cough (%)	3 (2.2)
Did Headache Awake Patient from Sleep (%)	23 (17.2)
Worst Headache of Life (%)	103 (76.9)
Similar Headache Quality in Past (%)	33 (24.6)
Occipital Area Only (%)	18 (13.4)
Unilateral (%)	46 (34.3)
Relieved with Anti-Migraine Treatment (%)	22 (21.4)
Transient Loss of Consciousness (%)	5 (3.8)
Obligated to Rest (%)	23 (17.2)
Photophobia (%)	50 (37.6)
Patient Complaint of Neck Pain (%)	50 (37.6)
Vomiting (%)	40 (29.9)

Table 12
Phase 1: Management and Outcomes of Patients from a 7-Month Prospective Cohort Study of 134 Emergency Patients with Acute Headache

Outcome	Number of Patients (N=134)
Diagnostic Procedures	
Computed Tomography (%)	114 (85.1)
Lumbar Puncture (%)	62 (46.3)
Computed Tomography **and** Lumbar Puncture (%)	57 (42.5)
Either Computed Tomography **or** Lumbar Puncture (%)	119 (88.8)
Only Lumbar Puncture (%)	5 (3.7)
Cerebral Angiogram (%)	17 (12.7)
Disposition	
Referral to Neurosurgery (%)	19 (14.2)
Admitted to Hospital (%)	18 (13.4)
Death (%)	2 (1.5)
Final Diagnosis	
Migraine Headache (%)	51 (38.1)
Other Benign Headache (%)	48 (35.8)
Subarachnoid Haemorrhage (%)	14 (10.4)
Viral Illness (%)	4 (3.0)
Ischemic Stroke or Transient Ischemic Attack (%)	3 (2.2)
Weakness Cause Not Determined (%)	3 (2.2)
Sinusitis (%)	2 (1.5)
Meningitis (%)	1 (0.7)
Intracerebral Haemorrhage (%)	1 (0.7)
Subdural Hematoma (%)	1 (0.7)
Neck Strain (%)	1 (0.7)
Cerebral Spinal Fluid Leak (%)	1 (0.7)
Temporal Mandibular Joint Inflammation (%)	1 (0.7)
Hypoglycemia (%)	1 (0.7)
Syncope Cause Not Determined (%)	1 (0.7)
Post Coital Headache (%)	1 (0.7)

Table 13

Phase 1: Univariate Correlation of Variables from History for Subarachnoid Haemorrhage from a 7-Month Prospective Cohort Study of 134 Emergency Patients with Acute Headache

Questions from History	No SAH [N=120]	Positive SAH [N=14]	p-value
Demographics			
Mean Age (SD)	41.2 (15.2)	56.9 (12.9)	<0.01
Female (%)	73 (60.8)	10 (71.4)	0.57
Timing of Headache			
Mean Time from Onset to Peak in Minutes (SD)	14.0 (28.2)	7.6 (17.1)	0.41
Range from Onset to Peak in Minutes	0-60	0.02-60	
Mean Duration of Headache in Minutes (SD)	693 (515)	1012 (542)	0.03
Range Duration of Headache in Minutes	0-1420	96-1395	
Mean Pain Severity at Peak [0-10] (SD)	8.7 (1.6)	8.9 (2.2)	0.68
Range of Pain Severity at Peak [0-10]	3-10	2-10	
Activity when Headache Began			
Onset During Exertional Activity (%)	8 (6.7)	4 (28.6)	0.02
Onset During Sexual Activity (%)	4 (3.3)	1 (7.1)	0.43
Onset During Cough (%)	3 (2.5)	0 (0)	1.0
Did Headache Awake from Sleep (%)	23 (19.2)	0 (0)	0.12
Description of Headache			
Worst Headache of Life (%)	89 (74.2)	14 (100)	0.04
Similar Headache Quality in Past (%)	30 (25.0)	3 (21.4)	1.0
Occipital Area Only (%)	14 (11.7)	4 (28.6)	0.10
Unilateral (%)	43 (35.8)	3 (23.1)	0.54
Relieved with Anti-Migraine Treatment (%)	20 (22.2)	2 (15.4)	0.73
Associated Features			
Transient Loss of Consciousness (%)	2 (1.7)	3 (21.4)	0.01
Obligated to Rest (%)	17 (14.2)	6 (42.9)	0.02
Photophobia (%)	44 (36.7)	6 (46.2)	0.55
Patient Complaint of Neck Pain (%)	40 (33.6)	10 (71.4)	0.01
Vomiting (%)	33 (27.5)	7 (50.0)	0.12
Transient Neurological Deficits (%)	22 (18.3)	3 (21.4)	0.73
Sympathomimetic Use (%)	4 (3.4)	0 (0)	1.0
Connective Tissue Disorder (%)	0 (0)	0 (0)	N/A
Adult Onset Polycystic Kidney Disease (%)	1 (0.9)	0 (0)	1.0
Family History of Subarachnoid Haemorrhage (%)	9 (7.7)	0 (0)	0.60

Table 14

Phase 1: Univariate Correlation of Variables from Physical Examination for Subarachnoid Haemorrhage over 7 Months from Prospective Cohort Data of 134 Patients Presenting to Emergency with an Acute Headache

Physical Examination Characteristics	No SAH [N=120]	Positive SAH [N=14]	p-value
Neck Stiffness (lateral rotation) (%)	10 (8.6)	5 (35.7)	0.01
Neck Stiffness (flexion/extension) (%)	11 (11.0)	6 (50)	<0.01
Mean Temperature in Celsius (SD)	36.3 (0.8)	35.8 (1.0)	0.08
Mean Heart Rate [BPM] (SD)	80.5 (13.7)	80.1 (11.1)	0.91
Mean Systolic Blood Pressure [mm of Hg] (SD)	144.2 (23.9)	150.9 (31.1)	0.34
Mean Diastolic Blood Pressure [mm of Hg] (SD)	80.6 (12.9)	86.1 (15.2)	0.14
Mean Patient Distress [0-10] (SD)	2.9 (2.7)	6.3 (2.3)	<0.01

Table 15
Phase 1: Characteristics of the 91 Missed Eligible Subjects from a 7-Month Prospective Cohort Study of Emergency Patients with Acute Headache

Characteristics	Number of Patients (N=91)
Mean Age (SD)	45.1 (17.6)
Age Range	17-87
Female (%)	54 (60.7)
Computed Tomography (%)	71 (79.8)
Lumbar Puncture (%)	36 (40.4)
Diagnosis Subarachnoid Haemorrhage (%)	2 (2.1)

Table 16

Phase 1: Hosmer Lemeshow Goodness of Fit of Final 5 Regression Models from a 7-Month Prospective Cohort Study of Patients Presenting to Emergency with an Acute Headache

Model (Variables included)	Significance
7 Variables (Occipital pain, Age > 40, Transient LOC or Buckling of Legs, Exertional or Sexual Activity, Neck Stiffness (lateral or flexion/extension), Diastolic Blood Pressure > 110, vomiting)	0.884
6 Variables (Age > 40, Transient LOC or Buckling of Legs, Exertional or Sexual Activity, Neck Stiffness (lateral or flexion/extension), Diastolic Blood Pressure > 110, Vomiting)	0.979
5 Variables (Age > 40, Transient LOC or Buckling of Legs, Neck Stiffness (lateral or flexion/extension), Diastolic Blood Pressure >110, Vomiting)	0.911
4 Variables (Age > 40, Transient LOC or Buckling of Legs, Neck Stiffness (lateral or flexion/extension), Diastolic Blood Pressure >110)	0.957
3 Variables (Age > 40, Transient LOC or Buckling of Legs, Neck Stiffness (lateral or flexion/extension))	0.926

Table 17
Phase 1: Final Model Developed by Stepwise Logistic Regression Analysis to Predict Subarachnoid Haemorrhage from a 7-Month Prospective Cohort Study of Patients Presenting to Emergency with an Acute Headache

Variable	Coefficient	Adjusted Odds Ratio (95% CI)
Intercept	-6.50	0.001
Age > 40	3.38	29.27 (2.63, 325.58)
Transient Loss of Consciousness or Obliged to Stop/Buckling of Legs	2.87	17.67 (3.33, 93.80)
Neck Stiffness (lateral or flexion/extension)	2.50	12.15 (2.42, 61.07)
Diastolic Blood Pressure > 110 mm Hg	2.61	13.61 (1.16, 159.19)

Table 18

Phase 1: Sensitivity and Specificity of Proposed Logistic Regression Model at Varying Cut Points to Determine Which Patients with an Acute Severe Headache Require Investigation for Subarachnoid Haemorrhage

Classification Cut Off	Sensitivity (95%CI)	Specificity (95%CI)
0.95	0 (0, 0.77)	1.0 (0.97, 1.0)
0.9	0.14 (0.03, 0.36)	0.99 (0.95, 1.0)
0.8	0.21 (0.06, 0.44)	0.99 (0.95, 1.0)
0.7	0.21 (0.06, 0.44)	0.99 (0.95, 1.0)
0.6	0.21 (0.06, 0.44)	0.99 (0.95, 1.0)
0.5	0.21 (0.06, 0.44)	0.99 (0.95, 1.0)
0.4	0.50 (0.24, 0.70)	0.96 (0.90, 0.98)
0.3	0.79 (0.49, 0.91)	0.90 (0.83, 0.94)
0.2	0.86 (0.56, 0.94)	0.89 (0.82, 0.93)
0.1	0.86 (0.56, 0.94)	0.89 (0.82, 0.93)
0.05	0.86 (0.56, 0.94)	0.89 (0.82, 0.93)
0.04	1.0 (0.77, 1.0)	0.51 (0.42, 0.59)
0.03	1.0 (0.77, 1.0)	0.51 (0.42, 0.59)
0.02	1.0 (0.77, 1.0)	0.41 (0.32, 0.49)
0.01	1.0 (0.77, 1.0)	0.34 (0.26, 0.43)

Table 19

Phase 1: Proposed Recursive Partitioning Models to Determine Which Patients with an Acute Severe Headache Require Investigation for Subarachnoid Haemorrhage

Recursive Partitioning Model	Sensitivity	Specificity
Age > 50, Obliged to Rest or Buckling of Legs at Onset of Headache, Systolic BP >160	100% (77-100)	55% (46-63)
Obliged to Rest or Buckling of Legs at Onset of Headache, Age >45	100% (77-100)	52% (43-61)
Age > 40, Obliged to Rest or Buckling of Legs at Onset of Headache,	100% (77-100)	42% (33-50)
Age > 50, Neck Stiffness with Flexion or Extension	100% (77-100)	56% (47-64)
Neck Stiffness with Lateral Rotation, Transient LOC, Age >45	100% (77-100)	52% (42-60)
Age >45, Neck Stiffness with Lateral Rotation	100% (77-100)	54% (45-62)

Table 20
Phase 1: Physician's Comfort in Performing a Lumbar Puncture Without First Obtaining Computed Tomography from a 7-Month Prospective Cohort Study of Patients Presenting to Emergency with an Acute Headache

Level of Comfort	Number (%) N=113
Uncomfortable	59 (52.2)
Comfortable	48 (42.5)
Very Comfortable	6 (5.3)

Table 21
Phase 1: Physicians' Comfort in Not Ordering Any Investigations from a 7-Month Prospective Cohort Study of Patients Presenting to Emergency with an Acute Headache

Level of Comfort	Number (%) N=121
Uncomfortable	97 (80.2)
Comfortable	14 (11.6)
Very Comfortable	10 (8.3)

Table 22

Phase 1: Physicians' Pre-test Probability that their Patient Had a Subarachnoid Haemorrhage from a 7-Month Prospective Cohort Study of Patients Presenting to Emergency with an Acute Headache

Pretest Probability of Patient Having Positive Subarachnoid Haemorrhage (%)	Negative for Subarachnoid Haemorrhage	Positive for Subarachnoid Haemorrhage
0	14	0
1	16	0
2	6	1
3	6	0
4	3	0
5	21	0
10	16	3
20	6	1
30	2	1
40	1	0
50	5	2
75	3	4
100	0	2

Figure 1
Flow Diagram of Electronic Database Study of Patients with Acute Headache or Syncope

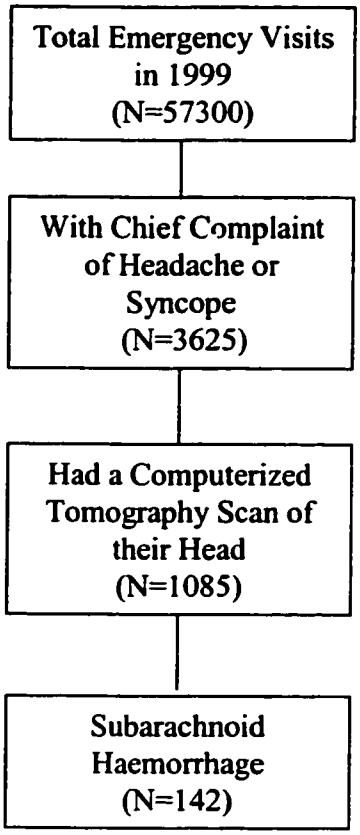


Figure 2
Phase 0: Trial Flow from a 10-Month Historical Cohort Study of Emergency Patients with Acute Headache or Syncope

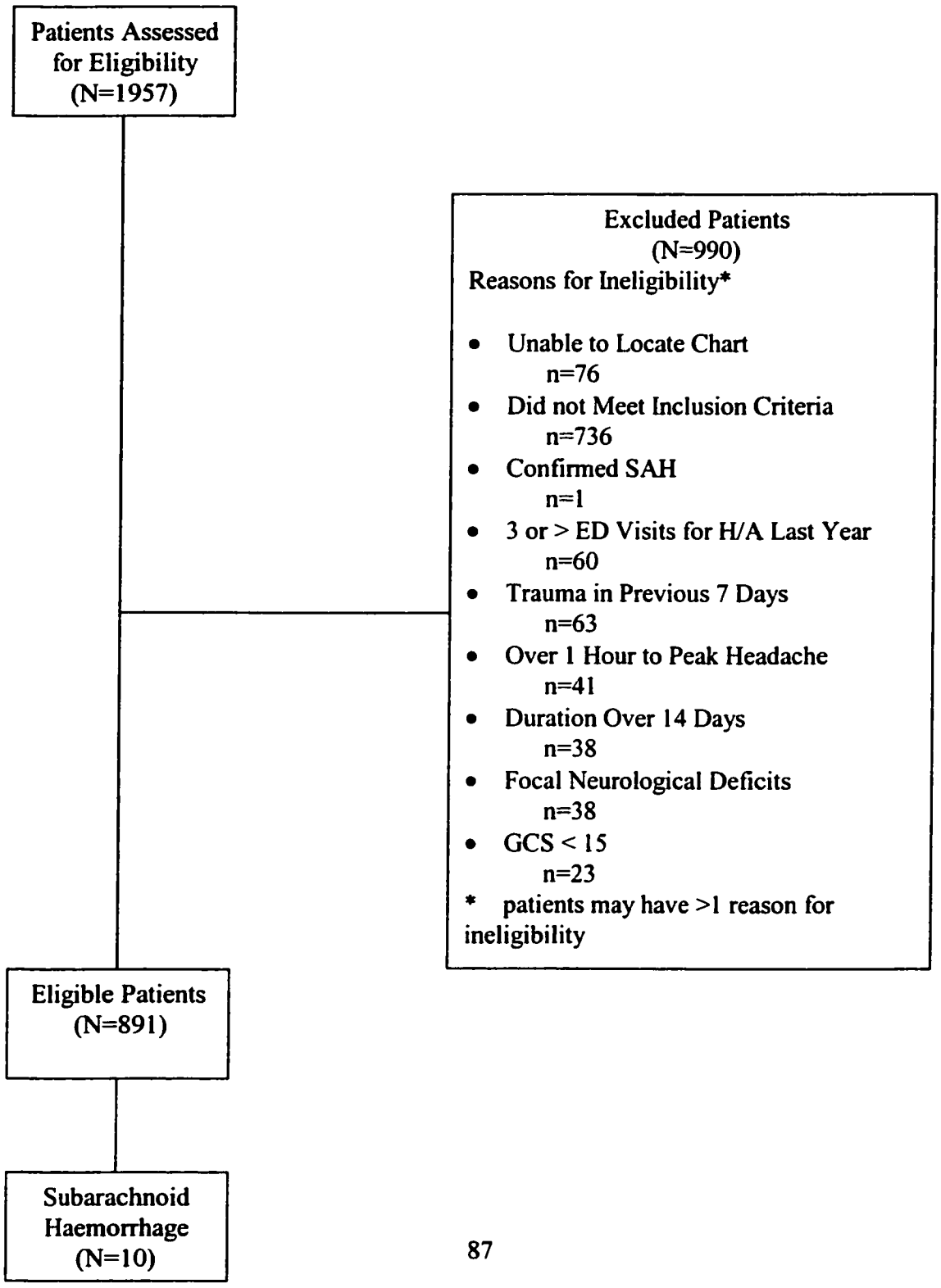


Figure 3
Phase 1: Trial Flow of 7-Month Prospective Cohort Study of Emergency Patients with an Acute Headache

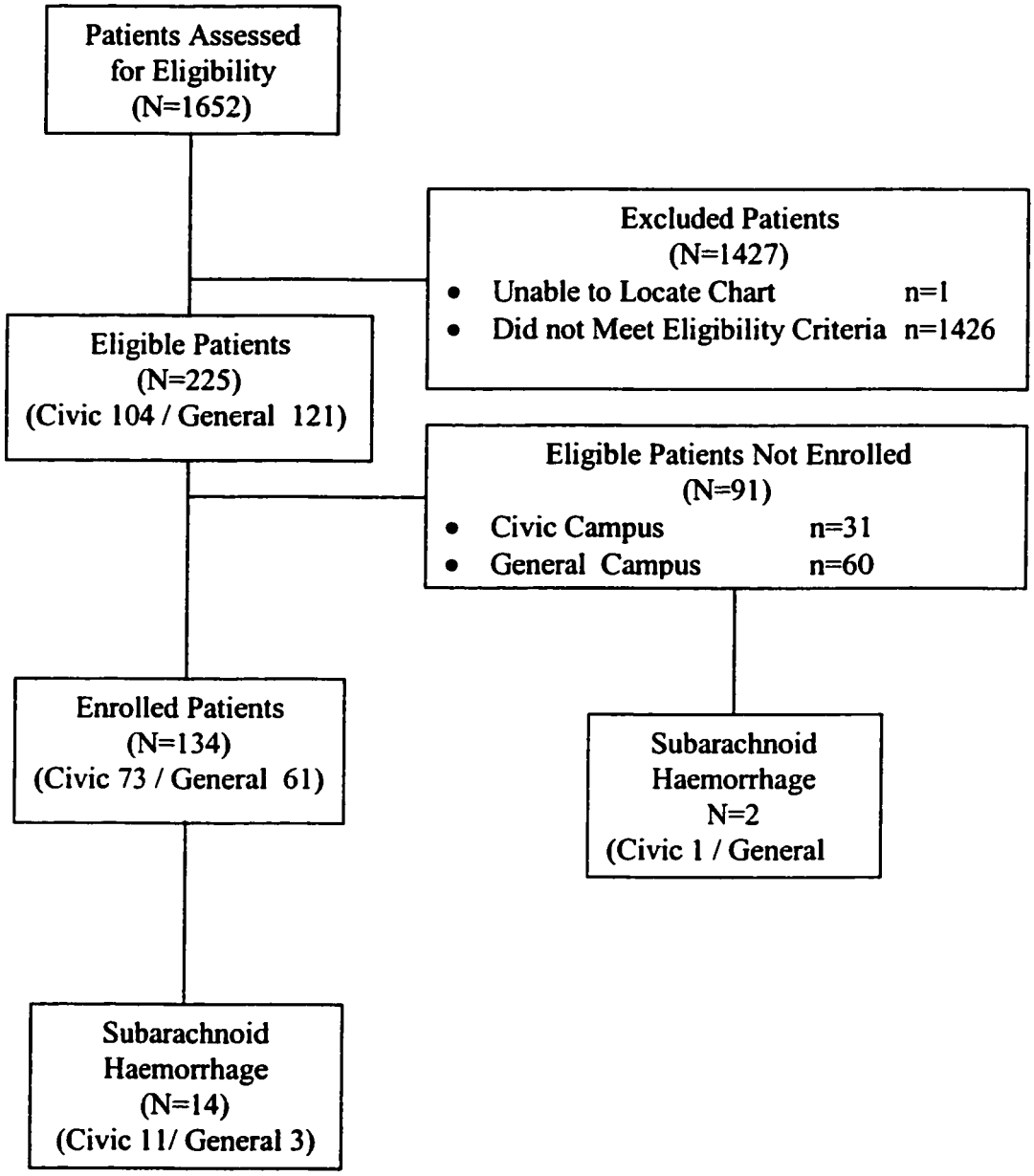


Figure 4
Phase 1: Receiver Operator Characteristic (ROC) Curve For the Outcome of Subarachnoid Haemorrhage Using the Logistic Regression Model Applied to the Patients from a 7-Month Prospective Cohort Study of Patients Presenting to Emergency with an Acute Headache

Figure 5
Phase 1: Flow Diagram of the Recursive Partitioning Model Using Age Over 45 Years and Neck Stiffness with Lateral Rotation

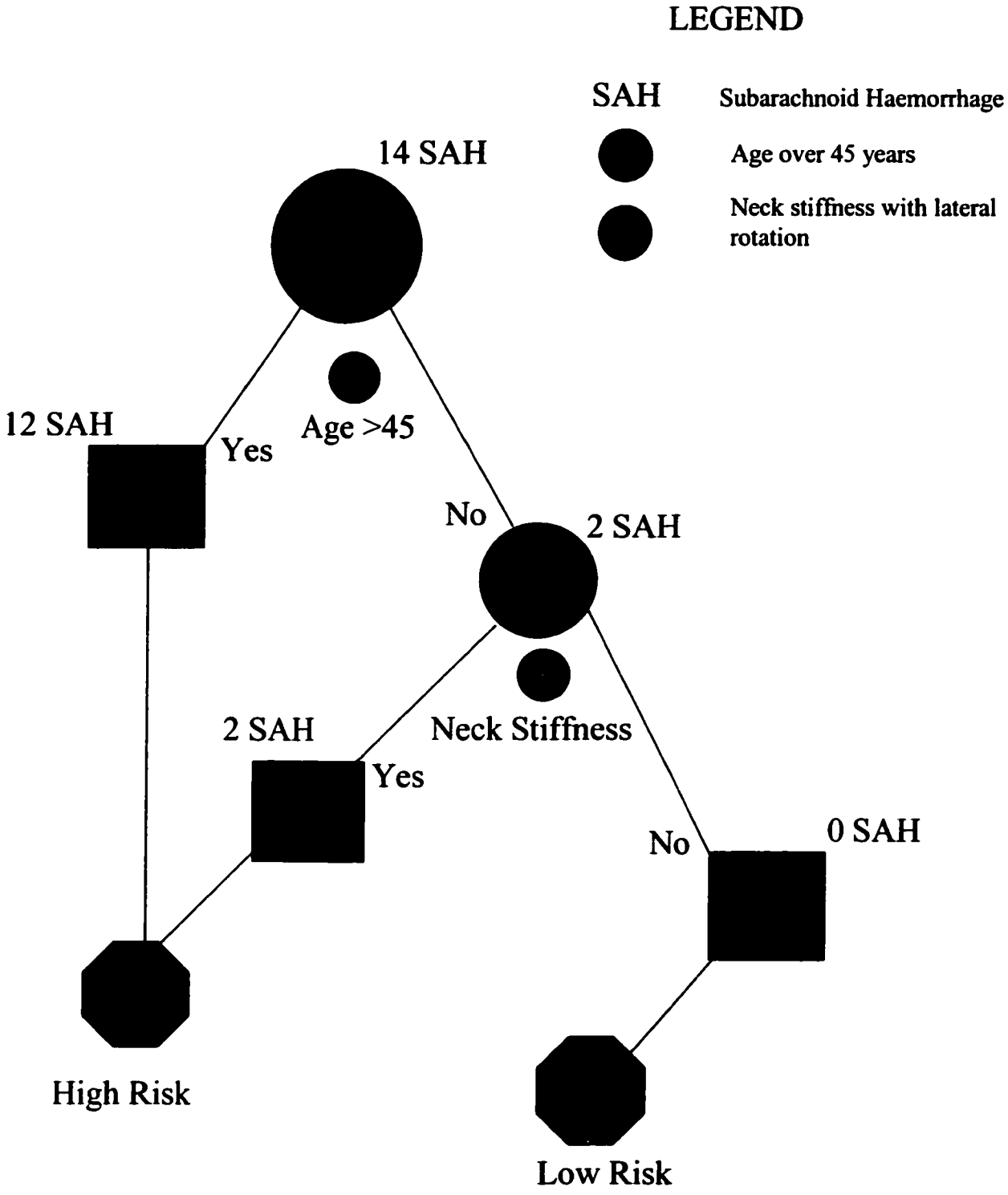


Figure 6
Phase 1: Preliminary Acute Headache Rule by Recursive Partitioning Analysis from a 7-Month Prospective Cohort Study of Patients Presenting to Emergency with an Acute Headache

1. **Neck Stiffness with Inability to Achieve Lateral Rotation of at least 45 Degrees**

OR

2. **Age over 45 years**

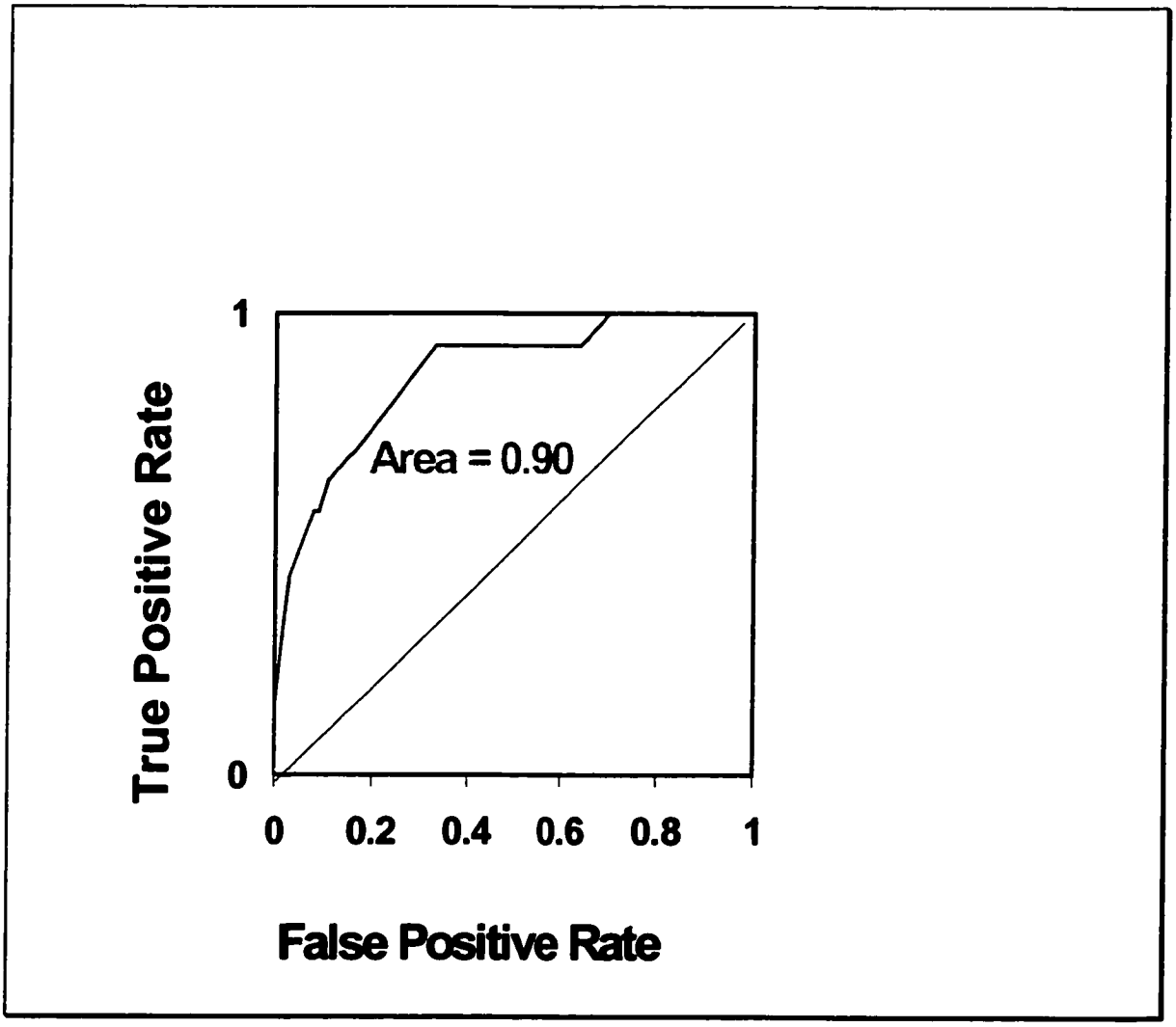
Figure 7
Phase 1: Classification Performance of the Preliminary Model to Determine Which Patients With an Acute Headache Require Investigations to Rule Out Subarachnoid Haemorrhage

Classification performance of the Acute Headache Rule for subarachnoid haemorrhage

	Subarachnoid Haemorrhage	
Decision Rule	Yes	No
Yes	14	52
No	0	68

Sensitivity	100% (77-100)
Specificity	57% (47-65)
Percent Requiring Testing	49.3%

Figure 8
Phase 1: Receiver Operator Characteristic (ROC) Curve of Physicians Pre-test Probability that their Patient Had a Subarachnoid Haemorrhage from a 7-Month Prospective Cohort Study of Patients Presenting to Emergency with an Acute Headache



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Appendix 1
Data Collection Form-Phase 0

Subject No.:_____ ED Visit Date: (y/m/d) ___-____-_____
Patient Initials.:_____

ACUTE HEADACHE STUDY (PHASE 0)

Data Collection Form

Inclusion Criteria
15 years of age or greater with a chief complaint of headache in 2000.
Does the patient meet the inclusion criteria? ○ Yes ○ No
IF 'NO' STOP HERE

Exclusion Criteria
Patients who have been referred from other centres with **confirmed** SAH by CT, LP (RBCs or xanthochromia), or angio. ○ Yes ○ No
Patients with 3 or more ED visits for headache in the last 12 months. ○ Yes ○ No
Recorded history of direct trauma to the head in the 7 days prior to presentation. ○ Yes ○ No
The headache is recorded to have reached maximal intensity in greater than one hour. ○ Yes ○ No
The headache is recorded to have been present continuously for greater than 14 days. ○ Yes ○ No
Patients recorded to have focal neurological deficits or papilledema on physical examination. ○ Yes ○ No
Patients recorded to have a GCS of less than 15. ○ Yes ○ No
Is the patient excluded by any of the exclusion criteria? ○ Yes ○ No
IF 'YES' STOP HERE

Reviewer's initials____ **PI**____

Demographics
Attending EP (code) ____
mode of arrival ○ Ambulance ○ Ambulatory ○ not recorded
age (years) _____
gender ○ Male ○ Female
transfer from other ED ○ Yes ○ No
Arrival time _____
Discharge time /or referral time (whichever is first) _____
Was patient referred to neurosurgery ○ Yes ○ No

Headache Characteristics
Has the patient been seen at this ED for either syncope or headache in last 6 months? ○ Yes ○ No ○ not recorded
Time from **onset to peak** ○ <1 hr ○ ≥1 hr ○ not recorded
If <1hr ____seconds or ____minutes
Pain severity at **peak** intensity (0-10) _____ ○ not recorded
Was this the worst headache the patient has ever had? ○ Yes ○ No ○ not recorded
History of similar type of headache in the past ○ Yes ○ No ○ not recorded
Previous SAH? ○ Yes ○ No ○ not recorded

Associated features
Transient loss of consciousness ○ Yes ○ No ○ not recorded
Photophobia ○ Yes ○ No ○ not recorded
Patient complaint of neck pain or stiffness ○ Yes ○ No ○ not recorded
Vomiting ○ Yes ○ No ○ not recorded
Transient motor deficits ○ Yes ○ No ○ not recorded
Family history of SAH ○ Yes ○ No ○ not recorded

Physical exam
Temperature _____°C Heart rate _____ BPM SBP _____ mm of Hg DBP _____ mm of Hg
Decreased level of consciousness (GCS < 15) ○ Yes ○ No ○ not recorded
Neck stiffness ○ Yes ○ No ○ not recorded

Investigations
CT head done ○ No ○ Yes-Normal ○ Yes-Abnormal, If abnormal describe_____
LP done ○ No ○ Yes-Normal ○ Yes-Abnormal, If abnormal describe_____
Final Diagnosis: ○ SAH ○ Migraine ○ Other Benign Headache ○ Tumor ○ Non CNS ○ Other
Disposition: ○ Home ○ Admitted

The Ottawa Hospital | L'Hôpital d'Ottawa

C
761-4146 ~ 761-4902 ~ 761-507
Fax No. ~ 761-431

Wednesday, October 25, 2000

Dr. Jeff Perry
Department of Emergency Medicine
Ground Floor
Ottawa Hospital - Civic Campus

Dear Dr. Perry:

Re: Protocol # 2000424-01H **Feasibility Study to Derive a Clinical Decision Rule for the Investigation of Alert Patients Suspected of Having a Subarachnoid Hemorrhage - Phase 0**

Protocol approval valid until - Wednesday, October 24, 2001

I am pleased to inform you that your protocol for chart review was reviewed by the Ottawa Hospital Research Ethics Board (OHREB) and approved. No changes, amendments or addenda may be made in the protocol without the OHREB review and approval.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Approximately one month prior to the expiration date listed above, a single renewal form should be sent to the Ottawa Hospital Research Ethics Board Office.

Yours sincerely,

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

Appendix 3a
Physician Data Collection Form

Please Stamp Patient Card

ACUTE HEADACHE STUDY

Data Collection Form

Staff Physicians / Emergency Medicine Residents

Chart No.:_____ ED Visit Date: (y/m/d) ____-____-____

Patient Name : _____

Physician _____

Site: ○ General ○ Civic

Inclusion Criteria

All alert patients 15 years of age or greater with any non-traumatic acute headache.
"Alert" is defined as a Glasgow Coma Scale (GCS) of 15
"Non Traumatic" is defined as no direct trauma to the head in the previous 7 days
"Acute" refers to reaching maximal intensity in less than one hour and the patient presents within 14 days of the headache's onset.

Does the patient meet all of the inclusion criteria? ○ Yes ○ No
(IF 'NO' STOP HERE)

Exclusion Criteria

Patients who have been referred from other centres with confirmed SAH by CT or LP.
Patients with 3 or more ED visits for headache in the last 12 months (at this ED)?.
Patients who return for the same headache who have already been investigated with CT and LP.
Patients with focal neurological deficits or papilledema on physical examination.
Patients with a previous diagnosis of SAH.

Is the patient excluded by any of the exclusion criteria? ○ Yes ○ No
(IF 'YES' STOP HERE)

Please inform patient that they may be contacted by telephone in 30 days for follow up.

Please complete the reverse side prior to sending the patient to CT or performing LP.

Interobserver? ○ Yes ○ No
If 'yes', Physician's name _____

Please return forms to emergency if found on wards

Appendix 3b
Physician Data Collection Form

Headache Characteristics

Time from onset to peak headache? _____seconds, or _____minutes

Time of onset? _____hours _____minutes ○AM ○ PM

Has the pain completely resolved? ○ Yes ○ No If resolved, what was the total duration? _____hours

Pain severity at peak intensity? (0-10) (0 = pain free, 10 = worst pain imaginable)_____

Onset during exertional activity? (e.g. weight lifting, exercise etc.)	○ Yes	○ No
Onset during sexual activity?	○ Yes	○ No
Onset during cough?	○ Yes	○ No
Did headache awake patient from sleep?	○ Yes	○ No
Is this the worst headache the patient has ever had in their life?	○ Yes	○ No
History of similar type of headache in the past?	○ Yes	○ No
Is the headache located only in the occipital area?	○ Yes	○ No
Is the headache unilateral?	○ Yes	○ No
Was the pain relieved with anti-migraine treatment?	○ Yes	○ No

If 'yes', what agent(s)? _____

Associated Features:

Transient loss of consciousness	○ Yes	○ No
Obligated to rest or buckling of legs at onset of headache	○ Yes	○ No
Photophobia	○ Yes	○ No
Symptom of neck pain or stiffness	○ Yes	○ No
Vomiting	○ Yes	○ No
Transient neurological deficits (as recalled by patient)	○ Yes	○ No

If yes, please explain: _____

Sympathomimetic use (cocaine or amphetamine use in the last 48 hours)	○ Yes	○ No
Connective tissue disorder (Ehlers-Danlos Syndrome, Neurofibromatosis, Marfan's, Alpha 1 anti-trypsan deficiency)	○ Yes	○ No
Adult onset polycystic kidney disease	○ Yes	○ No
Family history of SAH	○ Yes	○ No

Physical Exam

Neck stiffness (with lateral rotation)	○ Yes	○ No
Neck stiffness (with flexion and extension)	○ Yes	○ No
Localizing neurological signs	○ Yes	○ No

If 'yes', please explain:_____

Position of patient in room ○ walking ○ sitting ○ lying ○ lying still ○ lying still in dark room

Please describe patient's distress(0-10) (0 = no acute distress, 10 = very distressed)_____

Physician's Judgement

Comfort in performing only LP without CT ○uncomfortable○comfortable○very comfortable

Comfort in ordering no investigations ○ uncomfortable ○ comfortable ○ very comfortable

Clinical probability patient has a SAH(circle) 0% 1% 2% 3% 4% 5% 10% 20% 30% 40% 50% 75% 100%

Investigations

CT Ordered	○ Yes	○ No	If Yes :	○ Normal	○ Abnormal
LP Done	○ Yes	○ No	If Yes :	○ Normal	○ Abnormal

Chart No.:_____ ED Visit Date: (y/m/d) ____-____-____

Patient Initials : _____

ACUTE HEADACHE STUDY (PHASE 1)

Data Collection Form For Missed Patients

Inclusion Criteria

All alert patients 15 years of age or greater with a main complaint of a non-traumatic acute headache or syncope with a headache.

"Alert" is defined as a Glasgow Coma Scale (GCS) of 15

"Non Traumatic" is defined as no direct trauma to the head in the previous 7 days

"Acute" refers to reaching maximal intensity in less than one hour and the patient presents within 14 days of the headache's onset.

(IF 'NO' STOP HERE) ○ Yes ○ No

Exclusion Criteria

Patients who have been referred from other centres with **confirmed** SAH by CT, LP (RBCs or xanthochromia), or angio.

○ Yes ○ No

Patients with a documented history of chronic headaches (E.G. migraines)

○ Yes ○ No

Recorded history of direct trauma to the head in the 7 days prior to presentation.

○ Yes ○ No

The headache is recorded to have reached maximal intensity in greater than one hour.

○ Yes ○ No

The headache is recorded to have been present continuously for greater than 14 days.

○ Yes ○ No

Patients recorded to have focal neurological deficits or papilledema on physical examination.

○ Yes ○ No

Patients recorded to have a GCS of less than 15. ○ Yes ○ No

Is the patient excluded by any of the exclusion criteria? ○ Yes ○ No

(IF 'YES' STOP HERE)

Visit History

Physician (code) _____ Site: ○ General ○ Civic

Physician status ○ Full-time ○ Part-time ○ Housestaff

Transfer from another ED ○ Yes ○ No

If 'yes', with CT head ○ Yes ○ No

And/or LP results ○ Yes ○ No

Baseline Information

Gender ○ male ○ female

Age _____

Investigations

CT Ordered ○ Yes ○ No If Yes : ○ Normal ○ Abnormal

LP Done ○ Yes ○ No If Yes : ○ Normal ○ Abnormal

Diagnosis of SAH ○ Yes ○ No

Final Diagnosis if Not SAH _____

APPENDIX 5a
Research Nurse Data Form
Subject No. : _____
Initials:_____
Chart No:_____

ACUTE HEADACHE STUDY

Eligible Patient Data Collection Form Phase 1

Verification of eligibility Coordinator _____ Research Nurse _____ PI_____

Outstanding Information

(Completed)	(To be completed)	
_____	_____	Emergency Record of Treatment (ROT)
_____	_____	CT head results
_____	_____	LP results
_____	_____	Angiography (or MR Angio) results
_____	_____	RN notes / Vital Signs sheet / Ambulance Notes
_____	_____	Telephone follow-up
_____	_____	Admission Information
_____	_____	Discharge Summary (SAH only, if D/C from ED, consults)
_____	_____	Other_____

Final Diagnosis of SAH ○ Yes ○ No
Final Diagnosis if Not SAH _____
Death ○ Yes ○ No
If survived, neurological deficit ○ Yes ○ No

Visit History
Age (years): _____
Gender : ○ Male ○ Female
Physician (code): _____ Site: ○ General ○ Civic ○ KGH
Physician status ○ Full-time ○ Part-time ○ Housestaff
Interobserver? ○ Yes ○ No
If 'yes', Physician (code)_____
Arrived by Ambulance ○ Yes ○ No
Transfer from another ED ○ Yes ○ No
If 'yes', with CT head ○ Yes ○ No
And/or LP results ○ Yes ○ No

Time of Registration _____:_____ ○ Not documented
Time of initial assessment by physician _____:_____ ○ Not documented
Time of discharge / referral _____:_____ ○ Not documented

APPENDIX 5b
Research Nurse Data Form

Physical exam
Temperature _____°C
Heart rate _____ BPM
Systolic blood pressure _____ mm of Hg
Diastolic blood pressure _____ mm of Hg
CT Ordered ○ Yes ○ No If Yes : ○ Normal ○ Abnormal
If ordered, was it less than 6 hours since headache onset? ○ Yes ○ No
LP Done ○ Yes ○ No If Yes : ○ Normal ○ Abnormal
If done, was it over 12 hours since headache onset? ○ Yes ○ No
Requires follow-up ○ Yes ○ No
Admitted? ○ Yes ○ No

Did the patient require any neurological intervention ○ Yes ○ No
If 'yes', please indicate all interventions
○ Craniotomy
○ Intubation and ventilation
○ Medical management
○ Aneurysm clipping
○ Intracranial pressure monitoring

If abnormal CT scan
Subarachnoid hemorrhage ○ Yes ○ No
Subdural hematoma ○ Yes ○ No
Intracerebral hematoma ○ Yes ○ No
Cerebellar hematoma ○ Yes ○ No
Invtraventricular hemorrhage ○ Yes ○ No
Tumor (primary) ○ Yes ○ No
Tumor (mets) ○ Yes ○ No
Abscess ○ Yes ○ No
Other: _____

If abnormal LP
WBC > 5 ○ Yes ○ No If yes, Value_____
RBC Present (first tube) ○ Yes ○ No If yes, Value_____
RBC Present (last tube) ○ Yes ○ No If yes, Value_____
Xanthochromia ○ Yes ○ No
Bacteria on gram stain ○ Yes ○ No
If yes, Culture result _____

Results of Angiography (or MR Angiography)
○ Normal
○ Aneurysm
If Aneurysm, ○ Internal carotid artery ○ Middle cerebral artery ○ Anterior cerebral artery ○ Vertebrobasilar-posterior circulation ○ Other If Other Aneurysm, where?_____
Other Findings: _____

Appendix 6
One-Month Telephone Follow-Up Form

Subject No.:_____ Requires Telephone Call On:_____

SAH STUDY

TELEPHONE FOLLOW-UP (DAY 30)
For Patients Not Getting CT and LP Done in ED

Date and times of attempts:

_____

_____

Date reached: (y/m/d) _____-_____-_____

1) a) Do you still have a **headache?** ○ No ○ Yes
If '**no**', skip to question #2
b) If '**yes**' please rate your headache as: ○ mild ○ moderate ○ severe

2) a) Have you returned to see a physician since your initial emergency department visit? ○ No ○ Yes
b) If '**yes**', please explain - _____

3) a) Has your headache been diagnosed differently since your initial emergency department visit? ○ No ○ Yes
b) If '**yes**', what diagnosis have you been given? _____

4) a) Have you suffered any ill effects from your headache? ○ No ○ Yes
b) If '**yes**', please explain - _____

5) Have you had a CT scan of your head since you were discharged from the emergency department? ○ No ○ Yes
If '**yes**' where did you have the CT done?_____
If '**yes**' what was the result? ○ Normal ○ Abnormal

6) Have you had a Lumbar puncture test since you were discharged from the emergency department? ○ No ○ Yes
If '**yes**' where did you have the LP done?_____
If '**yes**' what was the result? ○ Normal ○ Abnormal

7) Did you ever require any surgical intervention (i.e. craniotomy, etc) ○ No ○ Yes
Comments: _____

The Ottawa Hospital | L'Hôpital d'Ottawa

C
761-[illegible]
Fax No. ~ 761-431

Thursday, October 05, 2000

Dr. Jeff Perry
Department of Emergency Medicine
Ground Floor
Ottawa Hospital - Civic Campus

Dear Dr. Perry:

Re: Protocol # 2000294-01H **A Feasibility Study to Derive a Clinical Decision Rule for the Alert Patients Suspected of Having Subarachnoid Haemorrhage**

Protocol approval valid until - Thursday, October 04, 2001

Thank you for your letter dated October 2, 2000. I am pleased to inform you that your study (listed above) was given expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. Approval is for the Protocol submitted June 23, 2000, the Data Collection Form, and the telephone Follow-up. No changes, amendments or addenda may be made in the protocol without the OHREB review and approval.

Approximately two months prior to the expiration date listed above, a single renewal form should be sent to the OHREB office.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. You must maintain as part of your records copies of the signed consent form. As well, you must inform the Board of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the Board review, either of which may impinge on the ethics of continuing the study. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely,

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

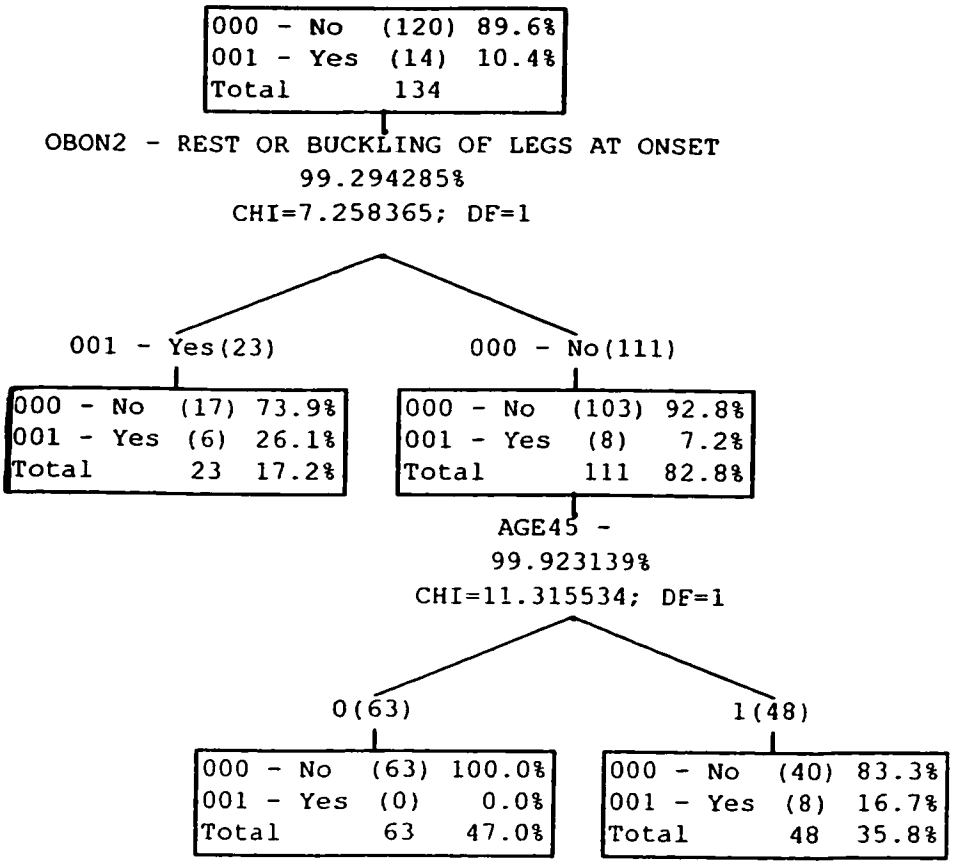
Appendix 8
Initial Logistic Regression Analysis of the Data from a 7-Month Prospective Cohort Study of Patients Presenting to Emergency with an Acute Headache

Logistic Regression with following variables in model alone	Beta	SE	P value	OR
Age (Continuous)	.065	.02	.001	1.07
Age 40	2.6	1.1	.013	13.9
Female	.476	.62	.443	1.6
Time from Onset to Peak in Minutes	-.014	.02	.421	1.00
Duration of Headache in Minutes	.001	.001	.04	1.00
Mean Pain Severity at Peak [0-10]	.079	.19	.672	1.08
Onset During Exertional Activity	1.72	.70	.013	5.6
Exertional or Sexual Activity	1.28	.66	.054	3.6
Onset During Sexual Activity	.802	1.1	.488	2.2
Onset During Cough	-5.1	21	.81	.01
Did Headache Awake from Sleep	-7.2	21	.729	.001
Worst Headache of Life	8.3	29	.77	4243
Similar Headache Quality in Past	-.2	.68	.77	.82
Occipital Area Only	1.1	.66	.091	3
Unilateral	-.62	.69	.36	.54
Relieved with Anti-Migraine Treatment	-.45	.81	.58	.64
Transient Loss of Consciousness	2.77	.97	.004	15.95
Obligated to Rest	1.5	.6	.12	4.54
Photophobia	.39	.58	.50	1.48
Patient Complaint of Neck Pain	1.6	.62	.010	4.94
Vomiting	.97	.57	.09	2.64
Transient Neurological Deficits	.19	.69	.779	1.22
Sympathomimetic Use	-6.1	30	.84	.002
Connective Tissue Disorder				
Adult Onset Polycystic Kidney Disease	-4.1	22	.854	.02
Family History of Subarachnoid Haemorrhage	-7.1	33	.831	.001

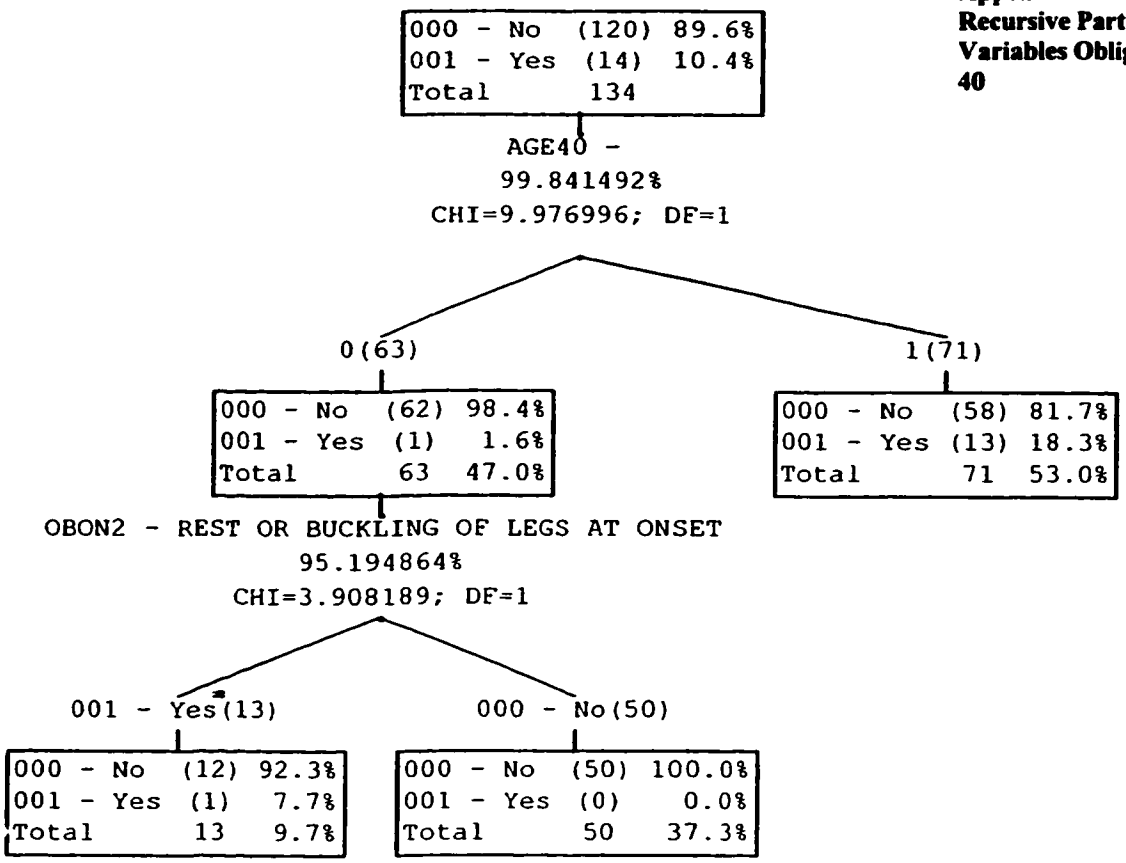
Appendix 9
Logistic Regression Model with the Data from a 7-Month Prospective Cohort Study of Patients Presenting to Emergency with an Acute Headache

Logistic Regression with following variables in model alone	Beta	SE	p-value	OR
Neck Stiffness (lateral rotation)	2.09	0.66	0.002	8.09
Neck Stiffness (flexion/extension)	1.77	0.65	0.006	5.89
Mean Temperature in Celsius	-0.645	0.37	0.080	0.53
Mean Heart Rate [BPM]	-0.002	0.02	0.911	1.0
Mean Systolic Blood Pressure [mm of Hg]	0.010	0.01	0.338	1.01
Mean Diastolic Blood Pressure [mm of Hg]	0.031	0.02	0.144	1.03
Patient Position in Room (4 dummy variables)			0.02	
Mean Physician Rating of Patient Distress [0-10]	0.45	0.14	0.001	1.57

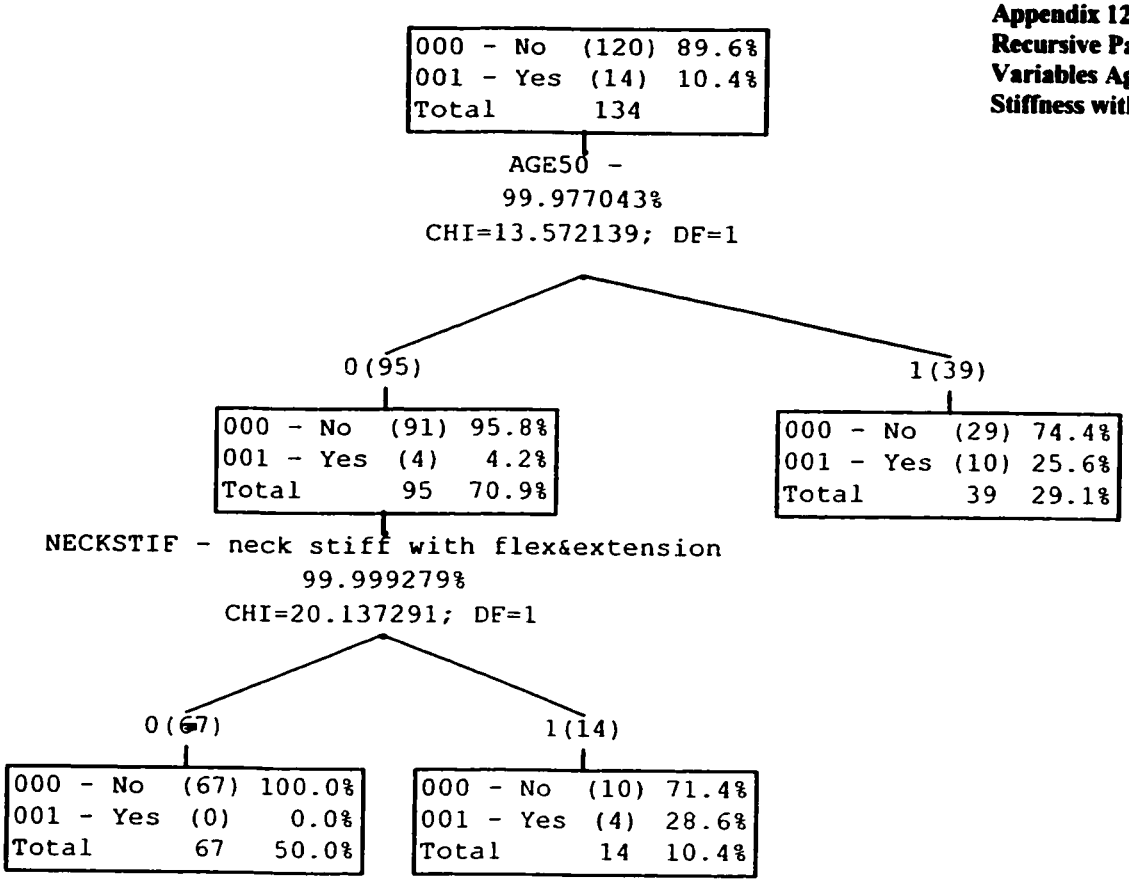
Appendix 10
Recursive Partitioning Model with Variables Obliged to Rest and Age Over 45



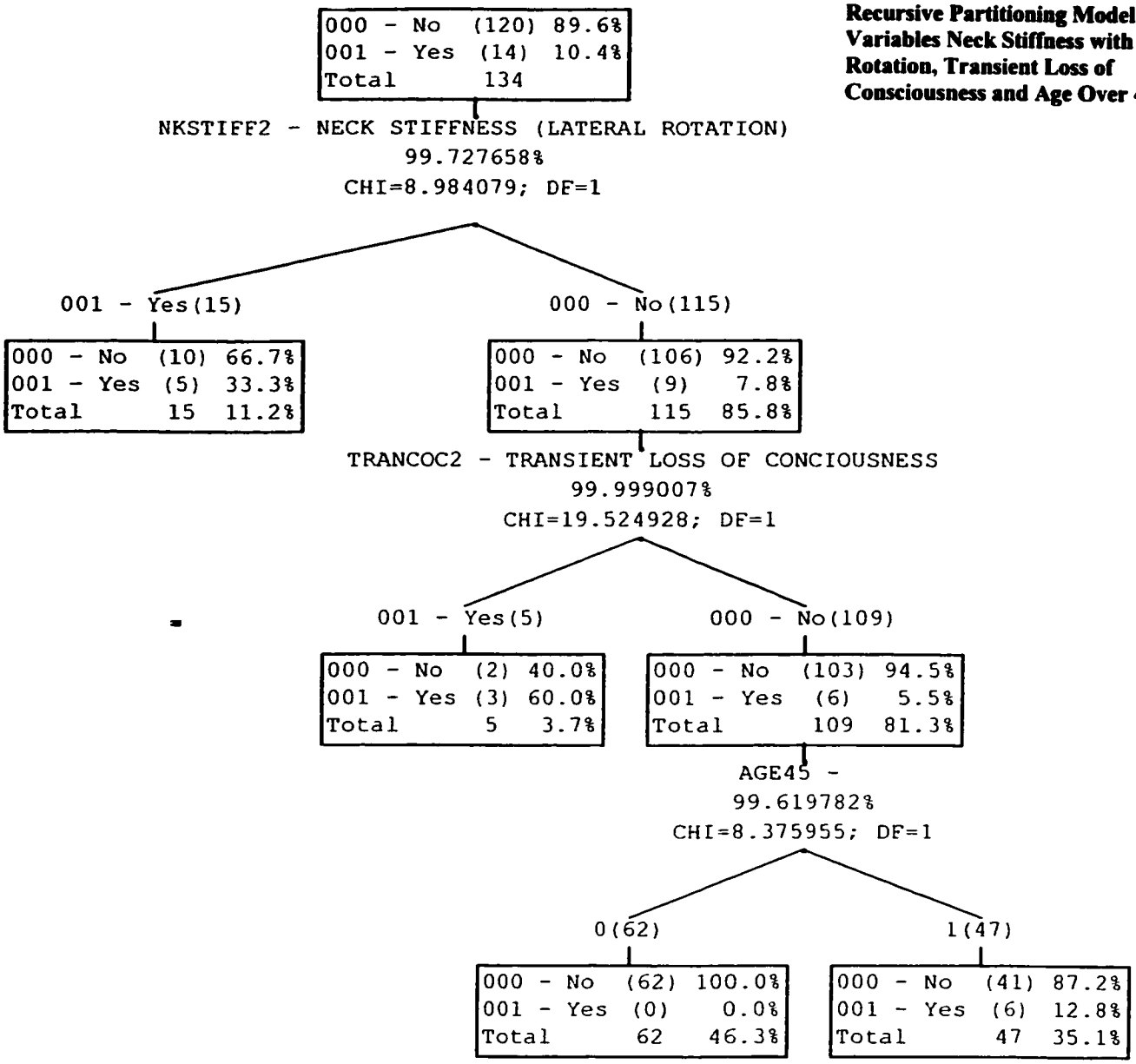
Appendix 11
Recursive Partitioning Model with Variables Obliged to Rest and Age Over 40



Appendix 12
Recursive Partitioning Model with Variables Age Over 50 and Neck Stiffness with Flexion/Extension



Appendix 13
Recursive Partitioning Model with Variables Neck Stiffness with Lateral Rotation, Transient Loss of Consciousness and Age Over 45



Appendix 14
Recursive Partitioning Model with Variables Age Over 50, Obliged to Re and Systolic Blood Pressure Over 160