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A Prospective Cohort Study of Self-Reported Computerized Medical History Taking for Acute Chest Pain: The Design of the CLEOS Chest Pain Danderyd Study (CLEOS-CPDS)

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A PROSPECTIVE COHORT STUDY OF SELF-REPORTED COMPUTERIZED MEDICAL HISTORY TAKING FOR ACUTE CHEST PAIN: THE DESIGN OF THE CLEOS CHEST PAIN DANDERYD STUDY (CLEOS-CPDS)

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ABSTRACT

Introduction

Management of acute chest pain focuses on diagnosis or safe rule-out of an acute coronary syndrome (ACS). We aim to determine the additional value of self-reported computerized history taking (CHT).

Methods and analysis

Prospective cohort study design with self-reported, medical histories collected by a CHT program (Clinical Expert Operating System, CLEOS) using a tablet. Women and men presenting with acute chest pain to the emergency department at Danderyd University Hospital (Stockholm, Sweden) are eligible. CHT will be compared with standard history taking for completeness of data required to calculate ACS risk scores such as HEART, GRACE, and TIMI. Clinical outcomes will be extracted from hospital electronic health records and national registries. The CLEOS-CPDS project includes (I) a feasibility study of CHT, (II) a validation study of CHT as compared with standard history taking, (III) a paired diagnostic accuracy study using data from CHT and established risk scores, (IV) a clinical utility study to evaluate the impact of CHT on management of chest pain and use of resources, and (V) data mining, aiming to generate an improved risk score for ACS. Primary outcomes will be analysed after 1,000 patients, but to allow for subgroup analysis, the study intends to recruit 2,000 or more patients. This project may lead to new and more effective ways for collecting thorough, accurate medical histories with have important implications for clinical practice.

Ethics and dissemination

This study has been reviewed and approved by the Ethics Committee in Stockholm. Results will be published, regardless of the outcome, in peer-reviewed international scientific journals.

Registration details

This study is registered at https://www.clinicaltrials.gov (unique identifier: NCT03439449).

ARTICLE SUMMARY

- This prospective cohort study aims to determine whether self-reported, patient-entered history data acquired by computer via a tablet will improve the management of patients with chest pain presenting to an emergency department.

- We will validate self-reported computerized history taking, perform a paired diagnostic accuracy study to compare the predictive accuracy of data collected by standard and computerized history taking and analyse the impact of the latter on resource utilization and costs of care.

Strengths and limitations of this study

- Strengths of this academic, investigator-driven study include the prospective study design, large study population, a highly structured computerized program that standardizes data collection, and the simultaneous evaluation of the technology on resource utilization and cost of care.

- Potential limitations include selection bias as some patients may not be able to carry through a computerized interview and that results may not be generalizable to other care provider settings.

INTRODUCTION

Chest pain is one of the most frequent presenting complaints in emergency departments (ED), accounting for as many as 30 % of all visits(1). Causes of chest pain range from benign conditions to life-threatening emergencies such as an acute coronary syndrome (ACS; *i.e.* unstable angina pectoris and acute myocardial infarction), which is the acute presentation of ischemic heart disease, the most common cause of death world-wide(2). A major challenge for physicians is to rule-in or rule-out ACS accurately because objective evidence for ACS, *e.g.* electrocardiograms (ECG) and circulating biomarkers of acute myocardial injury such as troponin, usually are imponderable in the early course of evaluation. Disease prevalence in patients presenting to the ED with chest pain can 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).

Current guidelines emphasize the importance of medical history taking for evaluating chest pain(3, 5). However, it has been argued that signs and symptoms of ACS are so variable that careful history taking by a physician is an imperfect tool and sometimes of little help for safely excluding ACS(6). It is argued too that history taking is time-consuming and can delay what are regarded as more precise examination methods such as coronary computed tomography angiography(6, 7). However, the majority of patients with chest pain in the ED do not have ACS or another emergent issue, so aggressive use of objective methods for finding lesions of the coronary arteries put many patients at risk for undergoing unnecessary, potentially harmful and costly examinations. Therefore, contemporary guidelines indicate that risk scores should be used to stratify risk for ACS on a patient-by-patient basis. Recommended scoring systems include the Thrombolysis in Myocardial Infarction (TIMI) score and Global Registry of Acute Coronary Events (GRACE) score(3, 5). More recently,

utilization of the HEART (History, ECG, Age, Risk factors and Troponin) score has been recommended as an effective tool for risk stratification in the ED setting(8). Typically, these scores include information on age, risk factors for coronary artery disease (family history, hypertension, hypercholesterolemia, diabetes, current smoker), heart failure, renal function, history suspicious for angina, current use of aspirin or diuretics, ST segment deviation on the ECG and elevated serum cardiac biomarkers(9, 10).

In a hectic ED setting, important information may be missed by medical history taking obtained by the physician (standard history taking). Other approaches have been suggested to ensure collection of more complete and accurate information(11). One way to address this issue is to collect self-reported medical histories *via* computerized history taking (CHT) programs. Herrick et al. conducted a cross-sectional study in an ED setting; 841 patients independently and easily engaged with CHT programs to input data with high accuracy(12). Other studies have shown that CHT performed well in evaluating risk for post-traumatic stress(13), stratifying cardiovascular risk in patients with hypercholesterolemia(14), and for generating a present illness in patients with gastrointestinal symptoms to improve clinic visit efficiency(15). However, in a recent a review of the literature for CHT *versus* oral-and-written history taking for prevention and management of cardiovascular disease only one other study(16) was identified. The authors concluded there is a need to develop an evidence base to support the use of CHT programs for cardiovascular disease.

Data from CHT together with computer-based decision support systems have demonstrated improved physician performance and better patient outcomes in some cases(17-20). An important prerequisite for useful computer-based decision support, however, is complete, accurate and standardized medical history data(11, 21). To date, the data in electronic health

records (EHR) in Swedish EDs does not meet the standards required as a basis for computer-based decision support(22). Accordingly, this study aims to determine the additional value of CHT for the management of patients presenting at the ED with chest pain. More specifically, we aim to determine whether self-reported CHT as compared with standard history taking (1) improves data quality, (2) adds to the accuracy of risk stratification to exclude ACS in patients with chest pain, and (3) saves time and resources.

METHODS AND ANALYSIS

Study design

The Clinical Expert Operating System - Chest Pain Danderyd Study (CLEOS-CPDS) is a prospective cohort study designed to determine the value of CHT in the management of acute chest pain (Study protocol version 1.7, dated May 16, 2019). This study follows the SPIRIT reporting guidelines(23). The project includes a feasibility study for CHT in the acute setting (*Study I*); a validation study of CHT as compared with standard history taking (*Study II*); a paired diagnostic accuracy study using data from CHT and established risk scores (*Study III*); a clinical utility study to evaluate the impact of CHT on chest pain management and use of resources (*Study IV*); and use of data mining to generate an improved risk score for ACS (*Study V*). A summary of the planned studies is presented in *Figure 1*.

Study population

Women and men, presenting consecutively at the ED at Danderyd University Hospital (Stockholm, Sweden) from October 1, 2017 until December 31, 2023 (preliminary date), with a chief complaint of chest pain are eligible if they meet the criteria in *Table 1*.

Table 1. Inclusion and exclusion criteria

Inclusion criteria:
- Women and men, aged 18 years and above
- Chest pain recorded by a triage nurse or registrar
- Fluency in Swedish
- Non-diagnostic first ECG and non-diagnostic serum markers of an acute disease requiring immediate care
- Clinically stable patients (RETTS level orange, yellow, green and blue)
- Informed consent
Exclusion criteria:
- Inability to carry out CHT on the dedicated device (*e.g.* confusion, agitation or inadequate eyesight)

ECG: Electrocardiogram, RETTS: Rapid Emergency Triage and Treatment System (triage level orange, yellow, green or blue indicating clinical stability), CHT: Computerized history taking. Standard blood biomarkers for an acute disease are haemoglobin, leukocytes, thrombocytes, high sensitive C-reactive protein, sodium, potassium, creatinine, glucose, high sensitive troponin T and d-dimer.

Danderyd University Hospital, one of four major hospitals in the greater Stockholm region, serves a population of approximately 550,000. The ED has 90,000 annual visits and dedicated units for internal medicine, cardiology, general surgery, orthopaedics and obstetrics/gynaecology. The cardiology unit manages about 20 % of acute visits. It is staffed by two (nights) to five (afternoons) junior doctors, who are supervised by a more senior physician, *e.g.* a cardiology consultant or senior resident in cardiology, day and night. As in most Swedish EDs, the triage protocol Rapid Emergency Triage and Treatment System

(RETTS) is used to assess the urgency of each patient's condition, to decide what work-up is needed and how the patient should be monitored. Based on vital signs and symptoms collected by a nurse and an assistant nurse, patients are divided into five priority levels depending on their need of urgent medical attention: red (immediate), orange (within 20 minutes), yellow (within 120 min), green (not in need of immediate care) and blue (not in need of emergency care or hospital facilities)(24).

Data collection

When presenting to the ED with chest pain, walk-in patients first report their complaint to the reception nurse, who will direct them to the cardiology ED. During weekdays, 10AM-4PM, these patients are triaged promptly by a physician, who is either a cardiology consultant or senior resident in cardiology. Triage includes a decision on the indicated work-up, which is based on a targeted medical history, a brief examination, vital signs and ECG. This data is used to determine whether a patient should be admitted to the cardiology ED, the day-care unit, or sent home. During out-of-office hours, all patients are triaged by a nurse. According to the RETTS protocol, ECG and biomarkers are acquired before the patient is transported to the cardiology ED. All patients then undergo a more thorough examination and standard history taking by a physician, who also decides whether further investigations are needed. Regional guidelines recommend risk stratification according to HEART score including high sensitivity cardiac troponin (hs-cTn) assays and the validated 0 h / 1 h rule-in and rule-out algorithm(3). Patients with signs of ST-elevation myocardial infarction on ECG or clinically unstable patients (RETTS level red) are evaluated immediately and admitted to the coronary care unit or brought to the coronary intervention laboratory for acute intervention, when indicated. Thus, critically ill patients are excluded in the present study. See *Figure 2* for an overview of the ED flow from arrival to referral.

Patients are asked by a member of the research staff to participate in the current study at the cardiology ED or day-care unit (*Figure 2*). After informed consent has been obtained, histories are collected with a CHT program during waiting times. CHT histories may occur before or after a patient is seen by a physician. Routine care takes precedence over CHT so that patients interact with the CHT program only during wait times. CHT will thus not interfere with workflow or patient care in the ED. CHT data will not be available to the care providers.

All answers to CHT-posed questions are time-stamped. The time at which the physician first meets the patient also is recorded. This will enable control for possible second-history effects. Patients are asked about technical, semantic and other problems they might have encountered after completing a CHT interview. This will be done as a basis for future corrections and improvements to the CHT program.

Self-reported medical history data, demographics and other baseline characteristics will be collected from CHT data.

Data from standard history, demographic and baseline characteristics, vital signs and lab data will be extracted from the EHR. Data on use of resources will be extracted from hospital EHR to generate the cost associated with routine care patient-by-patient. Cost will be correlated with different clinical outcomes by linking the diagnosis at the ED visit or when discharged with their Diagnosis Related Group (DRG) code, which is an estimate of costs associated with a specific diagnosis provided by the National Board of Health and Welfare and Swedish Association of Local Authorities and Regions.

The use of unique personal ID to all Swedish citizens allows linkage to national and regional registries for research purposes. Thus, clinical outcomes in the acute setting (*i.e.* within 7 days) will be extracted from the EHR of the hospital. Discharge diagnoses, at 30 days, and at 1 year, will be collected from the National Patient Register, which includes information on all hospital discharges in Sweden since 1964(25). Mortality status and causes of death will be extracted from the Cause of Death Register which provides official statistics, according to the International Statistical Classification of Diseases and Related Health Problems, in Sweden since 1961(26).

For the validation and future development of CHT, a questionnaire to assess overall patient experience in a larger sample of patients (n=500) will be developed through interviews with a subset of patients. Approximately 30 patients will be asked to participate in three to four focus group interviews for the evaluation of ease of use and usefulness of the CHT program. These interviews will take place one to three months after the ED visit.

Interventions

Computerized, self-reported medical histories will be collected with the software program CLEOS running on tablets (iPad, Apple Inc, Cupertino, CA, USA). CLEOS is developed by Zakim and colleagues and is owned by Karolinska Institutet, a public university. Details and validation of the CLEOS program have been described previously(14, 27). In brief, the participant answers questions by clicking on a variety of question types, *e.g.* yes/no answers, multiple-choice answers with one allowed answer and multiple-choice answers with more than one allowed answer. Most questions are in a text format but many are images as presented in *Figure 3*. The program determines dynamically the next most appropriate

question. This is done on the basis of the answer to a single prior question and with rules that interpret the clinical significance of all prior answers. Each patient is guided through an individually tailored, but comprehensive medical interview that includes demographics, present illness, organ systems review, past medical history, prescription and over the counter medications, socioeconomic issues, life-style risks, and family history. The program also searches for previous adverse drug reactions. Questions concerning established markers for cardiovascular risk are asked early in the interview for patients with a chief complaint of chest pain. *Table 2* shows the consecutive order of the major medical blocks of the interview. The occurrence of any block or subsection within a block in the pathway for a specific interview is determined, however, by a patient's chief complaint and answers to questions within specific blocks.

Table 2. Consecutive order of medical blocks in the interview

1. Chief complaint
2. Cardiovascular
3. Respiratory
4. Immunology/Rheumatology
5. Endocrinology
6. Gastroenterology/Gastrointestinal surgery
7. Hepatology
8. Nephrology and Urology
9. Obstetrics and Gynaecology
10. Neurology
11. Haematology/Oncology
12. Mental health

13. Past history medical/surgical events
14. Family history

The CLEOS interview is directed by > 17,000 decision nodes and can collect > 40,000 clinical data elements. The duration of interviews depends on the individual's pathway, but is approximately 60 minutes. The interview can be paused at any question as many times as necessary and resumed automatically at the last unanswered question. Previous studies concerning CHT programs have shown that self-reported, CHT with CLEOS is superior to standard history taking in terms of completeness of data collected(14, 27).

In previous studies with CLEOS, the interviews were conducted in English or German(14, 27). We have adapted the program to Swedish conditions. A professional translation agency with medical qualifications (Verbal i Nacka AB, Östersund, Sweden) processed all ~35,000 questions and answer sets in the program. This translation was tested for comprehensibility and cultural adaption in a random sample of 18 persons living in the Stockholm region including both women and men aged between 18-80 years. Age, gender, level of education, previous tablet use, issues during the interview and overall comments were tabulated for all these patients. All phrases were re-examined by a trained medical student and also, to get a non-medical perspective, an economy student. The language of all questions and answers was edited to account for country-specific differences (*e.g.* drug use, tobacco use and abuse) between Sweden, Germany and the U.S. The penultimate version was verified by a competent physician and then tested by 12 hospitalized patients before a pilot study was started in 400 patients. Additional errors in translation and poor use of language in the original English were resolved continuously in this phase of the work. No additional changes to language were

made after the start of the present study.

Sample size calculations

This is an exploratory study. The calculation of the size of the study population is based on the desired precision of sensitivity and specificity. Assuming that the prevalence of ACS is 0.5 (50 %), 1,000 patients are required to obtain a precision of sensitivity and specificity of ±0.03 (3 %) (nQuery version 7.0, Statistical Solutions Ltd, Boston, MA, USA). The more the extreme the result, *i.e.* sensitivity or specificity approaching 0 or 1 (100 %), the higher the precision. The models will be developed in the first 50 % of the data acquired (training data set) and validated in the last 50 % of the data acquired (validation data set). The primary outcome will be analysed after 1,000 patients (with no planned interim analyses), which is expected to be reached by December 31, 2020. We also intend to make estimates in subgroups. To allow these analyses, the study program intends to ultimately recruit data from at least 2,000 patients in total.

Outcomes

The primary objective is to determine whether the use of CHT is better than standard history taking obtained by the physician 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 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.

Secondary outcomes include 1) the ability of CHT, as compared to standard history taking obtained by the cardiologist in attendance to provide information required to calculate recommended risk scores for ACS; 2) a correct exclusion of an ACS up to 30 days and up to 1 year by use of CHT or standard history taking obtained by the cardiologist in attendance; 3) direct costs and resource utilization for a patient with a diagnosis of an ACS when patient selection is based on CHT, as compared to standard history taking obtained by the cardiologist in attendance; and 4) patient experience with CHT regarding feasibility, acceptance, comprehensible and technical aspects. Finally, we aim to use the collected data to explore the possibility to generate an improved risk score for ACS.

Data management and data analysis plan

The CLEOS interview program runs from a central server located at Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Stockholm, Sweden. Data collected will be stored on this server in the form of codes (not text) representing answers to questions posed. Data transmission and storage fulfil the high standards of security of Karolinska Institutet.

Other data stored are time stamps for completion of each question in an interview, and the pathway by which each interview proceeded. Data collected during routine care, which may be used for algorithm development, *e.g.* signs like heart rate, rhythm, body temperature, blood pressure, biochemistry, and findings from ECG recordings will be extracted from the EHRs and added manually to coded data fields in the CLEOS program.

Descriptive statistics will be used to describe demography and background characteristics. 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 test for significant difference of completeness of the risk scores.

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. Logistic regression will be used to describe the relationship with the predictions and actual outcomes (*i.e.* ACS or not ACS).

The potential impact on costs by use of information achieved from CHT in managing patients with acute chest pain, compared with standard history taking, will be calculated. Standard health economic principles and methods based on DRG codes and current Swedish tariffs for out-patient care and investigations will be used.

Patient and Public involvement

Patients participate at several stages of the study. Through interviews during the adaption of the CLEOS program to Swedish conditions, by providing feedback during the pilot study phase and also during the ongoing study after completion of the interview, the patient perspective has been well taken care of. Furthermore, interviews with a subset of patients for the evaluation of patient experience regarding feasibility, acceptance, comprehensiveness and technical aspects of answering the CLEOS interview will take place as part to the study protocol (see above). All participating patients are informed about how they can access the registered protocol.

Ethics and dissemination

This study has been reviewed and approved by the Ethics Committee in Stockholm (No 2015/1955-1). All participants will give their informed consent before taking part of the study. Results will be published, regardless of the results obtained, in peer-reviewed international scientific journals.

DISCUSSION

Chest pain is a common chief complaint in the ED and there are several health and resource benefits if ACS could be ruled-in or ruled-out more effectively. CHT may be a useful method, but has not been studied previously in an acute cardiology setting. The Swedish health care system offers a good opportunity to study this. There are high quality, comprehensive national health care registries and consistent use of EHRs. This ongoing study aims to determine the additional value of CHT for the management of patients with acute chest pain. The pilot phase of the CLEOS-CPDS study was performed May 1 to September 30, 2017 and the recruitment in the main study started on October 1, 2017.

The main strengths of this study include the focus on accurate prediction of risk for a life threatening condition among the large group of patients presenting to EDs with a common complaint(1). Second, we use a prospective, cohort study design; include a large study population; and use reliable outcome measures for which there are well-established, strict criteria(29). Third, the implications of the results on resource utilization could have a significant impact for health care providers. Fourth, the use of CHT does not require a specific EHR system, and CLEOS has a generic layout not specific for cardiology or the ED setting. Thus, the results could be potentially generalized to several other clinical issues and care-settings. Finally, our research is academically initiated and driven. The artificial

intelligence software in this study is owned by a public university. There are no commercial interests within this research project.

However, a number of possible limitations of this study should be considered. First, patients not able to accomplish CHT are excluded. This may limit the generalizability of the results to all people with chest pain. To address these issues, we will conduct a feasibility analysis on the first 500 patients to compare patient characteristics, their performance with the CHT, and demographics and background characteristics with the entire ED population for the same time period. Why patients decline to participate in the study will be reported specifically. Second, given the large number of possible questions during the interview, we cannot dismiss the risk of vague or misleading questions, as they are not all validated. A risk of recall bias caused by giving a medical history twice (CHT and standard history taking), cannot be excluded. To allow for a sensitive analysis for this possible bias, we will track the order of interview by physician and CLEOS. Third, as we compare data from CHT with data acquired by the attending physician, the performance of the physician can affect our results. Thus, our results may not be generalized to another ED setting.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study and to creating the study protocol. HB, TK, and DZ drafted the manuscript. DZ is the designer of the CLEOS program's method for making medical knowledge actionable and the developer of the program's medical knowledge base. All authors revised the manuscript for intellectual content and approved the final text. TK (chair), HB, JS, SK, CJS and DZ form the steering group of the CLEOS-CPDS study. CJS acts as the contact person for the trial sponsor (Karolinska Institutet). All steering group members will have full access to the final trial data set. The

corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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COMPETING INTERESTS STATEMENT

DZ is the inventor on US patents for technology related to the CLEOS program. All patent rights and copyrights to technology, language, images, and knowledge content are assigned without royalty rights by DZ to Karolinska Institutet, Stockholm, Sweden which is a public university. Apart from Karolinska Institutet and its subsidiaries, no individuals or companies may be owners or receive royalties or other revenue from use of CLEOS technology, language, images, knowledge content or from clinical insights and/or computer algorithms generated from analysis of data acquired by the program. There are no other competing interests financial or otherwise in study design, collection, management, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication. All CLEOS-CPDS steering group members (see above) will have full access to the final trial data set.

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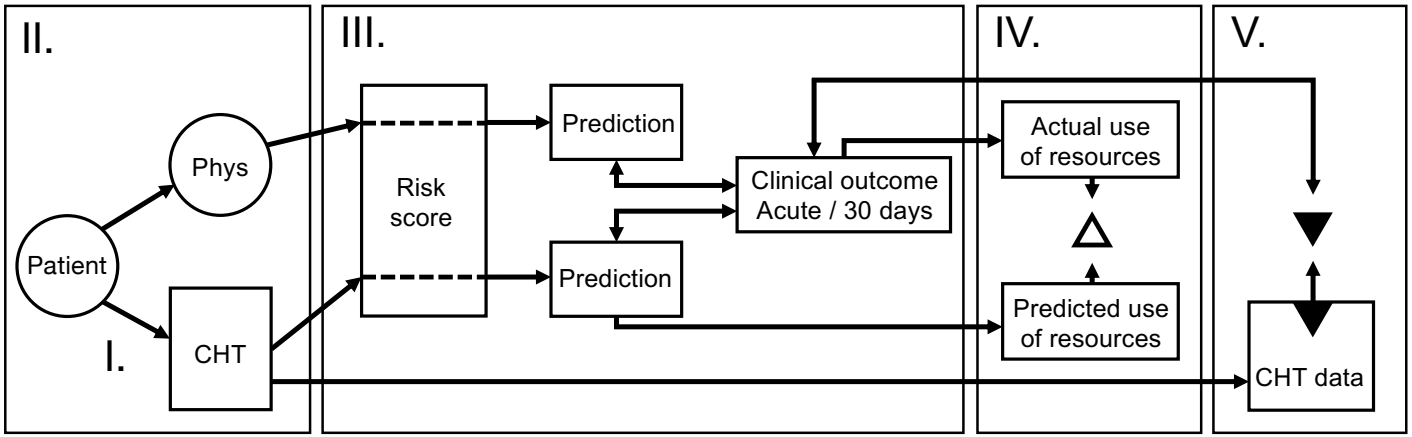
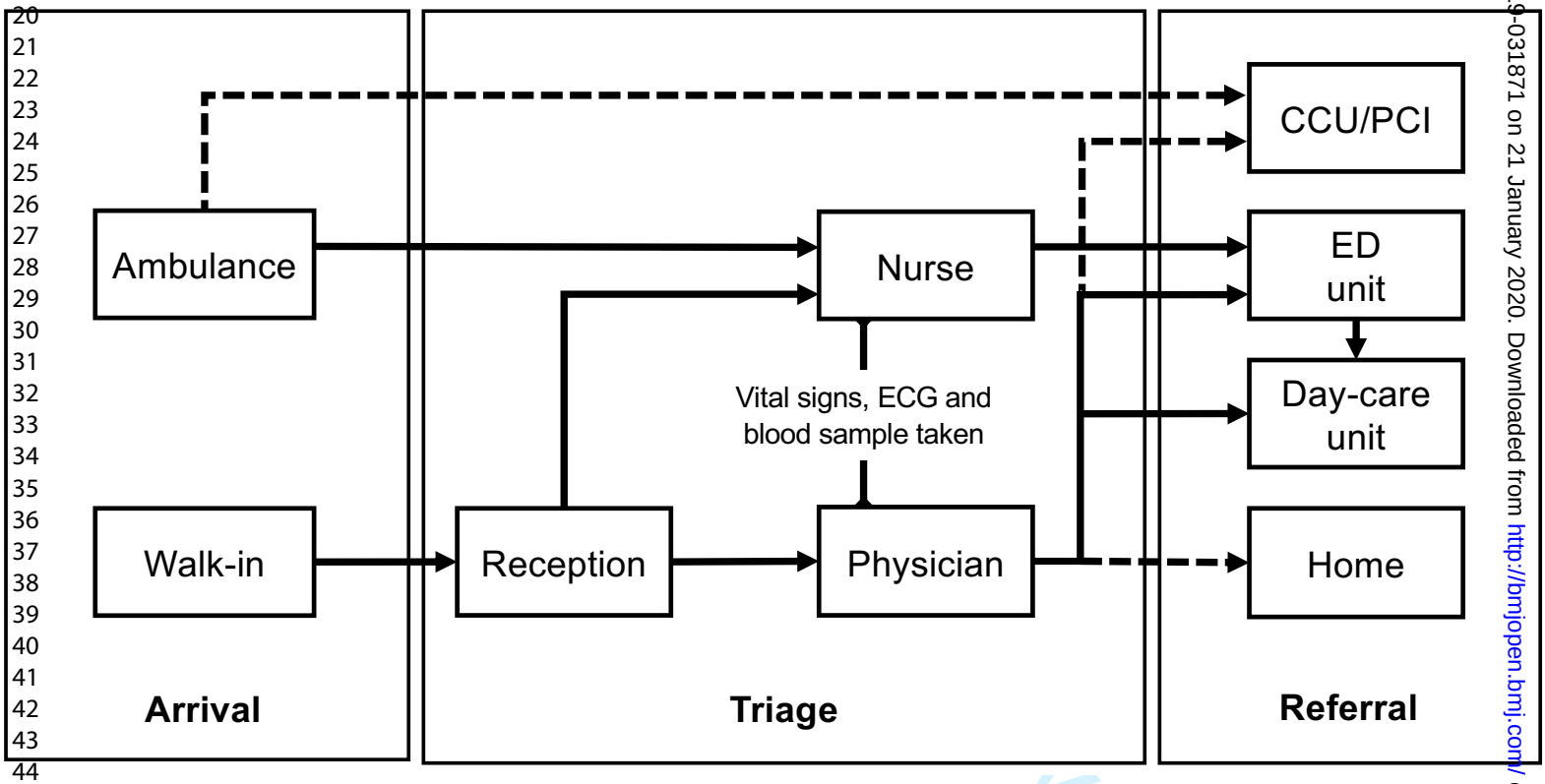
FIGURE LEGENDS

Figure 1. Overview of planned studies. Phys: history taking by physicians; CHT: computerized history taking.

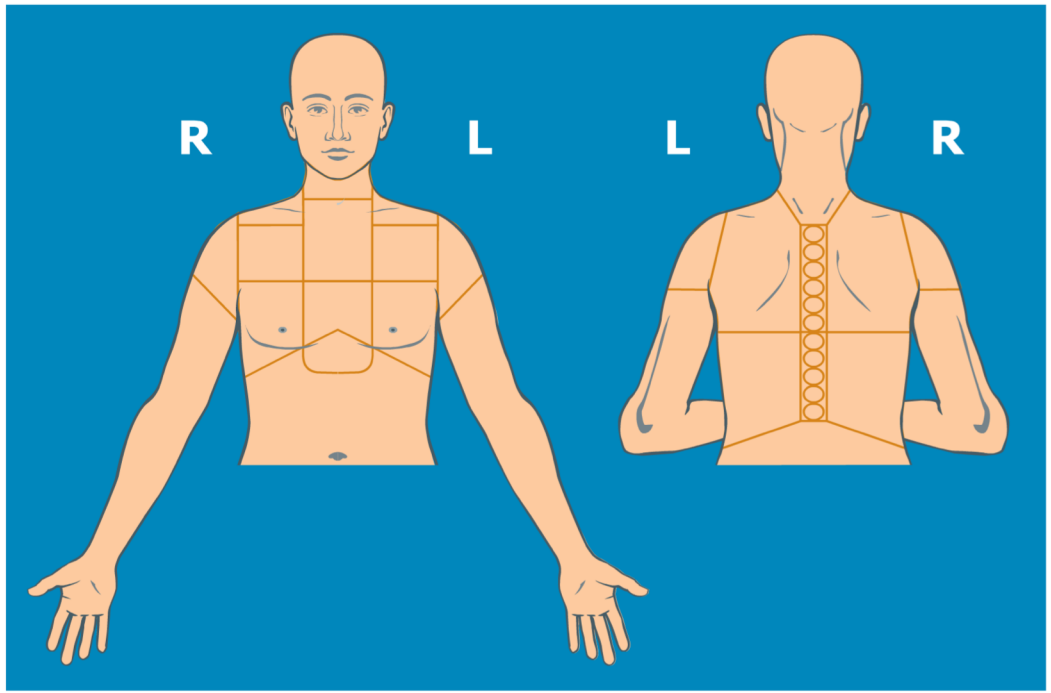
Figure 2. Overview of the ED flow from arrival to referral. Broken lines indicate patients who will not be eligible. ECG: electrocardiogram; CCU: Cardiac care unit; PCI: Percutaneous coronary intervention; ED: Emergency Department.

Figure 3. Example of the presentations of questions in CLEOS on the tablet.





When the pain/discomfort starts, where exactly do you feel it? Select all sites in which you have symptoms.



I have no pain/discomfort in any of these sites

IDM

QUESTION

Please indicate the kind of physical activity that causes or appears to cause the pain/discomfort .

ANSWER

- ❑ Walking on flat ground
- ❑ Walking up stairs
- ❑ Working with my arms
- ❑ Lifting heavy objects, running, bicycle riding, or another form of general physical activity
- ❑ Running, bicycle riding, or another form of general physical activity
- ❑ None of these activities cause the symptoms

IDM

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set *Comment: Embedded in manuscript. Also, see trial registration at clinicaltrials.gov (NCT03439449).*	4
Protocol version	#3	Date and version identifier	8
Funding	#4	Sources and types of financial, material, and other support	20

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2,19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1, 19
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6-8
Objectives	#7	Specific objectives or hypotheses	8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15-16
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8, figure 1 and 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 11, 15
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions *Comment: Not relevant for this observational cohort study.*	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned *Comment: Not relevant for this observational cohort study.*	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions *Comment: Not relevant for this observational cohort study.*	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how *Comment: Not relevant for this observational cohort study.*	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial *Comment: Not relevant for this observational cohort study.*	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	10-12

		Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols *Comment: When patients have provided data via the interview, outcome data are retrieved from registries and health records.*	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17, 19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring		*Comment: This will be addressed in the feasibility study (Study I).*	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed *Comment: Data is entered directly into the database.*	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11-12, 16

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17-18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) *Comment: Included in the regulations for ethical approval, which has been done to the ethical review authority. There, patient information, any amendments etc. can also be retrieved.*	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results	17-18

		databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code *Comment: No such plans at present.*	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates *Comment: The model consent form and other related documentation is available from the ethical review authority. These are public documents in Sweden.*	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

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)

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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)

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ABSTRACT

Introduction

Management of acute chest pain focuses on diagnosis or safe rule-out of an acute coronary syndrome (ACS). We aim to determine the additional value of self-reported computerized history taking (CHT).

Methods and analysis

Prospective cohort study design with self-reported, medical histories collected by a CHT program (Clinical Expert Operating System, CLEOS) using a tablet. Women and men presenting with acute chest pain to the emergency department at Danderyd University Hospital (Stockholm, Sweden) are eligible. CHT will be compared with standard history taking for completeness of data required to calculate ACS risk scores such as HEART, GRACE, and TIMI. Clinical outcomes will be extracted from hospital electronic health records and national registries. The CLEOS-CPDS project includes (I) a feasibility study of CHT, (II) a validation study of CHT as compared with standard history taking, (III) a paired diagnostic accuracy study using data from CHT and established risk scores, (IV) a clinical utility study to evaluate the impact of CHT on management of chest pain and use of resources, and (V) data mining, aiming to generate an improved risk score for ACS. Primary outcomes will be analysed after 1,000 patients, but to allow for subgroup analysis, the study intends to recruit 2,000 or more patients. This project may lead to new and more effective ways for collecting thorough, accurate medical histories with important implications for clinical practice.

Ethics and dissemination

This study has been reviewed and approved by the Ethics Committee in Stockholm. Results will be published, regardless of the outcome, in peer-reviewed international scientific journals.

Registration details

This study is registered at https://www.clinicaltrials.gov (unique identifier: NCT03439449).

Strengths and limitations of this study

- One strength of this study is the focus on accurate risk prediction for a life-threatening condition among the large group of patients presenting to the emergency department with a common complaint.

- Another strength is the prospective, cohort study design, and a large study population with reliable outcomes, for which there are well-established, strict criteria.

- The academic, investigator-initiated and investigator-driven study without any commercial interests adds further strength.

- Potential limitations include selection bias, as some patients may not be able to carry through a computerized interview; there may also be a risk of recall bias caused by giving a medical history twice.

- Furthermore, the generalizability of the study results may be limited with different structure and organization of emergency departments.

INTRODUCTION

Chest pain is one of the most frequent presenting complaints in emergency departments (ED), accounting for as many as 30 % of all visits(1). Causes of chest pain range from benign conditions to life-threatening emergencies such as an acute coronary syndrome (ACS; *i.e.* unstable angina pectoris and acute myocardial infarction), which is the acute presentation of ischemic heart disease, the most common cause of death world-wide(2). A major challenge for physicians is to rule-in or rule-out ACS accurately because objective evidence for ACS, *e.g.* electrocardiograms (ECG) and circulating biomarkers indicating acute myocardial injury such as troponin, usually are imponderable in the early course of evaluation. 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).

Current guidelines emphasize the importance of medical history taking for evaluating chest pain(3, 5). However, it has been argued that signs and symptoms of ACS are so variable that careful history taking by a physician is an imperfect tool and sometimes of little help for safely excluding ACS(6). It is argued too that history taking is time-consuming and can delay what are regarded as more precise examination methods such as coronary computed tomography angiography(6, 7). However, the majority of patients with chest pain in the ED do not have ACS or another emergent issue, so aggressive use of objective methods for finding lesions of the coronary arteries puts many patients at risk for undergoing unnecessary, potentially harmful and costly examinations. Therefore, contemporary guidelines indicate that risk scores should be used to stratify risk for ACS on a patient-by-patient basis. Recommended scoring systems include the Thrombolysis in Myocardial Infarction (TIMI)

score and Global Registry of Acute Coronary Events (GRACE) score(3, 5). More recently, utilization of the HEART (History, ECG, Age, Risk factors and Troponin) score has been recommended as an effective tool for risk stratification in the ED setting(8). Typically, these scores include information on age, risk factors for coronary artery disease (family history, hypertension, hypercholesterolemia, diabetes, current smoker), heart failure, renal function, history suspicious for angina, current use of aspirin or diuretics, ST segment deviation on the ECG and elevated serum cardiac biomarkers(9, 10).

In a hectic ED setting, important information may be missed by medical history taking obtained by the physician (standard history taking). Other approaches have been suggested to ensure collection of more complete and accurate information(11). One way to address this issue is to collect self-reported medical histories *via* computerized history taking (CHT) programs. Herrick et al. conducted a cross-sectional study in an ED setting; 841 patients independently and easily engaged with CHT programs to input data with high accuracy(12). Other studies have shown that CHT performed well in evaluating risk for post-traumatic stress(13), stratifying cardiovascular risk in patients with hypercholesterolemia(14), and for generating a present illness in patients with gastrointestinal symptoms to improve clinic visit efficiency(15). However, in a recent a review of the literature for CHT *versus* oral-and-written history taking for prevention and management of cardiovascular disease only one other study(16) was identified. The authors concluded there is a need to develop an evidence base to support the use of CHT programs for cardiovascular disease.

Data from CHT together with computer-based decision support systems have demonstrated improved physician performance and better patient outcomes in some cases(17-20). An important prerequisite for useful computer-based decision support, however, is complete,

accurate and standardized medical history data(11, 21). To date, the data in electronic health records (EHR) in Swedish EDs does not meet the standards required as a basis for computer-based decision support(22). Accordingly, this study aims to determine the additional value of CHT for the management of patients presenting at the ED with chest pain. More specifically, we aim to determine whether self-reported CHT as compared with standard history taking (1) improves data quality, (2) adds to the accuracy of risk stratification to exclude ACS in patients with chest pain, and (3) saves time and resources.

METHODS AND ANALYSIS

Study design

The Clinical Expert Operating System - Chest Pain Danderyd Study (CLEOS-CPDS) is a prospective cohort study designed to determine the value of CHT in the management of acute chest pain (Study protocol version 1.7, dated May 16, 2019). This study follows the SPIRIT reporting guidelines(23). The project includes a feasibility study for CHT in the acute setting (*Study I*); a validation study of CHT as compared with standard history taking (*Study II*); a paired diagnostic accuracy study using data from CHT and established risk scores (*Study III*); a clinical utility study to evaluate the impact of CHT on chest pain management and use of resources (*Study IV*); and use of data mining to generate an improved risk score for ACS (*Study V*). A summary of the planned studies is presented in *Figure 1*.

Study population

Women and men, presenting consecutively at the ED at Danderyd University Hospital (Stockholm, Sweden) from October 1, 2017 until December 31, 2023 (preliminary date), with a chief complaint of chest pain are eligible if they meet the criteria in *Table 1*.

Table 1. Inclusion and exclusion criteria

Inclusion criteria:
- Women and men, aged 18 years and above
- Chest pain recorded by a triage nurse or registrar
- Fluency in Swedish
- Non-diagnostic first ECG and non-diagnostic serum markers of an acute disease requiring immediate care
- Clinically stable patients (RETTS level orange, yellow, green and blue)
- Informed consent
Exclusion criteria:
- Inability to carry out CHT on the dedicated device (*e.g.* confusion, agitation or inadequate eyesight)

ECG: Electrocardiogram, RETTS: Rapid Emergency Triage and Treatment System (triage level orange, yellow, green or blue indicating clinical stability), CHT: Computerized history taking. Standard blood biomarkers for an acute disease are haemoglobin, leukocytes, thrombocytes, high sensitive C-reactive protein, sodium, potassium, creatinine, glucose, high sensitive troponin T and d-dimer.

Danderyd University Hospital, one of four major hospitals in the greater Stockholm region, serves a population of approximately 550,000. The ED has 90,000 annual visits and dedicated units for internal medicine, cardiology, general surgery, orthopaedics and obstetrics/gynaecology. The cardiology unit manages about 20 % of acute visits. It is staffed by two (nights) to five (afternoons) junior doctors, who are supervised by a more senior physician, *e.g.* a cardiology consultant or senior resident in cardiology, day and night. As in

most Swedish EDs, the triage protocol Rapid Emergency Triage and Treatment System (RETTS) is used to assess the urgency of each patient's condition, to decide what work-up is needed and how the patient should be monitored. Based on vital signs and symptoms collected by a nurse and an assistant nurse, patients are divided into five priority levels depending on their need of urgent medical attention: red (immediate), orange (within 20 minutes), yellow (within 120 min), green (not in need of immediate care) and blue (not in need of emergency care or hospital facilities)(24).

Data collection

When presenting to the ED with chest pain, walk-in patients first report their complaint to the reception nurse, who will direct them to the cardiology ED. During weekdays, 10AM-4PM, these patients are triaged promptly by a physician, who is either a cardiology consultant or senior resident in cardiology. The triage includes a decision on the indicated work-up, which is based on a targeted medical history, a brief examination, vital signs and ECG. This data is used to determine whether a patient should be admitted to the cardiology ED, the day-care unit, or sent home. During out-of-office hours, all patients are triaged by a nurse. According to the RETTS protocol, ECG and biomarkers are acquired before the patient is transported to the cardiology ED. All patients then undergo a more thorough examination and standard history taking by a physician, who also decides whether further investigations are needed. Regional guidelines recommend risk stratification according to HEART score including high sensitivity cardiac troponin (hs-cTn) assays and the validated 0 h / 1 h rule-in and rule-out algorithm(3). Patients with signs of ST-elevation myocardial infarction on ECG or clinically unstable patients (RETTS level red) are evaluated immediately and admitted to the coronary care unit or brought to the coronary intervention laboratory for acute intervention, when

indicated. Thus, critically ill patients are excluded in the present study. See *Figure 2* for an overview of the ED flow from arrival to referral.

Patients are asked by a member of the research staff to participate in the current study at the cardiology ED or day-care unit (*Figure 2*). After informed consent has been obtained, histories are collected with a CHT program during waiting times. CHT histories may occur before or after a patient is seen by a physician. Routine care takes precedence over CHT so that patients interact with the CHT program only during waiting times. CHT thus will not interfere with workflow or patient care in the ED. During the study period CHT data will not be available to the care providers.

All answers to CHT-posed questions are time-stamped. The time at which the physician first meets the patient also is recorded. This will enable control for possible second-history effects. Patients are asked about technical, semantic and other problems they might have encountered after completing a CHT interview. This will be done as a basis for future corrections and improvements to the CHT program.

Self-reported medical history data, demographics and other baseline characteristics will be collected from CHT data.

Data from standard history, demographic and baseline characteristics, vital signs and lab data will be extracted from the EHR. To generate the cost associated with routine care patient-by-patient data on use of resources will be extracted from the hospital EHR. Cost will be correlated with different clinical outcomes by linking the diagnosis at the ED visit or when discharged with their Diagnosis Related Group (DRG) code, which is an estimate of costs

associated with a specific diagnosis provided by the National Board of Health and Welfare and Swedish Association of Local Authorities and Regions.

The use of unique personal ID to all Swedish citizens allows linkage to national and regional registries for research purposes. Thus, clinical outcomes in the acute setting (*i.e.* within 7 days) will be extracted from the EHR of the hospital. Discharge diagnoses, at 30 days, and at 1 year, will be collected from the National Patient Register, which includes information on all hospital discharges in Sweden since 1964(25). Mortality status and causes of death will be extracted from the Cause of Death Register which provides official statistics, according to the International Statistical Classification of Diseases and Related Health Problems, in Sweden since 1961(26).

For the validation and future development of CHT, a questionnaire to assess overall patient experience in a larger sample of patients (n=500) will be developed through interviews with a subset of patients. Approximately 30 patients will be asked to participate in three to four focus group interviews for the evaluation of ease of use and usefulness of the CHT program. These interviews will take place one to three months after the ED visit.

Interventions

Computerized, self-reported medical histories will be collected with the software program CLEOS running on tablets (iPad, Apple Inc, Cupertino, CA, USA). CLEOS is developed by Zakim and colleagues and is owned by Karolinska Institutet, a public university. Details and validation of the CLEOS program have been described previously(14, 27). In brief, the participant answers questions by clicking on a variety of question types, *e.g.* yes/no answers, multiple-choice answers with one allowed answer and multiple-choice answers with more

than one allowed answer. Most questions are in a text format but many are images as presented in *Figure 3*. The program determines dynamically the next most appropriate question. This is done on the basis of the answer to a single prior question and rules that interpret the clinical significance of all prior answers. Each patient is guided through an individually tailored, comprehensive medical interview that includes demographics, present illness, organ systems review, past medical history, prescription and over the counter medications, socioeconomic issues, life-style risks, and family history. The program also searches for previous adverse drug reactions. Questions concerning established markers for cardiovascular risk are asked early in the interview for patients with a chief complaint of chest pain. *Table 2* shows the consecutive order of the major medical blocks of the interview. The occurrence of any block or subsection within a block in the pathway for a specific interview is determined, however, by a patient's chief complaint and answers to questions within specific blocks.

Table 2. Consecutive order of medical blocks in the interview

1. Chief complaint
2. Cardiovascular
3. Respiratory
4. Immunology/Rheumatology
5. Endocrinology
6. Gastroenterology/Gastrointestinal surgery
7. Hepatology
8. Nephrology and Urology
9. Obstetrics and Gynaecology
10. Neurology

11. Haematology/Oncology
12. Mental health
13. Past history medical/surgical events
14. Family history

The CLEOS interview is directed by > 17,000 decision nodes and can collect > 40,000 clinical data elements. 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. Previous studies concerning CHT programs have shown that self-reported, CHT with CLEOS is superior to standard history taking in terms of completeness of data collected(14, 27).

In previous studies with CLEOS, the interviews were conducted in English or German(14, 27). We have adapted the program to Swedish conditions. A professional translation agency with medical qualifications (Verbal i Nacka AB, Östersund, Sweden) processed all ~35,000 questions and answer sets in the program. This translation was tested for comprehensibility and cultural adaption in a random sample of 18 persons living in the Stockholm region including both women and men aged between 18-80 years. Age, gender, level of education, previous tablet use, issues during the interview and overall comments were tabulated for all these patients. All phrases were re-examined by a trained medical student and also, to get a non-medical perspective, an economics student. The language of all questions and answers was edited to account for country-specific differences (*e.g.* drug use, tobacco use and abuse) between Sweden, Germany and the U.S. The penultimate version was verified by a competent

physician and then tested by 12 hospitalized patients before a pilot study was started in 400 patients. Additional errors in translation and poor use of language in the original English were resolved continuously in this phase of the work. No additional changes to language were made after the start of the present study.

Sample size calculations

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. The models will be developed in the first 50 % of the data acquired (training data set) and validated in the last 50 % of the data acquired (validation data set). The primary outcome will be analysed after 1,000 patients (with no planned interim analyses), which is expected to be reached by December 31, 2020. We also intend to make estimates in subgroups. To allow these analyses, the study program intends to ultimately recruit data from at least 2,000 patients in total.

Outcomes

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.

Secondary outcomes include 1) the ability of CHT, as compared to standard history taking obtained by the cardiologist in attendance to provide information required to calculate recommended risk scores for ACS; 2) a correct exclusion of an ACS up to 30 days and up to 1 year by use of CHT or standard history taking obtained by the cardiologist in attendance; 3) direct costs and resource utilization for a patient with a diagnosis of an ACS when patient selection is based on CHT, as compared to standard history taking obtained by the cardiologist in attendance; and 4) patient experience with CHT regarding feasibility, acceptance, comprehensible and technical aspects. Finally, we aim to use the collected data to explore the possibility to generate an improved risk score for ACS.

Data management and data analysis plan

The CLEOS interview program runs from a central server located at Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Stockholm, Sweden. Data collected will be stored on this server in the form of codes (not text) representing answers to questions posed. Data transmission and storage fulfil the high standards of security of Karolinska Institutet.

Other data stored are time stamps for completion of each question in an interview, and the pathway by which each interview proceeded. Data collected during routine care, which may be used for algorithm development, *e.g.* signs like heart rate, rhythm, body temperature, blood pressure, biochemistry, and findings from ECG recordings will be extracted from the EHRs and added manually to coded data fields in the CLEOS program.

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).

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).

The potential impact on costs by use of information achieved from CHT in managing patients with acute chest pain, compared with standard history taking, will be calculated. Standard

health economic principles and methods based on DRG codes and current Swedish tariffs for out-patient care and investigations will be used.

Patient and Public involvement

Patients participate at several stages of the study. The patient perspective has been incorporated into this study through interviews during the adaption of the CLEOS program to Swedish conditions, by providing feedback during the pilot study phase and also during the ongoing study after completion of the interview. Furthermore, interviews with a subset of patients for the evaluation of patient experience regarding feasibility, acceptance, comprehensiveness and technical aspects of answering the CLEOS interview will take place as part to the study protocol (see above). All participating patients are informed about how they can access the registered protocol.

Ethics and dissemination

This study has been reviewed and approved by the Ethics Committee in Stockholm (No 2015/1955-1). All participants will give their informed consent before taking part of the study. Results will be published, regardless of the results obtained, in peer-reviewed international scientific journals.

DISCUSSION

Chest pain is a common chief complaint in the ED and there are several health and resource benefits if ACS could be ruled-in or ruled-out more effectively. CHT may be a useful method, but has not been studied previously in an acute cardiology setting. The Swedish health care system offers a good opportunity to study this. There are high quality, comprehensive national health care registries and consistent use of EHRs. This ongoing study aims to determine the

additional value of CHT for the management of patients with acute chest pain. The pilot phase of the CLEOS-CPDS study was performed May 1 to September 30, 2017 and the recruitment in the main study started on October 1, 2017.

The main strengths of this study include the focus on accurate prediction of risk for a life threatening condition among the large group of patients presenting to EDs with a common complaint(1). Second, we use a prospective, cohort study design; include a large study population; and use reliable outcome measures for which there are well-established, strict criteria(29). Third, the implications of the results on resource utilization could have a significant impact for health care providers. Fourth, the use of CHT does not require a specific EHR system, and CLEOS has a generic layout not specific for cardiology or the ED setting. Thus, the results could be potentially generalized to several other clinical issues and care-settings. Finally, our research is academically initiated and driven. The artificial intelligence software in this study is owned by a public university. There are no commercial interests within this research project.

However, a number of possible limitations of this study should be considered. First, patients not able to accomplish CHT are excluded. This may limit the generalizability of the results to all people with chest pain. To address these issues, we will conduct a feasibility analysis on the first 500 patients to compare patient characteristics, their performance with the CHT, and demographics and background characteristics with the entire ED population for the same time period. Why patients decline to participate in the study will be reported specifically. Second, given the large number of possible questions during the interview, we cannot dismiss the risk of vague or misleading questions, as they are not all validated. 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. A risk of recall bias caused by giving a medical history twice (CHT and standard history taking), cannot be excluded. To allow for a sensitivity analysis for this possible bias, we will track the order of interview by physician and CLEOS. 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. Fourth, as we compare data from CHT with data acquired by the attending physician, the performance of the physician can affect our results. 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.

AUTHOR CONTRIBUTIONS

All authors (HB, TK, JS, KS, SK, AA, CJS and DZ) contributed to the conception and design of the study and to creating the study protocol. HB, TK, and DZ drafted the manuscript. DZ is the designer of the CLEOS program's method for making medical knowledge actionable and the developer of the program's medical knowledge base. All authors (HB, TK, JS, KS, SK, AA, CJS and DZ) revised the manuscript for intellectual content and approved the final text. TK (chair), HB, JS, SK, CJS and DZ form the steering group of the CLEOS-CPDS study. CJS acts as the contact person for the trial sponsor (Karolinska Institutet). All steering group

members will have full access to the final trial data set. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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COMPETING INTERESTS STATEMENT

DZ is the inventor on US patents for technology related to the CLEOS program. All patent rights and copyrights to technology, language, images, and knowledge content are assigned without royalty rights by DZ to Karolinska Institutet, Stockholm, Sweden which is a public university. Apart from Karolinska Institutet and its subsidiaries, no individuals or companies may be owners or receive royalties or other revenue from use of CLEOS technology, language, images, knowledge content or from clinical insights and/or computer algorithms generated from analysis of data acquired by the program. There are no other competing interests financial or otherwise in study design, collection, management, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication. All CLEOS-CPDS steering group members (see above) will have full access to the final trial data set.

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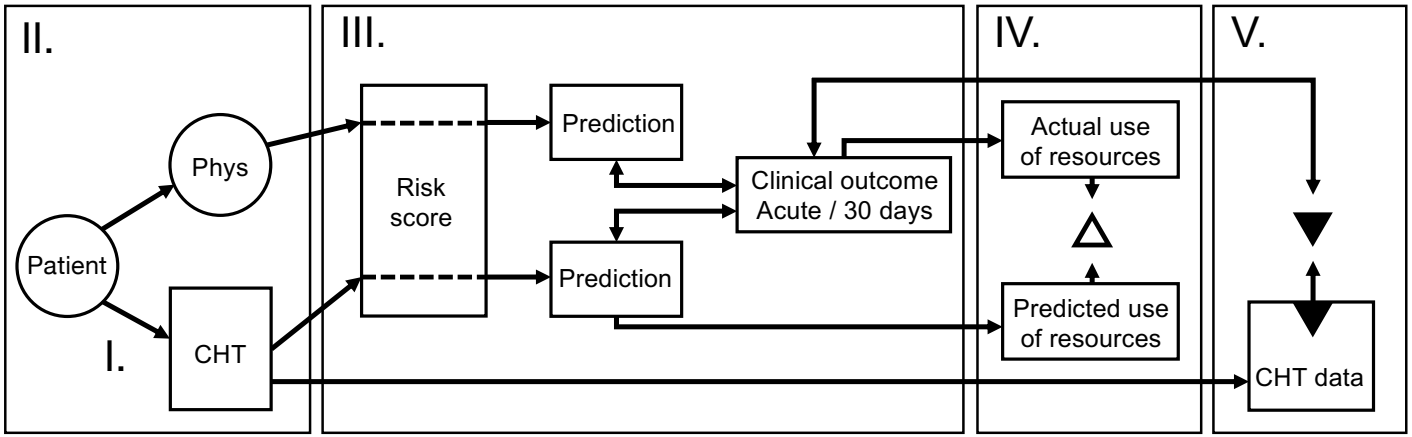
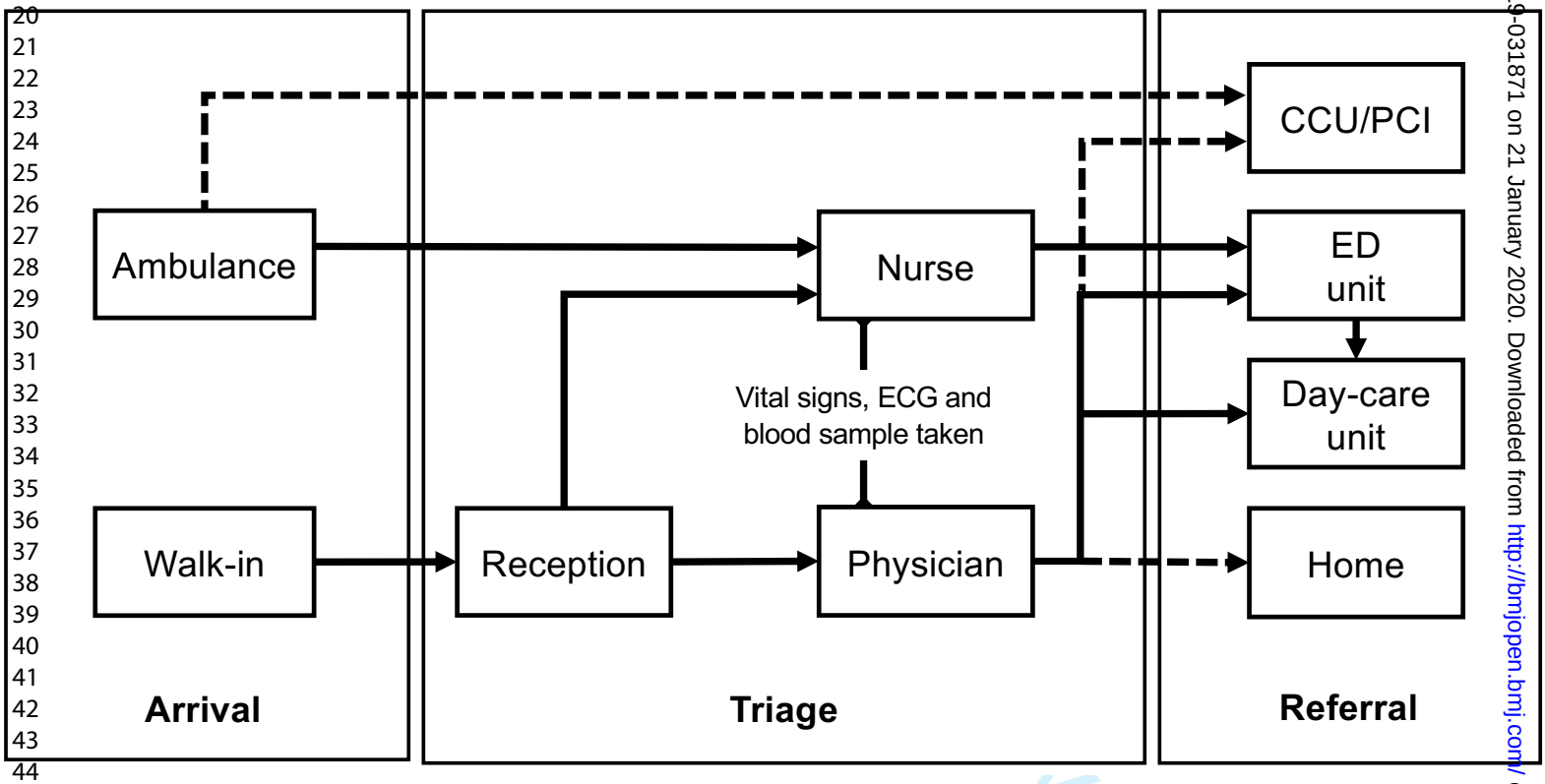
FIGURE LEGENDS

Figure 1. Overview of planned studies. Phys: history taking by physicians; CHT: computerized history taking.

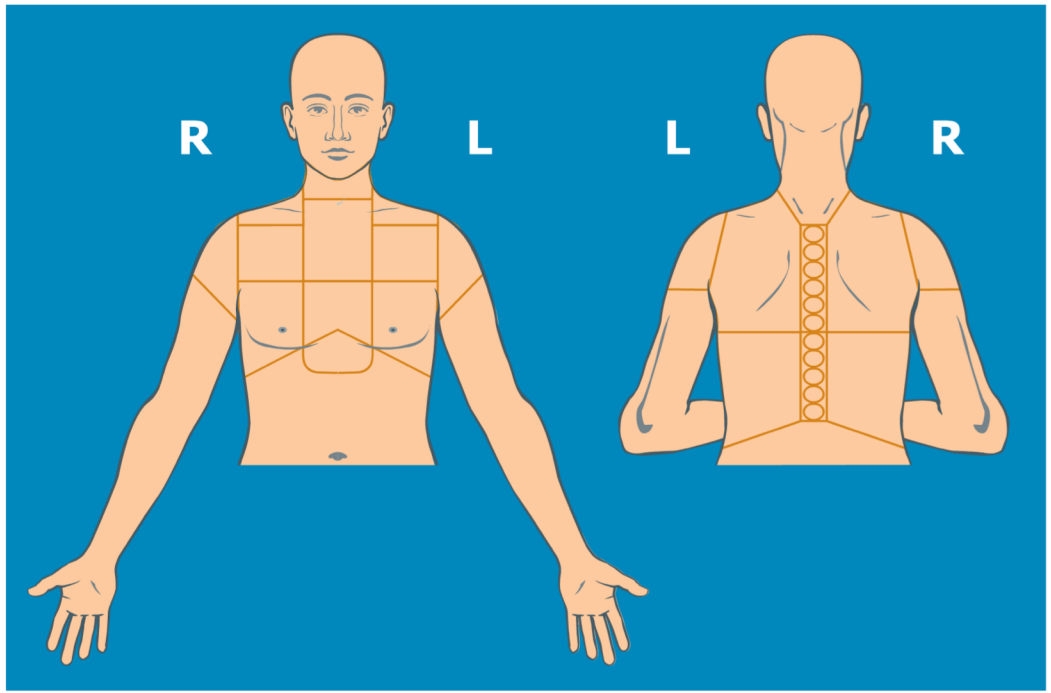
Figure 2. Overview of the ED flow from arrival to referral. Broken lines indicate patients who will not be eligible. ECG: electrocardiogram; CCU: Cardiac care unit; PCI: Percutaneous coronary intervention; ED: Emergency Department.

Figure 3. Example of the presentations of questions in CLEOS on the tablet.





When the pain/discomfort starts, where exactly do you feel it? Select all sites in which you have symptoms.



I have no pain/discomfort in any of these sites

IDM

QUESTION

Please indicate the kind of physical activity that causes or appears to cause the pain/discomfort .

ANSWER

- ❑ Walking on flat ground
- ❑ Walking up stairs
- ❑ Working with my arms
- ❑ Lifting heavy objects, running, bicycle riding, or another form of general physical activity
- ❑ Running, bicycle riding, or another form of general physical activity
- ❑ None of these activities cause the symptoms

IDM

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set *Comment: Embedded in manuscript. Also, see trial registration at clinicaltrials.gov (NCT03439449).*	4
Protocol version	#3	Date and version identifier	8
Funding	#4	Sources and types of financial, material, and other support	20

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2,19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1, 19
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6-8
Objectives	#7	Specific objectives or hypotheses	8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15-16
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8, figure 1 and 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 11, 15
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions *Comment: Not relevant for this observational cohort study.*	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned *Comment: Not relevant for this observational cohort study.*	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions *Comment: Not relevant for this observational cohort study.*	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how *Comment: Not relevant for this observational cohort study.*	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial *Comment: Not relevant for this observational cohort study.*	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	10-12

		Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols *Comment: When patients have provided data via the interview, outcome data are retrieved from registries and health records.*	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17, 19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring		*Comment: This will be addressed in the feasibility study (Study I).*	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed *Comment: Data is entered directly into the database.*	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11-12, 16

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17-18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) *Comment: Included in the regulations for ethical approval, which has been done to the ethical review authority. There, patient information, any amendments etc. can also be retrieved.*	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results	17-18

		databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code *Comment: No such plans at present.*	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates *Comment: The model consent form and other related documentation is available from the ethical review authority. These are public documents in Sweden.*	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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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)

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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)

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ABSTRACT

Introduction

Management of acute chest pain focuses on diagnosis or safe rule-out of an acute coronary syndrome (ACS). We aim to determine the additional value of self-reported computerized history taking (CHT).

Methods and analysis

Prospective cohort study design with self-reported, medical histories collected by a CHT program (Clinical Expert Operating System, CLEOS) using a tablet. Women and men presenting with acute chest pain to the emergency department at Danderyd University Hospital (Stockholm, Sweden) are eligible. CHT will be compared with standard history taking for completeness of data required to calculate ACS risk scores such as HEART, GRACE, and TIMI. Clinical outcomes will be extracted from hospital electronic health records and national registries. The CLEOS-CPDS project includes (I) a feasibility study of CHT, (II) a validation study of CHT as compared with standard history taking, (III) a paired diagnostic accuracy study using data from CHT and established risk scores, (IV) a clinical utility study to evaluate the impact of CHT on management of chest pain and use of resources, and (V) data mining, aiming to generate an improved risk score for ACS. Primary outcomes will be analysed after 1,000 patients, but to allow for subgroup analysis, the study intends to recruit 2,000 or more patients. This project may lead to new and more effective ways for collecting thorough, accurate medical histories with important implications for clinical practice.

Ethics and dissemination

This study has been reviewed and approved by the Stockholm Regional Ethical Committee (now Swedish Ethical Review Authority). Results will be published, regardless of the outcome, in peer-reviewed international scientific journals.

Registration details

This study is registered at https://www.clinicaltrials.gov (unique identifier: NCT03439449).

Strengths and limitations of this study

- One strength of this study is the focus on accurate risk prediction for a life-threatening condition among the large group of patients presenting to the emergency department with a common complaint.

- Another strength is the prospective, cohort study design, and a large study population with reliable outcomes, for which there are well-established, strict criteria.

- The academic, investigator-initiated and investigator-driven study without any commercial interests adds further strength.

- Potential limitations include selection bias, as some patients may not be able to carry through a computerized interview; there may also be a risk of recall bias caused by giving a medical history twice.

- Furthermore, the generalizability of the study results may be limited with different structure and organization of emergency departments.

INTRODUCTION

Chest pain is one of the most frequent presenting complaints in emergency departments (ED), accounting for as many as 30 % of all visits(1). Causes of chest pain range from benign conditions to life-threatening emergencies such as an acute coronary syndrome (ACS; *i.e.* unstable angina pectoris and acute myocardial infarction), which is the acute presentation of ischemic heart disease, the most common cause of death world-wide(2). A major challenge for physicians is to rule-in or rule-out ACS accurately because objective evidence for ACS, *e.g.* electrocardiograms (ECG) and circulating biomarkers indicating acute myocardial injury such as troponin, usually are imponderable in the early course of evaluation. 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).

Current guidelines emphasize the importance of medical history taking for evaluating chest pain(3, 5). However, it has been argued that signs and symptoms of ACS are so variable that careful history taking by a physician is an imperfect tool and sometimes of little help for safely excluding ACS(6). It is argued too that history taking is time-consuming and can delay what are regarded as more precise examination methods such as coronary computed tomography angiography(6, 7). However, the majority of patients with chest pain in the ED do not have ACS or another emergent issue, so aggressive use of objective methods for finding lesions of the coronary arteries puts many patients at risk for undergoing unnecessary, potentially harmful and costly examinations. Therefore, contemporary guidelines indicate that risk scores should be used to stratify risk for ACS on a patient-by-patient basis. Recommended scoring systems include the Thrombolysis in Myocardial Infarction (TIMI)

score and Global Registry of Acute Coronary Events (GRACE) score(3, 5). More recently, utilization of the HEART (History, ECG, Age, Risk factors and Troponin) score has been recommended as an effective tool for risk stratification in the ED setting(8). Typically, these scores include information on age, risk factors for coronary artery disease (family history, hypertension, hypercholesterolemia, diabetes, current smoker), heart failure, renal function, history suspicious for angina, current use of aspirin or diuretics, ST segment deviation on the ECG and elevated serum cardiac biomarkers(9, 10).

In a hectic ED setting, important information may be missed by medical history taking obtained by the physician (standard history taking). Other approaches have been suggested to ensure collection of more complete and accurate information(11). One way to address this issue is to collect self-reported medical histories *via* computerized history taking (CHT) programs. Herrick et al. conducted a cross-sectional study in an ED setting; 841 patients independently and easily engaged with CHT programs to input data with high accuracy(12). Other studies have shown that CHT performed well in evaluating risk for post-traumatic stress(13), stratifying cardiovascular risk in patients with hypercholesterolemia(14), and for generating a present illness in patients with gastrointestinal symptoms to improve clinic visit efficiency(15). However, in a recent a review of the literature for CHT *versus* oral-and-written history taking for prevention and management of cardiovascular disease only one other study(16) was identified. The authors concluded there is a need to develop an evidence base to support the use of CHT programs for cardiovascular disease.

Data from CHT together with computer-based decision support systems have demonstrated improved physician performance and better patient outcomes in some cases(17-20). An important prerequisite for useful computer-based decision support, however, is complete,

accurate and standardized medical history data(11, 21). To date, the data in electronic health records (EHR) in Swedish EDs does not meet the standards required as a basis for computer-based decision support(22). Accordingly, this study aims to determine the additional value of CHT for the management of patients presenting at the ED with chest pain. More specifically, we aim to determine whether self-reported CHT as compared with standard history taking (1) improves data quality, (2) adds to the accuracy of risk stratification to exclude ACS in patients with chest pain, and (3) saves time and resources.

METHODS AND ANALYSIS

Study design

The Clinical Expert Operating System - Chest Pain Danderyd Study (CLEOS-CPDS) is a prospective cohort study designed to determine the value of CHT in the management of acute chest pain (Study protocol version 1.7, dated May 16, 2019). This study follows the SPIRIT reporting guidelines(23). The project includes a feasibility study for CHT in the acute setting (*Study I*); a validation study of CHT as compared with standard history taking (*Study II*); a paired diagnostic accuracy study using data from CHT and established risk scores (*Study III*); a clinical utility study to evaluate the impact of CHT on chest pain management and use of resources (*Study IV*); and use of data mining to generate an improved risk score for ACS (*Study V*). A summary of the planned studies is presented in *Figure 1*.

Study population

Women and men, presenting consecutively at the ED at Danderyd University Hospital (Stockholm, Sweden) from October 1, 2017 until December 31, 2023 (preliminary date), with a chief complaint of chest pain are eligible if they meet the criteria in *Table 1*.

Table 1. Inclusion and exclusion criteria

Inclusion criteria:
- Women and men, aged 18 years and above
- Chest pain recorded by a triage nurse or registrar
- Fluency in Swedish
- Non-diagnostic first ECG and non-diagnostic serum markers of an acute disease requiring immediate care
- Clinically stable patients (RETTS level orange, yellow, green and blue)
- Informed consent
Exclusion criteria:
- Inability to carry out CHT on the dedicated device (*e.g.* confusion, agitation or inadequate eyesight)

ECG: Electrocardiogram, RETTS: Rapid Emergency Triage and Treatment System (triage level orange, yellow, green or blue indicating clinical stability), CHT: Computerized history taking. Standard blood biomarkers for an acute disease are haemoglobin, leukocytes, thrombocytes, high sensitive C-reactive protein, sodium, potassium, creatinine, glucose, high sensitive troponin T and d-dimer.

Danderyd University Hospital, one of four major hospitals in the greater Stockholm region, serves a population of approximately 550,000. The ED has 90,000 annual visits and dedicated units for internal medicine, cardiology, general surgery, orthopaedics and obstetrics/gynaecology. The cardiology unit manages about 20 % of acute visits. It is staffed by two (nights) to five (afternoons) junior doctors, who are supervised by a more senior physician, *e.g.* a cardiology consultant or senior resident in cardiology, day and night. As in

most Swedish EDs, the triage protocol Rapid Emergency Triage and Treatment System (RETTS) is used to assess the urgency of each patient's condition, to decide what work-up is needed and how the patient should be monitored. Based on vital signs and symptoms collected by a nurse and an assistant nurse, patients are divided into five priority levels depending on their need of urgent medical attention: red (immediate), orange (within 20 minutes), yellow (within 120 min), green (not in need of immediate care) and blue (not in need of emergency care or hospital facilities)(24).

Data collection

When presenting to the ED with chest pain, walk-in patients first report their complaint to the reception nurse, who will direct them to the cardiology ED. During weekdays, 10AM-4PM, these patients are triaged promptly by a physician, who is either a cardiology consultant or senior resident in cardiology. The triage includes a decision on the indicated work-up, which is based on a targeted medical history, a brief examination, vital signs and ECG. This data is used to determine whether a patient should be admitted to the cardiology ED, the day-care unit, or sent home. During out-of-office hours, all patients are triaged by a nurse. According to the RETTS protocol, ECG and biomarkers are acquired before the patient is transported to the cardiology ED. All patients then undergo a more thorough examination and standard history taking by a physician, who also decides whether further investigations are needed. Regional guidelines recommend risk stratification according to HEART score including high sensitivity cardiac troponin (hs-cTn) assays and the validated 0 h / 1 h rule-in and rule-out algorithm(3). Patients with signs of ST-elevation myocardial infarction on ECG or clinically unstable patients (RETTS level red) are evaluated immediately and admitted to the coronary care unit or brought to the coronary intervention laboratory for acute intervention, when

indicated. Thus, critically ill patients are excluded in the present study. See *Figure 2* for an overview of the ED flow from arrival to referral.

Patients are asked by a member of the research staff to participate in the current study at the cardiology ED or day-care unit (*Figure 2*). After informed consent has been obtained, histories are collected with a CHT program during waiting times. CHT histories may occur before or after a patient is seen by a physician. Routine care takes precedence over CHT so that patients interact with the CHT program only during waiting times. CHT thus will not interfere with workflow or patient care in the ED. During the study period CHT data will not be available to the care providers.

All answers to CHT-posed questions are time-stamped. The time at which the physician first meets the patient also is recorded. This will enable control for possible second-history effects. Patients are asked about technical, semantic and other problems they might have encountered after completing a CHT interview. This will be done as a basis for future corrections and improvements to the CHT program.

Self-reported medical history data, demographics and other baseline characteristics will be collected from CHT data.

Data from standard history, demographic and baseline characteristics, vital signs and lab data will be extracted from the EHR. To generate the cost associated with routine care patient-by-patient data on use of resources will be extracted from the hospital EHR. Cost will be correlated with different clinical outcomes by linking the diagnosis at the ED visit or when discharged with their Diagnosis Related Group (DRG) code, which is an estimate of costs

associated with a specific diagnosis provided by the National Board of Health and Welfare and Swedish Association of Local Authorities and Regions.

The use of unique personal ID to all Swedish citizens allows linkage to national and regional registries for research purposes. Thus, clinical outcomes in the acute setting (*i.e.* within 7 days) will be extracted from the EHR of the hospital. Discharge diagnoses, at 30 days, and at 1 year, will be collected from the National Patient Register, which includes information on all hospital discharges in Sweden since 1964(25). Mortality status and causes of death will be extracted from the Cause of Death Register which provides official statistics, according to the International Statistical Classification of Diseases and Related Health Problems, in Sweden since 1961(26).

For the validation and future development of CHT, a questionnaire to assess overall patient experience in a larger sample of patients (n=500) will be developed through interviews with a subset of patients. Approximately 30 patients will be asked to participate in three to four focus group interviews for the evaluation of ease of use and usefulness of the CHT program. These interviews will take place one to three months after the ED visit.

Interventions

Computerized, self-reported medical histories will be collected with the software program CLEOS running on tablets (iPad, Apple Inc, Cupertino, CA, USA). CLEOS is developed by Zakim and colleagues and is owned by Karolinska Institutet, a public university. Details and validation of the CLEOS program have been described previously(14, 27). In brief, the participant answers questions by clicking on a variety of question types, *e.g.* yes/no answers, multiple-choice answers with one allowed answer and multiple-choice answers with more

than one allowed answer. Most questions are in a text format but many are images as presented in *Figure 3*. The program determines dynamically the next most appropriate question. This is done on the basis of the answer to a single prior question and rules that interpret the clinical significance of all prior answers. Each patient is guided through an individually tailored, comprehensive medical interview that includes demographics, present illness, organ systems review, past medical history, prescription and over the counter medications, socioeconomic issues, life-style risks, and family history. The program also searches for previous adverse drug reactions. Questions concerning established markers for cardiovascular risk are asked early in the interview for patients with a chief complaint of chest pain. *Table 2* shows the consecutive order of the major medical blocks of the interview. The occurrence of any block or subsection within a block in the pathway for a specific interview is determined, however, by a patient's chief complaint and answers to questions within specific blocks.

Table 2. Consecutive order of medical blocks in the interview

1. Chief complaint
2. Cardiovascular
3. Respiratory
4. Immunology/Rheumatology
5. Endocrinology
6. Gastroenterology/Gastrointestinal surgery
7. Hepatology
8. Nephrology and Urology
9. Obstetrics and Gynaecology
10. Neurology

11. Haematology/Oncology
12. Mental health
13. Past history medical/surgical events
14. Family history

The CLEOS interview is directed by > 17,000 decision nodes and can collect > 40,000 clinical data elements. 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. Previous studies concerning CHT programs have shown that self-reported, CHT with CLEOS is superior to standard history taking in terms of completeness of data collected(14, 27).

In previous studies with CLEOS, the interviews were conducted in English or German(14, 27). We have adapted the program to Swedish conditions. A professional translation agency with medical qualifications (Verbal i Nacka AB, Östersund, Sweden) processed all ~35,000 questions and answer sets in the program. This translation was tested for comprehensibility and cultural adaption in a random sample of 18 persons living in the Stockholm region including both women and men aged between 18-80 years. Age, gender, level of education, previous tablet use, issues during the interview and overall comments were tabulated for all these patients. All phrases were re-examined by a trained medical student and also, to get a non-medical perspective, an economics student. The language of all questions and answers was edited to account for country-specific differences (*e.g.* drug use, tobacco use and abuse) between Sweden, Germany and the U.S. The penultimate version was verified by a competent

physician and then tested by 12 hospitalized patients before a pilot study was started in 400 patients. Additional errors in translation and poor use of language in the original English were resolved continuously in this phase of the work. No additional changes to language were made after the start of the present study.

Sample size calculations

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. The models will be developed in the first 50 % of the data acquired (training data set) and validated in the last 50 % of the data acquired (validation data set). The primary outcome will be analysed after 1,000 patients (with no planned interim analyses), which is expected to be reached by December 31, 2020. We also intend to make estimates in subgroups. To allow these analyses, the study program intends to ultimately recruit data from at least 2,000 patients in total.

Outcomes

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.

Secondary outcomes include 1) the ability of CHT, as compared to standard history taking obtained by the cardiologist in attendance to provide information required to calculate recommended risk scores for ACS; 2) a correct exclusion of an ACS up to 30 days and up to 1 year by use of CHT or standard history taking obtained by the cardiologist in attendance; 3) direct costs and resource utilization for a patient with a diagnosis of an ACS when patient selection is based on CHT, as compared to standard history taking obtained by the cardiologist in attendance; and 4) patient experience with CHT regarding feasibility, acceptance, comprehensible and technical aspects. Finally, we aim to use the collected data to explore the possibility to generate an improved risk score for ACS.

Data management and data analysis plan

The CLEOS interview program runs from a central server located at Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Stockholm, Sweden. Data collected will be stored on this server in the form of codes (not text) representing answers to questions posed. Data transmission and storage fulfil the high standards of security of Karolinska Institutet.

Other data stored are time stamps for completion of each question in an interview, and the pathway by which each interview proceeded. Data collected during routine care, which may be used for algorithm development, *e.g.* signs like heart rate, rhythm, body temperature, blood pressure, biochemistry, and findings from ECG recordings will be extracted from the EHRs and added manually to coded data fields in the CLEOS program.

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).

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).

The potential impact on costs by use of information achieved from CHT in managing patients with acute chest pain, compared with standard history taking, will be calculated. Standard

health economic principles and methods based on DRG codes and current Swedish tariffs for out-patient care and investigations will be used.

Patient and Public involvement

Patients participate at several stages of the study. The patient perspective has been incorporated into this study through interviews during the adaption of the CLEOS program to Swedish conditions, by providing feedback during the pilot study phase and also during the ongoing study after completion of the interview. Furthermore, interviews with a subset of patients for the evaluation of patient experience regarding feasibility, acceptance, comprehensiveness and technical aspects of answering the CLEOS interview will take place as part to the study protocol (see above). All participating patients are informed about how they can access the registered protocol.

Ethics and dissemination

This study has been reviewed and approved by the Stockholm Regional Ethical Committee (now Swedish Ethical Review Authority) (No 2015/1955-1). All participants will give their informed consent before taking part of the study. Results will be published, regardless of the results obtained, in peer-reviewed international scientific journals.

DISCUSSION

Chest pain is a common chief complaint in the ED and there are several health and resource benefits if ACS could be ruled-in or ruled-out more effectively. CHT may be a useful method, but has not been studied previously in an acute cardiology setting. The Swedish health care system offers a good opportunity to study this. There are high quality, comprehensive national health care registries and consistent use of EHRs. This ongoing study aims to determine the

additional value of CHT for the management of patients with acute chest pain. The pilot phase of the CLEOS-CPDS study was performed May 1 to September 30, 2017 and the recruitment in the main study started on October 1, 2017.

The main strengths of this study include the focus on accurate prediction of risk for a life threatening condition among the large group of patients presenting to EDs with a common complaint(1). Second, we use a prospective, cohort study design; include a large study population; and use reliable outcome measures for which there are well-established, strict criteria(29). Third, the implications of the results on resource utilization could have a significant impact for health care providers. Fourth, the use of CHT does not require a specific EHR system, and CLEOS has a generic layout not specific for cardiology or the ED setting. Thus, the results could be potentially generalized to several other clinical issues and care-settings. Finally, our research is academically initiated and driven. The artificial intelligence software in this study is owned by a public university. There are no commercial interests within this research project.

However, a number of possible limitations of this study should be considered. First, patients not able to accomplish CHT are excluded. This may limit the generalizability of the results to all people with chest pain. To address these issues, we will conduct a feasibility analysis on the first 500 patients to compare patient characteristics, their performance with the CHT, and demographics and background characteristics with the entire ED population for the same time period. Why patients decline to participate in the study will be reported specifically. Second, given the large number of possible questions during the interview, we cannot dismiss the risk of vague or misleading questions, as they are not all validated. 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. A risk of recall bias caused by giving a medical history twice (CHT and standard history taking), cannot be excluded. To allow for a sensitivity analysis for this possible bias, we will track the order of interview by physician and CLEOS. 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. 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. Fifth, as we compare data from CHT with data acquired by the attending physician, the performance of the physician can affect our results. 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.

AUTHOR CONTRIBUTIONS

All authors (HB, TK, JS, KS, SK, AA, CJS and DZ) contributed to the conception and design of the study and to creating the study protocol. HB, TK, and DZ drafted the manuscript. DZ is the designer of the CLEOS program's method for making medical knowledge actionable and the developer of the program's medical knowledge base. All authors (HB, TK, JS, KS, SK, AA, CJS and DZ) revised the manuscript for intellectual content and approved the final text.

TK (chair), HB, JS, SK, CJS and DZ form the steering group of the CLEOS-CPDS study. CJS acts as the contact person for the trial sponsor (Karolinska Institutet). All steering group members will have full access to the final trial data set. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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COMPETING INTERESTS STATEMENT

DZ is the inventor on US patents for technology related to the CLEOS program. All patent rights and copyrights to technology, language, images, and knowledge content are assigned without royalty rights by DZ to Karolinska Institutet, Stockholm, Sweden which is a public university. Apart from Karolinska Institutet and its subsidiaries, no individuals or companies may be owners or receive royalties or other revenue from use of CLEOS technology, language, images, knowledge content or from clinical insights and/or computer algorithms generated from analysis of data acquired by the program. There are no other competing interests financial or otherwise in study design, collection, management, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication. All CLEOS-CPDS steering group members (see above) will have full access to the final trial data set.

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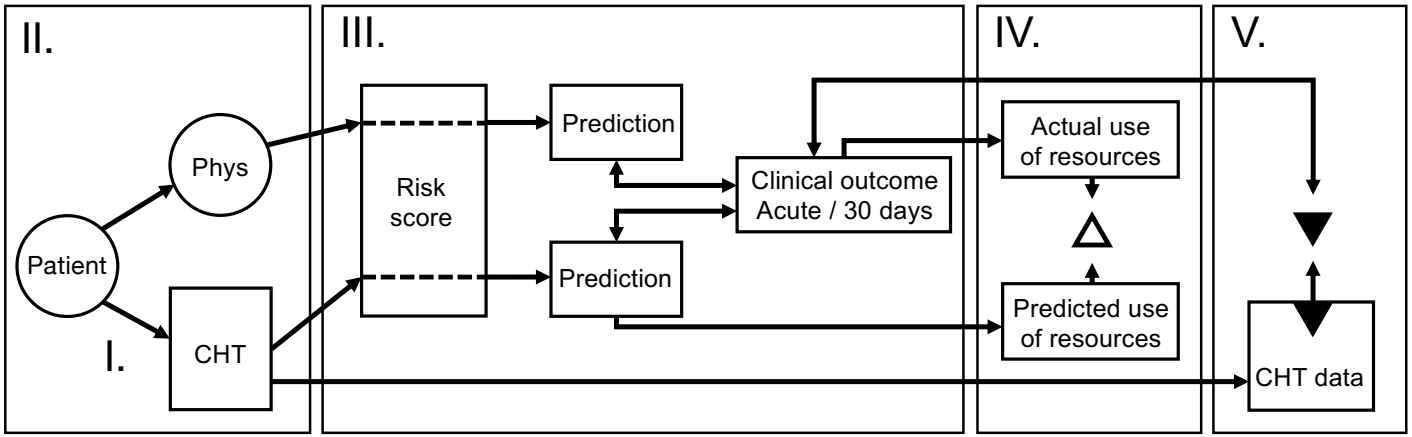
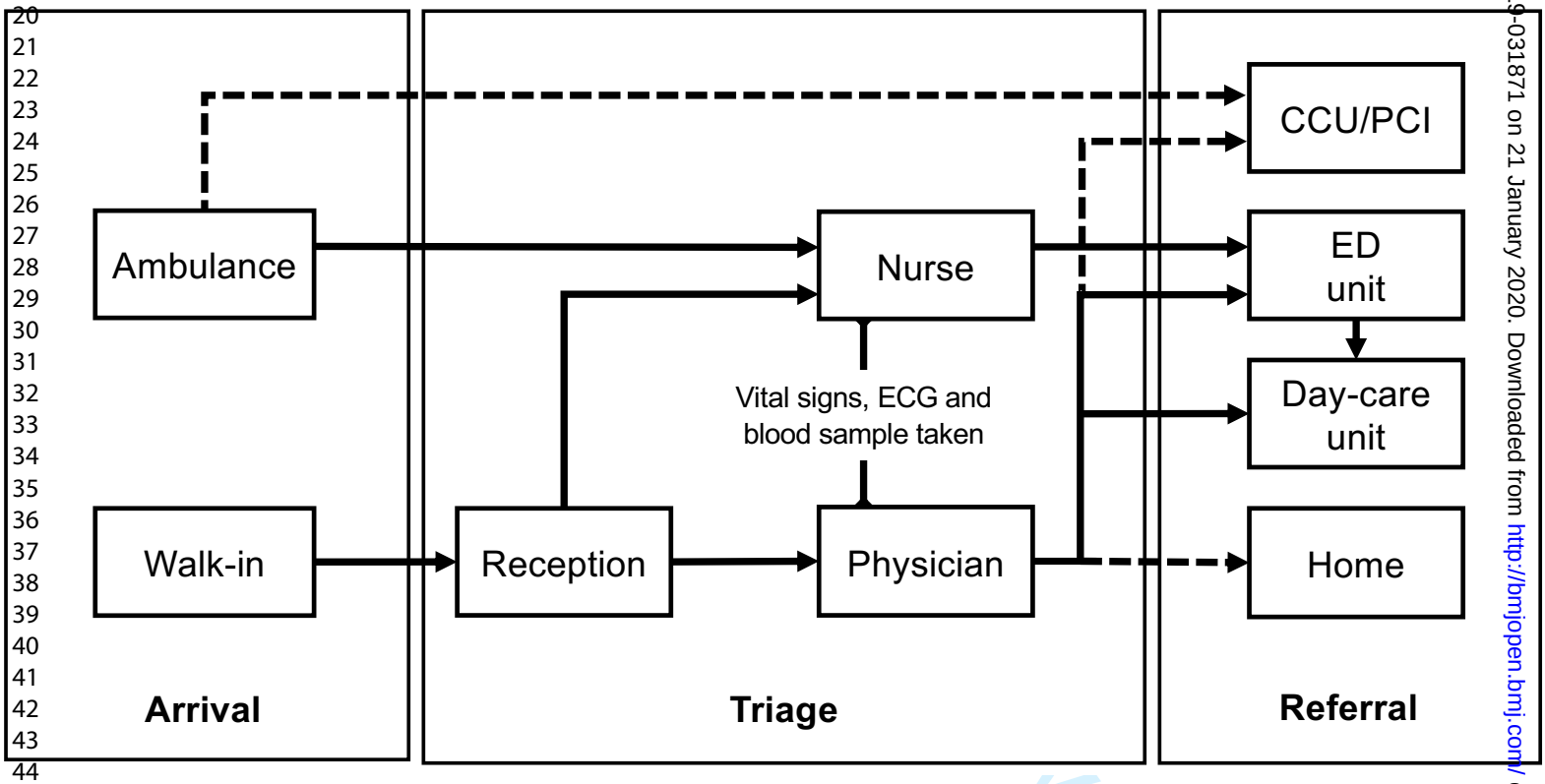
FIGURE LEGENDS

Figure 1. Overview of planned studies. Phys: history taking by physicians; CHT: computerized history taking.

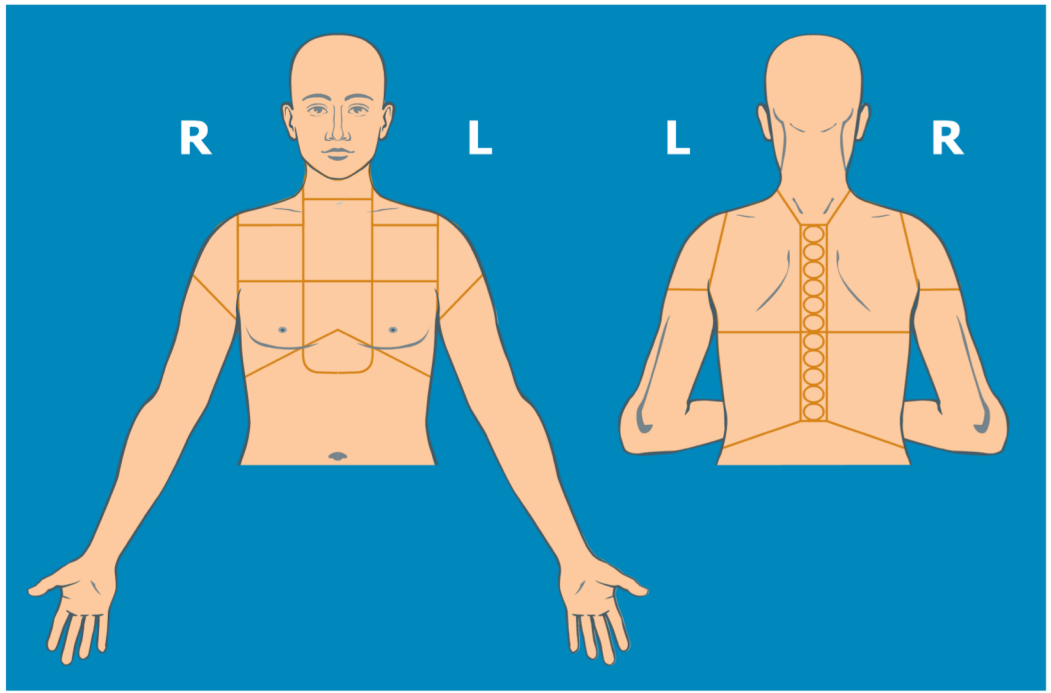
Figure 2. Overview of the ED flow from arrival to referral. Broken lines indicate patients who will not be eligible. ECG: electrocardiogram; CCU: Cardiac care unit; PCI: Percutaneous coronary intervention; ED: Emergency Department.

Figure 3. Example of the presentations of questions in CLEOS on the tablet.





When the pain/discomfort starts, where exactly do you feel it? Select all sites in which you have symptoms.



I have no pain/discomfort in any of these sites

IDM

QUESTION

Please indicate the kind of physical activity that causes or appears to cause the pain/discomfort .

ANSWER

- ❑ Walking on flat ground
- ❑ Walking up stairs
- ❑ Working with my arms
- ❑ Lifting heavy objects, running, bicycle riding, or another form of general physical activity
- ❑ Running, bicycle riding, or another form of general physical activity
- ❑ None of these activities cause the symptoms

IDM

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set *Comment: Embedded in manuscript. Also, see trial registration at clinicaltrials.gov (NCT03439449).*	4
Protocol version	#3	Date and version identifier	8
Funding	#4	Sources and types of financial, material, and other support	20

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2,19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1, 19
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6-8
Objectives	#7	Specific objectives or hypotheses	8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15-16
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8, figure 1 and 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 11, 15
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions *Comment: Not relevant for this observational cohort study.*	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned *Comment: Not relevant for this observational cohort study.*	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions *Comment: Not relevant for this observational cohort study.*	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how *Comment: Not relevant for this observational cohort study.*	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial *Comment: Not relevant for this observational cohort study.*	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	10-12

		Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols *Comment: When patients have provided data via the interview, outcome data are retrieved from registries and health records.*	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17, 19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring		*Comment: This will be addressed in the feasibility study (Study I).*	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed *Comment: Data is entered directly into the database.*	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11-12, 16

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17-18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) *Comment: Included in the regulations for ethical approval, which has been done to the ethical review authority. There, patient information, any amendments etc. can also be retrieved.*	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results	17-18

		databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code *Comment: No such plans at present.*	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates *Comment: The model consent form and other related documentation is available from the ethical review authority. These are public documents in Sweden.*	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a