METHODOLOGY

Canadian CT Head Rule Study for Patients With Minor Head Injury: Methodology for Phase II (Validation and Economic Analysis)

Prospective validation on a new set of patients is an essential test of a new decision rule. However, many clinical decision rules are not prospectively assessed to determine their accuracy, reliability, clinical sensibility, or potential impact on practice. This validation process is important because many statistically derived rules or guidelines do not perform well when tested in a new population. The methodologic standards for a validation study are similar to those described in the article on phase I for derivation studies in the August 2001 issue of Annals of Emergency Medicine. The goal of phase II is to prospectively assess the accuracy, reliability, and acceptability of the decision rule in a new set of patients with minor head injury. This will determine the clinical utility of the rule and is essential if such a rule is to be widely adopted into clinical practice.

or potential impact on practice. This validation process is very important because many statistically derived rules or guidelines do not perform well when tested in a new population.1a-3 The reason for this poor performance may be statistical (ie, overfitting or instability of the original derived model),4 or may be because of differences in prevalence of disease or differences in how the decision rule is applied.5,6 The methodologic standards for a validation study are similar to those described in phase I for derivation studies. Implementation to demonstrate the true effect on patient care is the ultimate test of a decision rule; transportability can be tested at this stage.7

**SPECIFIC OBJECTIVES FOR PHASE II: VALIDATION OF THE RULE**

1. To determine the accuracy or classification performance of the decision rule when applied prospectively.
2. To determine the reliability or interobserver agreement of the rule.
3. To determine the clinical sensibility (ie, physicians’ accuracy, comfort, and ease of use with applying the rule).
4. To determine the potential of the rule to reduce the use of computed tomography (CT).
5. To determine the potential for refinement of the rule (improved specificity).
6. To determine the potential savings associated with widespread implementation of the rule, in a preliminary economic evaluation.

**METHODS—PHASE II: VALIDATION OF THE RULE**

**Study population and setting**

Phase II will also constitute a 30-month prospective cohort study conducted at 8 large Canadian hospital emergency departments and enrolling new patients with the same inclusion and exclusion criteria as for phase I.

**Standardized patient assessment**

All eligible patients will be assessed by the same staff emergency physicians and residents to determine the patients’ status for each of the component variables within the decision rule derived in phase I. The physicians will record these findings along with their interpretation of the decision rule itself on the data collection sheets before radiography. Variables not found to be useful in phase I will not be assessed in phase II. When feasible, a subset of patients will be independently assessed by a second emergency physician to judge interobserver agreement for interpretation of the rule itself as well as for the component variables. In addition, the physicians will indicate, on a 5-point scale, their theoretical comfort in applying the rule for each patient.

**Outcome measures**

The primary outcome measure, “need for neurologic intervention,” will be ascertained in the same manner as in phase I by a research assistant who is unaware of the classification indicated on the data collection sheet. The secondary outcome, “clinically important brain injury,” will be determined by standard CT scanning of the head, which will be interpreted by a staff radiologist blinded to the contents of the data collection sheet. The treating physicians will be encouraged not to alter their normal radiography ordering practice. Consequently, we expect that some patients will have their outcome status determined by telephone follow-up, using the same proxy primary outcome as in phase I. Patients will be considered not to have acute brain injury if they fulfill the same criteria listed in “Proxy Secondary Outcome.” This judgment will be made at 14 days by a research assistant unaware of the classification on the data collection sheet.

**Data analysis**

The classification performance of the rule for predicting the 2 outcome measures will be assessed with 95% confidence intervals (CIs) for sensitivity, specificity, negative predictive value, and positive predictive value. The “criterion interpretation” of the rule (ie, positive or negative for need for neurologic intervention and for clinically important brain injury), will be made by the investigators based on the status of the patient for the component variables as documented by the treating physician. Calculation of likelihood ratios will allow estimation of the probability of the outcomes in patients, given a negative status for the Canadian CT Head Rule (Figure 1). The actual performance of the rule will be compared with the predictions of physicians made in phase I.

The interobserver agreement for each variable, as well as for interpretation of the rule itself, will be measured by calculating the κ coefficient, the proportion of potential agreement beyond chance, along with 95% CIs.8,9 For variables with 3 or more ordered categories, a weighted κ measure of interobserver agreement will be calculated.10 Accuracy will be calculated for interpretations of the rule by the treating physicians versus the criterion interpretations by the investigators. Data regarding physicians’ theoretical comfort and perceived ease of use of the rule will be given in a simple descriptive format.
The referral fraction for CT according to the Canadian CT Head Rule will be compared with the baseline referral fractions of phase I at the study hospitals. This will estimate the potential for reducing the number of CT scans ordered, if the rule had been applied.

The data collected will be further analyzed after approximately 1,500 patients have been enrolled to assess the potential for refining the Canadian CT Head Rule. The objective of this analysis would be to achieve a sensitivity of 1.0 for neurologic intervention with the highest possible specificity and the fewest number of variables. The statistical approach will be that used in phase I to derive the current rule and was previously used to refine the Ottawa Ankle Rules.11 (1) The interobserver agreement for each variable will be measured by calculating the $\kappa$ coefficient.8,9 (2) Univariate analyses will be used to determine the strength of association between each variable and the primary outcomes, need for neurologic intervention and important brain injury on CT. (3) Multivariate analyses will derive a model to predict acute brain injury by combining those variables found to be both reliable and strongly associated with the outcome measures ($P<0.05$). Recursive partitioning will be performed using KnowledgeSEEKER software (version 3.1, Angoss Software, Toronto, Ontario, Canada).12-15 (4) Further validation of the refined rule will be conducted with 1,000 patients.

Sample size

Two thousand five hundred patients will be enrolled over 30 months at the study sites. Because no hypothesis is being tested, sample size is based on estimation of the precision of the sensitivity of the derived decision rule. The sample size must accommodate the very low prevalence of cases requiring neurologic intervention (1.6% of patients enrolled in phase I) or having important brain injury (8.7%). A sample size of 2,500 eligible patients with minor head injury should yield approximately 40 cases requiring neurologic intervention and 230 cases with important brain injury. For a 100% sensitivity, this sample size would yield upper and lower limits of the 95% CIs of 100% to 91%, respectively, for neurologic intervention and 100% to 98% for important brain injury.10 Furthermore, for a cumulative sensitivity of 100% in phases I and II combined, the 95% CI limits would be 100% to 95% for 80 cases of neurologic intervention and 100% to 99% for 460 cases of important brain injury. We anticipate that a 30-month period should easily yield the required number of cases for phase II at the participating sites.

Two hundred patients will be assessed by 2 study physicians to determine interobserver agreement for the Canadian CT Head Rule as well as for the component variables. The number 200 is dictated primarily by considerations of feasibility as obtaining assessments by 2 physicians in a busy ED is very difficult. With 200 patients, the upper and lower 95% CIs for a $\kappa$ value of 0.6 are 0.73 and 0.47, respectively.16

METHODS: PRELIMINARY ECONOMIC EVALUATION

The objective of the preliminary economic analysis will be to identify the potential cost-effectiveness of the Canadian CT Head Rule if its use becomes widespread. The analysis will assist in determining the rationale for an implementation trial and will help in refining the methodology for a full economic analysis alongside such a trial. We will adopt a decision analytic approach similar to a previous cost-effectiveness analysis of the implementation of the Ottawa Ankle Rules.17 We will identify the incremental cost savings with widespread compliance with the Canadian CT Head Rule from both a health care sector and a societal perspective. The model will consider 2 hypothetical cohorts of patients: a “usual practice” cohort and a cohort for whom practice is guided by the Canadian CT Head Rule. In our baseline analysis, both cohorts of patients will adopt the characteristics of patients in phase II. The use of CT scanning and the brain injury rates will be estimated from the baseline rates of phase I for the usual practice cohort and from the pre-
dicted rates from phase II for the Canadian CT Head Rule cohort. The baseline CT rate is estimated to be 65%. The sensitivity of the results to the parameters relating to the usual practice cohort will be assessed by varying data found in Canadian EDs in phase 0 (ie, CT rate will be varied from 15% to 80%). Similarly, the robustness to changes in the sensitivity and specificity of the decision rule will be assessed.

The principal resources in this analysis will be the costs of CT and the associated patient time costs. Where appropriate, especially within the sensitivity analysis, the costs of litigation settlement, the incremental costs of follow-up treatment because of missed brain injury, and the costs of neurologic deficits will also be included. The probability that patients at each node will need neurologic intervention will be determined by the current validation study (phase II) of the Canadian CT Head Rule. By basing our estimate of the probability of CT on the phase II results, we are assuming that clinicians will be fully compliant in their use of the Canadian CT Head Rule. Thus, our base case analysis will identify the highest estimate of cost savings that could be attributable to the use of the rule. Detailed sensitivity analysis will be conducted to assess the robustness of the study’s results to changes in key parameters.

The design of the decision analytic model, sources of data, and range of sensitivity analysis are detailed in the following text and in Figure 2. For each terminal node within the decision tree, we will estimate the appropriate costs from both a health care and a societal perspective. Analysis will focus on identifying the significance of cost savings attributable to the use of the CT head decision rule. Interpretation of the analysis will focus on the cost savings relative to the clinical effects of the rule.

Estimates of the sensitivity and specificity of the decision rule will be obtained from the validation exercise. For sensitivity analysis, we will use the 95% CI relating to sensitivity and specificity. In addition, we will determine the threshold value for the specificity of the rule below which use of the rule would not be cost saving. For the baseline analysis, the cost of CT scanning will be obtained from both the Civic and General campuses of the Ottawa Hospital. For sensitivity analysis, costs will be obtained from other participating centers. The amount of patient

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**Figure 2.**
Structure of decision analytic model for economic analysis.
time saved because of the reduction in testing will be derived from data obtained in the phase I study. The value of this time will be represented by the mean wage rate. Incremental treatment for missed acute brain injuries and hematomas will be estimated by use of a clinical Delphi panel and chart audit. Costs of resource use will be obtained from the Ottawa Hospital and the Ontario Health Insurance Plan Schedule of Fees and Benefits. The proportion of missed brain injuries will be estimated by combining data from both the phase I study and the validation exercise. The rate and success of litigation for missed brain injuries will be estimated by a survey of experts in medicolegal issues in emergency medicine. The mean cost of compensation packages for litigation settlement for missed brain injuries will be obtained from the Canadian Medical Protective Association. For sensitivity analysis, the proportion of usual practice patients who receive CT scanning will be varied according to the results of the survey of current practice where practice varied from 15% to 80%.

Sensitivity analysis will address both uncertainty related to variability in data from the validation study and uncertainty relating to the generalizability of our base case results. Parameters for which sensitivity analysis will be conducted are (1) the proportion of patients treated under usual care who undergo CT scans of the head, (2) the sensitivity of the CT Head Rule, (3) the proportion of patients with injuries, (4) the costs of CT, and (5) the rate and success of litigation and the size of compensation package. Analysis will be both univariate and bivariate and will take the form of both simple sensitivity analysis using different parameter estimates and threshold analysis that will allow identification of parameter estimates associated with cost neutrality.

**Relevance**

We estimate that each year physicians in US EDs treat 800,000 adults with minor head injury (ie, loss of consciousness or amnesia with Glasgow Coma Scale scores of 13 to 15). Only 6.2% of these patients have incurred any type of brain injury visible on CT scan, and only 0.5% have a potentially life-threatening epidural hematoma. There are no widely accepted guidelines to help physicians standardize quality of care or to maximize the efficiency of their use of CT scans for minor head injury. Our data clearly show that emergency physicians accept and endorse the concept of selective ordering of CT scans. Currently, there is considerable variation among hospitals in the referral rate for CT. Use of CT is not efficient—

results of almost 80% of CT scans ordered are negative for any injury and 98% are negative for epidural hematoma. Despite this inefficiency, our data show that a number of important intracranial hematomas are being missed in patients with minor head injury. Inefficient use of CT scans significantly contributes to health care costs.

We will develop (phase I) and prospectively validate (phase II) a clinical decision rule that will permit physicians to be more accurate in their diagnosis of acute brain injury among patients with minor head injury and less likely to miss important intracranial hematomas. Furthermore, physicians could be more selective in their use of CT scanning without jeopardizing the quality of patient care. Such a decision rule should, therefore, lead to improved patient care and considerable savings for North American health care systems. The potential impact of this decision rule will be similar to that of the Ottawa Ankle Rules, which have been readily adopted by many physicians and which have been shown to significantly reduce health care costs.

**References**


