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Acute rule out of non ST-segment elevation acute coronary syndrome in the (pre)hospital setting by HEART score assessment and a single point of care troponin: Rationale and design of the ARTICA randomized trial.

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3 1 **Acute Rule out of non ST-segment elevation acute coronary syndrome in the**
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5 2 **(pre)hospital setting by HEART I score assessment and a single poInt of Care**
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7 3 **troponin: Rationale and design of the ARTICA randomized trial.**
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48 **Abstract**

49 *Introduction:* Because of the lack of pre-hospital protocols to rule out a non-ST elevation acute
50 coronary syndrome (NSTEMI-ACS), patients with chest pain are often transferred to the emergency
51 department (ED) for thorough evaluation. However, in low-risk patients, an ACS is rarely found,
52 resulting in unnecessary health-care consumption. Using the HEART score, low-risk patients are easily
53 identified. When a point-of-care (POC) troponin measurement is included in the HEART score, an ACS
54 can adequately be ruled out in low-risk patients in the pre-hospital setting. However, it remains
55 unclear whether a pre-hospital rule-out strategy using the HEART score and a POC troponin
56 measurement in suspected NSTEMI-ACS patients is cost-effective.

57 *Methods and analysis:* The ARTICA trial is a randomized trial in which the primary objective is to
58 investigate the cost-effectiveness after 30 days of an early rule-out strategy for low-risk patients
59 suspected of a NSTEMI-ACS, using a modified HEART score including a POC troponin T measurement.
60 Patients are included by ambulance paramedics and 1:1 randomized for 1) presentation at the ED
61 (control group) or 2) POC troponin T measurement (intervention group) and transfer of the care to
62 the general practitioner in case of a low troponin T value. In total, 866 patients will be included.
63 Follow-up will be performed after 30 days, 6 months and 12 months.

64 *Ethics and dissemination:* This trial has been accepted by the Medical Research Ethics Committee
65 region Arnhem-Nijmegen. The results of this trial will be disseminated in one main paper and in
66 additional papers with subgroup analyses.

68 **Article summary**

69 *Strengths and limitations of this study*

- 70 • The ARTICA trial is the first randomized trial with a primary focus on cost-effectiveness of an
71 early rule-out strategy for low-risk patients suspected of an acute coronary syndrome.
- 72 • When randomized for point-of-care troponin T measurement, the ambulance paramedics
73 can rule out an acute coronary syndrome on the spot and therefore comfort the patient
74 without having to transfer them to the emergency department.
- 75 • Underestimation of the HEART score could result in patients being misclassified as low-risk
76 patients, although the HEART score has proven to have an excellent inter-operator agreement
77 in both nurses and doctors.
- 78 • In order to calculate the HEART score correctly, the ambulance paramedics have to register
79 every component of the HEART score digitally before inclusion in the trial.
- 80 • The point-of-care troponin T measurement used in this trial is less sensitive than the high-
81 sensitive troponin T measurements in the hospital laboratory, but when combined with the

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82 other components of the HEART score, the sensitivity of this modified HEART score is still
83 high.

84

85 **Keywords**

86 Acute coronary syndrome, pre-hospital, ambulance, point-of-care troponin, modified HEART score,
87 cost-effectiveness

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88 **Background and rationale**

89 Acute chest pain poses a daily challenge for general practitioners and ambulance paramedics. Since
90 ischemic heart disease is the single most common cause of death worldwide, early risk stratification
91 is crucial.¹ The diagnostic foundation when an ACS is suspected is a combination of a 12-lead
92 electrocardiogram (ECG), clinical evaluation and cardiac troponin measurements.² In patients
93 presenting with an acute ST-segment elevation myocardial infarction (STEMI), the diagnosis is
94 relatively straightforward after obtaining an ECG. However, in more than one-third of the non-ST
95 elevation acute coronary syndrome (NSTEMI) patients, the ECG is normal.² Hence, the vast majority
96 of suspected ACS patients is in need of further evaluation and transferred to the emergency
97 department (ED). Chest pain is therefore one of the most chief complaints in the ED, accounting for
98 5-10% of all ED visits.³ The number of patients visiting the ED with chest pain is increasing, causing
99 overcrowding and even temporary closing of EDs^{4, 5}, which is associated with worse patient
100 outcomes.⁶ In addition to the increasing number of patients, health care costs are also increasing,
101 leading to a growing demand for efficiency.⁷ Only 10-20% of the chest pain patients have an ACS and
102 in patients at low risk for ACS, a NSTEMI is rarely found.⁸⁻¹⁰ Still, these ED visits often include
103 echocardiography, additional non-invasive ischemia detection and prolonged in-hospital stay.³ These
104 empirical strategies are costly, while low-risk patients are not likely to benefit from additional
105 testing.^{8, 11} A simple tool for risk stratification of chest pain patients is the HEART (History, ECG, Age,
106 Risk factors, Troponin) score [figure 1], which is widely validated for use in the ED.¹²⁻¹⁵ In the HEART
107 score, patients can be given 0 to 10 points and patients with 0 to 3 points are at low risk for having an
108 ACS. A recent meta-analysis showed that one-third of the patients presenting with chest pain have a
109 HEART score of 0 to 3, with a risk of 1.9% of developing short-term (30 days to 6 weeks) major
110 adverse cardiac events (MACE). The risk of MACE is even lower, 0.8%, when a modified low-risk, a
111 HEART score of 0 to 3 with a negative troponin, is used.¹⁶ Implementation of the HEART Pathway, a
112 protocol in which early discharge from the ED without further testing is recommended in low-risk
113 patients, resulted in significant cost savings without any MACE in the discharged patients.^{11, 17} The
114 HEART score has proven to have a high degree of reproducibility and an excellent inter-operator
115 agreement in both nurses and doctors.¹⁸ The FAMOUS triage study group has demonstrated that
116 HEART score assessment by ambulance paramedics is feasible and safe.¹⁹ Moreover, ambulance
117 paramedics can adequately assess a complete HEART score, using a point-of-care (POC) troponin T
118 measurement.²⁰ Thus, pre-hospital triage of patients suspected of a NSTEMI is possible. The cost-
119 effectiveness of this pre-hospital strategy has not been investigated yet. Therefore, it remains
120 unclear whether identification of low-risk patients presenting with chest pain in the pre-hospital
121 setting and accordingly not transferring them to the ED will lead to a reduction in health care costs.

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3 122 The aim of the ARTICA trial is to assess the cost-effectiveness of rule-out of a NSTEMI-ACS in low-risk
4 123 patients in the pre-hospital setting.

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7 124 **Methods**

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9 125 *Objectives*

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11 126 The primary objective of the ARTICA trial is to investigate the cost-effectiveness, assessed by health
12 127 care costs after 30 days, of a pre-hospital rule-out strategy for low-risk patients suspected of a NSTEMI-
13 128 ACS, using a modified HEART score and a POC troponin T measurement, compared with standard
14 129 transfer to the ED. The secondary objective is to determine safety of this pre-hospital rule-out
15 130 strategy, defined as the incidence of MACE.

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17 131 *Design and population*

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19 132 The ARTICA trial is a randomized, investigator-initiated, multi-center study. Patients with possible
20 133 ACS are screened for eligibility by trained ambulance paramedics [figure 2]. The patients are
21 134 screened using the Castor Electronic Data Capture (Castor EDC) platform, in which the ambulance
22 135 paramedics register every aspect of the HEAR(T) score and the in- and exclusion criteria in order to
23 136 check for eligibility. The paramedics are able to send the ECG to a cardiologist digitally, in case of
24 137 doubt. After being informed by the ambulance professional and having provided written consent, the
25 138 patients will be subjected to a digital 1:1 randomization in Castor EDC. The standard care arm will be
26 139 transferred to the ED for further evaluation, as is current practice in The Netherlands. The
27 140 intervention arm will undergo a POC troponin T measurement. If the POC troponin T is negative (<40
28 141 ng/L), the care for the patient will be transferred to the general practitioner. The general practitioner
29 142 will further evaluate the symptoms with focus on other non-cardiac causes of the chest pain. In order
30 143 to ensure the safety of this trial, a Data Safety and Monitoring Board (DSMB) has been assigned.
31 144 Furthermore, the study will be independently monitored by the Radboudumc technology center for
32 145 clinical studies according to Good Clinical Practice (GCP).

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34 146 *In- and exclusion criteria [table 1]*

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36 147 Patients are eligible if they are 18 years or older, are suspected of a NSTEMI-ACS, have symptom
37 148 duration of at least two hours and have a modified HEAR(T) score of ≤ 3 . Patients are not eligible if
38 149 they are suspected of another diagnosis requiring evaluation at the ED or if they are unable to be
39 150 fully informed about the trial, e.g. in case of a language barrier or cognitive impairment.

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41 151 *Modified HEART score [figure 3]*

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3 152 In the ARTICA trial a modified HEART score is used. This modification is based on the inclusion of a
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5 153 POC troponin T measurement. Furthermore, when patients are screened for eligibility, only the H, E,
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7 154 A and R components of the HEART score are evaluated. The HEAR score is turned into a HEART score
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9 155 either by POC troponin T measurement in the ambulance, or by high-sensitive troponin T
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11 156 measurement in the ED as part of standard care.

12 157 *Point-of-care troponin T*

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15 158 For the POC troponin T measurement, the Roche cobas h232 is used. The detection limit is 40-2000
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17 159 ng/L. According to Roche, the measurement should be performed in a temperature of 18-32 °C and a
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19 160 relative humidity of 10-80%.²¹ Blood is obtained in a heparinized tube by venipuncture or venous
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21 161 line. Using a Roche Cardiac pipette, 150 µL of blood is applied to the POC troponin T testing strip,
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23 162 after inserting the testing strip in the cobas h232 POC system. After 14 minutes, the results are
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25 163 available.

26 164 *Follow-up*

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28 165 Follow-up will be performed by phone after thirty days, six months and twelve months. All potential
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30 166 events, including hospital admissions, will be verified by review of medical record. Since the primary
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32 167 aim in this study is to assess the cost effectiveness of the pre-hospital rule-out strategy, all health
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34 168 care resources utilized by the patients will be collected in both arms.

35 36 169 *Patient involvement*

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38 170 During the development of the study protocol, a participant of “Harteraad”, a patient advisory
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40 171 council for patients with cardiovascular disease, was involved.

41 42 172 *Study endpoints and cost effectiveness analysis*

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45 173 The primary outcome is health care costs at 30 days. This economic evaluation investigates the cost-
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47 174 effectiveness of full implementation of a pre-hospital rule-out strategy compared to the standard
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49 175 transfer to the hospital to rule out ACS. This will be done from a societal perspective. The empirical
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51 176 cost effectiveness analysis (CEA) timeframe will adhere to the follow-up scheme of the secondary
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53 177 endpoint, being thirty days, six months and twelve months. Cost and quality adjusted life years
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55 178 (QALYs) will be measured on a per patient basis over the relevant time path in which the (most
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57 179 important) differences between both arms manifest themselves. The design of the economic
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59 180 evaluation follows the principles of a cost-utility analysis and adheres to the most recent Dutch
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181 guidelines for performing economic evaluations in health care.²² For reporting, the CHEERS checklist
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182 will be used where relevant.²³ Cost-effectiveness will be expressed in terms of costs per QALY gained.

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3 183 Quality of the health status of the patients is measured with a validated health-related quality of life
4 184 (HRQoL) instrument, the EuroQol-5D (EQ-5D-5L). This HRQoL instrument will be completed by the
5 185 patients and is available in a validated Dutch translation.²⁴ The EQ-5D is a generic HRQoL instrument
6 186 comprising five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
7
8 187 To assess productivity losses associated with chest pain, the Institute for Medical Technology
9 188 Assessment Productivity Cost Questionnaire (iMTA PCQ) will be used.²⁵ Uncertainty will be dealt with
10 189 by one-way sensitivity analysis (deterministic) and by parametric statistics ultimately presenting cost-
11 190 effectiveness acceptability curves. To ensure the quality of the economic evaluations, the
12 191 Radboudumc Technology Center Health Economics will be involved. Secondary endpoints will
13 192 determine the safety of the early rule-out strategy at 30 days, six months and twelve months, by
14 193 determining the incidence of MACE. MACE is defined as acute coronary syndrome (ACS), unplanned
15 194 revascularization and all cause death. Subgroup analyses will be performed according to gender,
16 195 assessment of the HEART score by paramedics or cardiologists, diabetic status and female-specific
17 196 risk factors.

197 *Sample size calculation*

198 The cost of hospital treatment is determined by the Dutch *Diagnose Behandel Combinatie (DBC)*
199 hospital reimbursement system and the *DBC* information system, similar to the international
200 diagnosis related groupings system (DRG).²⁶ When discharged from the ED after a negative
201 evaluation for ACS, 50% will undergo further outpatient evaluation. This percentage and the
202 percentages of further diagnostic testing (echocardiography and treadmill: 30%, non-invasive
203 ischemia detection: 10% and coronary angiography: 5%) are all based on the 2017 DBC
204 administration in the Radboudumc. In the pre-hospital rule out group, cost prices for diagnostics by
205 the cardiologist (e.g. non-invasive ischemia detection and coronary angiography) are included, even
206 when the probability of undergoing these tests is low. Based on the aforementioned percentages ,
207 the cost difference between both groups is estimated to be € 507. For the primary outcome we
208 assume a small effect size (0,2) and equal standard deviations in both arms of the trial. Group sample
209 sizes of 392 and 392 achieve 80% power to detect the difference of € 507 between both groups with
210 a significance level (alpha) of 0,05 using a two-sided two-sample t-test. To compensate for any loss of
211 follow-up, the sample size is enlarged by 10% to a total of 866 patients. The estimated inclusion rate
212 will be one patient per day.

213 **Discussion**

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3 214 The majority of patients suspected of a non ST-segment elevation acute coronary syndrome (NSTE-
4 215 ACS) is currently presented at emergency departments (ED) to rule out an ACS. EDs are increasingly
5 216 overcrowded and ambulance services are confronted with more patient transfers. However, in low-
6 217 risk patients an ACS is rarely found.¹⁰
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10 218 *Cost-effectiveness*

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13 219 Health care costs are increasing because of multiple factors, such as increases in health care service
14 220 price and intensity, population growth and aging.⁷ Low-risk patients suspected of a NSTE-ACS often
15 221 require an overnight stay in the hospital to undergo additional stress testing and imaging, but are not
16 222 likely to benefit from additional testing.⁸ In the year 2018 in the Netherlands, over one-fourth of the
17 223 patients who were evaluated for chest pain and eventually discharged with benign non-cardiac chest
18 224 pain were admitted to the hospital for at least one day. The average price for these admissions was €
19 225 1.355 in 2018 and is € 1.410 in 2019, while it was € 1.220 in 2012.⁵ The price for visiting the general
20 226 practitioner (GP) for 5-20 minutes is € 9,97 during working hours and € 117,50 after working hours.
21 227 However, it remains unclear how often the GPs will order additional tests or refer the patients to the
22 228 ED or outpatient clinic, after a NSTE-ACS has been ruled out in the ambulance. Furthermore, the
23 229 health care resource consumption in these patients represents the degree of reassurance in patients
24 230 and in health care professionals (e.g. the general practitioner).
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34 231 *The pre-hospital HEART score*

35 232 Recent studies have shown the safety of identifying low-risk chest pain patients in a pre-hospital
36 233 environment.^{19, 20} The FAMOUS triage study group has demonstrated that identifying low-risk chest
37 234 pain patients by ambulance staff using a modified HEART score is feasible and safe when using a
38 235 high-sensitive troponin T measurement in the hospital laboratory.¹⁹ They have also shown that using
39 236 a point of care (POC) troponin T measurement to turn the HEAR score into the HEART score in the
40 237 pre-hospital setting has important additional predictive value.²⁷ Furthermore, they have shown that
41 238 in patients suspected of NSTE-ACS, HEART score assessment using a POC troponin T measurement by
42 239 ambulance paramedics is accurate in identifying low-risk patients.²⁰
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50 240 *POC troponin T*

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52 241 The POC troponin T measured with the Roche cobas h232 yields very good analytical concordance
53 242 with high sensitive troponin T.²⁸ This POC-test can be used as a bedside test with a fast turn-around
54 243 time (<15 minutes) and was also used by the FAMOUS triage study group. The POC troponin T test
55 244 has already shown to have a high predictive value for mortality in high-risk patient.²⁹
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60 245 *The general practitioner*

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3 246 In the Netherlands, the GP is a gatekeeper to hospital- and specialist care. GPs offer out-of-hour
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5 247 services by GP cooperatives across the whole country.³⁰ Therefore, implementation of a rule-out
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7 248 strategy for NSTEMI-ACS in the ambulance is possible, without leaving the patients to fend for
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9 249 themselves when they are not transferred to the ED.

10 250 **Conclusion**

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13 251 The ARTICA trial is the first randomized trial on cost-effectiveness of an early rule-out strategy for
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15 252 low-risk patients suspected of an acute coronary syndrome, using a point-of-care troponin
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17 253 measurement outside the hospital setting. The results of this study are expected to have a major
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19 254 impact on the healthcare organization of chest pain patients.

20 255 **Ethics and dissemination**

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23 256 This trial has been accepted by the Medical Research Ethics Committee region Arnhem-Nijmegen.
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25 257 The results of this trial will be disseminated in one main paper and in additional papers with pre-
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27 258 defined subgroup analyses.

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31 260 The study is supported by ZonMw, grant number 852001942.

32 261 **Conflict of interest**

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35 262 The authors declare no conflict of interest.

36 263 **Authors' contributions**

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39 264 During the development of the study protocol, prof N. van Royen, C. Camaro and G.W.A. Aarts
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41 265 contributed equally. The other authors provided advice and comments.

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Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none">- Age \geq 18 years- Suspected NSTEMI-ACS- Symptom duration of at least two hours- Modified HEAR(T) score \leq 3- Provided written informed consent	<ul style="list-style-type: none">- ST-segment elevation- Suspected non-cardiac cause of the symptoms requiring evaluation at the emergency department- Comatose state, defined as an GCS $<$ 8- Known cognitive impairment- Pregnancy- Cardiogenic shock, defined as systolic blood pressure $<$90 mmHg, heart rate $>$ 100 bpm and peripheral oxygen saturation $<$90%- Syncope- Signs of heart failure- Heart rhythm disorders and second or third degree atrioventricular block- Known end-stage renal disease (dialysis and/or MDRD $<$ 30 ml/min)- Suspected aortic dissection or pulmonary embolism- Confirmed AMI, PCI or CABG $<$30 days prior to inclusion- Communication issues with the patient and/or language barrier- Decision of a present general practitioner to evaluate the patient at the emergency department- Decision of the consultant cardiologist to evaluate the patient at the emergency department- Any significant medical or mental condition, which in the investigator's opinion may interfere with optimal participation in the study

HEART

HEART score for chest pain patients

<u>H</u>istory (Anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
<u>E</u>CG	Significant ST-deviation	2	
	Non-specific repolarisation disturbance / LBBB / PM	1	
	Normal	0	
<u>A</u>ge	≥ 65 years	2	
	45 – 65 years	1	
	≤ 45 years	0	
<u>R</u>isk factors	≥ 3 risk factors <i>or</i> history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
<u>T</u>roponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

Risk factors for atherosclerotic disease:

Hypercholesterolemia

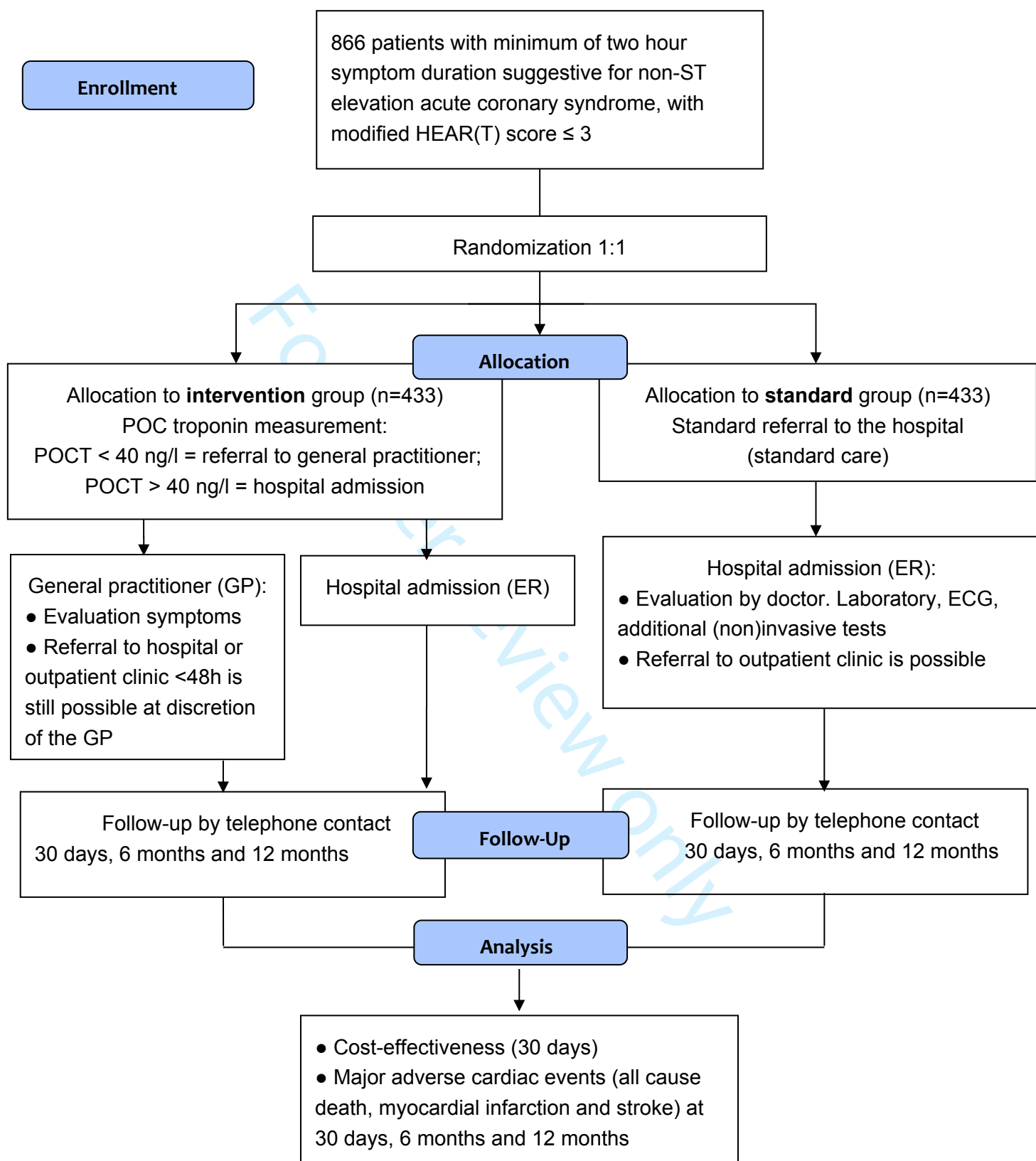
Cigarette smoking

Hypertension

Positive family history

Diabetes Mellitus

Obesity (BMI>30)





ARTICA

RANDOMIZED TRIAL

Modified HEART Score

History	Highly suspicious	2
	Moderately suspicious	1
	Slightly suspicious	0
ECG	Significant ST-segment depression	2
	Non specific repolarization disturbance	1
	LBBB or PM	1
	Normal	0
Age	≥65 years	2
	45-65 years	1
	<45 years	0
Risk factors	≥3 risk factors <i>OR</i> history of atherosclerotic disease	2
	1 or 2 risk factors	1
	No risk factors	0
Troponin T point of care	>60 ng/L	2
	40-60 ng/L	1
	<40 ng/L	0
Risk factors: <ul style="list-style-type: none"> • Smoking • Hypertension • Diabetes mellitus • Obesity (BMI > 30 kg/m²) • Hypercholesterolemia • Positive family history 		

BMJ Open

Acute rule out of non ST-segment elevation acute coronary syndrome in the (pre)hospital setting by HEART score assessment and a single point of care troponin: Rationale and design of the ARTICA randomized trial.

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Keywords:	Acute coronary syndrome, Pre-hospital, Ambulance, Point-of-care troponin, modified HEART score, Cost-effectiveness

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3 1 **Acute rule out of non ST-segment elevation acute coronary syndrome in the**
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5 2 **(pre)hospital setting by HEART score assessment and a single point of care**
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7 3 **troponin: Rationale and design of the ARTICA randomized trial.**
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48 Abstract

49 *Introduction:* Because of the lack of pre-hospital protocols to rule out a non-ST elevation acute
50 coronary syndrome (NSTEMI-ACS), patients with chest pain are often transferred to the emergency
51 department (ED) for thorough evaluation. However, in low-risk patients, an acute coronary syndrome
52 (ACS) is rarely found, resulting in unnecessary health-care consumption. Using the HEART (History,
53 Electrocardiogram, Age, Risk factors and Troponin) score, low-risk patients are easily identified.
54 When a point-of-care (POC) troponin measurement is included in the HEART score, an ACS can
55 adequately be ruled out in low-risk patients in the pre-hospital setting. However, it remains unclear
56 whether a pre-hospital rule-out strategy using the HEART score and a POC troponin measurement in
57 suspected NSTEMI-ACS patients is cost-effective.

58 *Methods and analysis:* The ARTICA trial is a randomized trial in which the primary objective is to
59 investigate the cost-effectiveness after 30 days of an early rule-out strategy for low-risk patients
60 suspected of a NSTEMI-ACS, using a modified HEART score including a POC troponin T measurement.
61 Patients are included by ambulance paramedics and 1:1 randomized for 1) presentation at the ED
62 (control group) or 2) POC troponin T measurement (intervention group) and transfer of the care to
63 the general practitioner in case of a low troponin T value. In total, 866 patients will be included.
64 Follow-up will be performed after 30 days, 6 months and 12 months.

65 *Ethics and dissemination:* This trial has been accepted by the Medical Research Ethics Committee
66 region Arnhem-Nijmegen. The results of this trial will be disseminated in one main paper and in
67 additional papers with subgroup analyses.

68 *Trial registration number:* Netherlands Trial Register (NL7148)

70 Article summary

71 *Strengths and limitations of this study*

- 72 • The ARTICA trial is the first randomized trial with a primary focus on cost-effectiveness of a
73 pre-hospital rule-out strategy for low-risk patients suspected of an acute coronary syndrome.
- 74 • When randomized for point-of-care troponin T measurement, the ambulance paramedics
75 can rule out an acute coronary syndrome on the spot and therefore comfort the patient
76 without having to transfer them to the emergency department.
- 77 • The results of this study will provide important insights in the effects of ruling out an acute
78 coronary syndrome without transfer to the hospital.
- 79 • In order to minimize the chance of miscalculation of the HEART score, the ambulance
80 paramedics have to register every component of the HEART score digitally before inclusion in
81 the trial.

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3 82 • The point-of-care troponin T measurement used in this trial is less sensitive than the high-
4 83 sensitive troponin T measurements in the hospital laboratory, but when combined with the
5 84 other components of the HEART score, the sensitivity of this modified HEART score is still
6 85 high.
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13 87 **Keywords**

14
15 88 Acute coronary syndrome, pre-hospital, ambulance, point-of-care troponin, modified HEART score,
16 89 cost-effectiveness
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90 Introduction

91 Acute chest pain poses a daily challenge for general practitioners and ambulance paramedics. Since
92 ischemic heart disease is the single most common cause of death worldwide, early risk stratification
93 is crucial.¹ The diagnostic foundation when an acute coronary syndrome (ACS) is suspected is a
94 combination of a 12-lead electrocardiogram (ECG), clinical evaluation and cardiac troponin
95 measurements.² In patients presenting with an acute ST-segment elevation myocardial infarction
96 (STEMI), the diagnosis is relatively straightforward after obtaining an ECG. However, in more than
97 one-third of the non-ST elevation acute coronary syndrome (NSTEMI) patients, the ECG is normal.²
98 Hence, the vast majority of suspected ACS patients is in need of further evaluation and transferred to
99 the emergency department (ED). Chest pain is therefore one of the most chief complaints in the ED,
100 accounting for up to over 10% of all ED visits.³⁻⁵ The number of patients visiting the ED is increasing
101 and ED overcrowding is a global public health phenomenon, which is associated with worse patient
102 outcomes.⁵⁻⁷ In addition to the increasing number of patients, health care costs and health
103 expenditure per capita are also increasing, leading to a growing demand for efficiency.^{8,9} Only 10-
104 20% of the chest pain patients have an ACS and in patients at low risk for ACS, a NSTEMI is rarely
105 found.¹⁰⁻¹² Still, these ED visits often include echocardiography, additional non-invasive ischemia
106 detection and prolonged in-hospital stay.^{10,13-15} These empirical strategies are costly, while low-risk
107 patients are not likely to benefit from additional testing.^{10,15,16} A simple tool for risk stratification of
108 chest pain patients is the HEART (History, ECG, Age, Risk factors, Troponin) score [figure 1], which is
109 widely validated for use in the ED.^{17,18} In the HEART score, patients can be given 0 to 10 points and
110 patients with 0 to 3 points are at low risk for having an ACS. A recent meta-analysis showed that one-
111 third of the patients presenting with chest pain have a HEART score of 0 to 3, with a risk of 1.9% of
112 developing short-term (30 days to 6 weeks) major adverse cardiac events (MACE).¹⁹ The risk of MACE
113 is even lower, 0.8%, when a modified low-risk HEART score is used, in which patients with a HEART
114 score of 0 to 3 are only classified as low-risk patients if the troponin value is below the 99th
115 percentile.¹⁹ Implementation of the HEART Pathway, a protocol in which early discharge from the ED
116 without further testing is recommended in low-risk patients, resulted in significant cost savings
117 without any MACE in the discharged patients.^{16,20} The HEART score has proven to have a high degree
118 of reproducibility and an excellent inter-operator agreement in both nurses and doctors.²¹ The
119 FAMOUS triage study group has demonstrated that HEART score assessment by ambulance
120 paramedics is feasible and safe.²² Moreover, ambulance paramedics can adequately assess a
121 complete HEART score, using a point-of-care (POC) troponin T measurement.²³ Thus, pre-hospital
122 triage of patients suspected of a NSTEMI is possible. The cost-effectiveness of this pre-hospital
123 strategy has not been investigated yet. Therefore, it remains unclear whether identification of low-

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3 124 risk patients presenting with chest pain in the pre-hospital setting and accordingly not transferring
4 125 them to the ED will lead to a reduction in health care costs. The aim of the ARTICA trial is to assess
5 126 the cost-effectiveness of rule-out of a NSTEMI-ACS in low-risk patients in the pre-hospital setting.
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8 9 127 **Methods and Analysis**

10 11 128 *Objectives*

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14 129 The primary objective of the ARTICA trial is to investigate the cost-effectiveness, assessed by health
15 130 care costs after 30 days, of a pre-hospital rule-out strategy for low-risk patients suspected of a NSTEMI-
16 131 ACS, using a modified HEART score and a POC troponin T measurement, compared with standard
17 132 transfer to the ED. The secondary objective is to determine safety of this pre-hospital rule-out
18 133 strategy, defined as the incidence of MACE.
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22 23 134 *Design and population*

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25 135 The ARTICA trial is a randomized, investigator-initiated, multi-center study. Patients with possible
26 136 ACS are screened for eligibility by trained ambulance paramedics [figure 2]. The patients are
27 137 screened using the Castor Electronic Data Capture (Castor EDC) platform, in which the ambulance
28 138 paramedics register every aspect of the HEART score (the HEART score without the Troponin
29 139 component) and the in- and exclusion criteria in order to check for eligibility. The paramedics are
30 140 able to send the ECG to a cardiologist digitally, in case of doubt. After being informed by the
31 141 ambulance professional and having provided written consent, the patients will be subjected to a
32 142 digital 1:1 randomization in Castor EDC. The standard care arm will be transferred to the ED for
33 143 further evaluation, as is current practice in The Netherlands. The intervention arm will undergo a
34 144 POC troponin T measurement. If the POC troponin T is negative (<40 ng/L), the care for the patient
35 145 will be transferred to the general practitioner. The general practitioner will further evaluate the
36 146 symptoms with focus on other non-cardiac causes of the chest pain. If the POC troponin T is elevated
37 147 (≥ 40 ng/L), the patient will be transferred to the ED, even if the total HEART score is less than or
38 148 equal to 3. In order to ensure the safety of this trial, a Data Safety and Monitoring Board (DSMB) has
39 149 been assigned. Furthermore, the study will be independently monitored by the Radboudumc
40 150 technology center for clinical studies according to Good Clinical Practice (GCP).
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52 53 151 *In- and exclusion criteria [table 1]*

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> - Age ≥ 18 years - Suspected NSTEMI-ACS 	<ul style="list-style-type: none"> - ST-segment elevation - Suspected non-cardiac cause of the

<ul style="list-style-type: none"> - Symptom duration of at least two hours - Modified HEAR(T) score ≤ 3 - Provided written informed consent 	<ul style="list-style-type: none"> symptoms requiring evaluation at the emergency department - Comatose state, defined as an GCS < 8 - Known cognitive impairment - Pregnancy - Cardiogenic shock, defined as systolic blood pressure < 90 mmHg, heart rate > 100 bpm and peripheral oxygen saturation $< 90\%$ - Syncope - Signs of heart failure - Heart rhythm disorders and second or third degree atrioventricular block - Known end-stage renal disease (dialysis and/or MDRD < 30 ml/min) - Suspected aortic dissection or pulmonary embolism - Confirmed AMI, PCI or CABG < 30 days prior to inclusion - Communication issues with the patient and/or language barrier - Decision of a present general practitioner to evaluate the patient at the emergency department - Decision of the consultant cardiologist to evaluate the patient at the emergency department - Any significant medical or mental condition, which in the investigator's opinion may interfere with optimal participation in the study
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152 **Table 1. In- and exclusion criteria. NSTEMI-ACS = non ST-segment elevation acute coronary syndrome,**
 153 **GCS = Glasgow Coma Scale, MDRD = Modification of Diet in Renal Disease formula, AMI = acute**
 154 **myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass**
 155 **grafting**

156 Patients are eligible if they are 18 years or older, are suspected of a NSTEMI-ACS, have symptom
 157 duration of at least two hours and have a modified HEAR score of ≤ 3 . Patients are not eligible if they

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2
3 158 are suspected of another diagnosis requiring evaluation at the ED or if they are unable to be fully
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5 159 informed about the trial, e.g. in case of a language barrier or cognitive impairment.
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7 160 *Modified HEART score [figure 3]*
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10 161 In the ARTICA trial a modified HEART score is used. This modification is based on the inclusion of a
11
12 162 POC troponin T measurement. Furthermore, when patients are screened for eligibility, only the H, E,
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14 163 A and R components of the HEART score are evaluated. The HEART score is turned into a HEART score
15
16 164 either by POC troponin T measurement in the ambulance, or by high-sensitive troponin T
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18 165 measurement in the ED as part of standard care.

19 166 *Point-of-care troponin T*
20

21 167 For the POC troponin T measurement, the Roche cobas h232 is used. The detection limit is 40-2000
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23 168 ng/L. According to Roche, the measurement should be performed in a temperature of 18-32 °C and a
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25 169 relative humidity of 10-80%.²⁴ Blood is obtained in a heparinized tube by venipuncture or venous
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27 170 line. Using a Roche Cardiac pipette, 150 µL of blood is applied to the POC troponin T testing strip,
28
29 171 after inserting the testing strip in the cobas h232 POC system. After 14 minutes, the results are
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31 172 available.
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33 173 *Follow-up*
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35 174 Follow-up will be performed by phone after thirty days, six months and twelve months. All potential
36
37 175 events, including hospital admissions, will be verified by review of medical record. Since the primary
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39 176 aim in this study is to assess the cost effectiveness of the pre-hospital rule-out strategy, all health
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41 177 care resources utilized by the patients will be collected in both arms.
42

43 178 *Patient involvement*
44

45 179 During the development of the study protocol, a participant of "Hareraad", a patient advisory
46
47 180 council for patients with cardiovascular disease, was involved. This patient representative is also
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49 181 involved during the duration of the trial and will be consulted in case of unpredicted adverse events.
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51 182 *Study endpoints and cost effectiveness analysis*
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53 183 The primary outcome is health care costs at 30 days. This economic evaluation investigates the cost-
54
55 184 effectiveness of full implementation of a pre-hospital rule-out strategy compared to the standard
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57 185 transfer to the hospital to rule out ACS. This will be done from a societal perspective. The empirical
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59 186 cost effectiveness analysis (CEA) timeframe will adhere to the follow-up scheme of the secondary
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187 endpoint, being thirty days, six months and twelve months. Cost and quality adjusted life years

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3 188 (QALYs) will be measured on a per patient basis over the relevant time path in which the (most
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5 189 important) differences between both arms manifest themselves. The design of the economic
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7 190 evaluation follows the principles of a cost-utility analysis and adheres to the most recent Dutch
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9 191 guidelines for performing economic evaluations in health care.²⁵ For reporting, the CHEERS checklist
10
11 192 will be used where relevant.²⁶ Cost-effectiveness will be expressed in terms of costs per QALY gained.
12
13 193 Quality of the health status of the patients is measured with a validated health-related quality of life
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15 194 (HRQoL) instrument, the EuroQoL-5D (EQ-5D-5L). This HRQoL instrument will be completed by the
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17 195 patients and is available in a validated Dutch translation.²⁷ The EQ-5D is a generic HRQoL instrument
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19 196 comprising five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
20
21 197 To assess productivity losses associated with chest pain, the Institute for Medical Technology
22
23 198 Assessment Productivity Cost Questionnaire (iMTA PCQ) will be used.²⁸ Uncertainty will be dealt with
24
25 199 by one-way sensitivity analysis (deterministic) and by parametric statistics ultimately presenting cost-
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27 200 effectiveness acceptability curves. To ensure the quality of the economic evaluations, the
28
29 201 Radboudumc Technology Center Health Economics will be involved. Secondary endpoints will
30
31 202 determine the safety of the early rule-out strategy at 30 days, six months and twelve months, by
32
33 203 determining the incidence of MACE. MACE is defined as acute coronary syndrome (ACS), unplanned
34
35 204 revascularization and all cause death. Subgroup analyses will be performed according to gender,
36
37 205 assessment of the HEART score by paramedics or cardiologists, diabetic status and female-specific
38
39 206 risk factors.

207 *Sample size calculation*

208 The cost of hospital treatment is determined by the Dutch *Diagnose Behandel Combinatie (DBC)*
209 hospital reimbursement system and the *DBC* information system, similar to the international
210 diagnosis related groupings system (DRG).²⁹ When discharged from the ED after a negative
211 evaluation for ACS, 50% will undergo further outpatient evaluation. This percentage and the
212 percentages of further diagnostic testing (echocardiography and treadmill: 30%, non-invasive
213 ischemia detection: 10% and coronary angiography: 5%) are all based on the 2017 DBC
214 administration in the Radboudumc. In the pre-hospital rule out group, cost prices for diagnostics by
215 the cardiologist (e.g. non-invasive ischemia detection and coronary angiography) are included, even
216 when the probability of undergoing these tests is low. Based on the aforementioned percentages ,
217 the cost difference between both groups is estimated to be € 507. For the primary outcome we
218 assume a small effect size (0,2) and equal standard deviations in both arms of the trial. Group sample
219 sizes of 392 and 392 achieve 80% power to detect the difference of € 507 between both groups with
220 a significance level (alpha) of 0,05 using a two-sided two-sample t-test. To compensate for any loss of

221 follow-up, the sample size is enlarged by 10% to a total of 866 patients. The estimated inclusion rate
222 will be one patient per day.

223 **Discussion**

224 The majority of patients suspected of a non ST-segment elevation acute coronary syndrome (NSTE-
225 ACS) is currently presented at emergency departments (ED) to rule out an ACS. EDs are increasingly
226 overcrowded and ambulance services are confronted with more patient transfers. However, in low-
227 risk patients an ACS is rarely found.¹²

228 *Cost-effectiveness*

229 Health care costs are increasing because of multiple factors, such as increases in health care service
230 price and intensity, population growth and aging.⁸ Low-risk patients suspected of a NSTE-ACS often
231 require an overnight stay in the hospital to undergo additional stress testing and imaging, but are not
232 likely to benefit from additional testing.¹⁰ Even in pre-hospital-adjudicated low-risk patients, acute
233 healthcare utilization and costs are high, with limited added value.¹⁵ In the year 2018 in the
234 Netherlands, over one-fourth of the patients who were evaluated for chest pain and eventually
235 discharged with benign non-cardiac chest pain were admitted to the hospital for at least one day.
236 The average price for these admissions was € 1.355 in 2018 and is € 1.410 in 2019, while it was €
237 1.220 in 2012.³⁰ The price for visiting the general practitioner (GP) for 5-20 minutes is € 9,97 during
238 working hours and € 117,50 after working hours. However, it remains unclear how often the GPs will
239 order additional tests or refer the patients to the ED or outpatient clinic, after a NSTE-ACS has been
240 ruled out in the ambulance. Furthermore, the health care resource consumption in these patients
241 represents the degree of reassurance in patients and in health care professionals (e.g. the general
242 practitioner).

243 *The pre-hospital HEART score*

244 Recent studies have shown the safety of identifying low-risk chest pain patients in a pre-hospital
245 environment.^{22, 23} The FAMOUS triage study group has demonstrated that identifying low-risk chest
246 pain patients by ambulance staff using a modified HEART score is feasible and safe when using a
247 high-sensitive troponin T measurement in the hospital laboratory.²² They have also shown that using
248 a point of care (POC) troponin T measurement to turn the HEAR score into the HEART score in the
249 pre-hospital setting has important additional predictive value.³¹ Furthermore, they have shown that
250 in patients suspected of NSTE-ACS, HEART score assessment using a POC troponin T measurement by
251 ambulance paramedics is accurate in identifying low-risk patients.²³

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3 252 *POC troponin T*
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6 253 The POC troponin T measured with the Roche cobas h232 yields very good analytical concordance
7 254 with high sensitive troponin T.³² This POC-test can be used as a bedside test with a fast turn-around
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9 255 time (<15 minutes) and was also used by the FAMOUS triage study group. The POC troponin T test
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11 256 has already shown to have a high predictive value for mortality in high-risk patient.³³
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13 257 *The general practitioner*
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16 258 In the Netherlands, the GP is a gatekeeper to hospital- and specialist care. GPs offer out-of-hour
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18 259 services by GP cooperatives across the whole country.³⁴ Therefore, implementation of a rule-out
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20 260 strategy for NSTEMI-ACS in the ambulance is possible, without leaving the patients to fend for
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22 261 themselves when they are not transferred to the ED.

23 262 **Conclusion**
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26 263 The ARTICA trial is the first randomized trial on cost-effectiveness of an early rule-out strategy for
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28 264 low-risk patients suspected of an acute coronary syndrome, using a point-of-care troponin
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30 265 measurement outside the hospital setting. The results of this study are expected to have a major
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32 266 impact on the healthcare organization of chest pain patients.

33 267 **Ethics and dissemination**
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36 268 This trial has been accepted by the Medical Research Ethics Committee region Arnhem-Nijmegen.
37
38 269 The results of this trial will be published in peer-reviewed journals and presented at national and
39
40 270 international conferences.

41 271 **Funding**
42

43
44 272 The study is supported by ZonMw, grant number 852001942.
45

46 273 **Conflict of interest**
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48
49 274 The authors declare no conflict of interest.
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51 275 **Authors' contributions**
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53
54 276 CC conceived the idea. GA, CC, RvG, EC, RvK, PD and NvR designed the study methodology. EA
55
56 277 designed the economical and statistical analyses. GA and CC drafted the manuscript. RvG, EC, RvK,
57
58 278 PD, PvG, EA, PG, MR, OO, MG and NvR provided critical revisions and substantial intellectual input.
59
60 280 GA takes full responsibility for the data acquisition. All authors agreed with the final version of the
manuscript.

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377 **Figure caption**

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3 378 **Figure 1.**

4 379 The original HEART score, with permission of the authors. ECG = electrocardiogram, LBBB = left
5 380 bundle branch block, PM = pacemaker, BMI = body mass index.

7
8 381 **Figure 2.**

9 382 The ARTICA trial flow chart. HEAR score = History, Electrocardiogram, Age, Risk factors score, POC =
10 383 Point of care, POCT = Point of care troponin, ED = Emergency department, GP = General practitioner.

12 384 **Figure 3.**

13 385 The modified HEART score in the ARTICA trial. ECG = electrocardiogram, LBBB = left bundle branch
14 386 block, PM = pacemaker, BMI = body mass index.

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For peer review only

HEART

HEART score for chest pain patients

<u>H</u>istory (Anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
<u>E</u>CG	Significant ST-deviation	2	
	Non-specific repolarisation disturbance / LBBB / PM	1	
	Normal	0	
<u>A</u>ge	≥ 65 years	2	
	45 – 65 years	1	
	≤ 45 years	0	
<u>R</u>isk factors	≥ 3 risk factors <i>or</i> history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
<u>T</u>roponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

Risk factors for atherosclerotic disease:

Hypercholesterolemia

Cigarette smoking

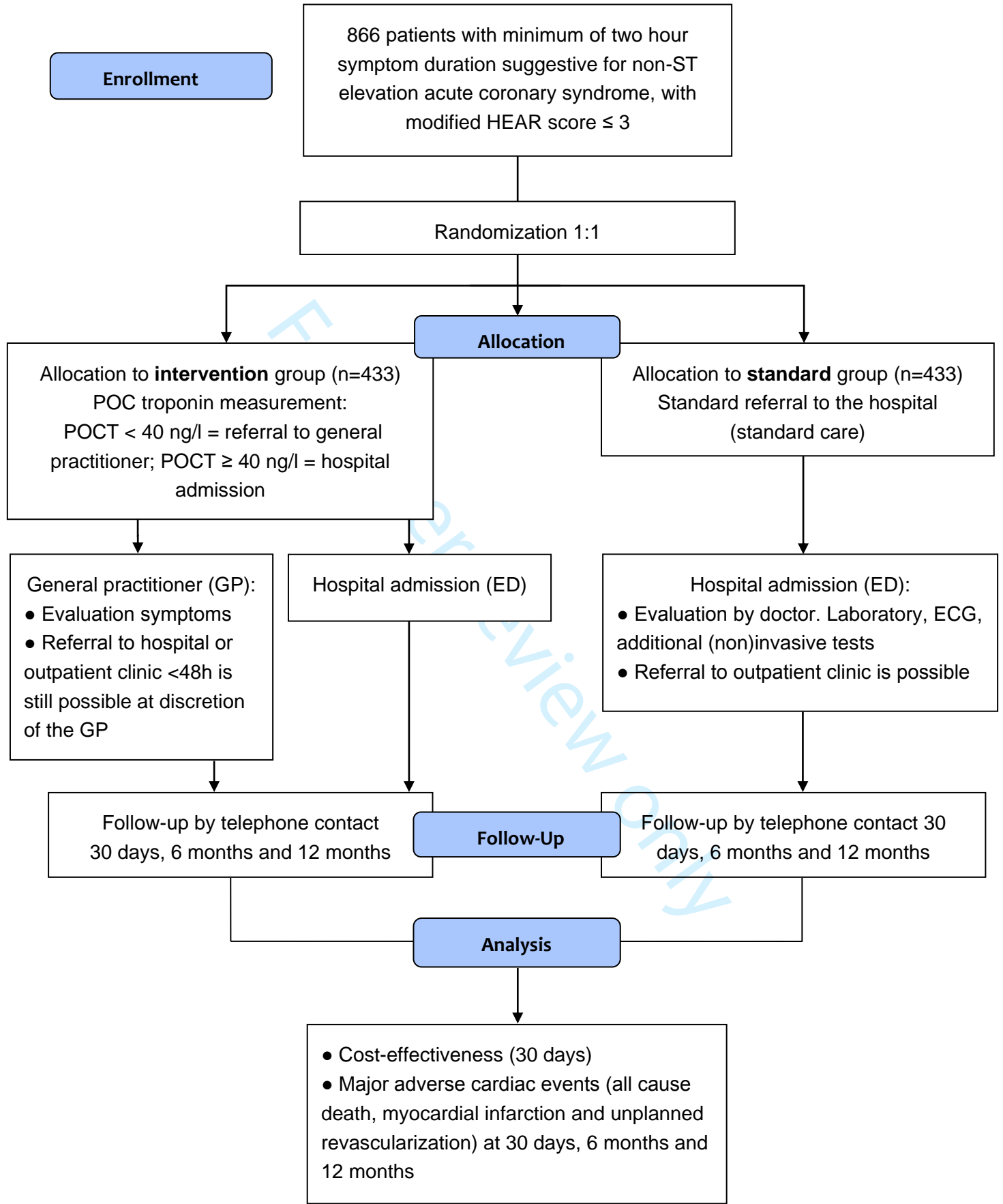
Hypertension

Positive family history

Diabetes Mellitus

Obesity (BMI>30)

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ARTICA

RANDOMIZED TRIAL

Modified HEART Score

History	Highly suspicious	2
	Moderately suspicious	1
	Slightly suspicious	0
ECG	Significant ST-segment depression	2
	Non specific repolarization disturbance	1
	LBBB or PM	1
	Normal	0
Age	≥65 years	2
	45-65 years	1
	<45 years	0
Risk factors	≥3 risk factors <i>OR</i> history of atherosclerotic disease	2
	1 or 2 risk factors	1
	No risk factors	0
Troponin T point of care	>60 ng/L	2
	40-60 ng/L	1
	<40 ng/L	0
Risk factors: <ul style="list-style-type: none"> • Smoking • Hypertension • Diabetes mellitus • Obesity (BMI > 30 kg/m²) • Hypercholesterolemia • Positive family history 		



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <u>Page 1, lines 1-3</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <u>Page 3, line 68</u>
	2b	All items from the World Health Organization Trial Registration Data Set https://www.trialregister.nl/trial/7148
Protocol version	3	Date and version identifier <u>Issue date:</u> 10 March 2019 <u>Version:</u> 1.9 The trial started while using protocol version 1.8. Reason for amendment: Addition of a second region in which the trial is conducted.
Funding	4	Sources and types of financial, material, and other support <u>Page 11, line 272</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <u>Page 11, lines 276-277</u>
	5b	Name and contact information for the trial sponsor <u>Trial sponsor:</u> Radboudumc Department of Cardiology Contact name: Prof. N. van Royen Address: Geert Grooteplein Zuid 10, 6525 GA Nijmegen Email: Niels.vanRoyen@radboudumc.nl

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- 5c Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities

The design of the study underwent peer review in order to gain funding by ZonMw. However, the funding source will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

- 5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Principal investigator and research physician

Design and conduct of ARTICA
Preparation of protocol and revisions
Preparation of case report forms and patient information
Education of paramedics
Maintenance of trial IT system, website and data entry
Follow-up of patients
Organising steering committee meetings
Publication of study reports
Responsible for trial master file
Budget administration and contractual issues with ambulance regions

ARTICA trial team

(see title page and protocol for members)
Agreement of final protocol
Reviewing progress of study and if necessary agreeing changes to the protocol.

Patient representative

Page 7, lines 179-181

Ambulance paramedics

Patient selection, screening, randomisation and primary data entry

Monitor

Data verification

Introduction

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- Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
Page 5, lines 91-126

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2		6b	Explanation for choice of comparators
3			<u>Pages 5-6, lines 118-126</u>
4			
5	Objectives	7	Specific objectives or hypotheses
6			<u>Page 6, lines 129-133</u>
7			
8	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
9			<u>Page 6, lines 135-150</u>
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14	Methods: Participants, interventions, and outcomes		
15			
16	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
17			<u>Page 6, lines 135-150</u>
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23			<u>List of study sites:</u> http://www.ARTICAtrial.nl
24	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)
25			<u>Pages 6-8, lines 151-159</u>
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30	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
31			<u>Page 6, lines 142-148</u>
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35		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)
36			<u>Not applicable.</u>
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41		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
42			<u>Not applicable.</u>
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46		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
47			<u>Not applicable.</u>
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50	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
51			<u>Pages 8-9, lines 183-206</u>
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2	Participant	13	Time schedule of enrolment, interventions (including any run-ins and
3	timeline		washouts), assessments, and visits for participants. A schematic
4			diagram is highly recommended (see Figure)
5			<u>Page 8, lines 174-177</u>
6			<u>Figure 2</u>
7			
8	Sample size	14	Estimated number of participants needed to achieve study objectives
9			and how it was determined, including clinical and statistical
10			assumptions supporting any sample size calculations
11			<u>Pages 9-10, lines 208-222</u>
12			
13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
14			target sample size
15			<u>Education of ambulance paramedics, frequent newsletters and</u>
16			<u>an instruction video (http://www.ARTICAtrial.nl).</u>
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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24	Sequence	16a	Method of generating the allocation sequence (eg, computer-
25	generation		generated random numbers), and list of any factors for stratification.
26			To reduce predictability of a random sequence, details of any planned
27			restriction (eg, blocking) should be provided in a separate document
28			that is unavailable to those who enrol participants or assign
29			interventions
30			<u>Page 6, lines 140-142</u>
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33	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
34	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
35	mechanism		describing any steps to conceal the sequence until interventions are
36			assigned
37			<u>Page 6, lines 140-142</u>
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40	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
41			and who will assign participants to interventions
42			<u>Page 6, lines 135-142</u>
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45	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
46	(masking)		participants, care providers, outcome assessors, data analysts), and
47			how
48			<u>Not applicable</u>
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51		17b	If blinded, circumstances under which unblinding is permissible, and
52			procedure for revealing a participant's allocated intervention during
53			the trial
54			<u>Not applicable</u>
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Methods: Data collection, management, and analysis

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2	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
3	methods		trial data, including any related processes to promote data quality (eg,
4			duplicate measurements, training of assessors) and a description of
5			study instruments (eg, questionnaires, laboratory tests) along with
6			their reliability and validity, if known. Reference to where data
7			collection forms can be found, if not in the protocol
8			<u>Page 8, lines 174-177</u>
9			<u>Page 9, lines 193-198</u>
10			
11		18b	Plans to promote participant retention and complete follow-up,
12			including list of any outcome data to be collected for participants who
13			discontinue or deviate from intervention protocols
14			<u>Page 8, lines 174-177</u>
15			
16	Data	19	Plans for data entry, coding, security, and storage, including any
17	management		related processes to promote data quality (eg, double data entry;
18			range checks for data values). Reference to where details of data
19			management procedures can be found, if not in the protocol
20			<u>Page 6, lines 136-139</u>
21			<u>Protocol version 1.9, chapter 10.1 (Handling and storage of data</u>
22			<u>and documents) and 10.2 (Monitoring and Quality Assurance)</u>
23			
24	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
25	methods		Reference to where other details of the statistical analysis plan can be
26			found, if not in the protocol
27			<u>Pages 8-9, lines 183-206</u>
28		20b	Methods for any additional analyses (eg, subgroup and adjusted
29			analyses)
30			<u>Page 9, lines 204-206</u>
31			
32		20c	Definition of analysis population relating to protocol non-adherence
33			(eg, as randomised analysis), and any statistical methods to handle
34			missing data (eg, multiple imputation)
35			<u>Page 9, lines 198-200</u>
36			
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44	Methods: Monitoring		
45	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
46			and reporting structure; statement of whether it is independent from
47			the sponsor and competing interests; and reference to where further
48			details about its charter can be found, if not in the protocol.
49			Alternatively, an explanation of why a DMC is not needed
50			<u>Page 6, lines 148-150</u>
51			
52		21b	Description of any interim analyses and stopping guidelines, including
53			who will have access to these interim results and make the final
54			decision to terminate the trial
55			<u>Not applicable</u>
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2	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
3			spontaneously reported adverse events and other unintended effects
4			of trial interventions or trial conduct
5			<u>Protocol version 1.9, chapter 7 (Safety Reporting)</u>
6			
7	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
8			whether the process will be independent from investigators and the
9			sponsor
10			<u>Page 6, lines 136-139</u>
11			<u>Protocol version 1.9, chapter 10.1 (Handling and storage of data</u>
12			<u>and documents) and 10.2 (Monitoring and Quality Assurance)</u>
13			
14			
15			
16	Ethics and dissemination		
17			
18	Research ethics	24	Plans for seeking research ethics committee/institutional review board
19	approval		(REC/IRB) approval
20			<u>Page 11, lines 268-270</u>
21			
22	Protocol	25	Plans for communicating important protocol modifications (eg,
23	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
24			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
25			regulators)
26			<u>Protocol version 1.9, chapter 10.3 (Amendments)</u>
27			
28			
29	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
30			participants or authorised surrogates, and how (see Item 32)
31			<u>Page 7, lines 135-142</u>
32			<u>Protocol version 1.9, chapter 9.2 (Recruitment and informed</u>
33			<u>consent)</u>
34			
35			
36		26b	Additional consent provisions for collection and use of participant data
37			and biological specimens in ancillary studies, if applicable
38			<u>Not applicable</u>
39			
40			
41	Confidentiality	27	How personal information about potential and enrolled participants will
42			be collected, shared, and maintained in order to protect confidentiality
43			before, during, and after the trial
44			<u>Page 7, lines 136-142</u>
45			<u>Protocol version 1.9, chapter 10.1 (Handling and storage of data</u>
46			<u>and documents)</u>
47			
48			
49	Declaration of	28	Financial and other competing interests for principal investigators for
50	interests		the overall trial and each study site
51			<u>Page 11, line 274</u>
52			
53			
54	Access to data	29	Statement of who will have access to the final trial dataset, and
55			disclosure of contractual agreements that limit such access for
56			investigators
57			https://www.trialregister.nl/trial/7148
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2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			<u>Protocol version 1.9, chapter 9.4 (Compensation for injury)</u>
5			
6	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
7	policy		participants, healthcare professionals, the public, and other relevant
8			groups (eg, via publication, reporting in results databases, or other
9			data sharing arrangements), including any publication restrictions
10			<u>Page 11, lines 269-270</u>
11			https://www.trialregister.nl/trial/7148 (IPD plan description)
12			
13		31b	Authorship eligibility guidelines and any intended use of professional
14			writers
15			<u>Assignment of writing committees:</u>
16			Topics suggested for presentation or publication will be shared with
17			the ARTICA trial team, after which authorship will be discussed in
18			team meetings.
19			
20		31c	Plans, if any, for granting public access to the full protocol, participant-
21			level dataset, and statistical code
22			https://www.trialregister.nl/trial/7148 (IPD plan description)
23			
24			
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28	Appendices		
29			
30	Informed consent	32	Model consent form and other related documentation given to
31	materials		participants and authorised surrogates
32			An English version of the Subject information and consent form
33			will be added to the manuscript
34			
35	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
36	specimens		specimens for genetic or molecular analysis in the current trial and for
37			future use in ancillary studies, if applicable
38			<u>Not applicable</u>
39			

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.