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HEART-GP: developing a rapid rule-out strategy for acute cardiac conditions in patients with acute-onset chest pain in out-of-hours primary care

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PROTOCOL TITLE ‘

HEART-GP: developing a rapid rule-out strategy for acute cardiac conditions in patients with acute-onset chest pain in out-of-hours primary care

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
ACS	**Acute coronary syndrome**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
ECG	**Electrocardiogram**
EU	**European Union**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
GP	**General practitioner**
Hs-troponin	**High sensitivity troponin**
IC	**Informed Consent**
MACE	**Major Adverse Cardiovascular Event**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
OOH-PC	**Out of hours primary health care services**
POCT	**Point of care test**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale

General practitioners (GPs) frequently assess patients with chest pain. The challenge in primary care is to make the distinction between acute cardiac conditions versus far more common, non-urgent diagnoses in an unselected case-mix of patients, with limited resources and time constraints. All while being fully aware that symptom characteristics and signs are at best a mediocre indicator in both male and female patients. Currently, both misdiagnosis and over-testing are key concerns, and standardized diagnostic strategies may help GPs to balance these risks. We propose that a recently developed fingerstick test for high-sensitivity(hs) troponin may present a breakthrough in this regard for safe rule out of acute cardiac conditions, particularly when integrated with a pretest probability assessment, using clinical risk scores.

Objectives

The goals of our study are: 1) to evaluate the performance of a single fingerstick-obtained hs-troponin measurement using universal and sex-specific cut-off values in out-of-hours primary care; 2) to evaluate whether embedding hs-troponin in a clinical risk score (HEART, INTERCHEST, Marburg Heart Score) will further improve performance, in terms of increased efficiency without compromising safety; 3) to evaluate experiences and preferences of GPs, triage nurses and patient participants in regards to the evaluated risk stratification tools; 4) to construct a chest pain decision rule that is safe, efficient, fit for use and implementable in out-of-hours primary care.

Central hypothesis

Modern decision support tools can help improve the evaluation of acute chest pain in out-of-hours primary care.

Study design

1) Comparative Diagnostic accuracy study
2) Qualitative study using interviews and focus group meetings

Study population:

Eligible patients are ≥18 years, with new onset, non-traumatic chest pain in which a cardiac etiology is considered possible, and who present to an out-of-hours primary care (OOH-PC) facility for a face-to-face consultation with a GP. Patients who are hemodynamically unstable or receive immediate ambulance activation following triage are excluded.

Intervention:

GPs will be asked to fill out a digital questionnaire containing the elements of the 3 clinical risk scores. A finger stick hs-troponin POCT will be assessed for each patient.

Main study parameters/endpoints:

Diagnostic test characteristics (sensitivity, specificity, accuracy, negative and positive predictive values) of hs-troponin alone or in combination with one of the three clinical risk scores for the occurrence of major adverse cardiovascular events (MACE) within 6 weeks of the index consultation.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The collection of relevant patient information will take additional time during the consultation, estimated at 10 minutes. The measurement of hs-troponin requires a finger stick blood sample, which brings little to no additional risk to the patient. The patient will experience a short sting when a few droplets are collected. The clinical course (i.e. referral and/or treatment) will be decided by the clinical judgement of the GP.

1. INTRODUCTION AND RATIONALE

1.1 Background

Chest pain is a common and challenging symptom in primary care. During office-hours 0.7-3.0% of general practice consultation are related to chest pain, and in Dutch out-of-hours settings, chest pain is the chief complaint in 125,000 patients annually, making it among the top 10 most common reasons for consultation (1-3). A minority (10-15 percent) of patients will have a potential life-threatening underlying condition, such as acute coronary syndrome (ACS), whereas the vast majority will have less-urgent problems, such as musculoskeletal, gastro-intestinal, or psychological conditions. (1, 3-6) Making this distinction can be quite challenging, as symptom characteristics and signs of ACS and less-urgent problems often overlap.

Current primary care practice is based on the guidelines of the Dutch College of General Practitioners. The guideline for (suspected) ACS states that individual signs and symptoms should lead the general practitioner (GP) in the decision whether to refer chest pain patients. It is well known, that the diagnostic value of these individual signs and symptoms is limited (reported sensitivity ranging from 69% up to 92-94% with a 6-17% miss rate). (7, 8) Due to the (often fatal) consequences of a missed ACS, missed ACS diagnoses form the most frequently reported cause of calamities (and medicolegal action) at the out-of-hours GP facilities in the Netherlands. (9) At the same time, GPs are cautious and refer most patients (40-70%) to emergency care, at the cost of a high number of unnecessary referrals. (2, 5, 9, 10) This low referral threshold is particularly notable during out-of-hours, since GPs work under different conditions during out-of-hours service when compared with daytime practice. Notable differences are a) the vast scale of the regional centers, resulting in GPs not knowing the patients that consult them, b) suboptimal working conditions, with incomplete past medical history data, due to no good linkage with daytime electronic health records, c) a different case mix (a priori risk), due to triage only urgent cases that cannot wait until the next office day are evaluated); d) Less experienced, locum GPs often represent the bulk of out-of-hours primary care. The net result is that a low referral threshold comes with unwanted side effects of overburdened ambulance and emergency department services, increased health care spending and unnecessary worry among patients. (11)

1.2 Proposed solution and potential impact

While every Dutch citizen benefits from a well-functioning out-of-hours primary care service, only limited resources are spent on helping GPs during out-of-hours to safely and efficiently fulfil their role as gatekeepers in our health care system. Given the vast volume of patients that require urgent care each year, on a background of a growing and aging population, and public expectations of high-quality and accessible care, we should provide out-of-hours primary care with better means to support those physicians on call perform their clinical duties. The recent development of point-of-care high-sensitivity troponin testing provides an important window of opportunity to further optimize acute chest pain care in primary care. Alone or combined with clinical risk scores these tests would bolster rapid, reliable decision making for patients with possible underlying cardiac conditions, resulting in less missed cases and more efficient use of health care resources. Moreover, this solution would complete a safety and efficiency improvement cycle for acute chest pain that started in the emergency department and more recently moved into the prehospital/ambulance setting, and now leads us to completion of the acute care chain with efforts in general practice settings.

Prior research has shown that GPs would be very receptive to start using a reliable diagnostic tool (preferably embedded in a clinical risk score) to aid clinical decision-making. (12) If GPs were to use a decision rule to exclude ACS safely, this could reduce 6-17% miss rate of ACS to about 1%, a percentage that is currently achieved in emergency care with the HEART score. This translates to thousands of patients (in whom ACS would previously have been missed), who could now reap the benefits from medical and procedural therapies that minimize myocardial damage and reduce morbidity and mortality. To illustrate this impact, a nationwide cohort study from the United Kingdom, found that 1 in 5 misdiagnosed cases of myocardial infarction had died within the first year, whereas those who were timely diagnosed and treated had a much lower fatality rate of 1 in 14 cases. (13) Furthermore, forestalling complications will also have a positive impact on quality of life, physical limitations, as well as psychological distress leading to anxiety or depression. (14)

Apart from safety, introducing a GP-based rapid rule out strategy for ACS could also tackle an important efficiency problem in Dutch health care by reinforcing GPs as gatekeepers, reducing diagnostic uncertainty, and diminishing unnecessary referrals and associated costs. The number of related ambulance activations could perhaps be cut in half, which would provide the much needed relief on this overstretched system. Finally, the aforementioned innovations may also be of relevance for other countries with comparable healthcare systems, such as the United Kingdom or Scandinavian countries.

1.3 Existing evidence

In secondary care, clinical judgment combined with hs-troponin testing and a risk stratification tool is an established strategy to assess chest pain patients (14). In emergency department settings, a strategy that combines a single hs-troponin measurement with a clinical assessment has been shown to perform safely for ruling out myocardial infarction in patients with chest pain >1 hour (14-16) A single measurement hs-troponin rule-out strategy is part of the ESC guideline for patients suspected of non ST-elevation ACS. (14) This means that for patients with a very low level of hs-troponin at baseline, myocardial infarction can be ruled out safely. For the Siemens POCT device, the rule-out threshold lies at 4ng/L, which demonstrated very high safety (sensitivity 98.8%, NPV=99.8%) in emergency department populations (n=2,572). In early presenters (symptom onset <2 hours), the sensitivity remained high at 94.1%, with a NPV of 98.3%. (17)

Studies in primary care on troponin testing and/or risk stratification tools for ruling out ACS are limited. An important study in this regard is OUT-ACS, a study conducted in Oslo, Norway, that applied the rule-out strategy, as proposed by the ESC, in a low-prevalence primary care setting and was able to rule out 33.3% of patients by a single hs-troponin measurement, without a missed case of ACS.(18,19) Other supportive evidence comes from a feasibility study in Dutch out-of-hours primary care, the URGENT study, which showed promising results by combining a clinical decision rule (HEART score) and troponin point of care test (POCT) for safely ruling out ACS by GPs in Dutch OOH-PC. (20) Of the 37 enrolled patients with low to intermediate suspicion of ACS, a total of 23 (62.2%) could be safely excluded, with no missed ACS during follow up. Additionally, unnecessary referrals were reduced. A study by our group also found that a modified/simplified version of the HEART score may also be used as a reliable risk stratification tool for chest pain in out-of-hours primary care. (21) Other easy-to-use risk scores, such as the Marburg Heart Score and INTERCHEST, may also be suitable for risk stratification purposes, when integrated with a troponin test. As a standalone tool, these risk scores appear less suitable, given that they may improve efficiency, but not safety when compared with unaided clinical judgement. (6,10,22)

1.4 Ongoing studies

The current HEART-GP study proposal builds on prior findings of the URGENT study and others, and will run in parallel with the ongoing POB HELP study *'Primary care decision rule for chest pain using the Marburg Heart Score and troponin point of care test'* (NL68784.058.19, registered at the METC Leiden-Den Haag-Delft under p20.013 and registered on trialregister.nl: NL9525) . The POB HELP study is a clustered randomized controlled trial in which a decision rule consisting of the Marburg Heart Score and hs-troponin

POCT is compared to current practice in primary care practices during office hours. Two other ongoing studies, the URGENT 2.0 (NCT04904107) and the ARTICA (NL7148) trials, use the HEART-score including troponin POCTs, in an ambulance setting to exclude ACS in patients with chest pain. Combined these efforts will make sure we will improve the future care of acute chest pain in the Netherlands across a spectrum of prehospital settings, in each setting has its own unique a priori risks and working conditions.

2. HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

The central hypothesis is that modern decision support tools can improve chest pain evaluation in out-of-hours primary care. A key opportunity in this regard, is the recent development of point-of-care tests for high sensitivity (hs-)troponin, which can reliably detect traces of myocardial injury using a mere drops of capillary blood. We postulate that introducing hs-troponin can help detect more cases with an acute coronary event. Moreover, we hypothesize that when integrating these hs-troponin tests in a clinical risk score that takes sex and pretest probability into account, we can develop a risk stratification tool that is not only safe (highly sensitive), but also efficient. Finally, these findings will be combined with the feedback from end-users, in which we develop a user-friendly chest pain decision support tool, that can help general practitioners make on-the-spot risk assessment, and make patient-tailored decisions in regards to referral and management decisions.

2.2 Key objectives

The development of a chest pain decision rule that is fit for future use in out-of-hours primary care requires to take a number of important steps, that are summarized in the following objectives.

Objective 1. To prospectively evaluate the performance of a single measurement quantitative high-sensitivity troponin fingerstick test using universal and sex-specific cut-off values in out-of-hours primary care setting

Objective 2. To compare the diagnostic performance of a stand-alone troponin test versus an integrated approach that involves previously developed risk scores (HEART, INTERCHEST, Marburg Heart Score)

Objective 3. To study experiences of primary end-users (GPs, triage nurses and patients) with the introduction of hs-troponin testing and risk scores at the participating sites

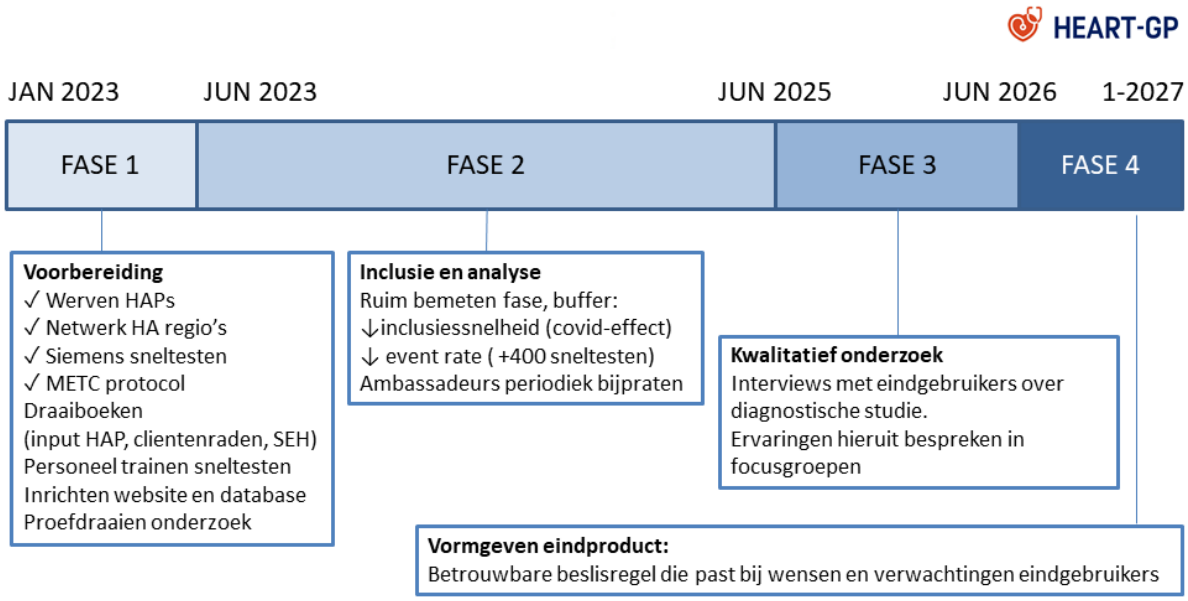
Objective 4. To integrate findings on the most favorable chest pain rule in terms of diagnostic properties (objectives 1 and 2), in conjunction with end-user experiences (objective 3) in order to settle on a chest pain decision rule that is both safe, fit for use and thus suitable for future implementation.

Overall, the above mentioned objectives are in line with national initiatives to improve chest pain care in the Netherlands as outlined in national policy agendas and efforts by the Dutch Heart Foundation, and as prioritized by academic societies, such as the Dutch National Science Agenda for General Practice.

3. STUDY DESIGN

This study will follow a prospective, comparative diagnostic accuracy study design to test the reliability a single measurement of hs-troponin as a stand-alone tool or in conjunction with a clinical risk score (objectives 1 and 2 = part A). Subsequently we will learn from end-user experiences on user-friendliness and pitfalls (objective 3 = part B) using qualitative research methods. From here on we will then adjust the concept to get to an implementable decision rule (objective 4 = part C). The projected timeline/timeframe of the HEART-GP study is illustrated below. In the first months we make sure the study can be started. This is followed by the inclusion and analysis phase for the diagnostic accuracy study (part A). The third phase involves qualitative research (= part B), and the final phase involves getting to the end-product, a reliable and implementable support tool (part C).

Figure 1. Projected timeline of HEART-GP study



3.1 PART A: Diagnostic accuracy study

The study will be coordinated by the department of general practice of the Amsterdam UMC. Prospective participants will be approached for enrolment at one of four out-of-hours primary care (OOH-PC) facilities in Alkmaar, Amersfoort, Leiden and Venlo regions. Patients, in whom ACS is considered in the differential diagnosis by the treating physician, will be asked for study participation by the treating physician during face-to-face consultation at the primary care facility. This will take place during operating hours, which means during weekends, holidays and during week days between 5PM and 8AM. Given that this study takes place in an acute care setting (in which delays should be kept to an absolute minimum), verbal initial consent will be asked initially, followed by a formal written consent procedure at a later stage, in which the latter will be done by research physicians and nurses from the Amsterdam UMC. This two-step approach is felt necessary due to safety (harm due to time delay) and acceptability concerns, and is also used in the POB-HELP trial, a troponin POCT strategy in daytime general practices (NL:9525).

We will investigate the diagnostic properties of a finger stick hs-troponin measurement alone or in combination with pretest probability assessment tools, consisting of the clinical risk scores: HEART, INTERCHEST, or Marburg Heart Score. For troponin and risk scores we will take sex-differences (i.e. specific cut-offs and stratified analyses) into consideration. We anticipate to include 900 patients at 4 OOH-PC facilities. We anticipate to need 24 months for inclusion, accounting for non-inclusion of 50% of consultations and a roll-in/start-up period.

3.1.1 Study flow

The study flow is as follows. Once the patient reaches the facility, the GP will evaluate the patient, ask for initial verbal consent and enter data required for the risk scores. After obtaining verbal consent, the GP asks the nurse to obtain a resting 12-lead electrocardiogram (ECG), and a hs-troponin measurement via a capillary sample. At the end of the consultation the physician provides the patient with an information leaflet regarding the study, including contact information of the study investigators. The study personnel will obtain the formal informed consent procedure at the earliest convenience, depending on the clinical condition of the patient, and after providing ample time after receiving the patient information folder. Please see paragraph *11.2* for more information on the informed consent procedure. All management decisions will be left to the discretion of the treating physician.

From a scientific perspective we would ideally like to blind the physician and the patient from the troponin test results. However, we have decided against blinding the treating physician for the ECG or troponin test findings, as we do not find this to be ethical nor easy to enforce. Instead we will provide information on what findings should be considered normal versus abnormal. It is important to stretch the safety aspect here. To be specific, we strongly recommend to immediately refer each patient with chest pain and an elevated troponin level, irrespective of clinical gestalt, for safety reasons. In addition, we will strongly advice GPs to immediately refer a patient with chest pain when there is a high clinical level of suspicion, even for those with a negative troponin test result. A safety decision flowchart can be found in the figure 2, and is also included in the instruction form for the GP. We acknowledge that providing this information will likely affect decision-making in the setting of chest pain. To semi-circumvent this, we will also ask GPs what their level of suspicion was prior to the results (i.e. clinical gestalt), and whether they acted based on clinical presentation alone or also based on the findings of the ECG and/or troponin test, and compare referral patterns using historic controls.

Figure 2. Decision support tool for the treating physician (aimed at maximizing safety)

(a pocket guide for enrolling physicians can be found attached, “F4 Zakkaartje huisarts 6-10-2022.pdf”)

To maximize feasibility we aim to minimally disrupt routine care, as the treating GPs will only be required to verbally ask patients for interest in study participation and minimal data

collection. All research related activities, such as the informed consent procedure, data collection (i.e. ECG, troponin) and follow-up will be performed by the research team.

Structured telephone follow-up will be conducted for all subjects by a study nurse, at 6 weeks after the index consultation. Patients will be asked whether they had consulted another physician, had experienced ACS, or had undergone any cardiac testing, including coronary angiography with or without invasive intervention. If the patient answers in the affirmative or was unsure of the answer to any of these questions, or when the patient could not be reached by telephone, the patient's own GP will be contacted to verify vital status and to obtain a copy of relevant documentation. Finally, we will also document the final diagnosis of each case with elevated troponin, to study whether it was due to myocardial infarction or another acute condition that warrants immediate evaluation (e.g. pulmonary embolism or myocarditis) or was due to a less urgent, chronic condition (such as renal failure).

3.1.2 Electrocardiogram

The nurse working at the facility attaches the electrodes on standardized positions at the patient's chest, arms, and legs. Subsequently a 12-lead ECG machine will make a recording, where after the electrodes are removed and discarded. The entire procedure takes about 5-7 minutes, is painless, and non-invasive. The primary care facilities are equipped with ECG machines and qualified personnel, and have protocols in place, as ECGs are already part of routine care at these facilities. Specifically for chest pain patients we will make sure that any abnormal ECG (either by ECG software or by the GPs own interpretation) will be discussed with a cardiologist. This recommendation is included in the GP instruction form.

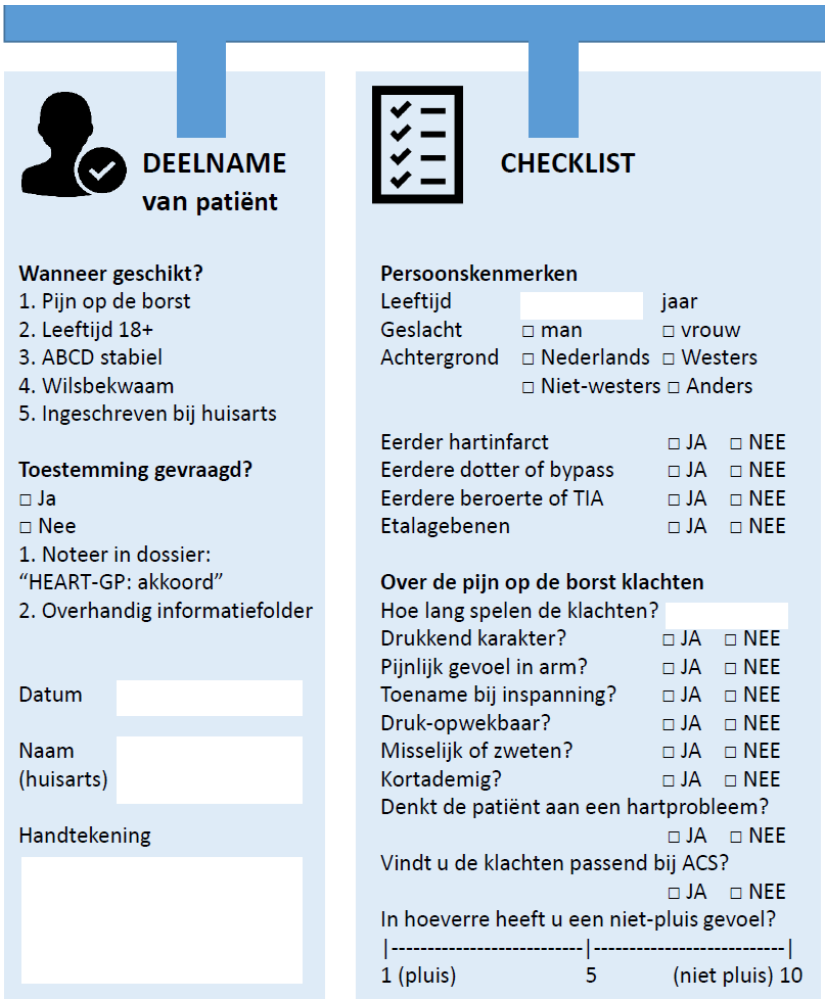
3.1.3 Cardiac troponin test

In this study we will use the Siemens Atellica VTLi (CE marked) point of care test for high sensitivity troponin-I. (17,23) The blood sample is collected by a finger stick and results are available within 7-8 minutes. Clinical validation of this POCT showed that it met the high sensitivity criteria, and is now commercially available. The 99th percentile (upper reference limit of normal) for rule-in is 23ng/L (90% CI 20–32 ng/L). (23) To ascertain maximum safety we will use the rule-out threshold of <4ng/L, which renders a negative predictive value of 99.8%, and is considered safe threshold for single-time point rule out of ACS. [17] More information can be found in paragraphs 7.1-7.3. In the GP instruction form, we will recommend the treating physician to immediately refer a patient with a troponin value that is 4ng/L or higher (see figure 2).

3.1.4 Checklist with elements of clinical risk scores

For this study we will also evaluate the diagnostic properties of HEART, INTERCHEST and Marburg Heart Score. Below we will discuss each of these scores, including the current evidence base. For this study, we will not ask the treating physician to actually calculate these scores, but instead to fill out a checklist with elements of these risk scores. An example can be found in the *table 1* below. The element of (migrant) background is not an item that was included in the risk scores, but is pivotal in order to capture whether our study will be representative, in terms of including men and women of different backgrounds.

Table 1. Checklist with questions for the treating physician that involve elements relevant for the clinical risk scores



DEELNAME van patiënt

Wanneer geschikt?
1. Pijn op de borst
2. Leeftijd 18+
3. ABCD stabiel
4. Wilsbekwaam
5. Ingeschreven bij huisarts

Toestemming gevraagd?
□ Ja
□ Nee
1. Noteer in dossier: "HEART-GP: akkoord"
2. Overhandig informatiefolder

Datum

Naam (huisarts)

Handtekening

CHECKLIST

Persoonskenmerken
Leeftijd ____ jaar
Geslacht □ man □ vrouw
Achtergrond □ Nederlands □ Westers □ Niet-westers □ Anders

Eerder hartinfarct □ JA □ NEE
Eerdere dotter of bypass □ JA □ NEE
Eerdere beroerte of TIA □ JA □ NEE
Etalagebenen □ JA □ NEE

Over de pijn op de borst klachten
Hoe lang spelen de klachten? ____
Drukkend karakter? □ JA □ NEE
Pijnlijk gevoel in arm? □ JA □ NEE
Toename bij inspanning? □ JA □ NEE
Druk-opwekbaar? □ JA □ NEE
Misselijk of zweten? □ JA □ NEE
Kortademig? □ JA □ NEE
Denkt de patiënt aan een hartprobleem? □ JA □ NEE
Vindt u de klachten passend bij ACS? □ JA □ NEE
In hoeverre heeft u een niet-pluis gevoel?
|----------|----------|
1 (pluis) 5 (niet pluis) 10

(a pocket guide for enrolling physicians can be found attached, "F4 Zakkaartje huisarts 6-10-2022.pdf")

3.1.5 HEART score

The HEART score is composed of 5 elements which can be assigned with either 0, 1 or 2 points. These elements are: a) history (2 points: highly suspicious, 1 point: moderately suspicious, 0 point: slightly suspicious), b) ECG (2 points: significant ST deviation, 1 point: non-specific repolarization abnormalities, 0 points: normal), c) Age (2 points: >=65, 1 point 45-64, 0 points <45), d) cardiovascular risk factors (2 points: >=3 risk factors or history of atherosclerotic disease, 1 point: 1-2 risk factors, 0 points: no known risk factors), e) initial troponin (2 points: >3 times normal limit, 1 point: 1-3 normal limit, 0 points <= normal limit). The HEART-score is routinely used in emergency care settings, in which the risk of missing MACE is 0.8% among low-risk patients (score<=3). (15) The HEART score has not been rigorously evaluated in primary care, except for a study in Norway (19), a Dutch feasibility study (URGENT) (20), and in a simplified version omitting troponin testing, which found this score to exceed unaided GP assessment. (21)

3.1.6 INTERCHEST

The INTERCHEST score consists of 6 components: 1) sex/age (female≥65, male≥55), 2) history of coronary artery disease, 3) chest pain related to effort, 4) pain reproducible by palpation, 5) physician initially suspected a serious condition, 6) chest discomfort feels like “pressure”. One point is assigned for each score variable that is present, except for pain reproducible by palpation, which results in minus 1 point. Prior studies on the performance of INTERCHEST found a C-statistic of 0.84, sensitivity of 82%-88% and specificity of 74%-82% when using a threshold of 2 points for ruling out CAD. (24) Furthermore, a recent study by our group compared INTERCHEST to unaided clinical judgement for predicting MACE. Here, INTERCHEST showed good discriminatory properties (C-statistic 0.85), sensitivity and specificity of 87.5% and 78.8%. (22) In this study, INTERCHEST also slightly improved risk stratification (as it resulted in fewer missed cases) when compared with unaided clinical judgement.

3.1.7 Marburg Heart Score

The MHS consists of a simple 5-item (yes/no) score: 1) sex/age (female≥65, male≥55), 2) history of cardiovascular disease, 3) patient assumes the pain is of cardiac origin, 4) pain gets worse with exercise, 5) pain is not reproducible by palpation. One point is assigned for each score variable that is present. Overall, MHS has good discriminatory ability (C-statistic of 0.84-0.90) for ruling out coronary artery disease, with a sensitivity of 87-91% and specificity of 61-81%, when using a threshold of 3 points. (6) As a standalone tool for ruling out ACS among high-risk primary care patients, the MHS performed less well, but incorporation of the MHS in GP’s consultation in one study led to fewer missed cases.

(10,22) There are no studies that have combined MHS with ECG or hs-troponin; there is however an ongoing study (POB-HELP).

3.2 PART B: End-user involvement and study evaluation

As we aim to develop a chest pain decision rule applicable for use in OOH-PC, we start out with consulting with our GPs and triage nurses from the four participating sites as well as patient representatives from Harteraad. We will use context mapping to make sure we have clarity in what context the study is conducted, for instance by identifying local stakeholders (cardiologists, paramedics) and to check their needs and expectations as well as how they may affect our study. Once the diagnostic accuracy study is (near) completion, we will perform in-depth interviews with GPs and triage nurses who participated in the study to evaluate their experiences with the troponin and risk stratification tools. We will explore whether they hold a preference for a specific decision rule and why, what is most important for them to make it work, in terms of practical use. Based on the output, we will subsequently hold focus group discussions on the most important topics. We will also hold interviews with enrolled patients (50% female, 25% with an ethnic minority background) and ask them to reflect on the point-of-care-test and the risk scores and how the physician discussed these with them, as well as on the flow-of-care and satisfaction.

3.3 PART C: Chest pain decision rule

In part C, we synthesize lessons on diagnostic properties as well as the practical input from GPs, triage nurses and patients in order to determine which of the studied options (hs-troponin, HEART, or hs-troponin + INTERCHEST or MHS) would be the best chest pain decision rule, in terms of diagnostic properties and implementability. Besides end-users, we will also consult other stakeholders (i.e. cardiologists, paramedics, professional societies) to obtain their input. The end product is a concept version of a chest pain decision rule.

4. STUDY POPULATION

4.1 Population for the diagnostic accuracy study

All patients ≥18 years with acute-onset chest pain in which a cardiac etiology is considered possible, and who present to the OOH-PC facility for GP consultation will be eligible for inclusion. ‘Acute-onset’ in an urgent primary care setting refers to the onset (or sudden worsening) of symptoms within the past 72 hours.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age 18 years or older
- Presence of chest pain at time of consultation of possible cardiac etiology
- Symptom onset (or worsening of preexisting symptoms) within the past 72 hours

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Signs of hemodynamic instability at consultation
- Chest trauma preceding chest pain
- Not able to provide informed consent
- Not registered with a GP in the Netherlands (needed for follow-up)

4.4 Sample size calculation

We calculated the sample size required for sensitivity and specificity in diagnostic studies using the Power Analysis and Sample Size (PASS) software, an approach that was previously published by Bujang and Adnan. (25) For our study, it is essential that the POCT test we evaluate is highly reliable in ruling out MACE, and hereby also an improvement with current GP evaluation (with a respective sensitivity of approximately 80% and specificity of 70%). We presume that the POCT troponin test alone will have a sensitivity of 90% and specificity of 80%. With an estimated MACE prevalence of 10-15%, a minimum sample size of 803 patients (including 107 with MACE) will then be required to achieve a minimum power of 80% (actual power 81.9%) in order to detect a change in the percentage value of sensitivity from 80% to 90%, based on a target significance level of <0.05 (actual p=0.040). This minimum sample size is also sufficient to detect a change in the value of specificity from 70 to 80%, which will only require a minimum sample of 183 patients (including 28 MACE cases). To err on the side of caution, we will include a margin to account for dropout (loss to follow-up, or withdrawal of consent), which will bring our final sample size to 900 patients. To ascertain equal representation of both women and men, enrollment will stop once both targets of 900 enrolled patients and 40% of female (or male) patients are met.

5. TREATMENT OF SUBJECTS

We will investigate the diagnostic properties of a hs-troponin POCT and three clinical risk scores for safely ruling-out MACE ≤6 weeks among patients with chest pain in OOH-PC. We will discuss the hs-troponin POCT in paragraphs 7.1-7.3 (non-investigational product). A detailed description of the risk scores (Marburg Heart Score INTERCHEST score and HEART-score) can be found in paragraphs 3.4-3.6.

6. INVESTIGATIONAL PRODUCT

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

The medical device used in this study: Siemens Atellica VTLi, bears the CE marking as a medical device, is used according to its intended purpose and is not part of the post market clinical follow-up (PMCF) of the manufacturer. Therefore it is subject to article 82 of the MDR. The EU declaration of conformity and the instructions for use are available.

7.1 Name and description of investigational product(s)

The POCT device is known as “Siemens Atellica VTLi”. User instruction guides can be found as PDF files “D6 Verkorte handleiding Troponine POCT 06-09-2022” and “D6 Gebruikershandleiding Troponine POCT 06-09-2022”. A CE certificate can be found as “D6 CE certificaat Troponine POCT 06-09-2022”.

7.2 Summary of findings from non-clinical studies

The information on data from non-clinical studies was obtained from the ‘instructions for use’’ of the Atellica VTLi. The precision of the platform was determined in plasma based on the EP05A3 document for evaluating quantitative measurement precision by the Clinical and Laboratory Standards Institute (CLSI). In essence, three controls and a native plasma pool were assayed in replicates of 2 at 2 separate times per day for 20 non-consecutive days on 2 different AtellicaVTLi Immunoassay analyzers per sample using 3 reagent lots (n=1920). (26) The data regarding the precision of this AtellicaVTLi hs-cTnI assay test is summarized in the following table:

	Car-tridge			Mean cTnI conc	Repeatability		Within laboratory precision	
Sample	Lot	Instru-ment	n	ng/L	SD (ng/L)	%CV (ng/L)	SD (ng/L)	%CV (ng/L)
Plasma panel	1	A	80	34.1	2.7	7.8%	2.9	8.4%
		B	80	32.6	2.2	6.7%	2.3	7.2%
	2	A	80	31.3	2.4	7.7%	2.7	8.6%
		B	80	30.8	2.7	8.7%	2.7	8.7%
	3	A	80	33.7	2.5	7.4%	2.7	8.1%
		B	80	33.0	2.4	7.3%	2.6	7.8%
Control 1	1	C	80	13.9	1.1	8.0%	1.1	8.0%
		D	80	14.0	1.3	9.0%	1.3	9.5%
	2	C	80	12.2	1.0	8.1%	1.1	9.0%
		D	80	12.9	1.2	9.3%	1.2	9.3%
	3	C	80	12.5	0.9	7.3%	1.0	8.3%
		D	80	13.0	0.8	6.3%	0.9	7.1%
Control 2	1	E	80	25.9	2.1	8.0%	2.1	8.0%
		F	80	27.8	2.1	7.4%	2.2	7.9%
	2	E	80	24.2	1.7	7.1%	1.9	7.8%
		F	80	25.2	2.1	8.4%	2.1	8.4%
	3	E	80	25.3	1.8	7.3%	2.0	8.0%
		F	80	26.0	2.1	8.2%	2.1	8.2%
Control 3	1	G	80	271	9.1	3.4%	11.3	4.2%
		H	80	267	13.0	4.9%	13.5	5.1%
	2	G	80	261	11.6	4.4%	12.1	4.6%
		H	80	259	9.3	3.6%	10.3	4.0%
	3	G	80	267	13.3	5.0%	13.3	5.0%
		H	80	266	10.1	3.8%	12.0	4.5%

7.3 Summary of findings from clinical studies

The Atellica VTLi hs-cTnI is also tested in a clinical setting and was found the meet the high sensitivity criteria. The 99th percentile for rule-in of a myocardial infarction is 23ng/L (90% CI 20–32 ng/L). The percentages of subjects having a measurable concentration above the level of detection was 83.7%. (15). In a study involving 1,089 patients who presented to the emergency department with acute chest pain, the POC device demonstrated comparable diagnostic accuracy for detecting myocardial infarction to central laboratory assays using 99th percentiles. (23) In other words, this portable POC device is as reliable as the gold standard for ruling out myocardial ischemia, namely high-sensitivity troponin assays based on machinery used in central laboratories of hospitals.

In a follow-up study, researchers studied the optimal threshold for *rule out* of acute MI using a single measurement of the Atellica VTli hs-cTnI in all-comers with acute chest pain at emergency departments in the USA (derivation, n=1,086, SEIGE) and Australia (validation, n=1,486, SAMIE). A hs-cTnI concentration of <4ng/L provided a sensitivity of 98.9% (93.8-100%) and NPV of 99.5% (95% CI: 97.2-100%) for ruling out MI in the derivation (SEIGE)

cohort. In the validation cohort, sensitivity was 98.8% (93.3-100%) and NPV was 99.8% (99.1-100%). 30-day adverse cardiac events were 0.1% (n=1) for the derivation and 0.8% (n=5) for the validation (SAMIE) cohort. Details for the overall cohort, as well as for early-presenters can be found in tables 2 and 3.

Table 2. Diagnostic Accuracy for Atellica VTLi POC hs-cTnI <4 ng/L Threshold for SEIGE and SAMIE Cohorts

	TP	FN	FP	TN	Sensitivity	NPV	Specificity	PPV
Index AMI (T1 and T2 MI)								
SEIGE	87	1	805	193	98.9% (93.8-100%)	99.5% (97.2-100%)	19.3% (16.9-21.9%)	9.8% (7.9-11.9%)
SAMIE	80	1	785	620	98.8% (93.3-100%)	99.8% (99.1-100%)	44.1% (41.5-46.8%)	9.2% (7.4-11.4%)
Index T1MI								
SEIGE	20	0	872	194	100% (83.2-100%)	100% (98.1-100%)	18.2% (15.9-20.6%)	2.2% (1.4-3.4%)
SAMIE	57	0	808	621	100% (93.7-100%)	100% (99.4-100%)	43.5% (40.9-46.1%)	6.6% (5.0-8.5%)
30-day MACE (MI, unplanned revascularisation or death during index or within 30 days)								
SEIGE	137	1	755	193	99.3% (96.0-100%)	99.5% (97.2-100%)	20.4% (17.8-23.1%)	15.4% (13.1-17.9%)
SAMIE	86	5	779	616	94.5% (87.6-98.2%)	99.2% (98.1-99.7%)	44.2% (41.5-46.8%)	9.9% (8.0-12.1%)
Index Injury (T1MI, T2MI, acute myocardial injury or chronic myocardial injury)								
SEIGE	289	5	603	189	98.3% (96.1-99.4%)	97.4% (94.1-99.2%)	23.9% (20.9-27.0%)	32.4% (29.3-35.6%)
SAMIE	165	6	700	615	96.5% (92.5-98.7%)	99.0% (97.9-99.6%)	48.8% (44.0-49.5%)	19.1% (16.5-21.9%)
30-day T1MI								
SEIGE*								
SAMIE	59	2	806	619	96.7% (88.7-99.6%)	99.7% (98.8-100%)	43.4% (40-8-46.1%)	6.8% (5.2-8.7%)

*Data not available for SIEGE

Table 3. Diagnostic Accuracy for Early Presenters for Atellica VTLi POC hs-cTnI <4 ng/L Threshold for Patients Presenting ≤2 Hours of Symptom Onset

	TP	FN	FP	TN	Sensitivity	NPV
Index AMI (T1 and T2 MI)						
SIEGE	16	1	134	59	94.1% (71.3-99.9%)	98.3% (91.1-100%)
SAMIE	21	1	201	140	95.5% (77.2-99.9)	99.3% (96.1-100%)
Index T1MI						
SIEGE	5	0	145	60	100% (47.8-100%)	100% (94.0-100%)
SAMIE	15	0	207	141	100% (78.2-100%)	100% (97.4-100%)
30-day MACE (MI, unplanned revascularisation or death)						
SIEGE	22	1	128	59	95.7% (78.1-99.9%)	98.3% (91.1-100%)
SAMIE	21	3	201	138	87.5% (67.6-97.3%)	97.9% (93.9-99.6%)

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Reference standard: major adverse cardiac events

The reference standard in our study will be the occurrence of major adverse cardiac events (MACE) within 6 weeks after the initial presentation. MACE consists of a composite of either: unstable angina, non-ST or ST elevation myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, coronary stenosis managed conservatively, cardiovascular death, non-cardiovascular death or death with unknown cause. An expert panel, consisting of a cardiologist and a GP with special interest in cardiovascular disease, blinded to the clinical decision rules, will adjudicate instances of MACE. Disagreements will be resolved by consensus. The rationale for using a 6-week (delayed-type) endpoint is to minimize the risk of selective verification, an accepted and commonly applied alternative when a single reference test (in this case rigorous cardiac evaluation) is not offered to all patients. The rationale is that due to clinical course (virtually) all initially missed cases will be detected within the 6 weeks following index GP consultation.

8.1.2 Diagnostic properties and definitions

Discrimination will be measured using c-statistics and diagnostic performance metrics will include sensitivity, specificity, positive and negative predictive values, based on various cut-offs for ‘high’ versus ‘low risk’ for each clinical decision rule. We will also include ‘failure rate’, which can be computed by the number of MACEs divided by the number of patients with a negative test within a risk category, and ‘efficiency’, which can be computed by the number of patients with a negative test within risk category divided by the number of enrolled patients. To categorize patients in low and high-risk groups we will use the cut-off values as mentioned for hs-troponin (based on sex specific thresholds), as well as the cut-offs for the HEART score, or the MHS or INTERCHEST in combination with a normal or abnormal ECG, troponin, or both. When calculating performance metrics based on these different thresholds we will be able to determine the most optimal combination. We will document which patients were referred during index presentation, as this will allow us to document the current referral rate.

8.1.3 Other study parameters

We will perform in-depth interviews with GPs and triage nurses who participated in the study to evaluate their experiences with the troponin and risk stratification tools, whether they hold a preference for a specific decision rule and why, what is most important for them to make it work, in terms of practical use and trust. The topics distilled from these interviews will be

used to hold focus group discussions. Finally we will synthesize the lessons on diagnostic properties and this input to determine which of the studied options would provide the best chest pain decision rules, based on the following metrics: safety, efficiency, acceptability, and implementability.

8.2 Randomisation, blinding and treatment allocation

Not applicable.

8.3 Study procedures

- The GP will fill out a checklist (see paragraph 3.1.4 for more details)
- Items we will collect via the OOHPC are:
    - Date of contact
    - Personal information: Name, Sex, Date of birth, contact information
    - Consultation details
    - Troponin measurement
    - ECG findings
- The ECG and hs-troponin measurement is performed by the assistant
- The informed consent form obtained by study personnel
- Occurrence of MACE is evaluated by an independent expert panel consisting of a cardiologist and general practitioner. In case of disagreement a third expert will be consulted.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. Previously collected data will be used for data analyses. In the scenario that a subject gave initial informed consent, but was unable to provide final written informed consent (i.e. the patient died prior to formal written consent), we will ask a surviving spouse or relative for consent, if this person cannot be traced, we propose to use the collected data of the patient for this study, given its direct relevance.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further

positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 (Serious) adverse events

Our study is observational in nature with extra (minimally invasive) diagnostic measurements. According to the CCMO ("Flowchart Ongewenste voorvallen: Observationeel en overig WMO-plichtig onderzoek"; https://www.ccmo.nl/publicaties/publicaties/2017/04/21/flowchart-ongewenste-voorvallen-observationeel-en-overig-wmo-plichtig-onderzoek), such a study does *not* mandate the reporting of serious adverse events (SAE) or adverse events (AE). In line with these regulations, we will therefore not directly report SAEs to the METC for this study. However, we will keep a list of medical occurrences that resulted in death or disability, and/or required hospitalization for medical or surgical intervention for each study participant from the date of verbal consent out to 6 weeks of follow-up. We will make a distinction between those events that naturally followed from index consultation (i.e. immediate referral for ACS) from those that followed later within the 6 week follow-up period. We will also record any undesirable experience (AE), such as skin infections at the fingerstick puncture site, that were reported spontaneously by the enrolled patient or observed/documented by the GP. We will report these findings to the data safety monitoring board (DSMB).

9.3 Data Safety Monitoring Board (DSMB)

In this study we will only collect data and perform a finger stick blood test. While we recommend the treating physician not to rely on a negative test result, there is a risk that physicians will ignore this recommendation. This means that there is a small risk of false negative results. To monitor this process we will install a DSMB.

10. STATISTICAL ANALYSIS

SPSS, R and MedCalc will be used for the statistical analyses. The investigators will perform the procedures and calculations. A biostatistician will be consulted for more advanced analyses.

10.1 Descriptive statistics

We collect demographic and baseline data at the moment of inclusion. These data will be summarized as means, medians, or proportions, depending on the data type and characteristics.

10.2 Primary study parameter(s)

Discrimination will be measured using c-statistics, and we will use the method of DeLong, that takes into account the paired nature of our data, as the three scores will be determined in each patient. For diagnostic performance metrics will include sensitivity, specificity, positive and negative predictive values, based on various cut-offs for 'high' versus 'low risk' for each clinical decision rule. We will also include 'failure rate', which can be computed by the number of MACEs divided by the number of patients with a negative test within a risk category, and 'efficiency', which can be computed by the number of patients with a negative test within risk category divided by the number of enrolled patients. To categorize patients in low and high-risk groups we will use the cut-off values as mentioned for hs-troponin (based on sex specific thresholds), as well as the cut-offs for the HEART score, or the MHS or INTERCHEST in combination with a normal or abnormal ECG, troponin, or both. When calculating performance metrics based on these different thresholds we will be able to determine the most optimal combination. We will document which patients were referred during index presentation, as this will allow us to document the current referral rate.

10.3 Study parameters of interviews and focus group meetings

Interviews and focus group meetings will be audio-recorded, translated into Dutch where appropriate and transcribed. Analysis will be performed using the qualitative data analysis software MAXQDA, which allows for open coding and thematic analysis by multiple researchers. The most important first step in this process is the transcribing of the interviews verbatim. From here on, two independent assessors will create initial codes, and those that are agreed upon will be put into a consensus document. This document will then be used to develop a thematic map of potential themes and sub-themes, followed by re-reading the collected data to make sure this map represents the data set, and by a discussion on whether data saturation was reached.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the 'declaration of Helsinki' (as amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and the Guideline for Good Clinical Practice (CPMH/ICH/135/95-17th July 1996).

11.2 Recruitment and consent

Patients with acute chest pain will be recruited at OOH-PC facilities by GPs during face-to-face consultations. Given the acute medical setting, in which delay due to informed consent procedures may be harmful (i.e. risk of potentially fatal arrhythmias or permanent myocardial damage), as well as that the studied investigations (i.e. fingerstick POCT, cannot be performed at a later stage in a non-acute medical setting), we followed the steps for deferred consent, such as reported by the CCMO ("Stappenplannen inzake uitgestelde toestemming ('deferred consent') bij onderzoek in noodsituaties"). We will carry out a two-staged informed consent procedure. In the first stage (in the acute setting), the treating physician will inform the patient of the study and verbally asks for permission to participate in the study, provides the patient (and accompanying family) with an information leaflet, and will ask to share the patients contact details with the research team. Within a week after the index consultation, the research team sends the patient the informed consent information (see document E1 E2 Informatiebrief en toestemmingsverklaring). To provide the patient ample time to read this information and to discuss it with others, the research team will contact the patient no earlier that the subsequent week. All patients have to review, understand, agree to, and personally sign and date the informed consent form. In case of death before final informed consent is obtained, we will consider the initial informed consent as valid.

Workflow

1. Index consultation at the general practitioner (10-minute consultation)
2. General practitioner performs normal anamnesis and physical examination and evaluates the possibility for inclusion
3. General practitioner asks for first stage spoken informed consent
4. General practitioner fills in the digital case report form and gives compact information including the compact patient leaflet.
5. Assistant performs the hs-troponin POCT test on the patient.
6. General practitioner treats or refers patient as he/she would normally do, in which she/he takes into account our safety recommendations
7. The research team sends the patient the information leaflet and the complete informed consent form by email and/or mail.
8. The research team contacts the patient by phone and will mention the possibility for a face-to-face appointment for extra information.
9. The patient sends the signed informed consent form to the research team, after which it will be signed and dated by the principal investigator.
10. Data on MACE outcomes will be collected by the research team after consent information is signed and dated by the participant and the principal investigator.

11.3 Benefits and risks assessment, group relatedness

The risk of this study is considered low since only data and a blood sample through a fingerstick are collected. Moreover, some patients may reap direct benefit from the researched intervention for the patient or GP. It is quite likely, that more cases of acute myocardial infarction will be detected, as the result of the hs-troponin assay test will be known to the treating physician resulting in immediate referral and treatment in secondary care. However, the biggest promise for benefit lies in the future, as a positive result of this study will ensure that future patients will experience less missed heart conditions as well as less uncertainty caused by unnecessary referrals and overall a higher quality of life. The eventual benefit for society will be the aimed reduction of the healthcare costs by reducing the number of false-positive referrals.

11.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Extracted data will be recorded in an electronic cloud-based, data capturing platform (CastorEDC, Amsterdam). This platform allows for secure data management, including the monitoring of patient inclusion, missing data elements, and importantly includes an audit trial. Each enrolled patient will be assigned a Castor-identification code. This identification code cannot be linked to an individual in Castor. Instead we keep this information in a separate, password-protected Access database, on a secure server of the Amsterdam UMC (G:\divjk\Huisartsgeneeskunde Onderzoek\). Access to this Access database will be restricted to members of the research team (e.g. principal investigator, research nurses), the monitor and IGJ (inspectie gezondheidszorg en jeugd).

Audio-recordings of focus group meetings as well as verbatim transcriptions of interviews will be digitally stored on a secure server of the Amsterdam UMC. Hard copy data will be stored in the trial master file (TMF) in a locked cabinet and will only be accessible to the research

group. Hard copy data will also be scanned and saved as digital data. Digital data will be stored in the Amsterdam UMC network storage, with access restricted to the research team. The network storage is backed-up automatically.

Future data analyses will be performed by exporting the final and locked Castor data file to our institutional secure data drives. From here we will use statistical software packages (including SPSS, R, MedCalc) to analyze our data.

All data will be handled according to the rules of the Amsterdam UMC and the General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. (in Dutch: Uitvoeringswet AVG, UAVG). Data will be kept until 15 years after finishing the study. When data will be used for publication, they will never relate to individual traceable patients.

12.2 Monitoring and Quality Assurance

Monitoring will be executed by (internal) monitors (clinical research associate) of the Clinical Monitoring Center.

12.3 Amendments

All substantial amendments will be notified to the METC. Non-substantial amendments will not be notified to the accredited METC, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

In accordance to the CCMO policy the results of the trial will be published unreservedly. As a condition for publication the trial will be registered in a public trial registry.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

The study adds the use of minimally invasive study procedures (single fingerstick blood test, Siemens Atellica VTLi for intended use), which in terms of risk are comparable to that of the standard medical care. We completed a structured risk analysis (CRU risk assessment document, see additional documentation), which classifies the risk of the study as negligible.

14. REFERENCES

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