PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Prospective Cohort Study of Self-Reported Computerized Medical History Taking for Acute Chest Pain: Protocol of the CLEOS Chest Pain Danderyd Study (CLEOS-CPDS)
AUTHORS	Brandberg, Helge; Kahan, Thomas; Spaak, Jonas; Sundberg, Kay; Koch, Sabine; Adeli, Athena; Sundberg, Carl Johan; Zakim, David

VERSION 1 – REVIEW

REVIEWER	Dylan Cooper, MD Indiana University School of Medicine, USA
REVIEW RETURNED	10-Jun-2019

GENERAL COMMENTS	Well designed and written submission. The study evaluates CHT as compared to physician histories. Please consider the following questions in your limitations / discussion. First, length of time is a concern as the CHT takes an average of 60 minutes to complete. This is much longer than time taken by physicians in a history, specifically in the Emergency Department where our average providers have seen 3-4 patients during this time. Second, there is significant differences in a patient reading questions as opposed to answering verbal questions - perhaps study the accuracy of CHT results as compared to the EMR / EHR? Third, the ED is specific to patients with chest pain, with evaluation by a cardiologist, which limits the application to an all-comer ED, where ED physicians evaluate all patients. Finally, the CHT is capturing every question asked, whereby the physician history is captured from the EMR / EHR, therefore some information will not be documented that was actually captured in the physician's history. Therefore one would expect the CHT to contain more data given the length of the interview and amount of data captured. Overall this is an interesting study with potential for future applications.

REVIEWER	William Alley Wake Forest Baptist Medical Center
REVIEW RETURNED	03-Sep-2019

GENERAL COMMENTS	This is a well-conceived and valuable study with potential to significantly improve the care of patients presenting with chest pain. As touched on in the limitations section, this data may not be generalizable to other settings, given the single-site design. The introduction also sites a markedly high expected disease prevalence compared to US data. In reviewing the citations for this number, I wonder if this disease prevalence could be better

	clarified, though I believe this to be a minor issue. I look forward to the dissemination of the results of this study.

REVIEWER	Karl Wegscheider Institute of Medical Biometrics and Epidemiology University Medical Center Hamburg-Eppendorf Germany
REVIEW RETURNED	29-Sep-2019

GENERAL COMMENTS	This cohort study has a skillful design which seems to be appropriate for the elaborate research questions given. However, more details are required. 1) Sample size calculation: A justification for the assumption of 50% ACS prevalence should be given 2) Statistical tests/statistical methods to be used should be precisely defined in the ‚Outcomes' section.They should be described in the required detail for an external statistician to perform the identical outcome evaluation once she has given access to the data. 3) Page 11 Line 17-20 ‚CHT data will not be available to the care providers.' Does this sentence relate to this study only, or is it a feature of CHT data not to be given to care providers even after the study is finished? Please clarify. 4) Abstract, last sentence: Page 3 Line 47 ‚with have' should presumably be ‚with' or ‚which have'. Please correct. I recommend a thorough review since more mistakes of that kind are in the manuscript.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1:

Comment 1: Please consider the following questions in your limitations / discussion:
First, length of time is a concern as the CHT takes an average of 60 minutes to complete. This is much longer than time taken by physicians in a history, specifically in the Emergency Department where our average providers have seen 3-4 patients during this time.

Response: Thank you, for mentioning this important point. We made further analyses from the pilot study on the interview duration and have chosen to exclude pauses longer than 2 minutes from the interview, with the assumption that this indicated that the patient was interrupted by e.g. blood sampling, radiology exam, or physician interview. With this analysis the mean duration of the interview was approximately 45 minutes. The text is now revised to include these results. Furthermore, this potential limitation is now specifically discussed in the revised text. Of note, the CHT in this study was performed only during waiting times in the ED and the time spent in the ED is comprised many other factors than the actual time spent for the physician to take a proper history. Please see p 14, 1st para; and p 19, 3rd para.

Revised/new text: The interview can be paused at any question as many times as necessary and resumed automatically at the last unanswered question. The duration of interviews depends on the individual's pathway, but is approximately 45 minutes when pauses > 2 minutes are excluded, with the assumption that this indicated the patient being interrupted by other activities such as blood testing, radiology, interview by physician or other staff.

Also, the time for CHT is longer than for a traditional history taken by a physician, which may be a

concern with time constraints in an ED setting. However, the results of the current study may help developing future CHT modules which are briefer but with equal or better performance.

Comment 2: Second, there is significant differences in a patient reading questions as opposed to answering verbal questions - perhaps study the accuracy of CHT results as compared to the EMR / EHR?

Response: Thank you for this suggestion. We agree on the importance of this analysis. The text has been revised to include this observation and our intention to further study the accuracy of CHT results, as compared to answering them verbally. Please see p 20, 1st para.

Revised/new text: Third, there might be a difference in patients reading questions as opposed to answering them verbally. Also, CHT will capture every question asked, whereby the data for standard history taking will be collected from the EHR. Therefore, information captured during standard history taking might not be documented and more complete data from CHT will be expected. These two issues will be addressed when analysing the congruency between CHT and EHR data.

Comment 3: Third, the ED is specific to patients with chest pain, with evaluation by a cardiologist, which limits the application to an all-comer ED, where ED physicians evaluate all patients.

Response: We agree that the ED setting can limit the applicability of our results. However, the ED setting in our study is not specific to patients with chest pain, as it includes all patients with potential cardiology related conditions in a very broad sense. Second, the use of ED physicians in the emergency setting is not a general rule and may be very different with different care provider systems. We have now revised the text to include this important limitation on the generalizability of our results. Please see p 20, 1st para.

Revised/new text: Furthermore, the ED in this study has a specific cardiology unit where the attending physician is a cardiologist. This may limit the application of the results to other settings with an ED with unsorted flow, and/or where ED physicians evaluate all patients.

Comment 4: Finally, the CHT is capturing every question asked, whereby the physician history is captured from the EMR / EHR, therefore some information will not be documented that was actually captured in the physician's history. Therefore one would expect the CHT to contain more data given the length of the interview and amount of data captured.

Response: Thank you for raising this important point. To highlight this concern, we have clarified this in the Discussion section. Please see p 20, 1st para.

Revised/new text: Also, CHT will capture every question asked, whereby the data for standard history taking will be collected from the EHR. Therefore, information captured during standard history taking might not be documented and more complete data from CHT will be expected.

REVIEWER 2:

Comment 1: The introduction also sites a markedly high expected disease prevalence compared to US data. In reviewing the citations for this number, I wonder if this disease prevalence could be better clarified, though I believe this to be a minor issue.

Response: Thank you for this comment. The seemingly high disease prevalence was obtained from the European Society of Cardiology guidelines for non-STEMI (Roffi et al, Eur Heart J 2015). We have

reviewed the sources of these figures, which are based on both European and American populations. A recently published review (Fitzgerald et al, Expert Rev Cardiovasc Ther, 2019 [e-pub before press]) reports 7-23% MI in acute chest pain patients. As suggested, we revised and expanded the text somewhat. Please see p 6, 1st para.

Revised/new text: According to an overview based on both European and US data disease prevalence in unselected patients presenting to the ED with acute chest pain may be as high as 5-10 % for ST-elevation myocardial infarction, 15-20 % for non-ST-elevation myocardial infarction and 10 % for unstable angina pectoris(3), which is consistent with Swedish data(4).

REVIEWER 3:

Comment 1: Sample size calculation: A justification for the assumption of 50% ACS prevalence should be given

Response: Thank you for this important comment. Together with our statistician (Jan Kowalski, JK Biostatistics AB, Stockholm) we have rewritten the text to clarify the background for our assumptions. Please see p 15, 2nd para.

Revised/new text: This is an exploratory study. The calculation of the sample size of the study population is based on the targeted precision of sensitivity and specificity. As the prevalence of ACS in the study population is unknown, we have based the calculation of the number of subjects based on the assumption that the prevalence is 0.5 (50 %) which maximizes the estimated sample size. To obtain a precision of sensitivity and specificity of ±0.03 (3 %) (nQuery version 7.0, Statistical Solutions Ltd, Boston, MA, USA) 1,000 patients are required. The more the extreme the result, i.e. sensitivity or specificity approaching 0 or 1 (100 %), the higher the precision and subsequently lower number of subjects needed for this study.

Comment 2: Statistical tests/statistical methods to be used should be precisely defined in the ‚Outcomes' section. They should be described in the required detail for an external statistician to perform the identical outcome evaluation once she has given access to the data.

Response: As suggested, we have now carefully revised the text to include more information on the major statistical methods we plan to use. Also, as requested, much of this text has been moved to “Outcome”; while some information is to be found under “Data Management and data analysis plan” when more appropriate. Please see p 15/16, 3rd/1st para; p 17, 2nd para; p 17, 3rd para.

Revised/new text: The primary objective is to determine whether the use of CHT (index test 1) is better than standard history taking obtained by the physician (index test 2) in attendance (generally a specialist or resident in cardiology) for the prediction and safe exclusion of an ACS in the acute setting in patients with non-diagnostic ECG or serum markers. Thus, the primary outcome (reference test) is the comparison of the accuracy between the two methods for the safe exclusion of ACS or a diagnosis of ACS in the acute setting i.e. within seven days from the ED visit. The diagnosis of ACS will be based on current European guidelines(3, 28). The diagnosis will be validated by an experienced cardiologist. A cross tabulation of the index test results against the reference test will allow estimations for sensitivity, specificity and predictive values. Confidence intervals will be calculated. The results will be presented graphically with a receiver operating characteristic (ROC) curve for each index test. Also, likelihood ratios will be calculated.

Revised/new text: Descriptive statistics will be used to describe demography and background characteristics (e.g. mean values and standard deviations or confidence values, median values and

interquartile ranges, or proportions, as appropriate). We will evaluate established risk scores, as populated with CLEOS data, and compare these results with data obtained during the concurrent ED visit and made available in the standard hospital EHR. Regression-based statistical analyses will be used, and appropriate tests for significant difference of completeness of the risk scores (e.g. the Chi-square test, Student's t-test and McNemar's test).

Revised/new text: Second, to assess how data collected with CLEOS in combination with established risk scores can rule-in and rule-out a diagnosis of an ACS, we will calculate sensitivity, specificity and negative and positive predictive values. The results will be presented with receiver operating characteristic (ROC) curves for each risk score and the Hanley and McNeil method to test for difference. Logistic regression will be used to describe the relationship with the predictions and actual outcomes (i.e. ACS or not ACS).

Comment 3: Page 11 Line 17-20 ‚CHT data will not be available to the care providers.' Does this sentence relate to this study only, or is it a feature of CHT data not to be given to care providers even after the study is finished? Please clarify.

Response: We have now revised the text to clarify that CHT data obtained during the study period will not be available to the care providers. Please see p 11, 1st para.

Revised/new text: During the study period CHT data will not be available to the care providers.

Comment 4: Abstract, last sentence: Page 3 Line 47 ‚with have' should presumably be ‚with' or ‚which have'. Please correct. I recommend a thorough review since more mistakes of that kind are in the manuscript.

Response: Thank you for catching this and other errors, which now has been corrected. The manuscript has been reviewed thoroughly again and as you noted, more errors were to be found. This has led to the following improvements in the manuscript:

Revised/new text:
Page 1 - Deleted recurrence of 'professor'
Page 3 - Deleted 'have' (1st para)
Page 6 - 'biomarkers of acute myocardial injury' changed to 'biomarkers indicating acute ...' (1st para)
Page 6 - 'coronary arteries put'' changed to 'coronary arteries puts' (2nd para)
Page 10 - 'The' added before 'triage'. (2nd para)
Page 11 - 'Wait times' changed to 'waiting times'. (2nd para)
Page 11 - Order of 'CHT will thus' changed to 'CHT thus will' (2nd para)
Page 11 - The sentence ' Data on use of resources will be extracted from hospital EHR to generate the cost associated with routine care patient-by-patient' is changed to ' To generate the cost associated with routine care patient-by-patient data on use of resources will be extracted from the hospital EHR' (5th para)
Page 13 - 'with' deleted (1st para)
Page 13 - 'but' deleted (1st para)
Page 14 - 'economy student' changed to 'economics student' (2nd para)
Page 18 - Order of 'the patient perspective have been...' changed. (2nd para)
Page 20 - 'sensitive analysis' changed to 'sensitivity analysis' (1st para)

VERSION 2 – REVIEW

REVIEWER	Dylan Cooper Indiana University, Indianapolis, IN, USA
REVIEW RETURNED	03-Dec-2019

GENERAL COMMENTS	My prior comments and concerns have been appropriately addressed in this revision, will be interesting to see the results. I would add one question to consider for future studies and analysis. Does the effect of patient data prior to the history (EKG, lab work) affect the history obtained by a physician? In this study, the physician will analyze this data before or while taking a patient history, whereas the CHT will not incorporate this data into history taking.

REVIEWER	Karl Wegscheider Universitätsklinikum Hamburg-Eppendorf Germany
REVIEW RETURNED	13-Nov-2019

GENERAL COMMENTS	Good luck with the study!

VERSION 2 – AUTHOR RESPONSE

REVIEWER 1:

Comment: I would add one question to consider for future studies and analysis. Does the effect of patient data prior to the history (EKG, lab work) affect the history obtained by a physician? In this study, the physician will analyze this data before or while taking a patient history, whereas the CHT will not incorporate this data into history taking.

Response: Thank you for this important and interesting comment. We agree on this potential confounding factor that may warrant further study. We have included this potential limitation in the discussion section. Please see page 20.

Revised/new text: Fourth, the effect of patient data collected prior to the history taking e.g. ECG or blood samples collected in the triage, is another potential confounding factor as the physician will have access to this data before obtaining history, whereas the CHT will not. This potential confounding may warrant further study.