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## A prospective multicentre randomised-controlled trial testing very early invasive angiography versus standard of care in higher-risk non-ST elevation myocardial infarction: rationale and design of the RAPID N-STEMI study

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**A prospective multicentre randomised-controlled trial testing very early invasive angiography versus standard of care in higher-risk non-ST elevation myocardial infarction: rationale and design of the RAPID N-STEMI study**

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## Abstract

**Introduction:** There are a paucity of randomised data on the optimal timing of invasive coronary angiography (ICA) in higher-risk patients with non-ST elevation myocardial infarction (N-STEMI). International guideline recommendations for early ICA are primarily based on retrospective subgroup analyses of neutral trials. The RAPID N-STEMI trial aims to determine whether very early percutaneous revascularisation improves clinical outcomes as compared to a standard of care strategy in higher-risk N-STEMI patients.

**Methods and analysis:** RAPID N-STEMI is a prospective, multi-centre, open-label, randomised-controlled, pragmatic strategy trial. Higher-risk N-STEMI patients, as defined by Global Registry of Acute Coronary Events (GRACE) 2.0 score  $\geq 118$ , or  $>90$  with at least one additional high-risk feature, were randomised to either: very early ICA +/- revascularisation or standard of care timing of ICA +/- revascularisation. The primary endpoint is a composite of all-cause mortality, non-fatal myocardial infarction, and hospital admission for heart failure at 12 months. Key secondary outcomes include major bleeding and stroke. A hypothesis generating cardiac magnetic resonance (CMR) substudy will provide mechanistic data on infarct size, myocardial salvage, and residual ischaemia post percutaneous coronary intervention. On 7<sup>th</sup> April 2021, the sponsor discontinued enrolment due to the impact of the COVID-19 pandemic and lower than expected event rates. 425 patients were enrolled, and 61 patients underwent CMR.

**Summary:** The optimal timing of revascularisation in higher-risk N-STEMI remains controversial. RAPID N-STEMI will provide insights into the impact of very early revascularisation in GRACE score defined high-risk N-STEMI patients and inform contemporary practice in this important patient cohort.

**Ethics and dissemination:** The study has full ethical approval. Data collection will be completed in December 2021. The study results will be submitted for publication within 6 months of completion

### Trial registration number

NCT03707314

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3 **Clinical trial registration**

4 NCT03707314  
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6  
7 **Protocol version**

8 v4.0  
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10 **Keywords**

11 Non-ST elevation myocardial infarction; percutaneous coronary intervention; timing; invasive  
12 strategy; GRACE score  
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### Strength and limitations of this study

- Prior data from subgroup analyses suggest that an early invasive strategy may improve clinical outcomes in high-risk patients with N-STEMI.
- RAPID N-STEMI is the first randomised-controlled trial to specifically investigate the impact of very early angiography and revascularisation in a high-risk N-STEMI population as defined by GRACE score.
- The RAPID N-STEMI cardiac magnetic resonance substudy will provide mechanistic insights into the effect of timing of revascularisation on myocardial injury and other novel cardiac magnetic resonance imaging markers.
- Recruitment to the study was discontinued prematurely due to the impact of the COVID-19 pandemic and lower than expected event rates.

## Introduction

Historical data indicate that an invasive strategy during index hospital admission in non-ST elevation myocardial infarction (N-STEMI) improves composite ischaemic outcomes, with maximal benefit seen in those at highest baseline risk for future major adverse cardiovascular events (MACE).<sup>1</sup> However, the optimal timing of invasive coronary angiography (ICA) and whether high-risk subgroups should be treated early remains controversial, despite it being a mandated management strategy in international guidelines.<sup>2,3</sup> Since N-STEMI is characterised by a risk-treatment paradox whereby higher-risk patients are less likely to receive aggressive pharmacotherapy and invasive management,<sup>4</sup> use and timing of ICA can differ significantly when compared to the precisely defined management of ST elevation myocardial infarction (STEMI). Clinically unstable patients require urgent revascularisation, whilst for others, the most appropriate timing of an invasive strategy is less certain.

A series of randomised trials have investigated this concept in unselected N-STEMI populations, thereby testing whether early revascularisation (<24 hours) improves clinical outcomes as compared to delayed or standard of care approaches.<sup>5-18</sup> Differences in study design, inclusion criteria, timing of ICA and endpoint definitions have resulted in conflicting results that are challenging to interpret and apply to current practice. When these data are evaluated in totality, patient level meta-analysis has demonstrated no significant difference in death or myocardial infarction (MI) between the two strategies.<sup>19</sup>

The application of the Global Registry of Acute Coronary Events (GRACE) score in prior trial subgroup analyses has potential for risk stratification of those patients that may benefit most from expeditious revascularisation (**Table 1**). A GRACE score >140 analysis of 961 patients

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3 from the TIMACS trial showed that an early invasive strategy (14 hours post randomisation)  
4 reduced the risk of death, non-fatal MI, and stroke at 6 months by 35% as compared to a  
5 delayed approach.<sup>9</sup> Moreover, the VERDICT study produced a similar finding, albeit in a  
6 subgroup of 1025 GRACE >140 N-STEMI patients who underwent a very early invasive strategy  
7 (4.7 hours post randomisation).<sup>15</sup> However, such analyses should only be considered  
8 hypothesis generating since; 1) the primary outcome in both overall trial populations was  
9 neutral, and 2) the studies were undertaken in the era of conventional troponin and CK-MB,  
10 with up to one-quarter of patients exhibiting no biomarker rise.<sup>9</sup>  
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25 Given that currently available data are inconsistent and of insufficient scientific quality to  
26 inform best practice, a contemporary trial that prospectively investigates the timing of  
27 revascularisation in GRACE score defined high-risk N-STEMI is required to confirm or refute  
28 these prior observations.  
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## 37 **Methods and analysis**

### 38 **Study design and inclusion criteria**

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40 The RAPID N-STEMI trial enrolled patients across 32 hospitals with on-site cardiac catheter  
41 laboratories in the United Kingdom (UK). Potential participants who experienced symptoms  
42 within 12 hours prior to admission were assessed on attendance to hospital and the research  
43 team alerted if a diagnosis of N-STEMI was suspected. N-STEMI was defined as: 1) the  
44 presence of cardiovascular symptoms suggestive of myocardial ischaemia and, 2) elevation in  
45 high-sensitivity troponin (hs-Tn) I or T. Risk stratification using the GRACE 2.0 score was then  
46 performed. Patients in whom the GRACE 2.0 score was  $\geq 118$ , or  $\geq 90$  with at least one  
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3 additional feature of high-risk presentation were deemed as higher risk. The full inclusion and  
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5 exclusion criteria are listed in **Table 2**.  
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10 Patients were enrolled after obtaining verbal consent once eligibility was confirmed in the  
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12 Emergency Department or appropriate receiving unit. Participants were then randomised in  
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14 a 1:1 fashion to either: Group A) very early ICA with a view to revascularisation; or Group B)  
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16 standard of care timing of ICA with a view to revascularisation. Research team members had  
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18 6 hours from hospital admission to randomise verbally consented patients who met all  
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20 eligibility criteria (**Figure 1**).  
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### 26 27 **Study procedures**

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29 Randomisation was performed via either a secure centralised web-based or telephone  
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31 assisted system provided by <http://www.sealedenvelope.com>. Those assigned to very early  
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33 angiography were transferred to the cardiac catheter laboratory as soon as possible. Teams  
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35 were encouraged, but not mandated to achieve a randomisation to vascular sheath insertion  
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37 time of less than 90 minutes. Timing of standard of care ICA was according to typical practice  
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39 at individual UK centres but encouraged to be within 72 hours of admission. Percutaneous  
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41 coronary intervention (PCI) and coronary artery bypass grafting (CABG) were performed  
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43 according to current international guidelines.<sup>20</sup> Requirement for multi-vessel  
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45 revascularisation to a non-infarct related artery was at the individual operator's discretion.  
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47 Optimal medical therapy, including the use of anti-platelet agents, was in accordance with  
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49 current clinical guidelines.<sup>2</sup> Drug eluting stents were used in all cases unless there were clear  
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51 contraindications. As this was a pragmatic strategy trial, all procedures performed were part  
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53 of guideline directed standard of care for N-STEMI.  
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6 Patients were invited to provide verbal consent to participate in the study after being read an  
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8 abridged consent form prior to randomisation. This was to avoid delay in those participants  
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10 that were subsequently allocated to a very early invasive strategy. In addition to the baseline  
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12 hs-Tn required for study inclusion, samples were obtained post-angiography in both trial arms  
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14 and prior to angiography in the standard of care arm. EQ-5D-5L and Seattle Angina  
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16 Questionnaires to assess quality of life were completed after angiography in both arms.<sup>21 22</sup>  
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18 All patients were then asked to provide written informed consent for continuation in the  
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20 study prior to hospital discharge. Study follow up visits via telephone occurred at 30 days, 6  
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22 months, and 12 months from randomisation. Clinical event reporting, EQ-5D-5L and Seattle  
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24 Angina Questionnaire completion were performed at each of these timepoints.  
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### 33 **The GRACE 2.0 score**

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35 Previous high-risk subgroup analyses utilised the original GRACE score, with a score of >140  
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37 stratifying those patients at highest baseline risk. In the TIMACS and VERDICT trials it was  
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39 these groups that benefited from an early invasive strategy.<sup>9 15</sup> However, the updated GRACE  
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41 2.0 score demonstrates equivalent performance and is easier to implement in clinical practice  
42  
43 as compared to the original GRACE Score.<sup>23</sup> A notable advantage of GRACE 2.0 is that Killip  
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45 Class and serum creatinine values are not required for risk calculation. This allows rapid  
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47 stratification very early during hospital admission once a hs-Tn result is available, thus  
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49 obviating the need to wait for renal biochemistry results.  
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57 Patients at intermediate risk (GRACE 2.0 score  $\geq 90$  to  $< 118$ ) were included to attenuate the  
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59 perceived age bias of the GRACE score, thereby allowing enrolment of younger patients  
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3 recognised to be at higher risk of future MACE. The following features: anterior ECG changes,  
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5 ST segment depression, diabetes mellitus on medication, and hs-Tn elevation three times the  
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7 upper limit of normal, have been demonstrated as determinants of poorer prognosis in N-  
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9 STEMI.<sup>24-26</sup>  
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### 15 **Study endpoints**

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17 The RAPID-NSTEMI trial will evaluate the effect of a very early invasive strategy on the  
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19 composite primary endpoint of all-cause mortality, non-fatal MI, and admission for heart  
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21 failure (HF) at 12 months following randomisation. The primary and secondary endpoints are  
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23 listed in **Table 3**.  
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### 30 **Sample size calculation and statistical analysis**

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32 RAPID N-STEMI is a superiority trial powered to detect a 25% risk reduction in the primary  
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34 endpoint. With a two-sided test of  $\alpha=0.05$  and 80% power, 964 patients were required in  
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36 each arm of the study. Assuming up to 5% withdrawal, 5% crossover and 8% requiring  
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38 coronary artery bypass grafting, 1157 patients were planned to be recruited to each group,  
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40 resulting in a recruitment target of 2314.  
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47 Sample size calculations were based primarily on the subgroup analysis of GRACE >140 high-  
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49 risk patients in the TIMACS study. The composite endpoint of death, non-fatal MI, and stroke  
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51 at 6 months occurred in 21.0% of patients in the standard care arm.<sup>9</sup> We decided to include  
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53 admission with HF since there is evidence of this being an important outcome following N-  
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55 STEMI hospitalisation. Data from *Kaul et al* show that at 12 months following N-STEMI the  
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57 incidence of admission with HF was 14.8%.<sup>27</sup> Based on these data and use of the GRACE 2.0  
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3 score, the standard care arm composite event rate of all-cause mortality, non-fatal MI, and  
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5 admission for HF in RAPID N-STEMI was estimated to be 19% at 12 months.  
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10 The CMR substudy is an exploratory mechanistic substudy that had a recruitment target of  
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12 200 patients. No formal power calculations were undertaken.  
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### 18 **RAPID N-STEMI CMR substudy**

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20 Imaging studies confined to N-STEMI are few and primarily descriptive, documenting smaller  
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22 infarct size than in STEMI.<sup>28</sup> Novel cardiac magnetic resonance (CMR) markers (such as  
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24 myocardial strain and salvage) may add incremental prognostic information to recognised  
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26 predictors such as left ventricular ejection fraction (LVEF).<sup>29 30</sup>  
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32 The RAPID N-STEMI CMR substudy applied multi-parametric CMR imaging to; 1) assess the  
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34 impact of the timing of revascularisation on infarct size, volumes and LVEF, myocardial strain,  
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36 myocardial salvage, and extracellular volume and 2) quantify ischaemic burden post-PCI to  
37  
38 ascertain whether this can predict risk of future MACE. The RAPID N-STEMI CMR substudy  
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40 endpoints are listed in **Table 4**.  
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47 Four centres with an established record of high-quality CMR research participated in the  
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49 substudy. As myocardial injury and infarct size reduces early following MI,<sup>31</sup> timing of CMR  
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51 was standardised and performed at 7 (+/-3) days post admission. This also ensured  
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53 angiography +/- PCI had been undertaken in both groups, as PCI itself may be associated with  
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55 further myocardial injury.<sup>32 33</sup> The protocol included cine imaging in long and short axes.  
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57 Adenosine stress perfusion was performed to assess for residual ischaemic burden and a  
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3 gadolinium-based contrast agent administered to allow detection of myocardial necrosis and  
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5 microvascular obstruction.<sup>33</sup> Where available, pre- and post-contrast T1 mapping sequences  
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7 will facilitate estimation of extracellular volume that may indicate more subtle changes in  
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9 myocardial architecture.<sup>34</sup>  
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15 All CMR images will be sent to the core laboratory at the National Institute for Health  
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17 Research Biomedical Research Centre in Leicester for quality control and central analysis, with  
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19 the interpreting clinicians blinded to patient information and allocated group.  
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### 25 **Patient and public involvement (PPI)**

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27 The University of Leicester and the Leicester NIHR Biomedical Research Centre have a very  
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29 active PPI group in cardiovascular sciences. The study outline was presented to our PPI groups  
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31 for feedback prior to designing the study protocol. Furthermore, the Trial Steering Committee  
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33 has a lay member for study oversight. All study participants and members of the public will  
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35 be invited to return for a lecture disseminating the study's key findings on completion.  
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### 42 **Trial coordination**

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44 Trial coordination is provided by the Leicester Clinical Trials Unit (LCTU) in collaboration with  
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46 the Chief Investigator (CI) and the Trial Management Group. LCTU is responsible for overall  
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48 trial conduct including data management, quality assurance and statistical reporting. LCTU  
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50 undertook site initiation visits, database training, and ensures all aspects of the trial are  
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52 performed to the highest ethical and research standards. The study is overseen by a Trial  
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54 Steering Committee consisting of three experienced clinicians, the CI, and a lay member. An  
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56 independent Data and Safety Monitoring Board convened to provide independent advice on  
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3 study conduct and safety issues. Clinical events will be adjudicated by an independent Clinical  
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5 Events Committee.  
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### 10 **Funding and sponsor**

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12 RAPID N-STEMI is funded by the British Heart Foundation (grant number: CS/17/1/32445).  
13  
14 The study sponsor is University Hospitals of Leicester National Health Service (NHS) Trust. The  
15  
16 study is registered at ClinicalTrials.gov (NCT03707314). All procedures have been reviewed  
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18 and approved by the UK National Research Ethics Service committee East of England  
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20 (18/EE/0222).  
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### 28 **Trial progress and impact of the COVID-19 pandemic**

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30 In March 2020, non-COVID-19 clinical research in the UK was suspended as NHS staff and  
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32 resources were repurposed to frontline services in preparation for the volume of COVID-19  
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34 patients expected to place severe pressure on the NHS.<sup>35</sup> During this time, admissions with  
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36 N-STEMI declined substantially.<sup>36 37</sup> Following the first wave in the UK, RAPID N-STEMI  
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38 restarted in late July 2020 at a limited number of sites that had sufficient resource to  
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40 recommence recruitment. However, due to the impending second wave of the COVID-19  
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42 pandemic the trial was once again suspended in December 2020. Discussions with the  
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44 funding body took place regarding the strategy for a successful restart, with it agreed an  
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46 interim pooled event rate (blinded to group allocation) should be calculated. Lower than  
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48 anticipated event rates were documented and it was agreed with the funder that enrolment  
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50 should be discontinued for two reasons: 1) the effect of the pandemic on clinical services and  
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52 2) the rate of the primary outcome. In summary, 425 (18.4% intended) patients were enrolled  
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54 to the main trial, with 61 of these participants included in the CMR substudy. The intention is  
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3 to perform in depth analyses of the available data from these populations and present these  
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5 in the near future.  
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## 10 **Discussion**

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12 The optimal timing of revascularisation in higher-risk N-STEMI is a controversial topic, not  
13  
14 least because international guidelines that mandate an early (<24 hr) invasive strategy are  
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16 not supported by prospective randomised-controlled clinical trial data that specifically  
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18 investigate this population.<sup>2 3</sup> RAPID N-STEMI addresses this knowledge gap. However, like  
19  
20 many other clinical trials during the COVID-19 pandemic, RAPID N-STEMI was discontinued  
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22 due to the emergency restructuring of healthcare and clinical research services. Despite  
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24 falling short of the recruitment target, RAPID N-STEMI has randomised 425 GRACE score  
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26 defined higher-risk patients admitted with N-STEMI, making it the third largest study to  
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28 specifically investigate this important patient population. It will therefore provide a significant  
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30 contribution to the current evidence base, with dissemination of results planned for 2022.  
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## 40 **COVID-19: implications for cardiovascular research**

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42 The major challenges faced due to COVID-19 were three-fold. First, significant reductions in  
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44 admissions with acute coronary syndrome and HF occurred during the pandemic in the UK,  
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46 with decreases of over to 40% in both disease entities, presumably due to fear of contagion  
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48 in healthcare settings.<sup>36 38 39</sup> Not only did this reduce potential research participants, but such  
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50 declines in admissions become a critical issue for clinical trial event reporting and thus may  
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52 be a contributory factor to the lower event rates observed in RAPID N-STEMI.  
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3 Second, the NHS underwent the largest workforce redeployment since its inception to  
4 support severely pressurised frontline services treat the vast numbers of COVID-19 patients  
5 attending UK hospitals. Research staff were moved to such clinical areas, resulting in all non-  
6 COVID-19 related research being left severely disrupted and placed on hiatus until further  
7 notice,<sup>40</sup> the ramifications of which are sure to be felt long after the initial effects of the  
8 COVID-19 pandemic have abated.<sup>41</sup>  
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20 Third, and perhaps most fundamentally for RAPID N-STEMI, elective cardiology activity across  
21 the UK was effectively cancelled from the beginning of the first wave in March 2020.<sup>35</sup>  
22 Suspension of planned cases created greater catheter laboratory capacity for acute MI  
23 patients and dramatically reduced the standard of care timing to ICA for N-STEMI in the UK.<sup>42</sup>  
24 Such changes to catheter laboratory throughput and working patterns resulted in an  
25 unmanageable task of ensuring adequate time separation between the very early ICA and  
26 standard of care ICA arms in RAPID N-STEMI – essentially the control arm was accelerated.  
27 Since any potential differences in clinical outcomes are related to the difference in timing  
28 between the trial arms, new systems of care enforced by the COVID-19 pandemic left the  
29 RAPID N-STEMI investigators in a position whereby restarting recruitment would inevitably  
30 jeopardise the scientific validity of the trial.  
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### 50 **Very early revascularisation in higher-risk N-STEMI: will optimal timing ever be defined?**

51 RAPID N-STEMI is the fifth randomised trial to investigate the timing of an invasive strategy in  
52 GRACE score defined higher-risk N-STEMI patients, albeit the first to specifically investigate  
53 this higher-risk population. Prior studies report pre-specified GRACE >140 subgroup analyses  
54 (Table 1). Favourable results were observed in TIMACS and VERDICT,<sup>9 15</sup> while ELISA-3 and  
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3 RIDDLE N-STEMI showed signals of benefit although were limited by small sample sizes.<sup>12 14</sup>  
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6 Since clinical event rates are greater in high-risk N-STEMI, it may be expected that an  
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8 adequately powered study to detect a clinically meaningful difference is achievable. Yet, in  
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10 recent years outcomes following N-STEMI have improved, largely due to enhanced  
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12 therapeutics and interventional techniques.<sup>43</sup> Therefore, demonstration of superiority for  
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14 hard clinical endpoints from a very early invasive strategy may not be feasible in the  
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16 contemporary era because the logistics of delivering an appropriately powered trial may be  
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18 prohibitive.  
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25 The choice of trial endpoints is also of note. The EARLY trial indicated benefit from a very early  
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27 invasive approach in European Society of Cardiology defined high-risk patients (median  
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29 GRACE score 122), but such benefit was driven by the softer endpoint of recurrent ischaemic  
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31 events in a cohort that did not receive P2Y12 inhibitor pre-treatment.<sup>17</sup> One may question the  
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33 clinical relevance of an endpoint, and as such it was not included in the composite primary  
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35 endpoint of RAPID N-STEMI. Given that practice in many centres is now shifting to a strategy  
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37 of early ICA in higher-risk N-STEMI patient groups, and that this strategy is now widely  
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39 accepted as without excess risk, it appears unlikely that the optimal timing of  
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41 revascularisation in higher-risk N-STEMI will ever be robustly defined.  
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## 50 **Conclusion**

51  
52 RAPID N-STEMI and its mechanistic CMR substudy will provide further insights into GRACE  
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54 score defined higher-risk N-STEMI and provide an additional contribution to the evidence  
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56 base.  
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## Author statement

AHG, GPM, ASB, APB, NC, CB, MF and MD conceived the idea for the study. AHG, GPM, ASB and MF designed the study protocol. TAK drafted the manuscript. SB provided statistical support. All authors critically reviewed and approved the final draft of the manuscript.

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## Competing interests

CB is employed by the University of Glasgow which holds consultancy and research agreements for his work with Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Causeway Therapeutics, Coroventis, Genentech, GSK, HeartFlow, Menarini, Neovasc, Siemens Healthcare, and Valo Health. The other co-authors have no relevant disclosures.

## Ethics and dissemination

The trial is conducted in accordance with the principles of the 1996 Helsinki Declarations, International Conference on Harmonisation-Good Clinical Practice Guidelines (ICH-GCP). It is

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2  
3 anticipated that data collection will be completed by December 2021. The study results will  
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5 be submitted for publication within 6 months of completion.  
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### 10 **Data statement**

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12 The deidentified participant data will be available upon reasonable request.  
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3 **Figure Legends**  
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6 **Figure 1: RAPID N-STEMI study flow diagram**  
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9 CMR: cardiac magnetic resonance; ECG: electrocardiogram; hs-Tn: high sensitivity troponin  
10 N-STEMI: non-ST elevation myocardial infarction; OMT: optimal medical therapy; SAQ: Seattle  
11 Angina Questionnaire; STEMI: ST elevation myocardial infarction; ULN: upper limit of normal  
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**Table 1: Higher-risk N-STEMI (GRACE score >140) subgroup analyses from randomised studies comparing early and delayed invasive strategies**

Trial	Patients	Time to ICA: early (median & IQR, h)	Time to ICA: delayed (median & IQR, h)	Primary outcome	Results
TIMACS 2009 <sup>9</sup>	961	14.0 (3.0 – 21.0)	50.0 (41.0 – 81.0)	6-month death, non-fatal MI, stroke	Early = 13.9% Delayed = 21.0% HR 0.65, 95% CI 0.48-0.89, p = 0.006
ELISA-3 2013 <sup>12</sup>	224	2.6 (1.2 – 6.2)	54.9 (44.2 – 74.5)	30-day death, non-fatal MI, recurrent ischaemia	Early = 10.5% Delayed = 19.1% HR 0.55, 95% CI 0.29-1.10, p=0.26
RIDDLE-NSTEMI 2016 <sup>14</sup>	123	1.4 (1.0 – 2.2)	61.0 (35.8 – 85.0)	30-day death, non-fatal MI	Early = 10.7% Delayed = 17.9% HR 0.56, 95% CI 0.21-1.51 p=0.12
VERDICT 2018 <sup>15</sup>	1025	4.7 (3.0 – 12.2)	61.6 (39.4 – 87.8)	Death, non-fatal MI, refractory ischaemia, admission for heart failure at median 4.3 years	Early = 34.0% Delayed = 40.1% HR 0.81, 95% CI 0.66-0.99, p = 0.023

CI: confidence interval; HR: hazard ratio; ICA: invasive coronary angiography; IQR: interquartile range; MI: myocardial infarction

**Table 2: RAPID N-STEMI inclusion and exclusion criteria**

Inclusion criteria	Exclusion criteria
>18 years of age	ST elevation myocardial infarction
Clinical diagnosis of N-STEMI comprising: <ul style="list-style-type: none"> <li>Cardiovascular symptoms suggestive of myocardial ischaemia</li> <li>Elevated high-sensitivity troponin I or T</li> </ul>	Evident type 2 myocardial infarction
Symptoms <12 hours prior to admission	Previous known cardiomyopathy
GRACE 2.0 score $\geq 118$ or if GRACE 2.0 score $\geq 90$ but $< 118$ must have at least one high-risk feature: <ul style="list-style-type: none"> <li>Anterior location of ECG changes (V2-V5)</li> <li>ST segment depression in 2 contiguous leads of 0.15mV/1.5mm</li> <li>Diabetes mellitus on medication</li> <li>Elevated high-sensitivity troponin 3x upper limit of normal</li> </ul>	Need for urgent PCI according to ESC Guidelines (haemodynamic instability, VT, VF, recurrent or persistent pain)
Intention to perform angiography and, if indicated, follow-on revascularisation	Cardiogenic shock
Provision of verbal assent followed by written informed consent	Severe valvular heart disease
	Any contraindication to PCI
	Current participation in another intervention trial

ECG: electrocardiogram; ESC: European Society of Cardiology; GRACE: Global Registry of Acute Coronary Events; N-STEMI: non-ST elevation myocardial infarction; PCI: percutaneous coronary intervention; VF: ventricular fibrillation; VT: ventricular tachycardia

**Table 3: RAPID N-STEMI study endpoints**

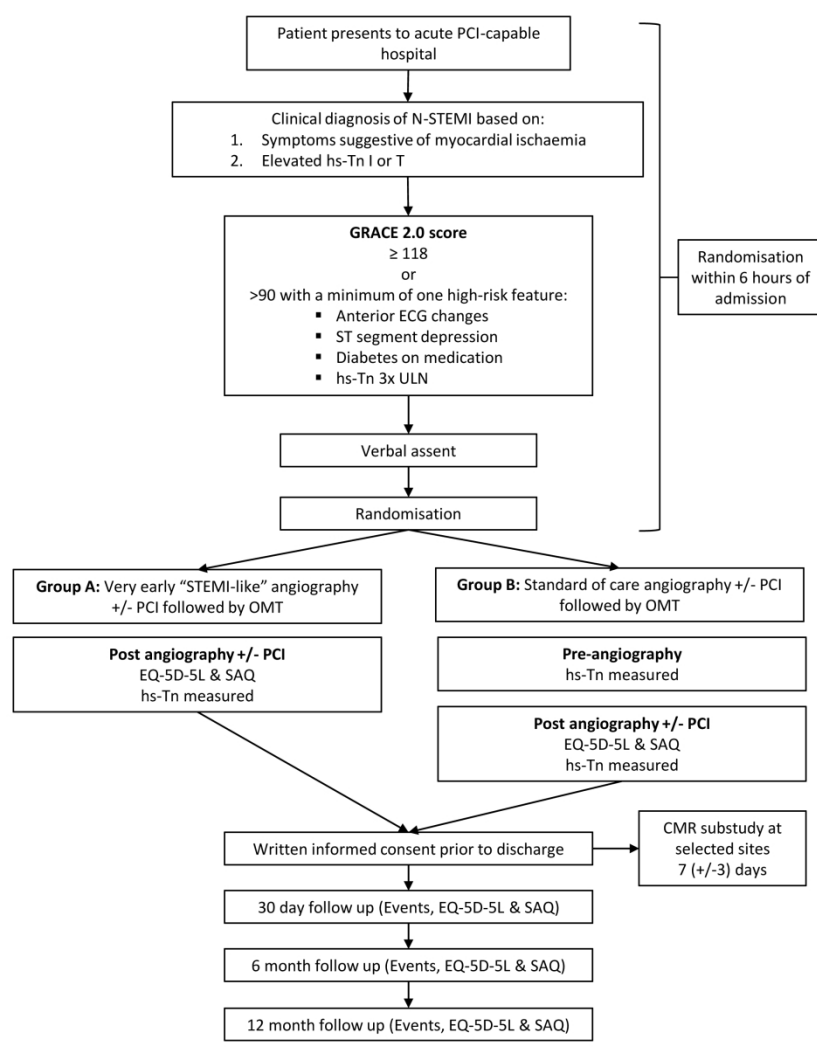
Primary outcome	Secondary outcomes
All-cause mortality, non-fatal myocardial infarction, and admission for heart failure at 12 months	Individual components of primary composite outcome
	Cardiovascular mortality
	Ischaemia-driven revascularisation
	BARC 3-5 major bleeding
	Stroke
	Length of inpatient stay
	Admission for any cause
	Events prior to angiography
	Quality of life (Seattle Angina Questionnaire and EQ-5D-5L questionnaires)
	Cost-efficacy analysis
	Proportion of patients requiring emergency revascularisation in group B
	Total VARC-2 classified access site complications
Major VARC-2 classified access site complications	

BARC: Bleeding Academic Research Consortium; VARC: Vascular Access Research Consortium

**Table 4: RAPID N-STEMI CMR study endpoints**

Primary outcome	Secondary outcomes
Infarct size (% left ventricular mass)	Left ventricular volumes and ejection fraction
	Myocardial salvage index
	Extracellular volume
	Ischaemic burden
	Global myocardial strain

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# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

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

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

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

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

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	<a href="#">#3</a>	Date and version identifier	3
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	20

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	8
2	responsibilities:			
3	sponsor contact			
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8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	20
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
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16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating centre,	11
17	responsibilities:		steering committee, endpoint adjudication committee, data	
18	committees		management team, and other individuals or groups overseeing the	
19			trial, if applicable (see Item 21a for data monitoring committee)	
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23	<b>Introduction</b>			
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25	Background and	<a href="#">#6a</a>	Description of research question and justification for undertaking	5
26	rationale		the trial, including summary of relevant studies (published and	
27			unpublished) examining benefits and harms for each intervention	
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30	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	5
31	rationale: choice of			
32	comparators			
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36	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	6
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38	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	6
39			group, crossover, factorial, single group), allocation ratio, and	
40			framework (eg, superiority, equivalence, non-inferiority,	
41			exploratory)	
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45	<b>Methods:</b>			
46	<b>Participants,</b>			
47	<b>interventions, and</b>			
48	<b>outcomes</b>			
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51	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	6
52			hospital) and list of countries where data will be collected.	
53			Reference to where list of study sites can be obtained	
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57	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable,	7
58			eligibility criteria for study centres and individuals who will	
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		perform the interventions (eg, surgeons, psychotherapists)	
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2	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	7
3	description	replication, including how and when they will be administered	
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5	Interventions:	<a href="#">#11b</a> Criteria for discontinuing or modifying allocated interventions for a	7
6	modifications	given trial participant (eg, drug dose change in response to harms,	
7		participant request, or improving / worsening disease)	
8			
9	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to intervention protocols, and any	7
10	adherence	procedures for monitoring adherence (eg, drug tablet return;	
11		laboratory tests)	
12	Interventions:	<a href="#">#11d</a> Relevant concomitant care and interventions that are permitted or	7
13	concomitant care	prohibited during the trial	
14			
15	Outcomes	<a href="#">#12</a> Primary, secondary, and other outcomes, including the specific	10
16		measurement variable (eg, systolic blood pressure), analysis metric	
17		(eg, change from baseline, final value, time to event), method of	
18		aggregation (eg, median, proportion), and time point for each	
19		outcome. Explanation of the clinical relevance of chosen efficacy	
20		and harm outcomes is strongly recommended	
21	Participant timeline	<a href="#">#13</a> Time schedule of enrolment, interventions (including any run-ins	10
22		and washouts), assessments, and visits for participants. A	
23		schematic diagram is highly recommended (see Figure)	
24			
25	Sample size	<a href="#">#14</a> Estimated number of participants needed to achieve study	10
26		objectives and how it was determined, including clinical and	
27		statistical assumptions supporting any sample size calculations	
28			
29	Recruitment	<a href="#">#15</a> Strategies for achieving adequate participant enrolment to reach	10
30		target sample size	
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45	<b>Methods: Assignment</b>		
46	<b>of interventions (for</b>		
47	<b>controlled trials)</b>		
48			
49			
50	Allocation: sequence	<a href="#">#16a</a> Method of generating the allocation sequence (eg, computer-	7
51	generation	generated random numbers), and list of any factors for	
52		stratification. To reduce predictability of a random sequence,	
53		details of any planned restriction (eg, blocking) should be provided	
54		in a separate document that is unavailable to those who enrol	
55		participants or assign interventions	
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1	Allocation concealment	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central	7
2	mechanism		telephone; sequentially numbered, opaque, sealed envelopes),	
3			describing any steps to conceal the sequence until interventions are	
4			assigned	
5				
6				
7				
8	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol	7
9	implementation		participants, and who will assign participants to interventions	
10				
11	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial	7
12			participants, care providers, outcome assessors, data analysts), and	
13			how	
14				
15				
16				
17	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible,	7
18	emergency unblinding		and procedure for revealing a participant's allocated intervention	
19			during the trial	
20				
21				
22	<b>Methods: Data</b>			
23	<b>collection,</b>			
24	<b>management, and</b>			
25	<b>analysis</b>			
26				
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28				
29	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and other	8
30			trial data, including any related processes to promote data quality	
31			(eg, duplicate measurements, training of assessors) and a	
32			description of study instruments (eg, questionnaires, laboratory	
33			tests) along with their reliability and validity, if known. Reference	
34			to where data collection forms can be found, if not in the protocol	
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39	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-up,	8
40	retention		including list of any outcome data to be collected for participants	
41			who discontinue or deviate from intervention protocols	
42				
43				
44	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including any	8
45			related processes to promote data quality (eg, double data entry;	
46			range checks for data values). Reference to where details of data	
47			management procedures can be found, if not in the protocol	
48				
49				
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51	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary outcomes.	11
52			Reference to where other details of the statistical analysis plan can	
53			be found, if not in the protocol	
54				
55				
56	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted	11
57	analyses		analyses)	
58				
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1	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	11
2	population and missing		adherence (eg, as randomised analysis), and any statistical methods	
3	data		to handle missing data (eg, multiple imputation)	
4				
5				
6	<b>Methods: Monitoring</b>			
7				
8	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary of its	11
9	formal committee		role and reporting structure; statement of whether it is independent	
10			from the sponsor and competing interests; and reference to where	
11			further details about its charter can be found, if not in the protocol.	
12			Alternatively, an explanation of why a DMC is not needed	
13				
14	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	n/a
15	interim analysis		including who will have access to these interim results and make	
16			the final decision to terminate the trial	
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22	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited	n/a
23			and spontaneously reported adverse events and other unintended	
24			effects of trial interventions or trial conduct	
25				
26				
27	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and	n/a
28			whether the process will be independent from investigators and the	
29			sponsor	
30				
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33	<b>Ethics and</b>			
34	<b>dissemination</b>			
35				
36				
37	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review	8
38	approval		board (REC / IRB) approval	
39				
40				
41	Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg,	n/a
42			changes to eligibility criteria, outcomes, analyses) to relevant	
43			parties (eg, investigators, REC / IRBs, trial participants, trial	
44			registries, journals, regulators)	
45				
46				
47	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial	n/a
48			participants or authorised surrogates, and how (see Item 32)	
49				
50				
51	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant	n/a
52	ancillary studies		data and biological specimens in ancillary studies, if applicable	
53				
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55	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled participants	n/a
56			will be collected, shared, and maintained in order to protect	
57			confidentiality before, during, and after the trial	
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1	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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3				
4				
5	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
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10	Ancillary and post trial care	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
11				
12				
13				
14	Dissemination policy: trial results	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
15				
16				
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20				
21	Dissemination policy: authorship	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of professional writers	n/a
22				
23				
24	Dissemination policy: reproducible research	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
25				
26				
27				
28	<b>Appendices</b>			
29				
30				
31	Informed consent materials	<a href="#">#32</a>	Model consent form and other related documentation given to participants and authorised surrogates	n/a
32				
33				
34	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a
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 42 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

## Very early invasive angiography versus standard of care in higher-risk non-ST elevation myocardial infarction: study protocol for the prospective multicentre randomised controlled RAPID N-STEMI trial

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**Very early invasive angiography versus standard of care in higher-risk non-ST elevation myocardial infarction: study protocol for the prospective multicentre randomised controlled RAPID N-STEMI trial**

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## Abstract

**Background:** There are a paucity of randomised data on the optimal timing of invasive coronary angiography (ICA) in higher-risk patients with non-ST elevation myocardial infarction (N-STEMI). International guideline recommendations for early ICA are primarily based on retrospective subgroup analyses of neutral trials.

**Aims:** The RAPID N-STEMI trial aims to determine whether very early percutaneous revascularisation improves clinical outcomes as compared to a standard of care strategy in higher-risk N-STEMI patients.

**Methods and analysis:** RAPID N-STEMI is a prospective, multi-centre, open-label, randomised-controlled, pragmatic strategy trial. Higher-risk N-STEMI patients, as defined by Global Registry of Acute Coronary Events (GRACE) 2.0 score  $\geq 118$ , or  $>90$  with at least one additional high-risk feature, were randomised to either: very early ICA +/- revascularisation or standard of care timing of ICA +/- revascularisation. The primary outcome is the proportion of participants with at least one of the following events (all-cause mortality, non-fatal myocardial infarction, and hospital admission for heart failure) at 12 months. Key secondary outcomes include major bleeding and stroke. A hypothesis generating cardiac magnetic resonance (CMR) substudy will provide mechanistic data on infarct size, myocardial salvage, and residual ischaemia post percutaneous coronary intervention. On 7<sup>th</sup> April 2021, the sponsor discontinued enrolment due to the impact of the COVID-19 pandemic and lower than expected event rates. 425 patients were enrolled, and 61 patients underwent CMR.

**Ethics and dissemination:** The trial has been reviewed and approved by the East of England Cambridge East Research Ethics Committee (18/EE/0222). The study results will be submitted for publication within 6 months of completion.

## Clinical trial registration

NCT03707314

## Keywords

Non-ST elevation myocardial infarction; percutaneous coronary intervention; timing; invasive strategy; GRACE score

### Strengths and limitations of this study:

-This randomised trial sought to test whether a very early invasive strategy in higher-risk N-STEMI patients improves clinical outcomes compared with standard care. An early invasive strategy in this group is recommended in international guidelines, but is as yet unsupported by the primary outcome of an appropriately sized randomised trial.

-Randomised-controlled pragmatic strategy design.

-A cardiac magnetic resonance sub-study will provide mechanistic data on infarct size, myocardial salvage, and residual ischaemia post-PCI.

-Due to the effects of the COVID-19 pandemic upon clinical services and a lower than expected primary outcome event rate, trial recruitment was terminated early after enrolment of 425 patients (18.4% of intended).

### Background and rationale

Historical data indicate that an invasive strategy during index hospital admission in non-ST elevation myocardial infarction (N-STEMI) improves composite ischaemic outcomes, with maximal benefit seen in those at highest baseline risk for future major adverse cardiovascular events (MACE) (1). However, the optimal timing of invasive coronary angiography (ICA) and whether high-risk subgroups should be treated early remains controversial, despite it being a mandated management strategy in international guidelines (2, 3). Since N-STEMI is



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3 characterised by a risk-treatment paradox whereby higher-risk patients are less likely to  
4 receive aggressive pharmacotherapy and invasive management (4), use and timing of ICA can  
5 differ significantly when compared to the precisely defined management of ST elevation  
6 myocardial infarction (STEMI). Clinically unstable patients require urgent revascularisation,  
7 whilst for others, the most appropriate timing of an invasive strategy is less certain.  
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18 A series of randomised trials have investigated this concept in unselected N-STEMI  
19 populations, thereby testing whether early revascularisation (<24 hours) improves clinical  
20 outcomes as compared to delayed or standard of care approaches (5-18). Differences in study  
21 design, inclusion criteria, timing of ICA and endpoint definitions have resulted in conflicting  
22 results that are challenging to interpret and apply to current practice. When these data are  
23 evaluated in totality, patient level meta-analysis has demonstrated no significant difference  
24 in death or myocardial infarction (MI) between the two strategies (19).  
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38 The application of the Global Registry of Acute Coronary Events (GRACE) score in prior trial  
39 subgroup analyses has potential for risk stratification of those patients that may benefit most  
40 from expeditious revascularisation (**Table 1**). A GRACE score >140 analysis of 961 patients  
41 from the TIMACS trial showed that an early invasive strategy (14 hours post randomisation)  
42 reduced the risk of death, non-fatal MI, and stroke at 6 months by 35% as compared to a  
43 delayed approach (9). Moreover, the VERDICT study produced a similar finding, albeit in a  
44 subgroup of 1025 GRACE >140 N-STEMI patients who underwent a very early invasive strategy  
45 (4.7 hours post randomisation) (15). However, such analyses should only be considered  
46 hypothesis generating since; 1) the primary outcome in both overall trial populations was  
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3 neutral, and 2) the studies were undertaken in the era of conventional troponin and CK-MB,  
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5 with up to one-quarter of patients exhibiting no biomarker rise (9).  
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10 Given that currently available data are inconsistent and of insufficient scientific quality to  
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12 inform best practice, a contemporary trial that prospectively investigates the timing of  
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14 revascularisation in GRACE score defined high-risk N-STEMI is required to confirm or refute  
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16 these prior observations.  
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## 20 21 22 **Methods and analysis**

### 23 24 **Study design and inclusion criteria**

25  
26 The RAPID N-STEMI trial enrolled patients across 32 hospitals with on-site cardiac catheter  
27  
28 laboratories in the United Kingdom (UK). Potential participants who experienced symptoms  
29  
30 within 12 hours prior to admission were assessed on attendance to hospital and the research  
31  
32 team alerted if a diagnosis of N-STEMI was suspected. N-STEMI was defined as: 1) the  
33  
34 presence of cardiovascular symptoms suggestive of myocardial ischaemia and, 2) elevation in  
35  
36 high-sensitivity troponin (hs-Tn) I or T. Risk stratification using the GRACE 2.0 score was then  
37  
38 performed. Patients in whom the GRACE 2.0 score was  $\geq 118$ , or  $\geq 90$  with at least one  
39  
40 additional feature of high-risk presentation were deemed as higher risk. The full inclusion and  
41  
42 exclusion criteria are listed in **Table 2**.  
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52 Patients were enrolled after obtaining verbal consent once eligibility was confirmed in the  
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54 Emergency Department or appropriate receiving unit. Participants were then randomised in  
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56 a 1:1 fashion to either: Group A) very early ICA with a view to revascularisation; or Group B)  
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58 standard of care timing of ICA with a view to revascularisation. Research team members had  
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3 6 hours from hospital admission to randomise verbally consented patients who met all  
4  
5 eligibility criteria (**Figure 1**).  
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### 10 **Study procedures**

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12 Randomisation was performed via either a secure centralised web-based or telephone  
13 assisted system provided by <http://www.sealedenvelope.com>. Those assigned to very early  
14  
15 angiography were transferred to the cardiac catheter laboratory as soon as possible. Teams  
16  
17 were encouraged, but not mandated to achieve a randomisation to vascular sheath insertion  
18  
19 time of less than 90 minutes. Timing of standard of care ICA was according to typical practice  
20  
21 at individual UK centres but encouraged to be within 72 hours of admission. Percutaneous  
22  
23 coronary intervention (PCI) and coronary artery bypass grafting (CABG) were performed  
24  
25 according to current international guidelines (20). Requirement for multi-vessel  
26  
27 revascularisation to a non-infarct related artery was at the individual operator's discretion.  
28  
29 Optimal medical therapy, including the use of anti-platelet agents, was in accordance with  
30  
31 current clinical guidelines (2). Drug eluting stents were used in all cases unless there were  
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33 clear contraindications. As this was a pragmatic strategy trial, all procedures performed were  
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35 part of guideline directed standard of care for N-STEMI.  
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47 Patients were invited to provide verbal consent to participate in the study after being read an  
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49 abridged consent form prior to randomisation. This was to avoid delay in those participants  
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51 that were subsequently allocated to a very early invasive strategy. In addition to the baseline  
52  
53 hs-Tn required for study inclusion, samples were obtained post-angiography in both trial arms  
54  
55 and prior to angiography in the standard of care arm. EQ-5D-5L (21) and Seattle Angina  
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57 Questionnaires (22) to assess quality of life were completed after angiography in both arms.  
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3 All patients were then asked to provide written informed consent for continuation in the  
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5 study prior to hospital discharge. Study follow up visits via telephone occurred at 30 days, 6  
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7 months, and 12 months from randomisation. Clinical event reporting, EQ-5D-5L and Seattle  
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9 Angina Questionnaire completion were performed at each of these timepoints.  
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### 12 13 **The GRACE 2.0 score**

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15 Previous high-risk subgroup analyses utilised the original GRACE score, with a score of >140  
16  
17 stratifying those patients at highest baseline risk. In the TIMACS and VERDICT trials it was  
18  
19 these groups that benefited from an early invasive strategy (9, 15). However, the updated  
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21 GRACE 2.0 score demonstrates equivalent performance and is easier to implement in clinical  
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23 practice as compared to the original GRACE Score (23). A notable advantage of GRACE 2.0 is  
24  
25 that Killip Class and serum creatinine values are not required for risk calculation. This allows  
26  
27 rapid stratification very early during hospital admission once a hs-Tn result is available, thus  
28  
29 obviating the need to wait for renal biochemistry results.  
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37 Patients at intermediate risk (GRACE 2.0 score  $\geq 90$  to  $< 118$ ) were included to attenuate the  
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39 perceived age bias of the GRACE score, thereby allowing enrolment of younger patients  
40  
41 recognised to be at higher risk of future MACE. The following features: anterior ECG changes,  
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43 ST segment depression, diabetes mellitus on medication, and hs-Tn elevation three times the  
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45 upper limit of normal, have been demonstrated as determinants of poorer prognosis in N-  
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47 STEMI (24-26).  
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### 52 53 **RAPID N-STEMI CMR substudy**

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55 Imaging studies confined to N-STEMI are few and primarily descriptive, documenting smaller  
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57 infarct size than in STEMI (27). Novel cardiac magnetic resonance (CMR) markers (such as  
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3 myocardial strain and salvage) may add incremental prognostic information to recognised  
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5 predictors such as left ventricular ejection fraction (LVEF) (28, 29).  
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10 The RAPID N-STEMI CMR substudy applied multi-parametric CMR imaging to; 1) assess the  
11  
12 impact of the timing of revascularisation on infarct size, volumes and LVEF, myocardial strain,  
13  
14 myocardial salvage, and extracellular volume and 2) quantify ischaemic burden post-PCI to  
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16 ascertain whether this can predict risk of future MACE. The RAPID N-STEMI CMR substudy  
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18 endpoints are listed in **Table 3**.  
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25 Four centres with an established record of high-quality CMR research participated in the  
26  
27 substudy. As myocardial injury and infarct size reduces early following MI (30), timing of CMR  
28  
29 was standardised and performed at 7 (+/-3) days post admission. This also ensured  
30  
31 angiography +/- PCI had been undertaken in both groups, as PCI itself may be associated with  
32  
33 further myocardial injury (31, 32). The protocol included cine imaging in long and short axes.  
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35 Adenosine stress perfusion was performed to assess for residual ischaemic burden and a  
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37 gadolinium-based contrast agent administered to allow detection of myocardial necrosis and  
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39 microvascular obstruction (32). Where available, pre- and post-contrast T1 mapping  
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41 sequences will facilitate estimation of extracellular volume that may indicate more subtle  
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43 changes in myocardial architecture (33).  
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52 All CMR images will be sent to the core laboratory at the National Institute for Health  
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54 Research Biomedical Research Centre in Leicester for quality control and central analysis, with  
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56 the interpreting clinicians blinded to patient information and allocated group.  
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## Study endpoints

The RAPID-NSTEMI trial will evaluate the effect of a very early invasive strategy on the binary primary endpoint which is composite of all-cause mortality, non-fatal MI, and admission for heart failure (HF) at 12 months following randomisation. The primary and secondary endpoints are listed in **Table 4**.

## Sample size calculation

RAPID N-STEMI is a superiority trial powered to detect a 25% risk reduction in the primary endpoint. With a two-sided test of  $\alpha=0.05$  and 80% power, 964 patients were required in each arm of the study. Assuming up to 5% withdrawal, 5% crossover and 8% requiring coronary artery bypass grafting, 1157 patients were planned to be recruited to each group, resulting in a recruitment target of 2314.

Sample size calculations were based primarily on the subgroup analysis of GRACE >140 high-risk patients in the TIMACS study. The composite endpoint of death, non-fatal MI, and stroke at 6 months occurred in 21.0% of patients in the standard care arm (9). We decided to include admission with HF since there is evidence of this being an important outcome following N-STEMI hospitalisation. Data from *Kaul et al* show that at 12 months following N-STEMI the incidence of admission with HF was 14.8% (34). Based on these data and use of the GRACE 2.0 score, the standard care arm composite event rate of all-cause mortality, non-fatal MI, and admission for HF in RAPID N-STEMI was estimated to be 19% at 12 months.

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2  
3 The CMR substudy is an exploratory mechanistic substudy that had a recruitment target of  
4  
5 200 patients. No formal power calculations were undertaken.  
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### 10 **Statistical analysis**

11  
12 A full statistical analysis plan will be completed prior to any analyses being undertaken.  
13  
14 Primary analysis will be carried out by intention to treat with imputation for individuals with  
15  
16 missing data due to loss to follow-up assessment as having no event. The primary outcome is  
17  
18 binary for each individual (yes or no) and therefore participants experiencing more than one  
19  
20 of the composite events will only be counted once. The treatment arms will be compared  
21  
22 using mixed effects logistic regression, which will be adjusted for randomisation stratification  
23  
24 factors hospital site (as a random effect) and GRACE score (as a fixed effect). Treatment  
25  
26 comparison estimates will be presented as adjusted odds ratios (OR) and 95% confidence  
27  
28 intervals (95% CI).  
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The analysis of binary secondary outcomes will be carried out in the intention to treat population as per the primary outcome analysis. All other secondary continuous outcomes will be analysed on a complete case approach, where participants will only be included if relevant data are available.

Quality of life data (EQ-5D) will be analysed using a mixed effects model with patient as a random effect to account for repeated measures over time. Each patient will contribute up to four postoperative repeated measures to the model. The model will be adjusted for the stratification variables as above. It is expected that some values at later time points will be

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3 missing. The mixed effects model specified here will include these patients with partially  
4  
5 observed data.  
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### 10 *Subgroup analyses*

11  
12 An exploratory analysis of the primary outcome in line with the primary analysis plan will be  
13  
14 repeated looking for indications of a randomised treatment arm interaction with the  
15  
16 following subgroups:  
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20 Gender; Female and Male  
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22  
23 Age at randomisation: <75 years and ≥75 years  
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25  
26 GRACE 2.0 score at admission; >140; >118 & <140; and 90-118  
27

28  
29 ECG normal vs ECG abnormalities at admission  
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### 32 *Exploratory analyses*

33  
34 The primary endpoint will also be analysed as a time-to-first-event outcome. The time will be  
35  
36 measured from randomisation and differences between treatment arms compared using  
37  
38 Cox's proportional hazards models, with treatment comparisons presented as hazard ratios  
39  
40 and 95% confidence interval. All time to event outcomes will be intention to treat with losses  
41  
42 to follow-up censored at date last seen.  
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49  
50 An exploratory analysis will be conducted repeating the analysis methods of the primary  
51  
52 outcome in the efficacy population. The efficacy population excludes individuals that were  
53  
54 randomised to Early Intervention not receiving angiography within 12 hours of randomisation  
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56 OR were randomised to Standard Care receiving angiography within 12 hours (unless  
57  
58 participant's procedure performed earlier than anticipated due to clinical deterioration).  
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6 The association between CMR outcomes and the primary outcome will be assessed by logistic  
7  
8 regression with each CMR variable being included in a separate model. Models will have the  
9  
10 clinical outcome as their dependant variable and include the CMR variable as explanatory  
11  
12 variable as well as adjusting for treatment arm, site, GRACE score, age and sex.  
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### 20 **Funding and sponsor**

21  
22  
23 RAPID N-STEMI is funded by the British Heart Foundation (grant number: CS/17/1/32445).  
24  
25 The study sponsor is University Hospitals of Leicester National Health Service (NHS) Trust. The  
26  
27 study is registered at ClinicalTrials.gov (NCT03707314).  
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### 32 **Ethics and dissemination**

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35 The study is conducted in accordance with the principles of the 1996 Helsinki Declarations,  
36  
37 International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines. The  
38  
39 trial has been reviewed and approved by the East of England Cambridge East Research Ethics  
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41 Committee (18/EE/0222). It is anticipated that data completion will be completed by the end  
42  
43 of December 2021, and the study results will be submitted for publication within 6 months of  
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45 completion.  
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### 49 **Public and patient involvement**

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52 The study was presented to the National Institute for Health Research (NIHR) University of  
53  
54 Leicester Biomedical Research Centre (BRC) Patient & Public Involvement Group.  
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56  
57 Development of the protocol, outcome measures, recruitment to the trial and conduct of  
58  
59 the study were discussed. There was a favourable response to the proposed study from the  
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3 group. Study progress has been fed back to the Patient & Public Involvement group during  
4  
5 the course of the trial. Participants are given a study newsletter when they attend their 12-  
6  
7 month clinic visit providing information about the study timelines and when the study  
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9 results will be known. Access to the findings of the study will be made available in a  
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11 contemporary and user-friendly way and full details of the results provided if the patient  
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13 requests them.  
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### 20 **Trial coordination**

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22 Trial coordination is provided by the Leicester Clinical Trials Unit (LCTU) in collaboration with  
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24 the Chief Investigator (CI) and the Trial Management Group. LCTU is responsible for overall  
25  
26 trial conduct including data management, quality assurance and statistical reporting. LCTU  
27  
28 undertook site initiation visits, database training, and ensures all aspects of the trial are  
29  
30 performed to the highest ethical and research standards. The study is overseen by a Trial  
31  
32 Steering Committee consisting of three experienced clinicians and the CI. An independent  
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34 Data and Safety Monitoring Board convened to provide independent advice on study conduct  
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36 and safety issues. Clinical events will be adjudicated by an independent Clinical Events  
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38 Committee.  
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### 47 **Trial progress and impact of the COVID-19 pandemic**

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49 In March 2020, non-COVID-19 clinical research in the UK was suspended as NHS staff and  
50  
51 resources were repurposed to frontline services in preparation for the volume of COVID-19  
52  
53 patients expected to place severe pressure on the NHS (35). During this time, admissions with  
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55 N-STEMI declined substantially (36, 37). Following the first wave in the UK, RAPID N-STEMI  
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57 restarted in late July 2020 at a limited number of sites that had sufficient resource to  
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3 recommence recruitment. However, due to the impending second wave of the COVID-19  
4  
5 pandemic the trial was once again suspended in December 2020. Discussions with the  
6  
7 funding body took place regarding the strategy for a successful restart, with it agreed an  
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9 interim pooled event rate (blinded to group allocation) should be calculated. Lower than  
10  
11 anticipated event rates were documented and it was agreed with the funder that enrolment  
12  
13 should be discontinued for two reasons: 1) the effect of the pandemic on clinical services and  
14  
15 2) the rate of the primary outcome. In summary, 425 (18.4% intended) patients were enrolled  
16  
17 to the main trial, with 61 of these participants included in the CMR substudy. The intention is  
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19 to perform in depth analyses of the available data from these populations and present these  
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21 in the near future.  
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### 30 **Discussion**

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32 The optimal timing of revascularisation in higher-risk N-STEMI is a controversial topic, not  
33  
34 least because international guidelines that mandate an early (<24 hr) invasive strategy are  
35  
36 not supported by prospective randomised-controlled clinical trial data (2, 3). RAPID N-STEMI  
37  
38 addresses this knowledge gap. However, like many other clinical trials during the COVID-19  
39  
40 pandemic, RAPID N-STEMI was discontinued due to the emergency restructuring of  
41  
42 healthcare and clinical research services. Despite falling short of the recruitment target,  
43  
44 RAPID N-STEMI has randomised 425 GRACE score defined higher-risk patients admitted with  
45  
46 N-STEMI, making it the third largest study to specifically investigate this important patient  
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48 population. It will therefore provide an significant contribution to the current evidence base,  
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50 with dissemination of results planned for 2022.  
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### 59 **COVID-19: implications for cardiovascular research**

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3 The major challenges faced due to COVID-19 were three-fold. First, significant reductions in  
4 admissions with acute coronary syndrome and HF occurred during the pandemic in the UK,  
5  
6 with decreases of over to 40% in both disease entities, presumably due to fear of contagion  
7  
8 in healthcare settings (36, 38, 39). Not only did this reduce potential research participants,  
9  
10 but such declines in admissions become a critical issue for clinical trial event reporting and  
11  
12 thus may be a contributory factor to the lower event rates observed in RAPID N-STEMI.  
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20 Second, the NHS underwent the largest workforce redeployment since its inception to  
21  
22 support severely pressurised frontline services treat the vast numbers of COVID-19 patients  
23  
24 attending UK hospitals. Research staff were moved to such clinical areas, resulting in all non-  
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26 COVID-19 related research being left severely disrupted and placed on hiatus until further  
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28 notice (40), the ramifications of which are sure to be felt long after the initial effects of the  
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30 COVID-19 pandemic have abated (41).  
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38 Third, and perhaps most fundamentally for RAPID N-STEMI, elective cardiology activity across  
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40 the UK was effectively cancelled from the beginning of the first wave in March 2020 (35).  
41  
42 Suspension of planned cases created greater catheter laboratory capacity for acute MI  
43  
44 patients and dramatically reduced the standard of care timing to ICA for N-STEMI in the UK  
45  
46 (42). Such changes to catheter laboratory throughput and working patterns resulted in an  
47  
48 unmanageable task of ensuring adequate time separation between the very early ICA and  
49  
50 standard of care ICA arms in RAPID N-STEMI – essentially the control arm was accelerated.  
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52 Since any potential differences in clinical outcomes are related to the difference in timing  
53  
54 between the trial arms, new systems of care enforced by the COVID-19 pandemic left the  
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3 RAPID N-STEMI investigators in a position whereby restarting recruitment would inevitably  
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5 jeopardise the scientific validity of the trial.  
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### 10 **Very early revascularisation in higher-risk N-STEMI: will optimal timing ever be defined?**

11  
12 RAPID N-STEMI is the fifth randomised trial to investigate the timing of an invasive strategy in  
13  
14 GRACE score defined higher-risk N-STEMI patients, albeit the first to specifically investigate  
15  
16 this higher-risk population. Prior studies report pre-specified GRACE >140 subgroup analyses  
17  
18 (**Table 1**). Favourable results were observed in TIMACS and VERDICT (9, 15), while ELISA-3 and  
19  
20 RIDDLE N-STEMI showed signals of benefit although were limited by small sample sizes (12,  
21  
22 14). Since clinical event rates are greater in high-risk N-STEMI, it may be expected that an  
23  
24 adequately powered study to detect a clinically meaningful difference is achievable. Yet, in  
25  
26 recent years outcomes following N-STEMI have improved, largely due to enhanced  
27  
28 therapeutics and interventional techniques (43). Therefore, demonstration of superiority for  
29  
30 hard clinical endpoints from a very early invasive strategy may not be feasible in the  
31  
32 contemporary era because the logistics of delivering an appropriately powered trial may be  
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34 prohibitive.  
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45 The choice of trial endpoints is also of note. The EARLY trial indicated benefit from a very early  
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47 invasive approach in European Society of Cardiology defined high-risk patients (median  
48  
49 GRACE score 122), but such benefit was driven by the softer endpoint of recurrent ischaemic  
50  
51 events in a cohort that did not receive P2Y12 inhibitor pre-treatment (17). One may question  
52  
53 the clinical relevance of an endpoint, and as such it was not included in the composite primary  
54  
55 endpoint of RAPID N-STEMI. Given that practice in many centres is now shifting to a strategy  
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57 of early ICA in higher-risk N-STEMI patient groups, and that this strategy is now widely  
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3 accepted as without excess risk, it appears unlikely that the optimal timing of  
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5 revascularisation in higher-risk N-STEMI will ever be robustly defined.  
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### 10 **Contributorship statement**

11  
12 AsB, MF, CB, NC, ApB, GPM & AHG conceived the idea for the study. AsB, GPM & AHG  
13  
14 designed the study protocol. TAK drafted the manuscript. AsB, AL, MF, CPG, JPG, MD, RH, SB,  
15  
16 EP, CB, NC, ApB & GPM critically reviewed and approved the final version of the manuscript.  
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### 23 **Competing interests**

24  
25 CB is employed by the University of Glasgow which holds consultancy and research  
26  
27 agreements for his work with Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Causeway  
28  
29 Therapeutics, Coroventis, Genentech, GSK, HeartFlow, Menarini, Neovasc, Siemens  
30  
31 Healthcare, and Valo Health. The other co-authors have no relevant disclosures.  
32  
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34  
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39  
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41  
42 grant providers were not involved in study design, data acquisition or management, or  
43  
44 analysis and writing of final reports.  
45  
46  
47  
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49

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51  
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53  
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55  
56 Research Clinical Research Facility.  
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3 **Figure Legends**  
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6 **Figure 1: RAPID N-STEMI study flow diagram**  
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9 CMR: cardiac magnetic resonance; ECG: electrocardiogram; hs-Tn: high sensitivity troponin N-STEMI: non-ST  
10 elevation myocardial infarction; OMT: optimal medical therapy; SAQ: Seattle Angina Questionnaire; STEMI: ST  
11 elevation myocardial infarction; ULN: upper limit of normal  
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**Table 1: Higher-risk N-STEMI (GRACE score >140) subgroup analyses from randomised studies comparing early and delayed invasive strategies**

Trial	Patients	Time to ICA: early (median & IQR, h)	Time to ICA: delayed (median & IQR, h)	Primary outcome	Results
TIMACS 2009	961	14.0 (3.0 – 21.0)	50.0 (41.0 – 81.0)	6-month death, non-fatal MI, stroke	Early = 13.9% Delayed = 21.0% HR 0.65, 95% CI 0.48-0.89, p = 0.006
ELISA-3 2013	224	2.6 (1.2 – 6.2)	54.9 (44.2 – 74.5)	30-day death, non-fatal MI, recurrent ischaemia	Early = 10.5% Delayed = 19.1% HR 0.55, 95% CI 0.29-1.10, p=0.26
RIDDLE-NSTEMI 2016	123	1.4 (1.0 – 2.2)	61.0 (35.8 – 85.0)	30-day death, non-fatal MI	Early = 10.7% Delayed = 17.9% HR 0.56, 95% CI 0.21-1.51 p=0.12
VERDICT 2018	1025	4.7 (3.0 – 12.2)	61.6 (39.4 – 87.8)	Death, non-fatal MI, refractory ischaemia, admission for heart failure at median 4.3 years	Early = 34.0% Delayed = 40.1% HR 0.81, 95% CI 0.66-0.99, p = 0.023

CI: confidence interval; HR: hazard ratio; ICA: invasive coronary angiography; IQR: interquartile range; MI: myocardial infarction

**Table 2: RAPID N-STEMI inclusion and exclusion criteria**

Inclusion criteria	Exclusion criteria
>18 years of age	ST elevation myocardial infarction
Clinical diagnosis of N-STEMI comprising: <ul style="list-style-type: none"> <li>▪ Cardiovascular symptoms suggestive of myocardial ischaemia</li> <li>▪ Elevated high-sensitivity troponin I or T</li> </ul>	Evident type 2 myocardial infarction
Symptoms <12 hours prior to admission	Previous known cardiomyopathy
GRACE 2.0 score $\geq 118$ or if GRACE 2.0 score $\geq 90$ but $< 118$ must have at least one high-risk feature: <ul style="list-style-type: none"> <li>▪ Anterior location of ECG changes (V2-V5)</li> <li>▪ ST segment depression in 2 contiguous leads of 0.15mV/1.5mm</li> <li>▪ Diabetes mellitus on medication</li> <li>▪ Elevated high-sensitivity troponin 3x upper limit of normal</li> </ul>	Need for urgent PCI according to ESC Guidelines (haemodynamic instability, VT, VF, recurrent or persistent pain)
Intention to perform angiography and, if indicated, follow-on revascularisation	Cardiogenic shock
Provision of verbal assent followed by written informed consent	Severe valvular heart disease
	Any contraindication to PCI
	Current participation in another intervention trial

ECG: electrocardiogram; ESC: European Society of Cardiology; GRACE: Global Registry of Acute Coronary Events; N-STEMI: non-ST elevation myocardial infarction; PCI: percutaneous coronary intervention; VF: ventricular fibrillation; VT: ventricular tachycardia

**Table 3: RAPID N-STEMI CMR study endpoints**

Primary outcome	Secondary outcomes
Infarct size (% left ventricular mass)	Left ventricular volumes and ejection fraction
	Myocardial salvage index
	Extracellular volume
	Ischaemic burden
	Global myocardial strain

**Table 4: RAPID N-STEMI study endpoints**

Primary outcome	Secondary outcomes
All-cause mortality, non-fatal myocardial infarction, and admission for heart failure at 12 months	Individual components of primary composite outcome
	Cardiovascular mortality
	Ischaemia-driven revascularisation
	BARC 3-5 major bleeding
	Stroke
	Length of inpatient stay
	Admission for any cause
	Events prior to angiography
	Quality of life (Seattle Angina Questionnaire and EQ-5D-5L questionnaires)
	Cost-efficacy analysis
	Proportion of patients requiring emergency revascularisation in group B
	Total VARC-2 classified access site complications
Major VARC-2 classified access site complications	

BARC: Bleeding Academic Research Consortium; VARC: Vascular Access Research Consortium

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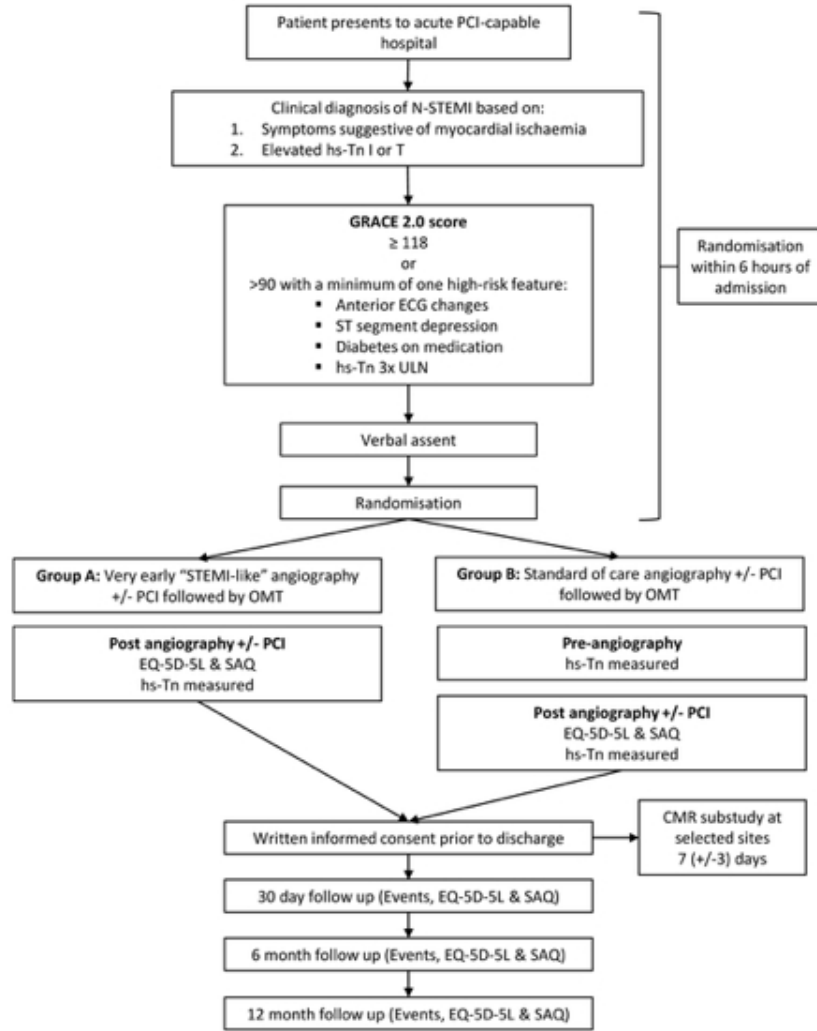


Figure 1: RAPID N-STEMI study flow diagram

CMR: cardiac magnetic resonance; ECG: electrocardiogram; hs-Tn: high sensitivity troponin N-STEMI: non-ST elevation myocardial infarction; OMT: optimal medical therapy; SAQ: Seattle Angina Questionnaire; STEMI: ST elevation myocardial infarction; ULN: upper limit of normal

38x54mm (300 x 300 DPI)



# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

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

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

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

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

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Page
	Reporting Item	Number
<b>Administrative information</b>		
Title	<a href="#">#1</a> Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

1	Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered,	2
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4			name of intended registry	
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6	Trial registration:	<a href="#">#2b</a>	All items from the World Health Organization Trial	2
7				
8	data set		Registration Data Set	
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11	Protocol version	<a href="#">#3</a>	Date and version identifier	3
12				
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15	Funding	<a href="#">#4</a>	Sources and types of financial, material, and other	20
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17			support	
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20	Roles and	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	20
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22	responsibilities:			
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24	contributorship			
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28	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	8
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30	responsibilities:			
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32	sponsor contact			
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34	information			
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38	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study	20
39				
40	responsibilities:		design; collection, management, analysis, and	
41				
42	sponsor and funder		interpretation of data; writing of the report; and the	
43				
44			decision to submit the report for publication, including	
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46			whether they will have ultimate authority over any of	
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48			these activities	
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52	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the	11
53				
54	responsibilities:		coordinating centre, steering committee, endpoint	
55				
56	committees		adjudication committee, data management team, and	
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other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

## Introduction

Background and rationale	<a href="#">#6a</a>	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	5
Background and rationale: choice of comparators	<a href="#">#6b</a>	Explanation for choice of comparators	5
Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	6
Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
<b>Methods:</b>			
<b>Participants, interventions, and outcomes</b>			
Study setting	<a href="#">#9</a>	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	6

1	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If	7
2				
3			applicable, eligibility criteria for study centres and	
4				
5			individuals who will perform the interventions (eg,	
6				
7			surgeons, psychotherapists)	
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11	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow	7
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13	description		replication, including how and when they will be	
14				
15			administered	
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19	Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	7
20				
21	modifications		interventions for a given trial participant (eg, drug dose	
22				
23			change in response to harms, participant request, or	
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25			improving / worsening disease)	
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29	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols,	7
30				
31	adherence		and any procedures for monitoring adherence (eg, drug	
32				
33			tablet return; laboratory tests)	
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35				
36	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	7
37				
38	concomitant care		permitted or prohibited during the trial	
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42	Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	10
43				
44			specific measurement variable (eg, systolic blood	
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46			pressure), analysis metric (eg, change from baseline, final	
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48			value, time to event), method of aggregation (eg, median,	
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50			proportion), and time point for each outcome. Explanation	
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52			of the clinical relevance of chosen efficacy and harm	
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54			outcomes is strongly recommended	
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1	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any	10
2			run-ins and washouts), assessments, and visits for	
3			participants. A schematic diagram is highly recommended	
4			(see Figure)	
5				
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11	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve	10
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any sample	
14			size calculations	
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21	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to	10
22			reach target sample size	
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26	<b>Methods:</b>			
27				
28	<b>Assignment of</b>			
29	<b>interventions (for</b>			
30	<b>controlled trials)</b>			
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36	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,	7
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
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53	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg,	7
54	concealment		central telephone; sequentially numbered, opaque,	
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58	mechanism			
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sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: [#16c](#) Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions 7

Blinding (masking) [#17a](#) Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how 7

Blinding (masking): [#17b](#) If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial 7

**Methods: Data collection, management, and analysis**

Data collection plan [#18a](#) Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol 8

1	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete	8
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
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11	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,	8
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
16				
17				
18	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary	11
19			outcomes. Reference to where other details of the	
20			statistical analysis plan can be found, if not in the protocol	
21				
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23	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and	11
24	analyses		adjusted analyses)	
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28	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	11
29	population and		adherence (eg, as randomised analysis), and any	
30	missing data		statistical methods to handle missing data (eg, multiple	
31			imputation)	
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36	<b>Methods: Monitoring</b>			
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39	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC);	11
40	formal committee		summary of its role and reporting structure; statement of	
41			whether it is independent from the sponsor and	
42			competing interests; and reference to where further	
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1 details about its charter can be found, if not in the  
 2 protocol. Alternatively, an explanation of why a DMC is  
 3 not needed  
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8	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping	n/a
9	interim analysis		guidelines, including who will have access to these	
10			interim results and make the final decision to terminate	
11			the trial	
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18	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing	n/a
19			solicited and spontaneously reported adverse events and	
20			other unintended effects of trial interventions or trial	
21			conduct	
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28	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if	n/a
29			any, and whether the process will be independent from	
30			investigators and the sponsor	
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35	<b>Ethics and</b>			
36	<b>dissemination</b>			
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41	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional	8
42	approval		review board (REC / IRB) approval	
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46	Protocol	<a href="#">#25</a>	Plans for communicating important protocol modifications	n/a
47	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
48			relevant parties (eg, investigators, REC / IRBs, trial	
49			participants, trial registries, journals, regulators)	
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1	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential	n/a
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
4				
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9	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	n/a
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
12				
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16	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	n/a
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
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26	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	20
27	interests		investigators for the overall trial and each study site	
28				
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31	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial	21
32			dataset, and disclosure of contractual agreements that	
33			limit such access for investigators	
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38				
39	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	n/a
40	trial care		compensation to those who suffer harm from trial	
41			participation	
42				
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47	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	20
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
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1 Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of n/a  
 2  
 3 authorship professional writers  
 4  
 5

6 Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full 20  
 7  
 8 reproducible protocol, participant-level dataset, and statistical code  
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 10 research  
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## 13 Appendices

14  
 15  
 16  
 17 Informed consent [#32](#) Model consent form and other related documentation n/a  
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 19 materials given to participants and authorised surrogates  
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22  
 23 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of n/a  
 24  
 25 biological specimens for genetic or molecular analysis in  
 26  
 27 the current trial and for future use in ancillary studies, if  
 28  
 29 applicable  
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