

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email editorial.bmjopen@bmj.com

BMJ Open

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)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-031871
Article Type:	Protocol
Date Submitted by the Author:	22-May-2019
Complete List of Authors:	<p>Brandberg, Helge; Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine</p> <p>Kahan, Thomas; Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine</p> <p>Spaak, Jonas; Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine</p> <p>Sundberg, Kay; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society</p> <p>Koch, Sabine; Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre</p> <p>Adeli, Athena; Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre</p> <p>Sundberg, Carl Johan; Karolinska Institutet, Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre; Karolinska Institutet, Department of Physiology & Pharmacology</p> <p>Zakim, David; Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre</p>
Keywords:	<p>Coronary heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY, MEDICAL HISTORY, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Information management < BIOTECHNOLOGY & BIOINFORMATICS, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT</p>

SCHOLARONE™
Manuscripts

1
2
3 **A PROSPECTIVE COHORT STUDY OF SELF-REPORTED COMPUTERIZED**
4
5 **MEDICAL HISTORY TAKING FOR ACUTE CHEST PAIN: THE DESIGN OF THE**
6
7 **CLEOS CHEST PAIN DANDERYD STUDY (CLEOS-CPDS)**
8
9
10
11

12 Helge Brandberg (0000-0003-1507-4099), Thomas Kahan (0000-0001-9909-4956), Jonas
13
14 Spaak (0000-0002-2135-1294), Kay Sundberg (0000-0002-4544-9798), Sabine Koch (0000-
15
16 0001-7144-8740), Athena Adeli, Carl Johan Sundberg (0000-0002-7000-466X), David Zakim
17
18 (0000-0002-7722-8148)
19
20
21
22

23 Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of
24
25 Cardiovascular Medicine, SE-182 88, Stockholm, Sweden
26
27

28 Helge Brandberg, MD

29
30 Professor Thomas Kahan, MD

31
32 Jonas Spaak, MD, associate professor
33
34
35
36

37 Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, SE-141 83,
38
39 Stockholm, Sweden
40
41

42 Kay Sundberg, PhD, assistant professor
43
44
45
46

47 Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical
48
49 Management Centre, and Health Informatics Centre, SE-171 77, Stockholm, Sweden
50
51

52 Professor Sabine Koch, PhD, professor

53 Athena Adeli, MD

54
55 Professor Carl Johan Sundberg, MD

56
57 Professor emeritus David Zakim, MD
58
59
60

1
2
3
4
5 Karolinska Institutet, Department of Physiology & Pharmacology, SE-171 77, Stockholm,
6
7 Sweden

8
9
10 Professor Carl Johan Sundberg, MD
11
12
13

14 Correspondence to: Dr Thomas Kahan, Department of Cardiology, Danderyd University
15 Hospital Corp, SE-182 88 Stockholm, Sweden. Email: thomas.kahan@ki.se. Telephone: +46
16
17 8 123 568 61.
18
19
20
21
22
23

24 Word count (excluding title page, abstract, references, figures and tables): 3,830
25
26
27

28 Keywords: Coronary heart disease, Myocardial infarction, Health informatics, Medical
29
30 History Information management, Risk management
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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).

For peer review only

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,

1
2
3 utilization of the HEART (History, ECG, Age, Risk factors and Troponin) score has been
4 recommended as an effective tool for risk stratification in the ED setting(8). Typically, these
5 scores include information on age, risk factors for coronary artery disease (family history,
6 hypertension, hypercholesterolemia, diabetes, current smoker), heart failure, renal function,
7 history suspicious for angina, current use of aspirin or diuretics, ST segment deviation on the
8 ECG and elevated serum cardiac biomarkers(9, 10).
9
10
11
12
13
14
15
16
17
18

19 In a hectic ED setting, important information may be missed by medical history taking
20 obtained by the physician (standard history taking). Other approaches have been suggested to
21 ensure collection of more complete and accurate information(11). One way to address this
22 issue is to collect self-reported medical histories *via* computerized history taking (CHT)
23 programs. Herrick et al. conducted a cross-sectional study in an ED setting; 841 patients
24 independently and easily engaged with CHT programs to input data with high accuracy(12).
25 Other studies have shown that CHT performed well in evaluating risk for post-traumatic
26 stress(13), stratifying cardiovascular risk in patients with hypercholesterolemia(14), and for
27 generating a present illness in patients with gastrointestinal symptoms to improve clinic visit
28 efficiency(15). However, in a recent a review of the literature for CHT *versus* oral-and-
29 written history taking for prevention and management of cardiovascular disease only one
30 other study(16) was identified. The authors concluded there is a need to develop an evidence
31 base to support the use of CHT programs for cardiovascular disease.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51 Data from CHT together with computer-based decision support systems have demonstrated
52 improved physician performance and better patient outcomes in some cases(17-20). An
53 important prerequisite for useful computer-based decision support, however, is complete,
54 accurate and standardized medical history data(11, 21). To date, the data in electronic health
55
56
57
58
59
60

1
2
3 records (EHR) in Swedish EDs does not meet the standards required as a basis for computer-
4 based decision support(22). Accordingly, this study aims to determine the additional value of
5 CHT for the management of patients presenting at the ED with chest pain. More specifically,
6 we aim to determine whether self-reported CHT as compared with standard history taking (1)
7 improves data quality, (2) adds to the accuracy of risk stratification to exclude ACS in
8 patients with chest pain, and (3) saves time and resources.
9
10
11
12
13
14
15
16
17
18

19 **METHODS AND ANALYSIS**

20 **Study design**

21
22 The Clinical Expert Operating System - Chest Pain Danderyd Study (CLEOS-CPDS) is a
23 prospective cohort study designed to determine the value of CHT in the management of acute
24 chest pain (Study protocol version 1.7, dated May 16, 2019). This study follows the SPIRIT
25 reporting guidelines(23). The project includes a feasibility study for CHT in the acute setting
26 (*Study I*); a validation study of CHT as compared with standard history taking (*Study II*); a
27 paired diagnostic accuracy study using data from CHT and established risk scores (*Study III*);
28 a clinical utility study to evaluate the impact of CHT on chest pain management and use of
29 resources (*Study IV*); and use of data mining to generate an improved risk score for ACS
30 (*Study V*). A summary of the planned studies is presented in *Figure 1*.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

47 **Study population**

48 Women and men, presenting consecutively at the ED at Danderyd University Hospital
49 (Stockholm, Sweden) from October 1, 2017 until December 31, 2023 (preliminary date), with
50 a chief complaint of chest pain are eligible if they meet the criteria in *Table 1*.
51
52
53
54
55
56
57

58 **Table 1. Inclusion and exclusion criteria**

1	
2	
3	Inclusion criteria:
4	
5	- Women and men, aged 18 years and above
6	
7	- Chest pain recorded by a triage nurse or registrar
8	
9	
10	- Fluency in Swedish
11	
12	- Non-diagnostic first ECG and non-diagnostic serum markers of an acute disease requiring
13	immediate care
14	
15	
16	
17	- Clinically stable patients (RETTS level orange, yellow, green and blue)
18	
19	
20	- Informed consent
21	
22	Exclusion criteria:
23	
24	- Inability to carry out CHT on the dedicated device (<i>e.g.</i> confusion, agitation or inadequate
25	eyesight)
26	
27	
28	

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

1
2
3 (RETTS) is used to assess the urgency of each patient's condition, to decide what work-up is
4
5 needed and how the patient should be monitored. Based on vital signs and symptoms
6
7 collected by a nurse and an assistant nurse, patients are divided into five priority levels
8
9 depending on their need of urgent medical attention: red (immediate), orange (within 20
10
11 minutes), yellow (within 120 min), green (not in need of immediate care) and blue (not in
12
13 need of emergency care or hospital facilities)(24).
14
15
16
17
18

19 **Data collection**

20
21 When presenting to the ED with chest pain, walk-in patients first report their complaint to the
22
23 reception nurse, who will direct them to the cardiology ED. During weekdays, 10AM-4PM,
24
25 these patients are triaged promptly by a physician, who is either a cardiology consultant or
26
27 senior resident in cardiology. Triage includes a decision on the indicated work-up, which is
28
29 based on a targeted medical history, a brief examination, vital signs and ECG. This data is
30
31 used to determine whether a patient should be admitted to the cardiology ED, the day-care
32
33 unit, or sent home. During out-of-office hours, all patients are triaged by a nurse. According
34
35 to the RETTS protocol, ECG and biomarkers are acquired before the patient is transported to
36
37 the cardiology ED. All patients then undergo a more thorough examination and standard
38
39 history taking by a physician, who also decides whether further investigations are needed.
40
41
42 Regional guidelines recommend risk stratification according to HEART score including high
43
44 sensitivity cardiac troponin (hs-cTn) assays and the validated 0 h / 1 h rule-in and rule-out
45
46 algorithm(3). Patients with signs of ST-elevation myocardial infarction on ECG or clinically
47
48 unstable patients (RETTS level red) are evaluated immediately and admitted to the coronary
49
50 care unit or brought to the coronary intervention laboratory for acute intervention, when
51
52 indicated. Thus, critically ill patients are excluded in the present study. See *Figure 2* for an
53
54 overview of the ED flow from arrival to referral.
55
56
57
58
59
60

1
2
3
4
5 Patients are asked by a member of the research staff to participate in the current study at the
6 cardiology ED or day-care unit (*Figure 2*). After informed consent has been obtained,
7
8 histories are collected with a CHT program during waiting times. CHT histories may occur
9
10 before or after a patient is seen by a physician. Routine care takes precedence over CHT so
11
12 that patients interact with the CHT program only during wait times. CHT will thus not
13
14 interfere with workflow or patient care in the ED. CHT data will not be available to the care
15
16 providers.
17
18
19
20
21
22

23 All answers to CHT-posed questions are time-stamped. The time at which the physician first
24 meets the patient also is recorded. This will enable control for possible second-history effects.
25
26 Patients are asked about technical, semantic and other problems they might have encountered
27
28 after completing a CHT interview. This will be done as a basis for future corrections and
29
30 improvements to the CHT program.
31
32
33
34
35
36
37

38 Self-reported medical history data, demographics and other baseline characteristics will be
39
40 collected from CHT data.
41
42
43
44

45 Data from standard history, demographic and baseline characteristics, vital signs and lab data
46
47 will be extracted from the EHR. Data on use of resources will be extracted from hospital EHR
48
49 to generate the cost associated with routine care patient-by-patient. Cost will be correlated
50
51 with different clinical outcomes by linking the diagnosis at the ED visit or when discharged
52
53 with their Diagnosis Related Group (DRG) code, which is an estimate of costs associated with
54
55 a specific diagnosis provided by the National Board of Health and Welfare and Swedish
56
57 Association of Local Authorities and Regions.
58
59
60

1
2
3
4
5 The use of unique personal ID to all Swedish citizens allows linkage to national and regional
6 registries for research purposes. Thus, clinical outcomes in the acute setting (*i.e.* within 7
7 days) will be extracted from the EHR of the hospital. Discharge diagnoses, at 30 days, and at
8 1 year, will be collected from the National Patient Register, which includes information on all
9 hospital discharges in Sweden since 1964(25). Mortality status and causes of death will be
10 extracted from the Cause of Death Register which provides official statistics, according to the
11 International Statistical Classification of Diseases and Related Health Problems, in Sweden
12 since 1961(26).
13
14
15
16
17
18
19
20
21
22
23
24
25

26 For the validation and future development of CHT, a questionnaire to assess overall patient
27 experience in a larger sample of patients (n=500) will be developed through interviews with a
28 subset of patients. Approximately 30 patients will be asked to participate in three to four focus
29 group interviews for the evaluation of ease of use and usefulness of the CHT program. These
30 interviews will take place one to three months after the ED visit.
31
32
33
34
35
36
37
38
39

40 **Interventions**

41 Computerized, self-reported medical histories will be collected with the software program
42 CLEOS running on tablets (iPad, Apple Inc, Cupertino, CA, USA). CLEOS is developed by
43 Zakim and colleagues and is owned by Karolinska Institutet, a public university. Details and
44 validation of the CLEOS program have been described previously(14, 27). In brief, the
45 participant answers questions by clicking on a variety of question types, *e.g.* yes/no answers,
46 multiple-choice answers with one allowed answer and multiple-choice answers with more
47 than one allowed answer. Most questions are in a text format but many are images as
48 presented in *Figure 3*. The program determines dynamically the next most appropriate
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 made after the start of the present study.
4
5
6

7 **Sample size calculations**

8
9
10 This is an exploratory study. The calculation of the size of the study population is based on
11 the desired precision of sensitivity and specificity. Assuming that the prevalence of ACS is
12 0.5 (50 %), 1,000 patients are required to obtain a precision of sensitivity and specificity of
13 ± 0.03 (3 %) (nQuery version 7.0, Statistical Solutions Ltd, Boston, MA, USA). The more the
14 extreme the result, *i.e.* sensitivity or specificity approaching 0 or 1 (100 %), the higher the
15 precision. The models will be developed in the first 50 % of the data acquired (training data
16 set) and validated in the last 50 % of the data acquired (validation data set). The primary
17 outcome will be analysed after 1,000 patients (with no planned interim analyses), which is
18 expected to be reached by December 31, 2020. We also intend to make estimates in
19 subgroups. To allow these analyses, the study program intends to ultimately recruit data from
20 at least 2,000 patients in total.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37

38 **Outcomes**

39
40 The primary objective is to determine whether the use of CHT is better than standard history
41 taking obtained by the physician in attendance (generally a specialist or resident in
42 cardiology) for the prediction and safe exclusion of an ACS in the acute setting in patients
43 with non-diagnostic ECG or serum markers. Thus, the primary outcome is the comparison of
44 the accuracy between the two methods for the safe exclusion of ACS or a diagnosis of ACS in
45 the acute setting *i.e.* within seven days from the ED visit. The diagnosis of ACS will be based
46 on current European guidelines(3, 28). The diagnosis will be validated by an experienced
47 cardiologist.
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Secondary outcomes include 1) the ability of CHT, as compared to standard history taking
4 obtained by the cardiologist in attendance to provide information required to calculate
5 recommended risk scores for ACS; 2) a correct exclusion of an ACS up to 30 days and up to 1
6 year by use of CHT or standard history taking obtained by the cardiologist in attendance; 3)
7 direct costs and resource utilization for a patient with a diagnosis of an ACS when patient
8 selection is based on CHT, as compared to standard history taking obtained by the
9 cardiologist in attendance; and 4) patient experience with CHT regarding feasibility,
10 acceptance, comprehensible and technical aspects. Finally, we aim to use the collected data to
11 explore the possibility to generate an improved risk score for ACS.
12
13
14
15
16
17
18
19
20
21
22
23
24
25

26 **Data management and data analysis plan**

27
28 The CLEOS interview program runs from a central server located at Karolinska Institutet,
29 Department of Learning, Informatics, Management and Ethics, Stockholm, Sweden. Data
30 collected will be stored on this server in the form of codes (not text) representing answers to
31 questions posed. Data transmission and storage fulfil the high standards of security of
32 Karolinska Institutet.
33
34
35
36
37
38
39
40
41

42 Other data stored are time stamps for completion of each question in an interview, and the
43 pathway by which each interview proceeded. Data collected during routine care, which may
44 be used for algorithm development, *e.g.* signs like heart rate, rhythm, body temperature, blood
45 pressure, biochemistry, and findings from ECG recordings will be extracted from the EHRs
46 and added manually to coded data fields in the CLEOS program.
47
48
49
50
51
52
53
54
55

56 Descriptive statistics will be used to describe demography and background characteristics. We
57 will evaluate established risk scores, as populated with CLEOS data, and compare these
58
59
60

1
2
3 results with data obtained during the concurrent ED visit and made available in the standard
4 hospital EHR. Regression-based statistical analyses will be used, and appropriate test for
5 significant difference of completeness of the risk scores.
6
7
8
9

10
11
12 Second, to assess how data collected with CLEOS in combination with established risk scores
13 can rule-in and rule-out a diagnosis of an ACS, we will calculate sensitivity, specificity and
14 negative and positive predictive values. The results will be presented with receiver operating
15 characteristic (ROC) curves for each risk score. Logistic regression will be used to describe
16 the relationship with the predictions and actual outcomes (*i.e.* ACS or not ACS).
17
18
19
20
21
22
23

24
25
26 The potential impact on costs by use of information achieved from CHT in managing patients
27 with acute chest pain, compared with standard history taking, will be calculated. Standard
28 health economic principles and methods based on DRG codes and current Swedish tariffs for
29 out-patient care and investigations will be used.
30
31
32
33
34
35

36 37 **Patient and Public involvement**

38
39 Patients participate at several stages of the study. Through interviews during the adaption of
40 the CLEOS program to Swedish conditions, by providing feedback during the pilot study
41 phase and also during the ongoing study after completion of the interview, the patient
42 perspective has been well taken care of. Furthermore, interviews with a subset of patients for
43 the evaluation of patient experience regarding feasibility, acceptance, comprehensiveness and
44 technical aspects of answering the CLEOS interview will take place as part to the study
45 protocol (see above). All participating patients are informed about how they can access the
46 registered protocol.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 intelligence software in this study is owned by a public university. There are no commercial
4
5 interests within this research project.
6
7
8
9

10 However, a number of possible limitations of this study should be considered. First, patients
11 not able to accomplish CHT are excluded. This may limit the generalizability of the results to
12 all people with chest pain. To address these issues, we will conduct a feasibility analysis on
13 the first 500 patients to compare patient characteristics, their performance with the CHT, and
14 demographics and background characteristics with the entire ED population for the same time
15 period. Why patients decline to participate in the study will be reported specifically. Second,
16 given the large number of possible questions during the interview, we cannot dismiss the risk
17 of vague or misleading questions, as they are not all validated. A risk of recall bias caused by
18 giving a medical history twice (CHT and standard history taking), cannot be excluded. To
19 allow for a sensitive analysis for this possible bias, we will track the order of interview by
20 physician and CLEOS. Third, as we compare data from CHT with data acquired by the
21 attending physician, the performance of the physician can affect our results. Thus, our results
22 may not be generalized to another ED setting.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41

42 **AUTHOR CONTRIBUTIONS**

43
44 All authors contributed to the conception and design of the study and to creating the study
45 protocol. HB, TK, and DZ drafted the manuscript. DZ is the designer of the CLEOS
46 program's method for making medical knowledge actionable and the developer of the
47 program's medical knowledge base. All authors revised the manuscript for intellectual content
48 and approved the final text. TK (chair), HB, JS, SK, CJS and DZ form the steering group of
49 the CLEOS-CPDS study. CJS acts as the contact person for the trial sponsor (Karolinska
50 Institutet). All steering group members will have full access to the final trial data set. The
51
52
53
54
55
56
57
58
59
60

1
2
3 corresponding author attests that all listed authors meet authorship criteria and that no others
4
5 meeting the criteria have been omitted.
6
7
8
9

10 **FUNDING STATEMENT**

11
12 This work was supported by the Robert Bosch Stiftung (Stuttgart, Germany), Karolinska
13
14 Institutet Research Foundation (Stockholm, Sweden) and Stiftelsen Hjärtat (Stockholm,
15
16
17 Sweden).
18
19
20

21 **COMPETING INTERESTS STATEMENT**

22
23 DZ is the inventor on US patents for technology related to the CLEOS program. All patent
24
25 rights and copyrights to technology, language, images, and knowledge content are assigned
26
27 without royalty rights by DZ to Karolinska Institutet, Stockholm, Sweden which is a public
28
29 university. Apart from Karolinska Institutet and its subsidiaries, no individuals or companies
30
31 may be owners or receive royalties or other revenue from use of CLEOS technology,
32
33 language, images, knowledge content or from clinical insights and/or computer algorithms
34
35 generated from analysis of data acquired by the program. There are no other competing
36
37 interests financial or otherwise in study design, collection, management, analysis, and
38
39 interpretation of data, writing of the report, and the decision to submit the report for
40
41 publication. All CLEOS-CPDS steering group members (see above) will have full access to
42
43 the final trial data set.
44
45
46
47
48
49
50

51 **REFERENCES**

52
53 1 Pitts SR, Niska RW, Xu J, et al. National Hospital Ambulatory Medical Care Survey: 2006
54
55 emergency department summary. *Natl Health Stat Report*. 2008:1-38.
56
57
58
59
60

1
2
3 2 Organization WH. Global Health Observatory (GHO) data: World Health Organization;
4
5 2019 [cited 2019 May 15]. Available from:

6
7 http://origin.who.int/gho/mortality_burden_disease/causes_death/top_10/en/.

8
9
10 3 Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute
11
12 coronary syndromes in patients presenting without persistent ST-segment elevation: Task
13
14 Force for the Management of Acute Coronary Syndromes in Patients Presenting without
15
16 Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*.
17
18 2016;37:267-315.

19
20
21 4 Ekelund U, Nilsson HJ, Frigyesi A, et al. Patients with suspected acute coronary syndrome
22
23 in a university hospital emergency department: an observational study. *BMC Emerg Med*.
24
25 2002;2:1.

26
27
28 5 Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the
29
30 management of patients with non-ST-elevation acute coronary syndromes: executive
31
32 summary: a report of the American College of Cardiology/American Heart Association Task
33
34 Force on Practice Guidelines. *Circulation*. 2014;130:2354-94.

35
36
37 6 Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of
38
39 patients with suspected acute coronary syndromes. *JAMA*. 2005;294:2623-9.

40
41
42 7 Nieman K, Hoffmann U. Cardiac computed tomography in patients with acute chest pain.
43
44 *Eur Heart J*. 2015;36:906-14.

45
46
47 8 Six AJ, Cullen L, Backus BE, et al. The HEART score for the assessment of patients with
48
49 chest pain in the emergency department: a multinational validation study. *Crit Pathw Cardiol*.
50
51 2013;12:121-6.

52
53
54 9 Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial
55
56 infarction in the six months after presentation with acute coronary syndrome: prospective
57
58 multinational observational study (GRACE). *BMJ*. 2006;333:1091.

- 1
2
3 10 Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST
4 elevation MI: A method for prognostication and therapeutic decision making. *JAMA*.
5
6 2000;284:835-42.
7
8
9
10 11 Cox JL, Zitner D, Courtney KD, et al. Undocumented patient information: an impediment
11 to quality of care. *Am J Med*. 2003;114:211-6.
12
13
14 12 Herrick DB, Nakhasi A, Nelson B, et al. Usability characteristics of self-administered
15 computer-assisted interviewing in the emergency department. *Appl Clin Inform*. 2013;4:276-
16
17 92.
18
19
20 21 13 Corrigan M, McWilliams R, Kelly KJ, et al. A computerized, self-administered
22 questionnaire to evaluate posttraumatic stress among firefighters after the World Trade Center
23 collapse. *Am J Public Health*. 2009;99 Suppl 3:S702-9.
24
25
26 27 14 Zakim D, Fritz C, Braun N, et al. Computerized history-taking as a tool to manage
28 dyslipidemia. *Vasc Health Risk Manag*. 2010;6:1039-46.
29
30
31 32 15 Almario CV, Chey W, Kaung A, et al. Computer-Generated Vs. Physician-Documented
33 History of Present Illness (HPI): Results of a Blinded Comparison. *Am J Gastroenterol*.
34
35 2015;110:170-9.
36
37
38 39 16 Pappas Y, Vseteckova J, Poduval S, et al. Computer-Assisted versus Oral-and-Written
40 History Taking for the Prevention and Management of Cardiovascular Disease: a Systematic
41
42 Review of the Literature. *Acta Medica (Hradec Kralove)*. 2017;60:97-107.
43
44
45 46 17 Hunt DL, Haynes RB, Hanna SE, et al. Effects of computer-based clinical decision support
47 systems on physician performance and patient outcomes: a systematic review. *JAMA*.
48
49 1998;280:1339-46.
50
51
52 53 18 Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision
54 support systems on practitioner performance and patient outcomes: a systematic review.
55
56
57
58
59
60 *JAMA*. 2005;293:1223-38.

- 1
2
3 19 Raschke RA, Gollihare B, Wunderlich TA, et al. A computer alert system to prevent injury
4 from adverse drug events: development and evaluation in a community teaching hospital.
5
6 *JAMA*. 1998;280:1317-20.
7
8
9
10 20 Chen R, Valladares C, Corbal I, et al. Early Experiences from a guideline-based
11 computerized clinical decision support for stroke prevention in atrial fibrillation. *Stud Health*
12 *Technol Inform*. 2013;192:244-7.
13
14
15
16 21 Berner ES, Kasiraman RK, Yu F, et al. Data quality in the outpatient setting: impact on
17 clinical decision support systems. *AMIA Annu Symp Proc*. 2005:41-5.
18
19
20
21 22 Skyttberg N, Chen R, Blomqvist H, et al. Exploring Vital Sign Data Quality in Electronic
22 Health Records with Focus on Emergency Care Warning Scores. *Appl Clin Inform*.
23
24 2017;8:880-92.
25
26
27
28 23 Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration:
29 guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.
30
31
32
33 24 Widgren BR, Jourak M. Medical Emergency Triage and Treatment System (METTS): a
34 new protocol in primary triage and secondary priority decision in emergency medicine. *J*
35 *Emerg Med*. 2011;40:623-8.
36
37
38
39
40 25 Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the
41 Swedish national inpatient register. *BMC Public Health*. 2011;11:450.
42
43
44
45 26 Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. *Eur J*
46 *Epidemiol*. 2017;32:765-73.
47
48
49
50 27 Zakim D, Braun N, Fritz P, et al. Underutilization of information and knowledge in
51 everyday medical practice: Evaluation of a computer-based solution. *BMC Med Inform Decis*
52 *Mak*. 2008;8.
53
54
55
56 28 Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute
57 myocardial infarction in patients presenting with ST-segment elevation: The Task Force for
58
59
60

1
2
3 the management of acute myocardial infarction in patients presenting with ST-segment
4 elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39:119-77.
5
6

7 29 Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction
8 (2018). *Eur Heart J.* 2018;40:237-69.
9
10
11
12

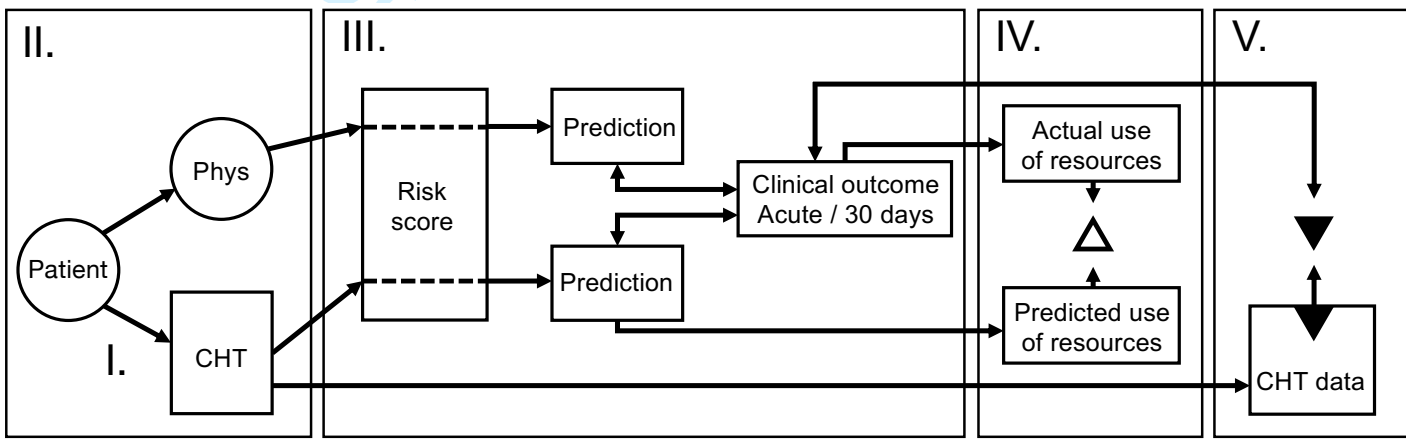
13 14 **FIGURE LEGENDS**

15
16
17 Figure 1. Overview of planned studies. Phys: history taking by physicians; CHT:
18 computerized history taking.
19
20

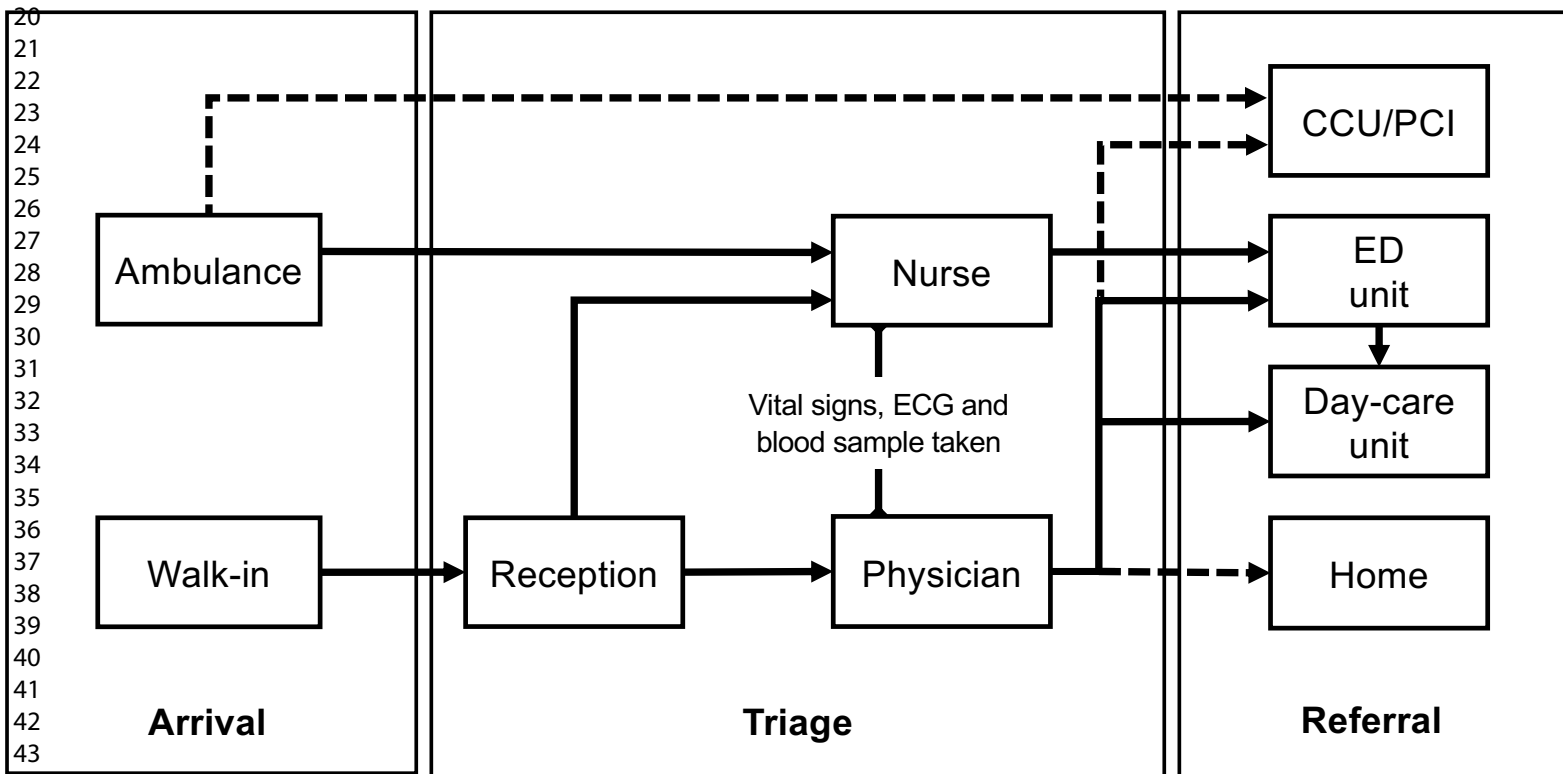
21
22
23 Figure 2. Overview of the ED flow from arrival to referral. Broken lines indicate patients who
24 will not be eligible. ECG: electrocardiogram; CCU: Cardiac care unit; PCI: Percutaneous
25 coronary intervention; ED: Emergency Department.
26
27
28
29

30
31
32 Figure 3. Example of the presentations of questions in CLEOS on the tablet.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

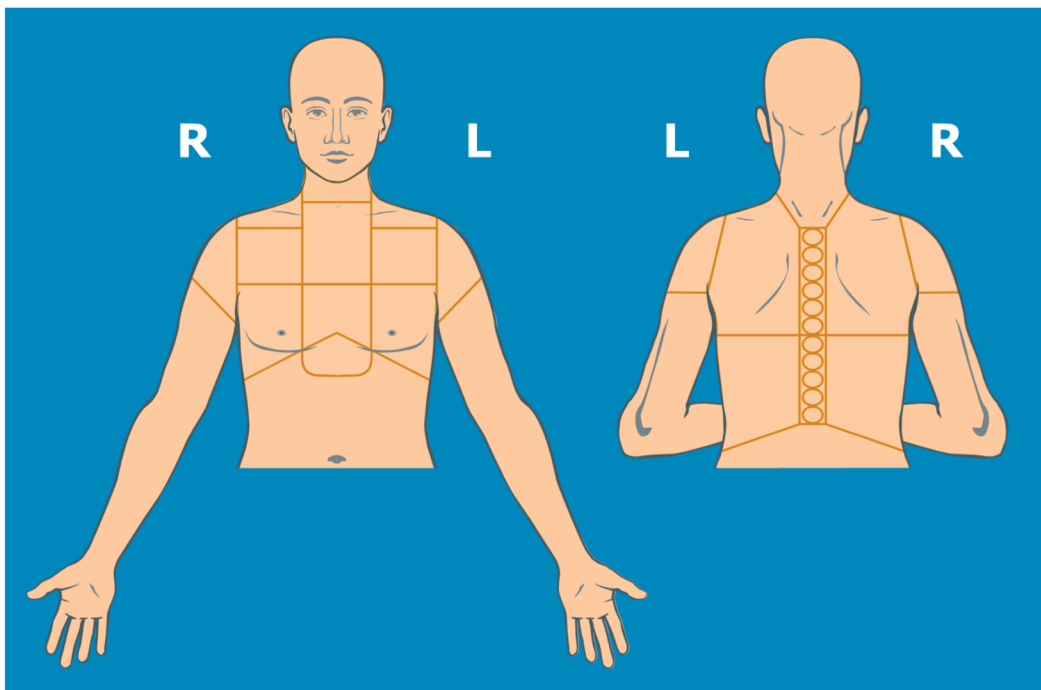
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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

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



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 <i>Comment: Embedded in manuscript. Also, see trial registration at clinicaltrials.gov (NCT03439449).</i>	4
Protocol version	#3	Date and version identifier	8
Funding	#4	Sources and types of financial, material, and other support	20

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1-2,19
2	responsibilities:			
3	contributorship			
4				
5				
6	Roles and	#5b	Name and contact information for the trial sponsor	1, 19
7	responsibilities:			
8	sponsor contact			
9	information			
10				
11				
12				
13	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	20
14	responsibilities:		collection, management, analysis, and interpretation of data;	
15	sponsor and funder		writing of the report; and the decision to submit the report for	
16			publication, including whether they will have ultimate authority	
17			over any of these activities	
18				
19				
20				
21	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	19
22	responsibilities:		centre, steering committee, endpoint adjudication committee,	
23	committees		data management team, and other individuals or groups	
24			overseeing the trial, if applicable (see Item 21a for data	
25			monitoring committee)	
26				
27				
28				
29				
30	Introduction			
31				
32	Background and	#6a	Description of research question and justification for undertaking	6-8
33	rationale		the trial, including summary of relevant studies (published and	
34			unpublished) examining benefits and harms for each intervention	
35				
36				
37	Background and	#6b	Explanation for choice of comparators	6-8
38	rationale: choice of			
39	comparators			
40				
41				
42	Objectives	#7	Specific objectives or hypotheses	8
43				
44				
45	Trial design	#8	Description of trial design including type of trial (eg, parallel	8
46			group, crossover, factorial, single group), allocation ratio, and	
47			framework (eg, superiority, equivalence, non-inferiority,	
48			exploratory)	
49				
50				
51				
52	Methods:			
53	Participants,			
54	interventions, and			
55	outcomes			
56				
57				
58				
59				
60				

1	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
2				
3				
4				
5				
6	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
7				
8				
9				
10				
11	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
12	description			
13				
14				
15	Interventions:	#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
16	modifications			
17				
18				
19				
20				
21	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-14
22	adherence			
23				
24				
25				
26	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
27	concomitant care			
28				
29				
30	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
31				
32				
33				
34				
35				
36				
37				
38				
39				
40	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
41				
42				
43				
44				
45	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
46				
47				
48				
49				
50	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 11, 15
51				
52				
53				

Methods: Assignment of interventions (for controlled trials)

1	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-	n/a
2	generation		generated random numbers), and list of any factors for	
3			stratification. To reduce predictability of a random sequence,	
4			details of any planned restriction (eg, blocking) should be	
5			provided in a separate document that is unavailable to those who	
6			enrol participants or assign interventions	
7				
8				
9				
10				
11			<i>Comment: Not relevant for this observational cohort study.</i>	
12				
13	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central	n/a
14	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
15	mechanism		describing any steps to conceal the sequence until interventions	
16			are assigned	
17				
18				
19				
20			<i>Comment: Not relevant for this observational cohort study.</i>	
21				
22	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	n/a
23	implementation		participants, and who will assign participants to interventions	
24				
25				
26			<i>Comment: Not relevant for this observational cohort study.</i>	
27				
28	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial	n/a
29			participants, care providers, outcome assessors, data analysts),	
30			and how	
31				
32				
33				
34			<i>Comment: Not relevant for this observational cohort study.</i>	
35				
36	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible,	n/a
37	emergency unblinding		and procedure for revealing a participant's allocated intervention	
38			during the trial	
39				
40				
41			<i>Comment: Not relevant for this observational cohort study.</i>	
42				
43				
44	Methods: Data			
45	collection,			
46	management, and			
47	analysis			
48				
49				
50	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and	10-12
51			other trial data, including any related processes to promote data	
52			quality (eg, duplicate measurements, training of assessors) and a	
53			description of study instruments (eg, questionnaires, laboratory	
54			tests) along with their reliability and validity, if known.	
55				
56				
57				
58				
59				
60				

Reference to where data collection forms can be found, if not in the protocol

1			
2			
3			
4	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, 12
5	retention		including list of any outcome data to be collected for participants
6			who discontinue or deviate from intervention protocols
7			
8			
9			<i>Comment: When patients have provided data via the interview,</i>
10			<i>outcome data are retrieved from registries and health records.</i>
11			
12			
13	Data management	#19	Plans for data entry, coding, security, and storage, including any 16
14			related processes to promote data quality (eg, double data entry;
15			range checks for data values). Reference to where details of data
16			management procedures can be found, if not in the protocol
17			
18			
19			
20	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary 16-17
21			outcomes. Reference to where other details of the statistical
22			analysis plan can be found, if not in the protocol
23			
24			
25	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted 16-17,
26	analyses		analyses) 19
27			
28			
29	Statistics: analysis	#20c	Definition of analysis population relating to protocol non- 8
30	population and missing		adherence (eg, as randomised analysis), and any statistical
31	data		methods to handle missing data (eg, multiple imputation)
32			
33			
34	Methods: Monitoring		<i>Comment: This will be addressed in the feasibility study (Study</i>
35			<i>I).</i>
36			
37			
38	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of n/a
39	formal committee		its role and reporting structure; statement of whether it is
40			independent from the sponsor and competing interests; and
41			reference to where further details about its charter can be found,
42			if not in the protocol. Alternatively, an explanation of why a
43			DMC is not needed
44			
45			<i>Comment: Data is entered directly into the database.</i>
46			
47			
48			
49			
50	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines, 15
51	interim analysis		including who will have access to these interim results and make
52			the final decision to terminate the trial
53			
54			
55			
56	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited 11-12,
57			and spontaneously reported adverse events and other unintended 16
58			effects of trial interventions or trial conduct
59			
60			

1	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
2				
3				
4				
5				
6	Ethics and			
7	dissemination			
8				
9				
10	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17-18
11				
12				
13				
14	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)	n/a
15				
16				
17				
18				
19				
20				
21			<i>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.</i>	
22				
23				
24				
25				
26	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
27				
28				
29				
30	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
31				
32				
33				
34				
35	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
36				
37				
38				
39				
40	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
41				
42				
43				
44	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
45				
46				
47				
48				
49	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
50				
51				
52				
53	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
54				
55				
56				
57				
58				
59				
60				

databases, or other data sharing arrangements), including any publication restrictions

Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of professional writers 19

Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code n/a

Comment: No such plans at present.

Appendices

Informed consent materials [#32](#) Model consent form and other related documentation given to participants and authorised surrogates n/a

Comment: The model consent form and other related documentation is available from the ethical review authority. These are public documents in Sweden.

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

None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. **This checklist can be completed online** using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

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)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-031871.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Oct-2019
Complete List of Authors:	<p>Brandberg, Helge; Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine</p> <p>Kahan, Thomas; Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine</p> <p>Spaak, Jonas; Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine</p> <p>Sundberg, Kay; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society</p> <p>Koch, Sabine; Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre</p> <p>Adeli, Athena; Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre</p> <p>Sundberg, Carl Johan; Karolinska Institutet, Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre; Karolinska Institutet, Department of Physiology & Pharmacology</p> <p>Zakim, David; Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre</p>
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Health informatics, Diagnostics, Medical management
Keywords:	Coronary heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY, MEDICAL HISTORY, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Information management < BIOTECHNOLOGY & BIOINFORMATICS, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ Open

v29-10-2019

**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)**

Helge Brandberg (0000-0003-1507-4099), Thomas Kahan (0000-0001-9909-4956), Jonas Spaak (0000-0002-2135-1294), Kay Sundberg (0000-0002-4544-9798), Sabine Koch (0000-0001-7144-8740), Athena Adeli, Carl Johan Sundberg (0000-0002-7000-466X), David Zakim (0000-0002-7722-8148)

Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine, SE-182 88, Stockholm, Sweden

Helge Brandberg, MD

Professor Thomas Kahan, MD

Jonas Spaak, MD, associate professor

Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, SE-141 83, Stockholm, Sweden

Kay Sundberg, PhD, assistant professor

Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre, SE-171 77, Stockholm, Sweden

Professor Sabine Koch, PhD

Athena Adeli, MD

Professor Carl Johan Sundberg, MD

1
2
3 Professor emeritus David Zakim, MD
4
5
6

7
8 Karolinska Institutet, Department of Physiology & Pharmacology, SE-171 77, Stockholm,
9
10 Sweden
11

12 Professor Carl Johan Sundberg, MD
13
14
15

16
17 Correspondence to: Dr Thomas Kahan, Department of Cardiology, Danderyd University
18
19 Hospital Corp, SE-182 88 Stockholm, Sweden. Email: thomas.kahan@sll.se, Telephone: +46
20
21 8 123 568 61.
22
23

24
25
26 Word count (excluding title page, abstract, references, figures and tables): 4,166
27
28

29
30 Keywords: Coronary heart disease, Myocardial infarction, Health informatics, Medical
31
32 History, Information management, Risk management
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3 **Registration details**
4

5 This study is registered at <https://www.clinicaltrials.gov> (unique identifier: NCT03439449).
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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)

1
2
3 score and Global Registry of Acute Coronary Events (GRACE) score(3, 5). More recently,
4
5 utilization of the HEART (History, ECG, Age, Risk factors and Troponin) score has been
6
7 recommended as an effective tool for risk stratification in the ED setting(8). Typically, these
8
9 scores include information on age, risk factors for coronary artery disease (family history,
10
11 hypertension, hypercholesterolemia, diabetes, current smoker), heart failure, renal function,
12
13 history suspicious for angina, current use of aspirin or diuretics, ST segment deviation on the
14
15 ECG and elevated serum cardiac biomarkers(9, 10).
16
17
18
19
20

21 In a hectic ED setting, important information may be missed by medical history taking
22
23 obtained by the physician (standard history taking). Other approaches have been suggested to
24
25 ensure collection of more complete and accurate information(11). One way to address this
26
27 issue is to collect self-reported medical histories *via* computerized history taking (CHT)
28
29 programs. Herrick et al. conducted a cross-sectional study in an ED setting; 841 patients
30
31 independently and easily engaged with CHT programs to input data with high accuracy(12).
32
33 Other studies have shown that CHT performed well in evaluating risk for post-traumatic
34
35 stress(13), stratifying cardiovascular risk in patients with hypercholesterolemia(14), and for
36
37 generating a present illness in patients with gastrointestinal symptoms to improve clinic visit
38
39 efficiency(15). However, in a recent a review of the literature for CHT *versus* oral-and-
40
41 written history taking for prevention and management of cardiovascular disease only one
42
43 other study(16) was identified. The authors concluded there is a need to develop an evidence
44
45 base to support the use of CHT programs for cardiovascular disease.
46
47
48
49
50
51
52

53 Data from CHT together with computer-based decision support systems have demonstrated
54
55 improved physician performance and better patient outcomes in some cases(17-20). An
56
57 important prerequisite for useful computer-based decision support, however, is complete,
58
59
60

1
2
3 accurate and standardized medical history data(11, 21). To date, the data in electronic health
4 records (EHR) in Swedish EDs does not meet the standards required as a basis for computer-
5 based decision support(22). Accordingly, this study aims to determine the additional value of
6 CHT for the management of patients presenting at the ED with chest pain. More specifically,
7 we aim to determine whether self-reported CHT as compared with standard history taking (1)
8 improves data quality, (2) adds to the accuracy of risk stratification to exclude ACS in
9 patients with chest pain, and (3) saves time and resources.
10
11
12
13
14
15
16
17
18
19
20

21 **METHODS AND ANALYSIS**

22 **Study design**

23
24 The Clinical Expert Operating System - Chest Pain Danderyd Study (CLEOS-CPDS) is a
25 prospective cohort study designed to determine the value of CHT in the management of acute
26 chest pain (Study protocol version 1.7, dated May 16, 2019). This study follows the SPIRIT
27 reporting guidelines(23). The project includes a feasibility study for CHT in the acute setting
28 (*Study I*); a validation study of CHT as compared with standard history taking (*Study II*); a
29 paired diagnostic accuracy study using data from CHT and established risk scores (*Study III*);
30 a clinical utility study to evaluate the impact of CHT on chest pain management and use of
31 resources (*Study IV*); and use of data mining to generate an improved risk score for ACS
32 (*Study V*). A summary of the planned studies is presented in *Figure 1*.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

50 **Study population**

51 Women and men, presenting consecutively at the ED at Danderyd University Hospital
52 (Stockholm, Sweden) from October 1, 2017 until December 31, 2023 (preliminary date), with
53 a chief complaint of chest pain are eligible if they meet the criteria in *Table 1*.
54
55
56
57
58
59
60

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 (<i>e.g.</i> 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

1
2
3 most Swedish EDs, the triage protocol Rapid Emergency Triage and Treatment System
4 (RETTS) is used to assess the urgency of each patient's condition, to decide what work-up is
5
6 (RETTS) is used to assess the urgency of each patient's condition, to decide what work-up is
7
8 needed and how the patient should be monitored. Based on vital signs and symptoms
9
10 collected by a nurse and an assistant nurse, patients are divided into five priority levels
11
12 depending on their need of urgent medical attention: red (immediate), orange (within 20
13
14 minutes), yellow (within 120 min), green (not in need of immediate care) and blue (not in
15
16 need of emergency care or hospital facilities)(24).
17
18
19
20

21 **Data collection**

22
23 When presenting to the ED with chest pain, walk-in patients first report their complaint to the
24
25 reception nurse, who will direct them to the cardiology ED. During weekdays, 10AM-4PM,
26
27 these patients are triaged promptly by a physician, who is either a cardiology consultant or
28
29 senior resident in cardiology. The triage includes a decision on the indicated work-up, which
30
31 is based on a targeted medical history, a brief examination, vital signs and ECG. This data is
32
33 used to determine whether a patient should be admitted to the cardiology ED, the day-care
34
35 unit, or sent home. During out-of-office hours, all patients are triaged by a nurse. According
36
37 to the RETTS protocol, ECG and biomarkers are acquired before the patient is transported to
38
39 the cardiology ED. All patients then undergo a more thorough examination and standard
40
41 history taking by a physician, who also decides whether further investigations are needed.
42
43
44 Regional guidelines recommend risk stratification according to HEART score including high
45
46 sensitivity cardiac troponin (hs-cTn) assays and the validated 0 h / 1 h rule-in and rule-out
47
48 algorithm(3). Patients with signs of ST-elevation myocardial infarction on ECG or clinically
49
50 unstable patients (RETTS level red) are evaluated immediately and admitted to the coronary
51
52 care unit or brought to the coronary intervention laboratory for acute intervention, when
53
54
55
56
57
58
59
60

1
2
3 indicated. Thus, critically ill patients are excluded in the present study. See *Figure 2* for an
4
5 overview of the ED flow from arrival to referral.
6
7
8
9

10 Patients are asked by a member of the research staff to participate in the current study at the
11
12 cardiology ED or day-care unit (*Figure 2*). After informed consent has been obtained,
13
14 histories are collected with a CHT program during waiting times. CHT histories may occur
15
16 before or after a patient is seen by a physician. Routine care takes precedence over CHT so
17
18 that patients interact with the CHT program only during waiting times. CHT thus will not
19
20 interfere with workflow or patient care in the ED. During the study period CHT data will not
21
22 be available to the care providers.
23
24
25
26
27

28 All answers to CHT-posed questions are time-stamped. The time at which the physician first
29
30 meets the patient also is recorded. This will enable control for possible second-history effects.
31
32 Patients are asked about technical, semantic and other problems they might have encountered
33
34 after completing a CHT interview. This will be done as a basis for future corrections and
35
36 improvements to the CHT program.
37
38
39
40
41

42 Self-reported medical history data, demographics and other baseline characteristics will be
43
44 collected from CHT data.
45
46
47
48

49 Data from standard history, demographic and baseline characteristics, vital signs and lab data
50
51 will be extracted from the EHR. To generate the cost associated with routine care patient-by-
52
53 patient data on use of resources will be extracted from the hospital EHR. Cost will be
54
55 correlated with different clinical outcomes by linking the diagnosis at the ED visit or when
56
57 discharged with their Diagnosis Related Group (DRG) code, which is an estimate of costs
58
59
60

1
2
3 associated with a specific diagnosis provided by the National Board of Health and Welfare
4 and Swedish Association of Local Authorities and Regions.
5
6
7
8
9

10 The use of unique personal ID to all Swedish citizens allows linkage to national and regional
11 registries for research purposes. Thus, clinical outcomes in the acute setting (*i.e.* within 7
12 days) will be extracted from the EHR of the hospital. Discharge diagnoses, at 30 days, and at
13 1 year, will be collected from the National Patient Register, which includes information on all
14 hospital discharges in Sweden since 1964(25). Mortality status and causes of death will be
15 extracted from the Cause of Death Register which provides official statistics, according to the
16 International Statistical Classification of Diseases and Related Health Problems, in Sweden
17 since 1961(26).
18
19
20
21
22
23
24
25
26
27
28
29

30 For the validation and future development of CHT, a questionnaire to assess overall patient
31 experience in a larger sample of patients (n=500) will be developed through interviews with a
32 subset of patients. Approximately 30 patients will be asked to participate in three to four focus
33 group interviews for the evaluation of ease of use and usefulness of the CHT program. These
34 interviews will take place one to three months after the ED visit.
35
36
37
38
39
40
41
42
43
44

45 **Interventions**

46 Computerized, self-reported medical histories will be collected with the software program
47 CLEOS running on tablets (iPad, Apple Inc, Cupertino, CA, USA). CLEOS is developed by
48 Zakim and colleagues and is owned by Karolinska Institutet, a public university. Details and
49 validation of the CLEOS program have been described previously(14, 27). In brief, the
50 participant answers questions by clicking on a variety of question types, *e.g.* yes/no answers,
51 multiple-choice answers with one allowed answer and multiple-choice answers with more
52
53
54
55
56
57
58
59
60

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

1
2
3 physician and then tested by 12 hospitalized patients before a pilot study was started in 400
4 patients. Additional errors in translation and poor use of language in the original English were
5 resolved continuously in this phase of the work. No additional changes to language were
6 made after the start of the present study.
7
8
9
10
11
12
13

14 **Sample size calculations**

15
16 This is an exploratory study. The calculation of the sample size of the study population is
17 based on the targeted precision of sensitivity and specificity. As the prevalence of ACS in the
18 study population is unknown, we have based the calculation of the number of subjects based
19 on the assumption that the prevalence is 0.5 (50 %) which maximizes the estimated sample
20 size. To obtain a precision of sensitivity and specificity of ± 0.03 (3 %) (nQuery version 7.0,
21 Statistical Solutions Ltd, Boston, MA, USA) 1,000 patients are required. The more the
22 extreme the result, *i.e.* sensitivity or specificity approaching 0 or 1 (100 %), the higher the
23 precision and subsequently lower number of subjects needed for this study. The models will
24 be developed in the first 50 % of the data acquired (training data set) and validated in the last
25 50 % of the data acquired (validation data set). The primary outcome will be analysed after
26 1,000 patients (with no planned interim analyses), which is expected to be reached by
27 December 31, 2020. We also intend to make estimates in subgroups. To allow these analyses,
28 the study program intends to ultimately recruit data from at least 2,000 patients in total.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48

49 **Outcomes**

50
51 The primary objective is to determine whether the use of CHT (index test 1) is better than
52 standard history taking obtained by the physician (index test 2) in attendance (generally a
53 specialist or resident in cardiology) for the prediction and safe exclusion of an ACS in the
54 acute setting in patients with non-diagnostic ECG or serum markers. Thus, the primary
55
56
57
58
59
60

1
2
3 outcome (reference test) is the comparison of the accuracy between the two methods for the
4 safe exclusion of ACS or a diagnosis of ACS in the acute setting *i.e.* within seven days from
5 the ED visit. The diagnosis of ACS will be based on current European guidelines(3, 28). The
6 diagnosis will be validated by an experienced cardiologist. A cross tabulation of the index test
7 results against the reference test will allow estimations for sensitivity, specificity and
8 predictive values. Confidence intervals will be calculated. The results will be presented
9 graphically with a receiver operating characteristic (ROC) curve for each index test. Also,
10 likelihood ratios will be calculated.
11
12
13
14
15
16
17
18
19
20
21
22

23
24 Secondary outcomes include 1) the ability of CHT, as compared to standard history taking
25 obtained by the cardiologist in attendance to provide information required to calculate
26 recommended risk scores for ACS; 2) a correct exclusion of an ACS up to 30 days and up to 1
27 year by use of CHT or standard history taking obtained by the cardiologist in attendance; 3)
28 direct costs and resource utilization for a patient with a diagnosis of an ACS when patient
29 selection is based on CHT, as compared to standard history taking obtained by the
30 cardiologist in attendance; and 4) patient experience with CHT regarding feasibility,
31 acceptance, comprehensible and technical aspects. Finally, we aim to use the collected data to
32 explore the possibility to generate an improved risk score for ACS.
33
34
35
36
37
38
39
40
41
42
43
44
45
46

47 **Data management and data analysis plan**

48
49 The CLEOS interview program runs from a central server located at Karolinska Institutet,
50 Department of Learning, Informatics, Management and Ethics, Stockholm, Sweden. Data
51 collected will be stored on this server in the form of codes (not text) representing answers to
52 questions posed. Data transmission and storage fulfil the high standards of security of
53 Karolinska Institutet.
54
55
56
57
58
59
60

1
2
3
4
5 Other data stored are time stamps for completion of each question in an interview, and the
6
7 pathway by which each interview proceeded. Data collected during routine care, which may
8
9 be used for algorithm development, *e.g.* signs like heart rate, rhythm, body temperature, blood
10
11 pressure, biochemistry, and findings from ECG recordings will be extracted from the EHRs
12
13 and added manually to coded data fields in the CLEOS program.
14
15
16
17

18
19 Descriptive statistics will be used to describe demography and background characteristics
20
21 (*e.g.* mean values and standard deviations or confidence values, median values and
22
23 interquartile ranges, or proportions, as appropriate). We will evaluate established risk scores,
24
25 as populated with CLEOS data, and compare these results with data obtained during the
26
27 concurrent ED visit and made available in the standard hospital EHR. Regression-based
28
29 statistical analyses will be used, and appropriate tests for significant difference of
30
31 completeness of the risk scores (*e.g.* the Chi-square test, Student's *t*-test and McNemar's test).
32
33
34
35
36
37

38 Second, to assess how data collected with CLEOS in combination with established risk scores
39
40 can rule-in and rule-out a diagnosis of an ACS, we will calculate sensitivity, specificity and
41
42 negative and positive predictive values. The results will be presented with receiver operating
43
44 characteristic (ROC) curves for each risk score and the Hanley and McNeil method to test for
45
46 difference. Logistic regression will be used to describe the relationship with the predictions
47
48 and actual outcomes (*i.e.* ACS or not ACS).
49
50
51
52

53 The potential impact on costs by use of information achieved from CHT in managing patients
54
55 with acute chest pain, compared with standard history taking, will be calculated. Standard
56
57
58
59
60

1
2
3 health economic principles and methods based on DRG codes and current Swedish tariffs for
4 out-patient care and investigations will be used.
5
6
7
8
9

10 **Patient and Public involvement**

11 Patients participate at several stages of the study. The patient perspective has been
12 incorporated into this study through interviews during the adaption of the CLEOS program to
13 Swedish conditions, by providing feedback during the pilot study phase and also during the
14 ongoing study after completion of the interview. Furthermore, interviews with a subset of
15 patients for the evaluation of patient experience regarding feasibility, acceptance,
16 comprehensiveness and technical aspects of answering the CLEOS interview will take place
17 as part to the study protocol (see above). All participating patients are informed about how
18 they can access the registered protocol.
19
20
21
22
23
24
25
26
27
28
29
30
31
32

33 **Ethics and dissemination**

34 This study has been reviewed and approved by the Ethics Committee in Stockholm (No
35 2015/1955-1). All participants will give their informed consent before taking part of the
36 study. Results will be published, regardless of the results obtained, in peer-reviewed
37 international scientific journals.
38
39
40
41
42
43
44
45
46

47 **DISCUSSION**

48 Chest pain is a common chief complaint in the ED and there are several health and resource
49 benefits if ACS could be ruled-in or ruled-out more effectively. CHT may be a useful method,
50 but has not been studied previously in an acute cardiology setting. The Swedish health care
51 system offers a good opportunity to study this. There are high quality, comprehensive national
52 health care registries and consistent use of EHRs. This ongoing study aims to determine the
53
54
55
56
57
58
59
60

1
2
3 additional value of CHT for the management of patients with acute chest pain. The pilot phase
4 of the CLEOS-CPDS study was performed May 1 to September 30, 2017 and the recruitment
5
6 in the main study started on October 1, 2017.
7
8
9

10
11
12 The main strengths of this study include the focus on accurate prediction of risk for a life
13 threatening condition among the large group of patients presenting to EDs with a common
14 complaint(1). Second, we use a prospective, cohort study design; include a large study
15 population; and use reliable outcome measures for which there are well-established, strict
16 criteria(29). Third, the implications of the results on resource utilization could have a
17 significant impact for health care providers. Fourth, the use of CHT does not require a
18 specific EHR system, and CLEOS has a generic layout not specific for cardiology or the ED
19 setting. Thus, the results could be potentially generalized to several other clinical issues and
20 care-settings. Finally, our research is academically initiated and driven. The artificial
21 intelligence software in this study is owned by a public university. There are no commercial
22 interests within this research project.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39

40 However, a number of possible limitations of this study should be considered. First, patients
41 not able to accomplish CHT are excluded. This may limit the generalizability of the results to
42 all people with chest pain. To address these issues, we will conduct a feasibility analysis on
43 the first 500 patients to compare patient characteristics, their performance with the CHT, and
44 demographics and background characteristics with the entire ED population for the same time
45 period. Why patients decline to participate in the study will be reported specifically. Second,
46 given the large number of possible questions during the interview, we cannot dismiss the risk
47 of vague or misleading questions, as they are not all validated. Also, the time for CHT is
48 longer than for a traditional history taken by a physician, which may be a concern with time
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 constraints in an ED setting. However, the results of the current study may help developing
4 future CHT modules which are briefer but with equal or better performance. A risk of recall
5 bias caused by giving a medical history twice (CHT and standard history taking), cannot be
6 excluded. To allow for a sensitivity analysis for this possible bias, we will track the order of
7 interview by physician and CLEOS. Third, there might be a difference in patients reading
8 questions as opposed to answering them verbally. Also, CHT will capture every question
9 asked, whereby the data for standard history taking will be collected from the EHR.
10 Therefore, information captured during standard history taking might not be documented and
11 more complete data from CHT will be expected. These two issues will be addressed when
12 analysing the congruency between CHT and EHR data. Fourth, as we compare data from
13 CHT with data acquired by the attending physician, the performance of the physician can
14 affect our results. Furthermore, the ED in this study has a specific cardiology unit where the
15 attending physician is a cardiologist. This may limit the application of the results to other
16 settings with an ED with unsorted flow, and/or where ED physicians evaluate all patients.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41

42 **AUTHOR CONTRIBUTIONS**

43
44 All authors (HB, TK, JS, KS, SK, AA, CJS and DZ) contributed to the conception and design
45 of the study and to creating the study protocol. HB, TK, and DZ drafted the manuscript. DZ is
46 the designer of the CLEOS program's method for making medical knowledge actionable and
47 the developer of the program's medical knowledge base. All authors (HB, TK, JS, KS, SK,
48 AA, CJS and DZ) revised the manuscript for intellectual content and approved the final text.
49 TK (chair), HB, JS, SK, CJS and DZ form the steering group of the CLEOS-CPDS study. CJS
50 acts as the contact person for the trial sponsor (Karolinska Institutet). All steering group
51
52
53
54
55
56
57
58
59
60

1
2
3 members will have full access to the final trial data set. The corresponding author attests that
4
5 all listed authors meet authorship criteria and that no others meeting the criteria have been
6
7 omitted.
8
9

10 11 12 **FUNDING STATEMENT**

13
14 This work was funded by the Robert Bosch Stiftung (Stuttgart, Germany), grant number
15
16 11.5.1000.0258.0, Karolinska Institutet Research Foundation (Stockholm, Sweden) and
17
18 Stiftelsen Hjärtat (Stockholm, Sweden).
19
20
21
22

23 24 **COMPETING INTERESTS STATEMENT**

25
26 DZ is the inventor on US patents for technology related to the CLEOS program. All patent
27
28 rights and copyrights to technology, language, images, and knowledge content are assigned
29
30 without royalty rights by DZ to Karolinska Institutet, Stockholm, Sweden which is a public
31
32 university. Apart from Karolinska Institutet and its subsidiaries, no individuals or companies
33
34 may be owners or receive royalties or other revenue from use of CLEOS technology,
35
36 language, images, knowledge content or from clinical insights and/or computer algorithms
37
38 generated from analysis of data acquired by the program. There are no other competing
39
40 interests financial or otherwise in study design, collection, management, analysis, and
41
42 interpretation of data, writing of the report, and the decision to submit the report for
43
44 publication. All CLEOS-CPDS steering group members (see above) will have full access to
45
46 the final trial data set.
47
48
49
50
51
52

53 54 **REFERENCES**

55
56 1 Pitts SR, Niska RW, Xu J, et al. National Hospital Ambulatory Medical Care Survey: 2006
57
58 emergency department summary. *Natl Health Stat Report*. 2008:1-38.
59
60

1
2
3 2 Organization WH. Global Health Observatory (GHO) data: World Health Organization;
4
5 2019 [cited 2019 May 15]. Available from:

6
7 http://origin.who.int/gho/mortality_burden_disease/causes_death/top_10/en/.

8
9
10 3 Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute
11
12 coronary syndromes in patients presenting without persistent ST-segment elevation: Task
13
14 Force for the Management of Acute Coronary Syndromes in Patients Presenting without
15
16 Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*.
17
18 2016;37:267-315.

19
20 4 Ekelund U, Nilsson HJ, Frigyesi A, et al. Patients with suspected acute coronary syndrome
21
22 in a university hospital emergency department: an observational study. *BMC Emerg Med*.
23
24 2002;2:1.

25
26 5 Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the
27
28 management of patients with non-ST-elevation acute coronary syndromes: executive
29
30 summary: a report of the American College of Cardiology/American Heart Association Task
31
32 Force on Practice Guidelines. *Circulation*. 2014;130:2354-94.

33
34 6 Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of
35
36 patients with suspected acute coronary syndromes. *JAMA*. 2005;294:2623-9.

37
38 7 Nieman K, Hoffmann U. Cardiac computed tomography in patients with acute chest pain.
39
40
41
42
43
44
45 *Eur Heart J*. 2015;36:906-14.

46
47 8 Six AJ, Cullen L, Backus BE, et al. The HEART score for the assessment of patients with
48
49 chest pain in the emergency department: a multinational validation study. *Crit Pathw Cardiol*.
50
51 2013;12:121-6.

52
53 9 Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial
54
55 infarction in the six months after presentation with acute coronary syndrome: prospective
56
57 multinational observational study (GRACE). *BMJ*. 2006;333:1091.

- 1
2
3 10 Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST
4 elevation MI: A method for prognostication and therapeutic decision making. *JAMA*.
5
6 2000;284:835-42.
7
8
9
10 11 Cox JL, Zitner D, Courtney KD, et al. Undocumented patient information: an impediment
11 to quality of care. *Am J Med*. 2003;114:211-6.
12
13
14 12 Herrick DB, Nakhasi A, Nelson B, et al. Usability characteristics of self-administered
15 computer-assisted interviewing in the emergency department. *Appl Clin Inform*. 2013;4:276-
16
17 92.
18
19
20
21 21 Corrigan M, McWilliams R, Kelly KJ, et al. A computerized, self-administered
22 questionnaire to evaluate posttraumatic stress among firefighters after the World Trade Center
23 collapse. *Am J Public Health*. 2009;99 Suppl 3:S702-9.
24
25
26
27 28 Zakim D, Fritz C, Braun N, et al. Computerized history-taking as a tool to manage
29 dyslipidemia. *Vasc Health Risk Manag*. 2010;6:1039-46.
30
31
32
33 33 Almario CV, Chey W, Kaung A, et al. Computer-Generated Vs. Physician-Documented
34 History of Present Illness (HPI): Results of a Blinded Comparison. *Am J Gastroenterol*.
35
36 2015;110:170-9.
37
38
39
40 40 Pappas Y, Vseteckova J, Poduval S, et al. Computer-Assisted versus Oral-and-Written
41 History Taking for the Prevention and Management of Cardiovascular Disease: a Systematic
42
43 Review of the Literature. *Acta Medica (Hradec Kralove)*. 2017;60:97-107.
44
45
46
47 47 Hunt DL, Haynes RB, Hanna SE, et al. Effects of computer-based clinical decision support
48 systems on physician performance and patient outcomes: a systematic review. *JAMA*.
49
50 1998;280:1339-46.
51
52
53
54 54 Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision
55 support systems on practitioner performance and patient outcomes: a systematic review.
56
57
58
59
60

- 1
2
3 19 Raschke RA, Gollihare B, Wunderlich TA, et al. A computer alert system to prevent injury
4 from adverse drug events: development and evaluation in a community teaching hospital.
5
6 *JAMA*. 1998;280:1317-20.
7
8
9
10 20 Chen R, Valladares C, Corbal I, et al. Early Experiences from a guideline-based
11 computerized clinical decision support for stroke prevention in atrial fibrillation. *Stud Health*
12 *Technol Inform*. 2013;192:244-7.
13
14
15
16 21 Berner ES, Kasiraman RK, Yu F, et al. Data quality in the outpatient setting: impact on
17 clinical decision support systems. *AMIA Annu Symp Proc*. 2005:41-5.
18
19
20
21 22 Skyttberg N, Chen R, Blomqvist H, et al. Exploring Vital Sign Data Quality in Electronic
22 Health Records with Focus on Emergency Care Warning Scores. *Appl Clin Inform*.
23
24 2017;8:880-92.
25
26
27
28 23 Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration:
29 guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.
30
31
32
33 24 Widgren BR, Jourak M. Medical Emergency Triage and Treatment System (METTS): a
34 new protocol in primary triage and secondary priority decision in emergency medicine. *J*
35 *Emerg Med*. 2011;40:623-8.
36
37
38
39
40 25 Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the
41 Swedish national inpatient register. *BMC Public Health*. 2011;11:450.
42
43
44
45 26 Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. *Eur J*
46 *Epidemiol*. 2017;32:765-73.
47
48
49
50 27 Zakim D, Braun N, Fritz P, et al. Underutilization of information and knowledge in
51 everyday medical practice: Evaluation of a computer-based solution. *BMC Med Inform Decis*
52 *Mak*. 2008;8.
53
54
55
56 28 Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute
57 myocardial infarction in patients presenting with ST-segment elevation: The Task Force for
58
59
60

1
2
3 the management of acute myocardial infarction in patients presenting with ST-segment
4 elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39:119-77.
5
6

7 29 Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction
8 (2018). *Eur Heart J.* 2018;40:237-69.
9
10
11
12

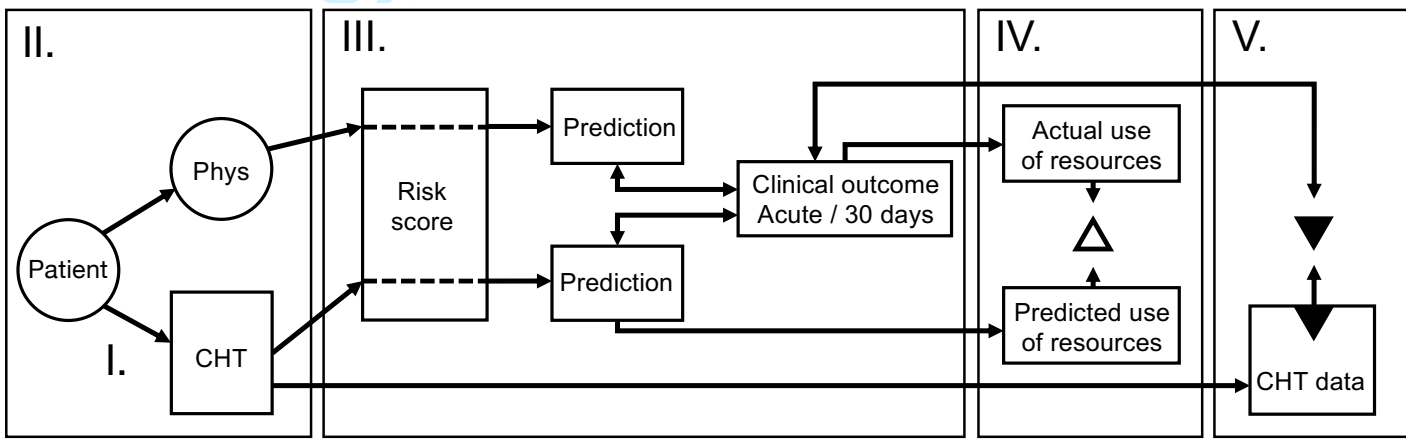
13 14 **FIGURE LEGENDS**

15
16
17 Figure 1. Overview of planned studies. Phys: history taking by physicians; CHT:
18 computerized history taking.
19
20

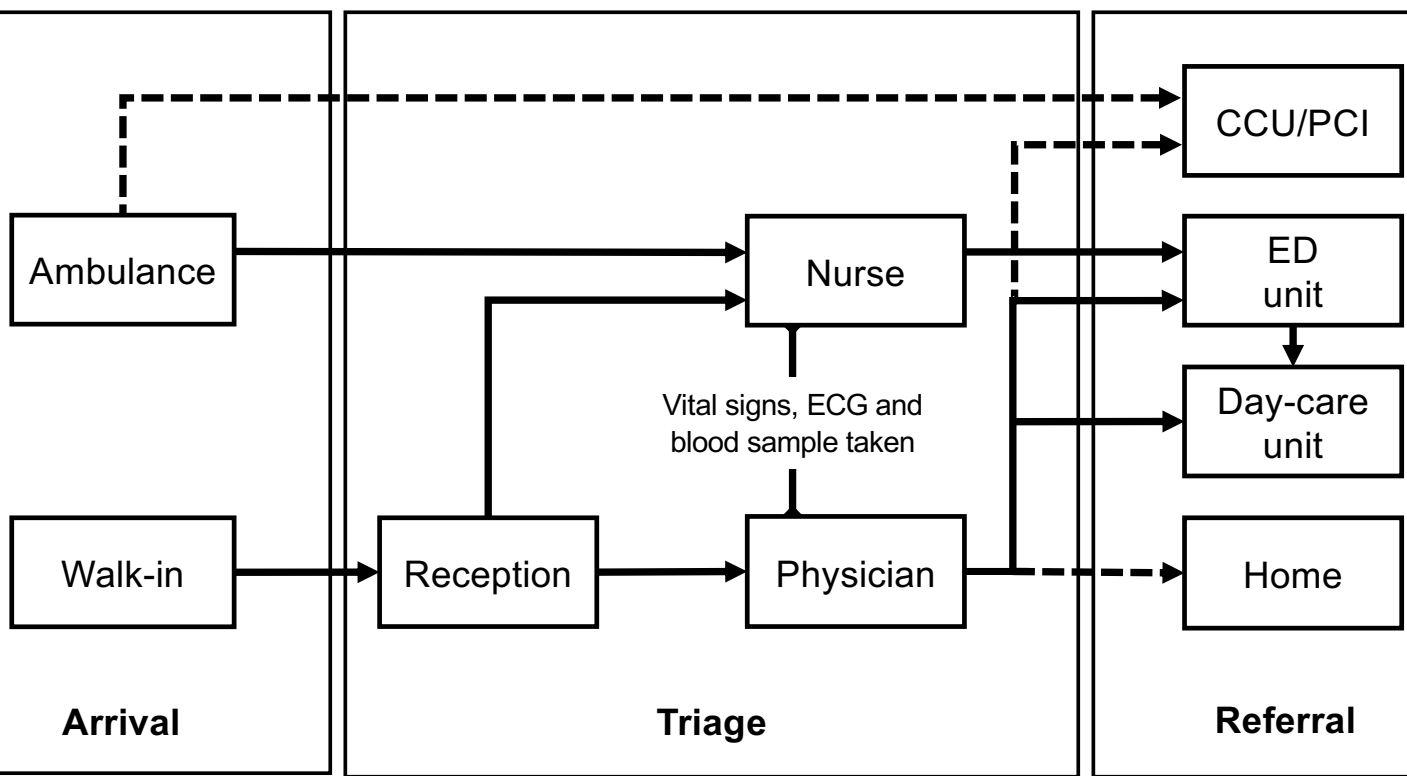
21
22
23 Figure 2. Overview of the ED flow from arrival to referral. Broken lines indicate patients who
24 will not be eligible. ECG: electrocardiogram; CCU: Cardiac care unit; PCI: Percutaneous
25 coronary intervention; ED: Emergency Department.
26
27
28
29

30
31
32
33 Figure 3. Example of the presentations of questions in CLEOS on the tablet.
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

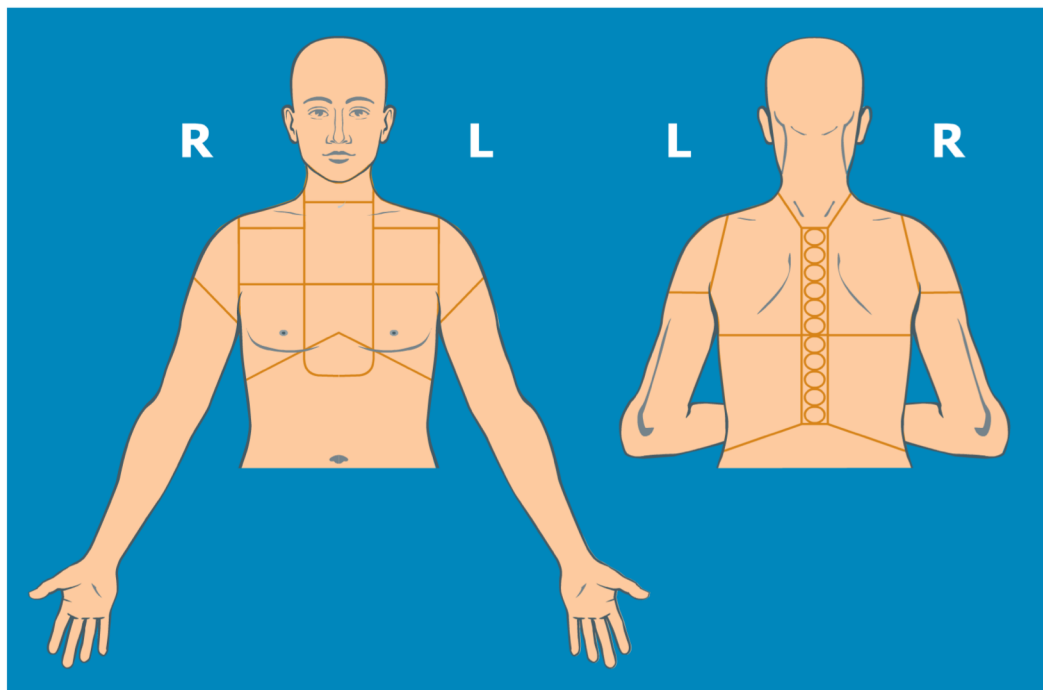
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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

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



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 <i>Comment: Embedded in manuscript. Also, see trial registration at clinicaltrials.gov (NCT03439449).</i>	4
Protocol version	#3	Date and version identifier	8
Funding	#4	Sources and types of financial, material, and other support	20

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1-2,19
2	responsibilities:			
3	contributorship			
4				
5				
6	Roles and	#5b	Name and contact information for the trial sponsor	1, 19
7	responsibilities:			
8	sponsor contact			
9	information			
10				
11				
12				
13	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	20
14	responsibilities:		collection, management, analysis, and interpretation of data;	
15	sponsor and funder		writing of the report; and the decision to submit the report for	
16			publication, including whether they will have ultimate authority	
17			over any of these activities	
18				
19				
20				
21	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	19
22	responsibilities:		centre, steering committee, endpoint adjudication committee,	
23	committees		data management team, and other individuals or groups	
24			overseeing the trial, if applicable (see Item 21a for data	
25			monitoring committee)	
26				
27				
28				
29				
30	Introduction			
31				
32	Background and	#6a	Description of research question and justification for undertaking	6-8
33	rationale		the trial, including summary of relevant studies (published and	
34			unpublished) examining benefits and harms for each intervention	
35				
36				
37	Background and	#6b	Explanation for choice of comparators	6-8
38	rationale: choice of			
39	comparators			
40				
41				
42	Objectives	#7	Specific objectives or hypotheses	8
43				
44				
45	Trial design	#8	Description of trial design including type of trial (eg, parallel	8
46			group, crossover, factorial, single group), allocation ratio, and	
47			framework (eg, superiority, equivalence, non-inferiority,	
48			exploratory)	
49				
50				
51				
52	Methods:			
53	Participants,			
54	interventions, and			
55	outcomes			
56				
57				
58				
59				
60				

1	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
2				
3				
4				
5				
6	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
7				
8				
9				
10				
11	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
12	description			
13				
14				
15	Interventions:	#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
16	modifications			
17				
18				
19				
20				
21	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-14
22	adherence			
23				
24				
25				
26	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
27	concomitant care			
28				
29				
30	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
31				
32				
33				
34				
35				
36				
37				
38				
39				
40	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
41				
42				
43				
44				
45	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
46				
47				
48				
49				
50	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 11, 15
51				
52				
53				

Methods: Assignment of interventions (for controlled trials)

1	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-	n/a
2	generation		generated random numbers), and list of any factors for	
3			stratification. To reduce predictability of a random sequence,	
4			details of any planned restriction (eg, blocking) should be	
5			provided in a separate document that is unavailable to those who	
6			enrol participants or assign interventions	
7				
8				
9				
10				
11			<i>Comment: Not relevant for this observational cohort study.</i>	
12				
13	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central	n/a
14	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
15	mechanism		describing any steps to conceal the sequence until interventions	
16			are assigned	
17				
18				
19				
20			<i>Comment: Not relevant for this observational cohort study.</i>	
21				
22	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	n/a
23	implementation		participants, and who will assign participants to interventions	
24				
25				
26			<i>Comment: Not relevant for this observational cohort study.</i>	
27				
28	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial	n/a
29			participants, care providers, outcome assessors, data analysts),	
30			and how	
31				
32				
33				
34			<i>Comment: Not relevant for this observational cohort study.</i>	
35				
36	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible,	n/a
37	emergency unblinding		and procedure for revealing a participant's allocated intervention	
38			during the trial	
39				
40				
41			<i>Comment: Not relevant for this observational cohort study.</i>	
42				
43				
44	Methods: Data			
45	collection,			
46	management, and			
47	analysis			
48				
49				
50	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and	10-12
51			other trial data, including any related processes to promote data	
52			quality (eg, duplicate measurements, training of assessors) and a	
53			description of study instruments (eg, questionnaires, laboratory	
54			tests) along with their reliability and validity, if known.	
55				
56				
57				
58				
59				
60				

Reference to where data collection forms can be found, if not in the protocol

1			
2			
3			
4	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, 12
5	retention		including list of any outcome data to be collected for participants
6			who discontinue or deviate from intervention protocols
7			
8			
9			<i>Comment: When patients have provided data via the interview,</i>
10			<i>outcome data are retrieved from registries and health records.</i>
11			
12			
13	Data management	#19	Plans for data entry, coding, security, and storage, including any 16
14			related processes to promote data quality (eg, double data entry;
15			range checks for data values). Reference to where details of data
16			management procedures can be found, if not in the protocol
17			
18			
19			
20	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary 16-17
21			outcomes. Reference to where other details of the statistical
22			analysis plan can be found, if not in the protocol
23			
24			
25	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted 16-17,
26	analyses		analyses) 19
27			
28			
29	Statistics: analysis	#20c	Definition of analysis population relating to protocol non- 8
30	population and missing		adherence (eg, as randomised analysis), and any statistical
31	data		methods to handle missing data (eg, multiple imputation)
32			
33			
34	Methods: Monitoring		<i>Comment: This will be addressed in the feasibility study (Study</i>
35			<i>I).</i>
36			
37			
38	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of n/a
39	formal committee		its role and reporting structure; statement of whether it is
40			independent from the sponsor and competing interests; and
41			reference to where further details about its charter can be found,
42			if not in the protocol. Alternatively, an explanation of why a
43			DMC is not needed
44			
45			<i>Comment: Data is entered directly into the database.</i>
46			
47			
48			
49			
50	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines, 15
51	interim analysis		including who will have access to these interim results and make
52			the final decision to terminate the trial
53			
54			
55			
56	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited 11-12,
57			and spontaneously reported adverse events and other unintended 16
58			effects of trial interventions or trial conduct
59			
60			

1	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
2				
3				
4				
5				
6	Ethics and			
7	dissemination			
8				
9				
10	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17-18
11				
12				
13				
14	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)	n/a
15				
16				
17				
18				
19				
20				
21			<i>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.</i>	
22				
23				
24				
25				
26	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
27				
28				
29				
30	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
31				
32				
33				
34				
35	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
36				
37				
38				
39				
40	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
41				
42				
43				
44	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
45				
46				
47				
48				
49	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
50				
51				
52				
53	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
54				
55				
56				
57				
58				
59				
60				

databases, or other data sharing arrangements), including any publication restrictions

Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of professional writers 19

Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code n/a

Comment: No such plans at present.

Appendices

Informed consent materials [#32](#) Model consent form and other related documentation given to participants and authorised surrogates n/a

Comment: The model consent form and other related documentation is available from the ethical review authority. These are public documents in Sweden.

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

None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. **This checklist can be completed online** using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

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)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-031871.R2
Article Type:	Protocol
Date Submitted by the Author:	13-Dec-2019
Complete List of Authors:	Brandberg, Helge; Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine Kahan, Thomas; Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine Spaak, Jonas; Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine Sundberg, Kay; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society Koch, Sabine; Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre Adeli, Athena; Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre Sundberg, Carl Johan; Karolinska Institutet, Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre; Karolinska Institutet, Department of Physiology & Pharmacology Zakim, David; Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Health informatics, Diagnostics, Medical management
Keywords:	Coronary heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY, MEDICAL HISTORY, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Information management < BIOTECHNOLOGY & BIOINFORMATICS, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ Open

v13-12-2019

**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)**

Helge Brandberg (0000-0003-1507-4099), Thomas Kahan (0000-0001-9909-4956), Jonas Spaak (0000-0002-2135-1294), Kay Sundberg (0000-0002-4544-9798), Sabine Koch (0000-0001-7144-8740), Athena Adeli, Carl Johan Sundberg (0000-0002-7000-466X), David Zakim (0000-0002-7722-8148)

Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine, SE-182 88, Stockholm, Sweden

Helge Brandberg, MD

Professor Thomas Kahan, MD

Jonas Spaak, MD, associate professor

Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, SE-141 83, Stockholm, Sweden

Kay Sundberg, PhD, assistant professor

Karolinska Institutet, Department of Learning, Informatics, Management and Ethics, Medical Management Centre, and Health Informatics Centre, SE-171 77, Stockholm, Sweden

Professor Sabine Koch, PhD

Athena Adeli, MD

Professor Carl Johan Sundberg, MD

1
2
3 Professor emeritus David Zakim, MD
4
5
6

7 Karolinska Institutet, Department of Physiology & Pharmacology, SE-171 77, Stockholm,
8
9 Sweden
10

11 Professor Carl Johan Sundberg, MD
12
13
14
15

16
17 Correspondence to: Dr Thomas Kahan, Department of Cardiology, Danderyd University
18 Hospital Corp, SE-182 88 Stockholm, Sweden. Email: thomas.kahan@sll.se, Telephone: +46
19 8 123 568 61.
20
21
22

23
24
25
26 Word count (excluding title page, abstract, references, figures and tables): 4,166
27

28
29
30 Keywords: Coronary heart disease, Myocardial infarction, Health informatics, Medical
31 History, Information management, Risk management
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3 **Registration details**
4

5 This study is registered at <https://www.clinicaltrials.gov> (unique identifier: NCT03439449).
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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)

1
2
3 score and Global Registry of Acute Coronary Events (GRACE) score(3, 5). More recently,
4
5 utilization of the HEART (History, ECG, Age, Risk factors and Troponin) score has been
6
7 recommended as an effective tool for risk stratification in the ED setting(8). Typically, these
8
9 scores include information on age, risk factors for coronary artery disease (family history,
10
11 hypertension, hypercholesterolemia, diabetes, current smoker), heart failure, renal function,
12
13 history suspicious for angina, current use of aspirin or diuretics, ST segment deviation on the
14
15 ECG and elevated serum cardiac biomarkers(9, 10).
16
17
18
19
20

21 In a hectic ED setting, important information may be missed by medical history taking
22
23 obtained by the physician (standard history taking). Other approaches have been suggested to
24
25 ensure collection of more complete and accurate information(11). One way to address this
26
27 issue is to collect self-reported medical histories *via* computerized history taking (CHT)
28
29 programs. Herrick et al. conducted a cross-sectional study in an ED setting; 841 patients
30
31 independently and easily engaged with CHT programs to input data with high accuracy(12).
32
33 Other studies have shown that CHT performed well in evaluating risk for post-traumatic
34
35 stress(13), stratifying cardiovascular risk in patients with hypercholesterolemia(14), and for
36
37 generating a present illness in patients with gastrointestinal symptoms to improve clinic visit
38
39 efficiency(15). However, in a recent a review of the literature for CHT *versus* oral-and-
40
41 written history taking for prevention and management of cardiovascular disease only one
42
43 other study(16) was identified. The authors concluded there is a need to develop an evidence
44
45 base to support the use of CHT programs for cardiovascular disease.
46
47
48
49
50
51
52

53 Data from CHT together with computer-based decision support systems have demonstrated
54
55 improved physician performance and better patient outcomes in some cases(17-20). An
56
57 important prerequisite for useful computer-based decision support, however, is complete,
58
59
60

1
2
3 accurate and standardized medical history data(11, 21). To date, the data in electronic health
4 records (EHR) in Swedish EDs does not meet the standards required as a basis for computer-
5 based decision support(22). Accordingly, this study aims to determine the additional value of
6 CHT for the management of patients presenting at the ED with chest pain. More specifically,
7 we aim to determine whether self-reported CHT as compared with standard history taking (1)
8 improves data quality, (2) adds to the accuracy of risk stratification to exclude ACS in
9 patients with chest pain, and (3) saves time and resources.
10
11
12
13
14
15
16
17
18
19
20

21 **METHODS AND ANALYSIS**

22 **Study design**

23
24 The Clinical Expert Operating System - Chest Pain Danderyd Study (CLEOS-CPDS) is a
25 prospective cohort study designed to determine the value of CHT in the management of acute
26 chest pain (Study protocol version 1.7, dated May 16, 2019). This study follows the SPIRIT
27 reporting guidelines(23). The project includes a feasibility study for CHT in the acute setting
28 (*Study I*); a validation study of CHT as compared with standard history taking (*Study II*); a
29 paired diagnostic accuracy study using data from CHT and established risk scores (*Study III*);
30 a clinical utility study to evaluate the impact of CHT on chest pain management and use of
31 resources (*Study IV*); and use of data mining to generate an improved risk score for ACS
32 (*Study V*). A summary of the planned studies is presented in *Figure 1*.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

50 **Study population**

51 Women and men, presenting consecutively at the ED at Danderyd University Hospital
52 (Stockholm, Sweden) from October 1, 2017 until December 31, 2023 (preliminary date), with
53 a chief complaint of chest pain are eligible if they meet the criteria in *Table 1*.
54
55
56
57
58
59
60

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 (<i>e.g.</i> 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

1
2
3 most Swedish EDs, the triage protocol Rapid Emergency Triage and Treatment System
4 (RETTS) is used to assess the urgency of each patient's condition, to decide what work-up is
5
6 (RETTS) is used to assess the urgency of each patient's condition, to decide what work-up is
7
8 needed and how the patient should be monitored. Based on vital signs and symptoms
9
10 collected by a nurse and an assistant nurse, patients are divided into five priority levels
11
12 depending on their need of urgent medical attention: red (immediate), orange (within 20
13
14 minutes), yellow (within 120 min), green (not in need of immediate care) and blue (not in
15
16 need of emergency care or hospital facilities)(24).
17
18
19
20

21 **Data collection**

22
23 When presenting to the ED with chest pain, walk-in patients first report their complaint to the
24
25 reception nurse, who will direct them to the cardiology ED. During weekdays, 10AM-4PM,
26
27 these patients are triaged promptly by a physician, who is either a cardiology consultant or
28
29 senior resident in cardiology. The triage includes a decision on the indicated work-up, which
30
31 is based on a targeted medical history, a brief examination, vital signs and ECG. This data is
32
33 used to determine whether a patient should be admitted to the cardiology ED, the day-care
34
35 unit, or sent home. During out-of-office hours, all patients are triaged by a nurse. According
36
37 to the RETTS protocol, ECG and biomarkers are acquired before the patient is transported to
38
39 the cardiology ED. All patients then undergo a more thorough examination and standard
40
41 history taking by a physician, who also decides whether further investigations are needed.
42
43
44 Regional guidelines recommend risk stratification according to HEART score including high
45
46 sensitivity cardiac troponin (hs-cTn) assays and the validated 0 h / 1 h rule-in and rule-out
47
48 algorithm(3). Patients with signs of ST-elevation myocardial infarction on ECG or clinically
49
50 unstable patients (RETTS level red) are evaluated immediately and admitted to the coronary
51
52 care unit or brought to the coronary intervention laboratory for acute intervention, when
53
54
55
56
57
58
59
60

1
2
3 indicated. Thus, critically ill patients are excluded in the present study. See *Figure 2* for an
4
5 overview of the ED flow from arrival to referral.
6
7
8
9

10 Patients are asked by a member of the research staff to participate in the current study at the
11
12 cardiology ED or day-care unit (*Figure 2*). After informed consent has been obtained,
13
14 histories are collected with a CHT program during waiting times. CHT histories may occur
15
16 before or after a patient is seen by a physician. Routine care takes precedence over CHT so
17
18 that patients interact with the CHT program only during waiting times. CHT thus will not
19
20 interfere with workflow or patient care in the ED. During the study period CHT data will not
21
22 be available to the care providers.
23
24
25
26
27

28 All answers to CHT-posed questions are time-stamped. The time at which the physician first
29
30 meets the patient also is recorded. This will enable control for possible second-history effects.
31
32 Patients are asked about technical, semantic and other problems they might have encountered
33
34 after completing a CHT interview. This will be done as a basis for future corrections and
35
36 improvements to the CHT program.
37
38
39
40
41

42 Self-reported medical history data, demographics and other baseline characteristics will be
43
44 collected from CHT data.
45
46
47
48

49 Data from standard history, demographic and baseline characteristics, vital signs and lab data
50
51 will be extracted from the EHR. To generate the cost associated with routine care patient-by-
52
53 patient data on use of resources will be extracted from the hospital EHR. Cost will be
54
55 correlated with different clinical outcomes by linking the diagnosis at the ED visit or when
56
57 discharged with their Diagnosis Related Group (DRG) code, which is an estimate of costs
58
59
60

1
2
3 associated with a specific diagnosis provided by the National Board of Health and Welfare
4
5 and Swedish Association of Local Authorities and Regions.
6
7
8
9

10 The use of unique personal ID to all Swedish citizens allows linkage to national and regional
11 registries for research purposes. Thus, clinical outcomes in the acute setting (*i.e.* within 7
12 days) will be extracted from the EHR of the hospital. Discharge diagnoses, at 30 days, and at
13
14 1 year, will be collected from the National Patient Register, which includes information on all
15 hospital discharges in Sweden since 1964(25). Mortality status and causes of death will be
16
17 extracted from the Cause of Death Register which provides official statistics, according to the
18
19 International Statistical Classification of Diseases and Related Health Problems, in Sweden
20
21 since 1961(26).
22
23
24
25
26
27
28
29

30 For the validation and future development of CHT, a questionnaire to assess overall patient
31
32 experience in a larger sample of patients (n=500) will be developed through interviews with a
33
34 subset of patients. Approximately 30 patients will be asked to participate in three to four focus
35
36 group interviews for the evaluation of ease of use and usefulness of the CHT program. These
37
38 interviews will take place one to three months after the ED visit.
39
40
41
42
43
44

45 **Interventions**

46 Computerized, self-reported medical histories will be collected with the software program
47
48 CLEOS running on tablets (iPad, Apple Inc, Cupertino, CA, USA). CLEOS is developed by
49
50 Zakim and colleagues and is owned by Karolinska Institutet, a public university. Details and
51
52 validation of the CLEOS program have been described previously(14, 27). In brief, the
53
54 participant answers questions by clicking on a variety of question types, *e.g.* yes/no answers,
55
56 multiple-choice answers with one allowed answer and multiple-choice answers with more
57
58
59
60

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

1
2
3 physician and then tested by 12 hospitalized patients before a pilot study was started in 400
4 patients. Additional errors in translation and poor use of language in the original English were
5 resolved continuously in this phase of the work. No additional changes to language were
6 made after the start of the present study.
7
8
9
10
11
12
13

14 **Sample size calculations**

15
16 This is an exploratory study. The calculation of the sample size of the study population is
17 based on the targeted precision of sensitivity and specificity. As the prevalence of ACS in the
18 study population is unknown, we have based the calculation of the number of subjects based
19 on the assumption that the prevalence is 0.5 (50 %) which maximizes the estimated sample
20 size. To obtain a precision of sensitivity and specificity of ± 0.03 (3 %) (nQuery version 7.0,
21 Statistical Solutions Ltd, Boston, MA, USA) 1,000 patients are required. The more the
22 extreme the result, *i.e.* sensitivity or specificity approaching 0 or 1 (100 %), the higher the
23 precision and subsequently lower number of subjects needed for this study. The models will
24 be developed in the first 50 % of the data acquired (training data set) and validated in the last
25 50 % of the data acquired (validation data set). The primary outcome will be analysed after
26 1,000 patients (with no planned interim analyses), which is expected to be reached by
27 December 31, 2020. We also intend to make estimates in subgroups. To allow these analyses,
28 the study program intends to ultimately recruit data from at least 2,000 patients in total.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48

49 **Outcomes**

50
51 The primary objective is to determine whether the use of CHT (index test 1) is better than
52 standard history taking obtained by the physician (index test 2) in attendance (generally a
53 specialist or resident in cardiology) for the prediction and safe exclusion of an ACS in the
54 acute setting in patients with non-diagnostic ECG or serum markers. Thus, the primary
55
56
57
58
59
60

1
2
3 outcome (reference test) is the comparison of the accuracy between the two methods for the
4 safe exclusion of ACS or a diagnosis of ACS in the acute setting *i.e.* within seven days from
5 the ED visit. The diagnosis of ACS will be based on current European guidelines(3, 28). The
6 diagnosis will be validated by an experienced cardiologist. A cross tabulation of the index test
7 results against the reference test will allow estimations for sensitivity, specificity and
8 predictive values. Confidence intervals will be calculated. The results will be presented
9 graphically with a receiver operating characteristic (ROC) curve for each index test. Also,
10 likelihood ratios will be calculated.
11
12
13
14
15
16
17
18
19
20
21
22

23
24 Secondary outcomes include 1) the ability of CHT, as compared to standard history taking
25 obtained by the cardiologist in attendance to provide information required to calculate
26 recommended risk scores for ACS; 2) a correct exclusion of an ACS up to 30 days and up to 1
27 year by use of CHT or standard history taking obtained by the cardiologist in attendance; 3)
28 direct costs and resource utilization for a patient with a diagnosis of an ACS when patient
29 selection is based on CHT, as compared to standard history taking obtained by the
30 cardiologist in attendance; and 4) patient experience with CHT regarding feasibility,
31 acceptance, comprehensible and technical aspects. Finally, we aim to use the collected data to
32 explore the possibility to generate an improved risk score for ACS.
33
34
35
36
37
38
39
40
41
42
43
44
45
46

47 **Data management and data analysis plan**

48
49 The CLEOS interview program runs from a central server located at Karolinska Institutet,
50 Department of Learning, Informatics, Management and Ethics, Stockholm, Sweden. Data
51 collected will be stored on this server in the form of codes (not text) representing answers to
52 questions posed. Data transmission and storage fulfil the high standards of security of
53 Karolinska Institutet.
54
55
56
57
58
59
60

1
2
3
4
5 Other data stored are time stamps for completion of each question in an interview, and the
6
7 pathway by which each interview proceeded. Data collected during routine care, which may
8
9 be used for algorithm development, *e.g.* signs like heart rate, rhythm, body temperature, blood
10
11 pressure, biochemistry, and findings from ECG recordings will be extracted from the EHRs
12
13 and added manually to coded data fields in the CLEOS program.
14
15
16
17

18
19 Descriptive statistics will be used to describe demography and background characteristics
20
21 (*e.g.* mean values and standard deviations or confidence values, median values and
22
23 interquartile ranges, or proportions, as appropriate). We will evaluate established risk scores,
24
25 as populated with CLEOS data, and compare these results with data obtained during the
26
27 concurrent ED visit and made available in the standard hospital EHR. Regression-based
28
29 statistical analyses will be used, and appropriate tests for significant difference of
30
31 completeness of the risk scores (*e.g.* the Chi-square test, Student's *t*-test and McNemar's test).
32
33
34
35
36
37

38 Second, to assess how data collected with CLEOS in combination with established risk scores
39
40 can rule-in and rule-out a diagnosis of an ACS, we will calculate sensitivity, specificity and
41
42 negative and positive predictive values. The results will be presented with receiver operating
43
44 characteristic (ROC) curves for each risk score and the Hanley and McNeil method to test for
45
46 difference. Logistic regression will be used to describe the relationship with the predictions
47
48 and actual outcomes (*i.e.* ACS or not ACS).
49
50
51
52
53

54 The potential impact on costs by use of information achieved from CHT in managing patients
55
56 with acute chest pain, compared with standard history taking, will be calculated. Standard
57
58
59
60

1
2
3 health economic principles and methods based on DRG codes and current Swedish tariffs for
4 out-patient care and investigations will be used.
5
6
7
8
9

10 **Patient and Public involvement**

11
12 Patients participate at several stages of the study. The patient perspective has been
13 incorporated into this study through interviews during the adaption of the CLEOS program to
14 Swedish conditions, by providing feedback during the pilot study phase and also during the
15 ongoing study after completion of the interview. Furthermore, interviews with a subset of
16 patients for the evaluation of patient experience regarding feasibility, acceptance,
17 comprehensiveness and technical aspects of answering the CLEOS interview will take place
18 as part to the study protocol (see above). All participating patients are informed about how
19 they can access the registered protocol.
20
21
22
23
24
25
26
27
28
29
30
31
32

33 **Ethics and dissemination**

34
35 This study has been reviewed and approved by the Stockholm Regional Ethical Committee
36 (now Swedish Ethical Review Authority) (No 2015/1955-1). All participants will give their
37 informed consent before taking part of the study. Results will be published, regardless of the
38 results obtained, in peer-reviewed international scientific journals.
39
40
41
42
43
44
45
46

47 **DISCUSSION**

48
49 Chest pain is a common chief complaint in the ED and there are several health and resource
50 benefits if ACS could be ruled-in or ruled-out more effectively. CHT may be a useful method,
51 but has not been studied previously in an acute cardiology setting. The Swedish health care
52 system offers a good opportunity to study this. There are high quality, comprehensive national
53 health care registries and consistent use of EHRs. This ongoing study aims to determine the
54
55
56
57
58
59
60

1
2
3 additional value of CHT for the management of patients with acute chest pain. The pilot phase
4 of the CLEOS-CPDS study was performed May 1 to September 30, 2017 and the recruitment
5
6 in the main study started on October 1, 2017.
7
8
9

10
11
12 The main strengths of this study include the focus on accurate prediction of risk for a life
13 threatening condition among the large group of patients presenting to EDs with a common
14 complaint(1). Second, we use a prospective, cohort study design; include a large study
15 population; and use reliable outcome measures for which there are well-established, strict
16 criteria(29). Third, the implications of the results on resource utilization could have a
17 significant impact for health care providers. Fourth, the use of CHT does not require a
18 specific EHR system, and CLEOS has a generic layout not specific for cardiology or the ED
19 setting. Thus, the results could be potentially generalized to several other clinical issues and
20 care-settings. Finally, our research is academically initiated and driven. The artificial
21 intelligence software in this study is owned by a public university. There are no commercial
22 interests within this research project.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39

40 However, a number of possible limitations of this study should be considered. First, patients
41 not able to accomplish CHT are excluded. This may limit the generalizability of the results to
42 all people with chest pain. To address these issues, we will conduct a feasibility analysis on
43 the first 500 patients to compare patient characteristics, their performance with the CHT, and
44 demographics and background characteristics with the entire ED population for the same time
45 period. Why patients decline to participate in the study will be reported specifically. Second,
46 given the large number of possible questions during the interview, we cannot dismiss the risk
47 of vague or misleading questions, as they are not all validated. Also, the time for CHT is
48 longer than for a traditional history taken by a physician, which may be a concern with time
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 constraints in an ED setting. However, the results of the current study may help developing
4 future CHT modules which are briefer but with equal or better performance. A risk of recall
5 bias caused by giving a medical history twice (CHT and standard history taking), cannot be
6 excluded. To allow for a sensitivity analysis for this possible bias, we will track the order of
7 interview by physician and CLEOS. Third, there might be a difference in patients reading
8 questions as opposed to answering them verbally. Also, CHT will capture every question
9 asked, whereby the data for standard history taking will be collected from the EHR.
10
11 Therefore, information captured during standard history taking might not be documented and
12 more complete data from CHT will be expected. These two issues will be addressed when
13 analysing the congruency between CHT and EHR data. Fourth, the effect of patient data
14 collected prior to the history taking *e.g.* ECG or blood samples collected in the triage, is
15 another potential confounding factor as the physician will have access to this data before
16 obtaining history, whereas the CHT will not. This potential confounding may warrant further
17 study. Fifth, as we compare data from CHT with data acquired by the attending physician, the
18 performance of the physician can affect our results. Furthermore, the ED in this study has a
19 specific cardiology unit where the attending physician is a cardiologist. This may limit the
20 application of the results to other settings with an ED with unsorted flow, and/or where ED
21 physicians evaluate all patients.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

47 **AUTHOR CONTRIBUTIONS**

48 All authors (HB, TK, JS, KS, SK, AA, CJS and DZ) contributed to the conception and design
49 of the study and to creating the study protocol. HB, TK, and DZ drafted the manuscript. DZ is
50 the designer of the CLEOS program's method for making medical knowledge actionable and
51 the developer of the program's medical knowledge base. All authors (HB, TK, JS, KS, SK,
52 AA, CJS and DZ) revised the manuscript for intellectual content and approved the final text.
53
54
55
56
57
58
59
60

1
2
3 TK (chair), HB, JS, SK, CJS and DZ form the steering group of the CLEOS-CPDS study. CJS
4 acts as the contact person for the trial sponsor (Karolinska Institutet). All steering group
5 members will have full access to the final trial data set. The corresponding author attests that
6
7 all listed authors meet authorship criteria and that no others meeting the criteria have been
8
9 omitted.
10
11
12
13
14
15
16

17 **FUNDING STATEMENT**

18
19 This work was funded by the Robert Bosch Stiftung (Stuttgart, Germany), grant number
20
21 11.5.1000.0258.0, Karolinska Institutet Research Foundation (Stockholm, Sweden) and
22
23 Stiftelsen Hjärtat (Stockholm, Sweden).
24
25
26
27

28 **COMPETING INTERESTS STATEMENT**

29
30 DZ is the inventor on US patents for technology related to the CLEOS program. All patent
31
32 rights and copyrights to technology, language, images, and knowledge content are assigned
33
34 without royalty rights by DZ to Karolinska Institutet, Stockholm, Sweden which is a public
35
36 university. Apart from Karolinska Institutet and its subsidiaries, no individuals or companies
37
38 may be owners or receive royalties or other revenue from use of CLEOS technology,
39
40 language, images, knowledge content or from clinical insights and/or computer algorithms
41
42 generated from analysis of data acquired by the program. There are no other competing
43
44 interests financial or otherwise in study design, collection, management, analysis, and
45
46 interpretation of data, writing of the report, and the decision to submit the report for
47
48 publication. All CLEOS-CPDS steering group members (see above) will have full access to
49
50 the final trial data set.
51
52
53
54
55
56
57

58 **REFERENCES**

59
60

1
2
3 1 Pitts SR, Niska RW, Xu J, et al. National Hospital Ambulatory Medical Care Survey: 2006
4 emergency department summary. *Natl Health Stat Report*. 2008:1-38.

5
6
7 2 Organization WH. Global Health Observatory (GHO) data: World Health Organization;
8
9 2019 [cited 2019 May 15]. Available from:
10
11 http://origin.who.int/gho/mortality_burden_disease/causes_death/top_10/en/.

12
13
14 3 Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute
15 coronary syndromes in patients presenting without persistent ST-segment elevation: Task
16 Force for the Management of Acute Coronary Syndromes in Patients Presenting without
17 Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*.
18 2016;37:267-315.

19
20
21 4 Ekelund U, Nilsson HJ, Frigyesi A, et al. Patients with suspected acute coronary syndrome
22 in a university hospital emergency department: an observational study. *BMC Emerg Med*.
23 2002;2:1.

24
25
26 5 Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the
27 management of patients with non-ST-elevation acute coronary syndromes: executive
28 summary: a report of the American College of Cardiology/American Heart Association Task
29 Force on Practice Guidelines. *Circulation*. 2014;130:2354-94.

30
31
32 6 Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of
33 patients with suspected acute coronary syndromes. *JAMA*. 2005;294:2623-9.

34
35
36 7 Nieman K, Hoffmann U. Cardiac computed tomography in patients with acute chest pain.
37 *Eur Heart J*. 2015;36:906-14.

38
39
40 8 Six AJ, Cullen L, Backus BE, et al. The HEART score for the assessment of patients with
41 chest pain in the emergency department: a multinational validation study. *Crit Pathw Cardiol*.
42 2013;12:121-6.

- 1
2
3 9 Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial
4 infarction in the six months after presentation with acute coronary syndrome: prospective
5 multinational observational study (GRACE). *BMJ*. 2006;333:1091.
6
7
8
9
10 Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST
11 elevation MI: A method for prognostication and therapeutic decision making. *JAMA*.
12 2000;284:835-42.
13
14
15
16
17 11 Cox JL, Zitner D, Courtney KD, et al. Undocumented patient information: an impediment
18 to quality of care. *Am J Med*. 2003;114:211-6.
19
20
21
22 12 Herrick DB, Nakhasi A, Nelson B, et al. Usability characteristics of self-administered
23 computer-assisted interviewing in the emergency department. *Appl Clin Inform*. 2013;4:276-
24 92.
25
26
27
28
29 13 Corrigan M, McWilliams R, Kelly KJ, et al. A computerized, self-administered
30 questionnaire to evaluate posttraumatic stress among firefighters after the World Trade Center
31 collapse. *Am J Public Health*. 2009;99 Suppl 3:S702-9.
32
33
34
35
36 14 Zakim D, Fritz C, Braun N, et al. Computerized history-taking as a tool to manage
37 dyslipidemia. *Vasc Health Risk Manag*. 2010;6:1039-46.
38
39
40
41 15 Almario CV, Chey W, Kaung A, et al. Computer-Generated Vs. Physician-Documented
42 History of Present Illness (HPI): Results of a Blinded Comparison. *Am J Gastroenterol*.
43 2015;110:170-9.
44
45
46
47 16 Pappas Y, Vseteckova J, Poduval S, et al. Computer-Assisted versus Oral-and-Written
48 History Taking for the Prevention and Management of Cardiovascular Disease: a Systematic
49 Review of the Literature. *Acta Medica (Hradec Kralove)*. 2017;60:97-107.
50
51
52
53
54 17 Hunt DL, Haynes RB, Hanna SE, et al. Effects of computer-based clinical decision support
55 systems on physician performance and patient outcomes: a systematic review. *JAMA*.
56 1998;280:1339-46.
57
58
59
60

- 1
2
3 18 Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision
4 support systems on practitioner performance and patient outcomes: a systematic review.
5
6
7 *JAMA*. 2005;293:1223-38.
8
9
10 19 Raschke RA, Gollihare B, Wunderlich TA, et al. A computer alert system to prevent injury
11 from adverse drug events: development and evaluation in a community teaching hospital.
12
13
14 *JAMA*. 1998;280:1317-20.
15
16
17 20 Chen R, Valladares C, Corbal I, et al. Early Experiences from a guideline-based
18 computerized clinical decision support for stroke prevention in atrial fibrillation. *Stud Health*
19 *Technol Inform*. 2013;192:244-7.
20
21
22
23 21 Berner ES, Kasiraman RK, Yu F, et al. Data quality in the outpatient setting: impact on
24 clinical decision support systems. *AMIA Annu Symp Proc*. 2005:41-5.
25
26
27
28 22 Skyttberg N, Chen R, Blomqvist H, et al. Exploring Vital Sign Data Quality in Electronic
29 Health Records with Focus on Emergency Care Warning Scores. *Appl Clin Inform*.
30
31
32 2017;8:880-92.
33
34
35 23 Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration:
36 guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.
37
38
39
40 24 Widgren BR, Jourak M. Medical Emergency Triage and Treatment System (METTS): a
41 new protocol in primary triage and secondary priority decision in emergency medicine. *J*
42 *Emerg Med*. 2011;40:623-8.
43
44
45
46 25 Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the
47 Swedish national inpatient register. *BMC Public Health*. 2011;11:450.
48
49
50
51 26 Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. *Eur J*
52 *Epidemiol*. 2017;32:765-73.
53
54
55
56
57
58
59
60

1
2
3 27 Zakim D, Braun N, Fritz P, et al. Underutilization of information and knowledge in
4
5 everyday medical practice: Evaluation of a computer-based solution. *BMC Med Inform Decis*
6
7 *Mak.* 2008;8.

8
9
10 28 Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute
11
12 myocardial infarction in patients presenting with ST-segment elevation: The Task Force for
13
14 the management of acute myocardial infarction in patients presenting with ST-segment
15
16 elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39:119-77.

17
18 29 Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction
19
20 (2018). *Eur Heart J.* 2018;40:237-69.
21
22

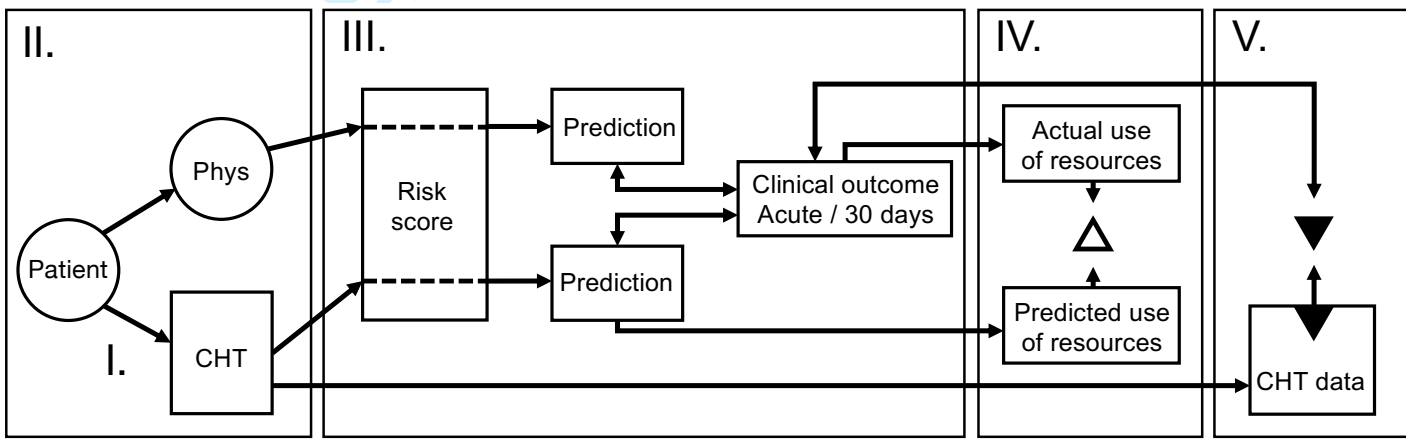
23 24 25 26 **FIGURE LEGENDS**

27
28 Figure 1. Overview of planned studies. Phys: history taking by physicians; CHT:
29
30 computerized history taking.
31
32

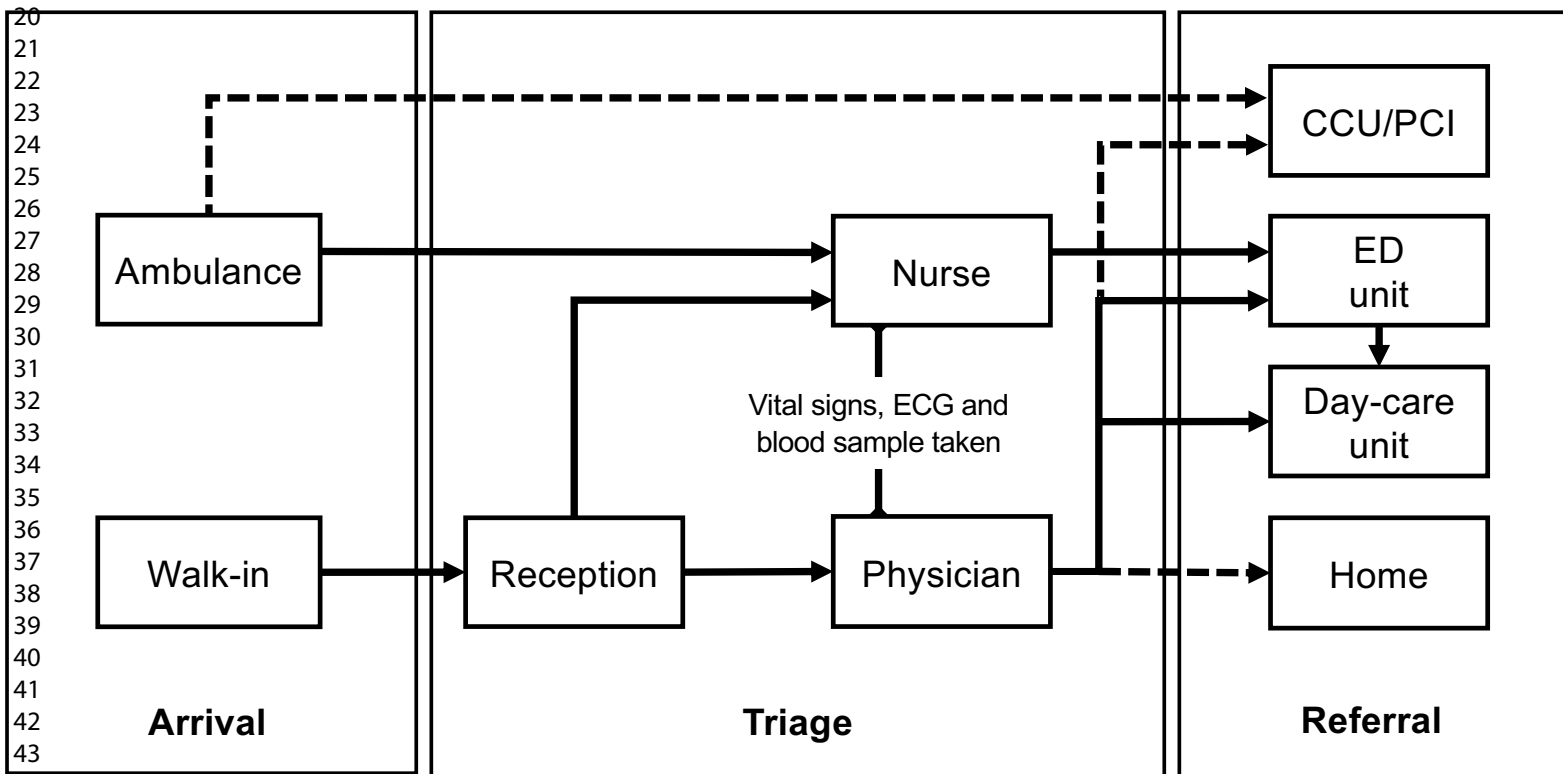
33
34
35 Figure 2. Overview of the ED flow from arrival to referral. Broken lines indicate patients who
36
37 will not be eligible. ECG: electrocardiogram; CCU: Cardiac care unit; PCI: Percutaneous
38
39 coronary intervention; ED: Emergency Department.
40
41

42
43
44 Figure 3. Example of the presentations of questions in CLEOS on the tablet.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

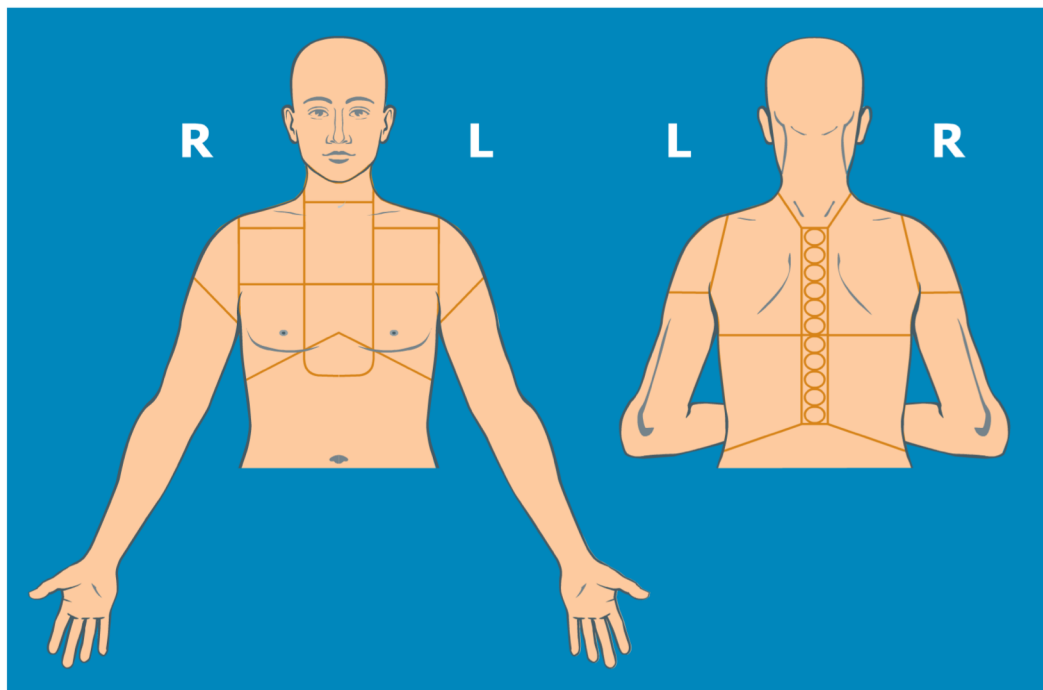
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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

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



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 <i>Comment: Embedded in manuscript. Also, see trial registration at clinicaltrials.gov (NCT03439449).</i>	4
Protocol version	#3	Date and version identifier	8
Funding	#4	Sources and types of financial, material, and other support	20

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1-2,19
2	responsibilities:			
3	contributorship			
4				
5				
6	Roles and	#5b	Name and contact information for the trial sponsor	1, 19
7	responsibilities:			
8	sponsor contact			
9	information			
10				
11				
12				
13	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	20
14	responsibilities:		collection, management, analysis, and interpretation of data;	
15	sponsor and funder		writing of the report; and the decision to submit the report for	
16			publication, including whether they will have ultimate authority	
17			over any of these activities	
18				
19				
20				
21	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	19
22	responsibilities:		centre, steering committee, endpoint adjudication committee,	
23	committees		data management team, and other individuals or groups	
24			overseeing the trial, if applicable (see Item 21a for data	
25			monitoring committee)	
26				
27				
28				
29				
30	Introduction			
31				
32	Background and	#6a	Description of research question and justification for undertaking	6-8
33	rationale		the trial, including summary of relevant studies (published and	
34			unpublished) examining benefits and harms for each intervention	
35				
36				
37	Background and	#6b	Explanation for choice of comparators	6-8
38	rationale: choice of			
39	comparators			
40				
41				
42	Objectives	#7	Specific objectives or hypotheses	8
43				
44				
45	Trial design	#8	Description of trial design including type of trial (eg, parallel	8
46			group, crossover, factorial, single group), allocation ratio, and	
47			framework (eg, superiority, equivalence, non-inferiority,	
48			exploratory)	
49				
50				
51				
52	Methods:			
53	Participants,			
54	interventions, and			
55	outcomes			
56				
57				
58				
59				
60				

1	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
2				
3				
4				
5				
6	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
7				
8				
9				
10				
11	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
12	description			
13				
14				
15	Interventions:	#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
16	modifications			
17				
18				
19				
20				
21	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-14
22	adherence			
23				
24				
25				
26	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
27	concomitant care			
28				
29				
30	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
31				
32				
33				
34				
35				
36				
37				
38				
39				
40	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
41				
42				
43				
44				
45	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
46				
47				
48				
49				
50	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 11, 15
51				
52				
53				

Methods: Assignment of interventions (for controlled trials)

1	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-	n/a
2	generation		generated random numbers), and list of any factors for	
3			stratification. To reduce predictability of a random sequence,	
4			details of any planned restriction (eg, blocking) should be	
5			provided in a separate document that is unavailable to those who	
6			enrol participants or assign interventions	
7				
8				
9				
10				
11			<i>Comment: Not relevant for this observational cohort study.</i>	
12				
13	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central	n/a
14	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
15	mechanism		describing any steps to conceal the sequence until interventions	
16			are assigned	
17				
18				
19				
20			<i>Comment: Not relevant for this observational cohort study.</i>	
21				
22	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	n/a
23	implementation		participants, and who will assign participants to interventions	
24				
25				
26			<i>Comment: Not relevant for this observational cohort study.</i>	
27				
28	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial	n/a
29			participants, care providers, outcome assessors, data analysts),	
30			and how	
31				
32				
33				
34			<i>Comment: Not relevant for this observational cohort study.</i>	
35				
36	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible,	n/a
37	emergency unblinding		and procedure for revealing a participant's allocated intervention	
38			during the trial	
39				
40				
41			<i>Comment: Not relevant for this observational cohort study.</i>	
42				
43				
44	Methods: Data			
45	collection,			
46	management, and			
47	analysis			
48				
49				
50	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and	10-12
51			other trial data, including any related processes to promote data	
52			quality (eg, duplicate measurements, training of assessors) and a	
53			description of study instruments (eg, questionnaires, laboratory	
54			tests) along with their reliability and validity, if known.	
55				
56				
57				
58				
59				
60				

Reference to where data collection forms can be found, if not in the protocol

1			
2			
3			
4	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, 12
5	retention		including list of any outcome data to be collected for participants
6			who discontinue or deviate from intervention protocols
7			
8			
9			<i>Comment: When patients have provided data via the interview,</i>
10			<i>outcome data are retrieved from registries and health records.</i>
11			
12			
13	Data management	#19	Plans for data entry, coding, security, and storage, including any 16
14			related processes to promote data quality (eg, double data entry;
15			range checks for data values). Reference to where details of data
16			management procedures can be found, if not in the protocol
17			
18			
19			
20	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary 16-17
21			outcomes. Reference to where other details of the statistical
22			analysis plan can be found, if not in the protocol
23			
24			
25	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted 16-17,
26	analyses		analyses) 19
27			
28			
29	Statistics: analysis	#20c	Definition of analysis population relating to protocol non- 8
30	population and missing		adherence (eg, as randomised analysis), and any statistical
31	data		methods to handle missing data (eg, multiple imputation)
32			
33			
34	Methods: Monitoring		<i>Comment: This will be addressed in the feasibility study (Study</i>
35			<i>I).</i>
36			
37			
38	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of n/a
39	formal committee		its role and reporting structure; statement of whether it is
40			independent from the sponsor and competing interests; and
41			reference to where further details about its charter can be found,
42			if not in the protocol. Alternatively, an explanation of why a
43			DMC is not needed
44			
45			<i>Comment: Data is entered directly into the database.</i>
46			
47			
48			
49			
50	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines, 15
51	interim analysis		including who will have access to these interim results and make
52			the final decision to terminate the trial
53			
54			
55			
56	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited 11-12,
57			and spontaneously reported adverse events and other unintended 16
58			effects of trial interventions or trial conduct
59			
60			

1	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
2				
3				
4				
5				
6	Ethics and			
7	dissemination			
8				
9				
10	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17-18
11				
12				
13				
14	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)	n/a
15				
16				
17				
18				
19				
20				
21			<i>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.</i>	
22				
23				
24				
25				
26	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
27				
28				
29				
30	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
31				
32				
33				
34				
35	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
36				
37				
38				
39				
40	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
41				
42				
43				
44	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
45				
46				
47				
48				
49	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
50				
51				
52				
53	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
54				
55				
56				
57				
58				
59				
60				

databases, or other data sharing arrangements), including any publication restrictions

Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of professional writers 19

Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code n/a

Comment: No such plans at present.

Appendices

Informed consent materials [#32](#) Model consent form and other related documentation given to participants and authorised surrogates n/a

Comment: The model consent form and other related documentation is available from the ethical review authority. These are public documents in Sweden.

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

None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. **This checklist can be completed online** using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)