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# BMJ Open

## Study protocol for IMPROVE: a multicentre prospective observational cohort study of the incidence, impact and mechanisms of perioperative right ventricular dysfunction.

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Manuscripts

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3 1 **Title: Study protocol for IMPROVE: a multicentre prospective observational cohort**  
4 2 **study of the incidence, impact and mechanisms of perioperative right ventricular**  
5 3 **dysfunction**  
6 4

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## 29 Abstract

### 30 Introduction

31 Perioperative myocardial injury evidenced by elevated cardiac biomarkers (both natriuretic  
32 peptides and troponin) is common after major non-cardiac surgery. It is unclear however if  
33 the rise in cardiac biomarkers represents global or more localised cardiac injury. We have  
34 previously shown isolated right ventricular (RV) dysfunction in patients following lung  
35 resection surgery, with no change in left ventricular (LV) function. Given that perioperative  
36 RV dysfunction (RVD) can manifest insidiously, we hypothesise there may be a substantial  
37 burden of covert yet clinically important perioperative RVD in other major non-cardiac  
38 surgical groups. The Incidence, impact and Mechanisms of Perioperative Right Ventricular  
39 dysfunction (IMPRoVE) study has been designed to address this knowledge gap.

### 41 Methods and analysis

42 A multicentre prospective observational cohort study across four centres in the West of  
43 Scotland and London. One-hundred and seventy-five patients will be recruited from five  
44 surgical specialties; thoracic, upper gastrointestinal, vascular, colorectal, and orthopaedic  
45 surgery (35 patients from each group). All patients will undergo pre- and postoperative (day  
46 2-4) echocardiography, with contemporaneous cardiac biomarker testing. Ten patients from  
47 each surgical specialty (50 patients in total) will undergo T1-cardiovascular magnetic  
48 resonance (CMR) imaging preoperatively and postoperatively. The co-primary outcomes are  
49 the incidence of perioperative RVD (diagnosed by RV speckle tracking echocardiography)  
50 and the effect that RVD has on days alive and at home at 30-days postoperatively. Secondary  
51 outcomes include LV dysfunction and clinical outcomes informed by Standardised Endpoints  
52 in Perioperative Medicine (StEP) consensus definitions. T1 CMR will be used to investigate  
53 for imaging correlates of myocardial inflammation as a possible mechanism driving  
54 perioperative RVD.

### 56 Ethics and dissemination

57 Approval was gained from Oxford C Research Ethics Committee (REC reference  
58 22/SC/0442). Findings will be disseminated by various methods including social media,  
59 international presentations, and publication in peer-reviewed journals.

### 61 Trial registration

62 ClinicalTrials.gov registration in progress.

### 64 Strengths and limitations of this study

65 This is the first study to investigate the incidence of perioperative RVD after major non-  
66 cardiac surgery, and the association between RVD and patient outcomes in this group.

68 T1-CMR sub-study to investigate whether inflammation is a mechanism underlying  
69 perioperative RVD.

71 A large prospective multicentre study with appropriate statistical power analysis.

73 It is difficult to predict the incidence of perioperative RVD in surgical groups other than  
74 lung resection since there is such limited data.

## 76 **Introduction**

77 Perioperative myocardial injury (PMI) is common after major non-cardiac surgery, with a  
78 recent large international observational study demonstrating an elevated postoperative high-  
79 sensitivity troponin (hsTn) level in 19.7% of patients undergoing major non-cardiac surgery<sup>1</sup>.  
80 Perioperative PMI has also been shown to be associated with poor cardiovascular outcomes  
81 in patients undergoing non-cardiac surgery<sup>2</sup>. Similarly, natriuretic peptides increase following  
82 surgery, and this is associated with an increased risk of cardiovascular complications and  
83 mortality<sup>3</sup>. Our group has demonstrated that peak postoperative brain natriuretic peptide  
84 (BNP) is associated with postoperative complications and length of hospital stay after  
85 thoracic surgery<sup>4</sup>. Although an increase in cardiac biomarkers after major non-cardiac is well  
86 described, there has been little research to investigate the location of the myocardial injury  
87 (although it is frequently attributed to injury of the left ventricle with little evidence to  
88 substantiate this assertion). A study in a mixed surgical population requiring “rescue”  
89 echocardiography demonstrated that postoperative right ventricular (RV) dysfunction was as  
90 prevalent as left ventricular (LV) dysfunction, occurring in 24.1% of patients.<sup>5</sup> Postoperative  
91 RV dysfunction (RVD) is difficult to diagnose, manifesting with subtle clinical signs; it is  
92 therefore unsurprising that its importance may have been overlooked.<sup>6</sup> In addition to  
93 postoperative RVD, it has been shown that there may be a considerable burden of preoperative  
94 RVD in patients undergoing non-cardiac surgery, a study in patients undergoing major  
95 vascular surgery found a prevalence of preoperative RVD of 10%, and this was associated  
96 with postoperative major cardiac complications<sup>7</sup>. The incidence and significance of  
97 perioperative RVD in other non-cardiac surgical populations has been poorly described. We  
98 have previously shown that patients undergoing lung resection experience significant  
99 impairment of RV function postoperatively with no change in LV function<sup>8</sup>. Further research  
100 is needed to investigate the incidence and impact of perioperative RVD on patient outcomes

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3 101 in other non-cardiac surgery groups. Additionally, the mechanisms underlying perioperative  
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5 102 RVD require elucidation to allow effective preventative and treatment strategies to be  
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7  
8 103 devised. The IMPROVE study has been conceived to address this gap in our understanding of  
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10 104 perioperative RVD.

105

#### 106 Potential mechanisms of perioperative RV dysfunction

107 The mechanisms of postoperative RVD likely reflect a complex interplay between pre-  
108 existing RVD, patient susceptibility, surgical risk and a multitude of potential perioperative  
109 insults.

110

111 As described above<sup>7</sup>, RVD may pre-date surgery. In the general population, RVD is more  
112 prevalent in the elderly, and in people with hypertension, diabetes mellitus, ischaemic heart  
113 disease, and lung disease<sup>9</sup>; risk factors which are overrepresented in the surgical population.  
114 As anticipated, in our previous thoracic surgery cohort we found a high prevalence of pre-  
115 existing RV dysfunction of 50%<sup>8</sup>.

116

117 The perioperative period exposes patients to many insults that may contribute to RVD.

118 Excess pre-load may occur in the form of injudicious IV fluid administration, resulting in RV  
119 distension and tricuspid regurgitation<sup>6,10</sup>. Impaired contractility may occur due to myocardial  
120 ischaemia. RV afterload may increase by many mechanisms, including;

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122 - *Pulmonary thromboembolism (PTE)*- occurring sub-clinically in up to 28% of patients  
123 undergoing elective intermediate to high risk noncardiac surgery<sup>11</sup>.

124

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3 125 - *Lung injury and inflammation*- due to pre-existing lung disease and the combined  
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5 126 deleterious effects of ventilator induced lung injury, systemic inflammation and fluid  
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8 127 overload<sup>6</sup>.

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11  
12 129 - *Positive-pressure mechanical ventilation*<sup>6</sup>

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17 131 - *Lung resection*- recently we have demonstrated the pulsatile component of RV  
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19 132 afterload significantly increases after lung resection<sup>12</sup>.

20  
21 133

### 22 23 134 Inflammation and Perioperative Myocardial Injury

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26 135 Whilst it is widely hypothesised that PMI results predominantly from ischaemia secondary to  
27  
28 136 myocardial oxygen supply/demand imbalance, this hypothesis remains unproven and is  
29  
30 137 challenged by important observations; in excess of 90% of patients with PMI have no  
31  
32 138 ischaemic symptoms to support a diagnosis of myocardial infarction<sup>1</sup>, and the extent and  
33  
34 139 severity of coronary artery disease does not correlate closely with the occurrence of PMI<sup>13</sup>.

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39 141 The inflammatory response is an important contributor to the myocardial injury seen after  
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41 142 myocardial infarction and cardiac surgery, but the extent to which systemic inflammation is  
42  
43 143 involved in the pathogenesis of PMI after non-cardiac surgery is not known. Ackland et al  
44  
45 144 recently demonstrated that PMI was associated with an elevated neutrophil-lymphocyte ratio,  
46  
47 145 suggesting systemic inflammation may predispose patients to PMI<sup>14</sup>. Using T1-weighted  
48  
49 146 Cardiovascular Magnetic Resonance (T1-CMR) our group has described the presence of  
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51 147 imaging correlates of perioperative RV (but not LV) myocardial inflammation in patients  
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53 148 undergoing lung resection<sup>15</sup>.

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3 150 In summary, with greater understanding of the incidence, impact and underlying mechanisms  
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5 151 of perioperative RV dysfunction provided through this investigation, preventative  
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7 152 interventions targeted at patients at greatest risk may offer a unique therapeutic opportunity to  
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9 153 provide a personalised approach to perioperative management, and improve patient outcomes  
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11 154 across a wide range of surgical populations.  
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### 17 156 **Hypotheses**

18  
19 157 1. Right ventricular dysfunction (RVD) after major non-cardiac surgery is a common covert  
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21 158 contributor to perioperative morbidity.  
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26 160 2. Inflammatory injury to the right ventricle (RV) is a significant contributing factor to  
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28 161 perioperative myocardial injury.  
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33 163 3. Prevention of RVD in high-risk patients undergoing major non-cardiac surgery will lead to  
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35 164 improved outcomes. This underlying hypothesis justifies the workstream of our group,  
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37 165 however it is not directly tested by IMPRoVE study.  
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### 42 167 **Methods and Analysis**

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44 168 Summary: A multicentre prospective observational cohort study in patients undergoing major  
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46 169 non-cardiac surgery in five surgical specialties. Main study: 175 patients to undergo  
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48 170 transthoracic echocardiography (TTE) pre- and postoperatively (Figure 1). Sub-study: 50  
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50 171 patients to undergo T1-CMR pre- and postoperatively.  
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3 173 Centres: three hospitals in the West of Scotland (Golden Jubilee National Hospital [GJNH],  
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5 174 Queen Elizabeth University Hospital, and Glasgow Royal Infirmary). and one London  
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8 175 hospital (Royal London Hospital).  
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12 177 Study status: Grant funding was secured 12/02/2021, with ethical approval on 12/01/2023  
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14 178 (REC reference 22/SC/0442). First recruit anticipated April 2023.  
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19 **180 Selection of study subjects**

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21 **181 Inclusion Criteria**

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24 182 1. Patient aged >18 years

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26 183 2. Patient undergoing planned elective primary hip or knee joint replacement under spinal  
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28 184 anaesthesia, major colorectal, major vascular surgery, or major surgery requiring one lung  
29  
30 185 ventilation with or without lung resection  
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33 186 3. Provision of informed consent  
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38 **188 Main Study Exclusion Criteria**

39  
40 189 1. Pregnancy

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42 190 2. On-going participation in any investigational research which could undermine the  
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44 191 scientific basis of the study  
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47 192 3. Previous major surgery within previous 3 months

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49 193 4. Previous participation in the IMPRoVE study

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51 194 5. Inadequate comprehension of English resulting in inability to comply with instructions  
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53 195 while undergoing interventions required for main study and sub-study  
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3 **198 T1-CMR Sub-study Exclusion Criteria**  
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5 199 1. Contraindication to T1-CMR (see supplementary material)  
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8 200 2. Atrial fibrillation at baseline  
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10 201 3. Acute or chronic kidney disease  
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12 202 4. Allergy to intravenous contrast  
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17 204 **Study Conduct**  
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19 205 **Recruitment**  
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21 206 Patients will be identified from hospital waiting lists. Patients will be informed of the study,  
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23 207 offered a patient information sheet, and invited to participate at the earliest possible  
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25 208 opportunity after they have been informed of their decision for surgery. Following  
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27 209 appropriate time to consider participation, informed consent will be obtained by a member of  
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29 210 the research team.  
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35 212 **Consent**  
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37 213 Written informed consent will be obtained, following a face-to-face discussion about the  
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39 214 study by a member of the study team. Signing of consent form and preoperative blood  
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41 215 sampling and imaging may take place at any time in the 30 days prior to surgery or on the  
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43 216 day of surgery.  
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49 218 **Medical Management**  
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51 219 Medical management will be according to the standard of care at each treating site and is not  
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53 220 influenced by this study protocol.  
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3 **223 Study Interventions**

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5 224 Table 1 shows the general schedule of assessments/study interventions that patients will  
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8 225 undergo.

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11  
12 227 Table 1. Schedule of Assessments

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15 **Table 1. Schedule of assessments for all patients enrolled into IMPRoVE study**

Visit Window	Pre-op	Day of surgery (Day 0)	POD1	POD2	Day of Echo (POD 2-4)	Discharge	30 days	3 months	12 months
Informed consent	x								
Inclusion/exclusion criteria	x								
Baseline demographics and risk scoring	x								
BNP/HsTn	x		x	x	x				
NT-proBNP	x								
Immediate perioperative data		x							
Echocardiography	x				x				
T1-CMR <sup>A</sup>	x				x				
QoR-15	x				x				
Organ specific complications (Clavien-Dindo $\geq 2$ )			x	x	x	x	x		
Unplanned ICU Admission			x	x	x	x			
Length of Hospital stay						x			
Length of ICU/HDU stay					x	x			
Mortality					x	x	x	x	x
DAH <sub>30</sub>							x		
Hospital readmission							x		
EQ-5D-5L	x						x	x	x
WHODAS 2.0	x						x	x	x

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<sup>A</sup>= Ten patients from each of the five surgical groups (50 in total)

48 228 POD = postoperative day, echo = echocardiography, BNP = brain natriuretic peptide, HsTn = high sensitivity

49  
50 229 troponin, NT-proBNP = N-terminal prohormone of brain natriuretic peptide, T1-CMR = T1 cardiovascular

51  
52 230 magnetic resonance, QoR-15 = quality of recovery-15 score, ICU = intensive care unit, HDU = high

53  
54 231 dependency unit, DAH<sub>30</sub> = days alive and at home at 30-days, EQ-5D-5L = EuroQol-5 Dimension Health

55  
56 232 Related Quality of Life Questionnaire, WHODAS 2.0 = World Health Organisation Disability Assessment

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58 233 Schedule 2.0.

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### 235 **Echocardiography Conduct and Analysis**

236 Transthoracic echocardiography will be performed on all 175 patients by a British Society of  
237 Echocardiography (BSE) accredited echocardiographers preoperatively and between  
238 postoperative days 2-4. Echocardiography will acquire the minimum BSE image dataset<sup>16</sup>. In  
239 addition to this minimum image dataset, we will acquire a RV focussed apical four chamber  
240 view for RV free-wall peak longitudinal strain (FWLS) analysis (optimising feasibility as per  
241 consensus guidelines<sup>17 18</sup>). All echocardiography study images will be sent centrally for  
242 offline analysis: anonymised images will be transferred via routine clinical imaging systems  
243 to the GJNH.

244

245 A full echocardiography data set will be used to assess for RVD (the primary outcome) and  
246 LV dysfunction (LVD). Offline RV and LV 2D speckle tracking strain analysis will be  
247 performed using Tomtec 2D Cardiac Performance Analysis software. Twenty  
248 echocardiography scans will be randomly selected and re-reported by the same reporter a  
249 minimum of two weeks after initial reporting, and reported by a second reporter, to allow  
250 assessment of intra- and inter-observer agreement. Reproducibility will be assessed by  
251 intraclass correlation co-efficient (ICC) using two-way mixed effects with absolute  
252 agreement and Bland–Altman plots.

253

### 254 **T1-CMR Conduct**

255 A sub-cohort of 50 patients (10 from each surgical group) will undergo T1-CMR  
256 preoperatively and on day 2-4 postoperatively. Replicating our previous protocol<sup>8</sup>, CMR will  
257 be undertaken on a 1.5 or 3.0 Tesla scanner, by band 7 Health and Care Professions Council  
258 accredited radiographers. T1 weighted scans will be performed pre- and post- intravenous  
259 gadolinium administration. Post-processing will be protocolised and dual reported by blinded  
260 observers.

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3 **261 Laboratory sampling**  
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5 262 Where possible samples will be drawn contemporaneously with routine clinical blood tests.  
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8 263 Cardiac biomarkers will be batch analysed at University of Glasgow Laboratories.  
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12 **265 DAH<sub>30</sub> Conduct**  
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14 266 Days alive and at home at 30-days postoperatively (DAH<sub>30</sub>) will be assessed by telephone on  
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17 267 postoperative day 30 (up to + 5 days). A script will be used to ensure that DAH<sub>30</sub> is reliably  
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19 268 and consistently recorded.  
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24 **270 Data collection and management**  
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26 271 Data collection will be performed by the local study team on case report forms (CRFs) which  
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28 272 will be filed and securely stored at participating sites. The data will be anonymised at site and  
29

30 273 a unique numeric study number allocated. Completed CRFs will be entered onto a secure  
31

32 274 online database in a linked anonymised form. Electronic data will be stored in an encrypted  
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34 275 and anonymised format for 15 years following the completion of the trial. At the end of this  
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36 276 period, the dataset will be destroyed according to DoD 5220.22-M standards. All data will be  
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38 277 held in accordance with The General Data Protection Regulation (2018).  
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44 **279 Laboratory data**  
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46 280 Laboratory data will be obtained from the local biochemistry and haematology laboratory  
47

48 281 reporting systems preoperatively, on the day of echocardiography and at follow-up.  
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53 **283 Clinical data**  
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55 284 Baseline demographic information will be collected including chronic co-morbidities. We  
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57 285 will specifically gather information on sleep apnoea status and previous COVID-19 infection  
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3 286 since these may affect baseline RV function. Preoperative data will include previous  
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5 287 pulmonary function tests, cardiopulmonary exercise testing, computed tomography (CT)  
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7 288 thorax imaging (for coronary artery calcium scoring), American College of Surgeons  
8  
9 289 National Surgical Quality Improvement Program risk scoring, and baseline questionnaires  
10  
11 290 (Duke activity status index [DASI], quality of recovery-15 [QoR-15], EuroQol-5 Dimension  
12  
13 291 Health Related Quality of Life Questionnaire [EQ-5D-5L], and WHO Disability Assessment  
14  
15 292 Schedule 2.0 [WHODAS 2.0]). Immediate perioperative data will include the operation  
16  
17 293 performed, duration of surgery and anaesthesia, duration of one lung ventilation (if  
18  
19 294 applicable), and use of vasopressor/inotropic support.  
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## 26 296 **Study outcomes**

### 27 297 **Co-primary outcomes**

#### 28 298 Incidence of postoperative RVD

29 299 RVD, defined as:

30 300

31 301 • 2D-speckle tracking derived RVFWLS less negative than -20%<sup>17,19</sup>.

32 302

33 303 • Or, (when RVFWLS not available) two of Tricuspid Annular Plane Systolic Excursion

34 304 <16mm, S' Wave velocity at the tricuspid annulus <10cm/s or tissue doppler RV index of

35 305 myocardial performance >0.55<sup>20</sup>.

36 306

#### 37 307 Clinical impact of postoperative RVD

38 308 Days alive and at home at 30 days postoperatively (DAH<sub>30</sub>). DAH<sub>30</sub> is a continuous number

39 309 between 0 and 30 which reflects, out of the 30 days following surgery, the total number of

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3 310 those days that a patient spends alive and at home. If a patient dies within those 30 days, their  
4  
5 311 value is set to 0.  
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10 313 **Justification for co-primary outcomes**

11  
12 314 Incidence of postoperative RVD

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14 315 There is currently no consensus on how best to measure RV function in the context of clinical  
15  
16 316 trials<sup>21</sup>. Recent work however (by our group and others) has demonstrated the superiority and  
17  
18 317 increased reproducibility of RVFWLS in identifying RVD compared to ‘conventional  
19  
20 318 indices’<sup>22-24</sup>. A recent American Thoracic Society Research Statement has advocated the use  
21  
22 319 of RVFWLS due to its ability to assess RVD at an early stage and to detect differences when  
23  
24 320 other traditional measurements fail to do so<sup>21</sup>.  
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28  
29  
30 322 Clinical impact of perioperative RV

31  
32 323 Days alive and at home at 30 days postoperatively (DAH<sub>30</sub>) is a novel, well validated clinical  
33  
34 324 endpoint describing all facets of the perioperative experience and has been recommended as a  
35  
36 325 patient centred outcome by the Standardising Endpoints in Perioperative (StEP) Medicine  
37  
38 326 initiative. DAH<sub>30</sub> is sensitive to prolonged stay due to complications, discharge to a  
39  
40 327 rehabilitation or nursing care facility, readmission to hospital after discharge and mortality  
41  
42 328 thus integrating efficacy, quality, and safety<sup>25,26</sup>.  
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335 **Exploratory outcomes**

336 Exploratory outcomes that we will investigate are shown in Table 2.

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<b>Table 2. Exploratory Outcomes</b>	
Left ventricular dysfunction	Defined by 2D-echocardiography derived biplane ejection fraction
Cardiac biomarkers	NT-proBNP, BNP, hsTn
<i>Clinical outcomes informed by StEP trials consensus definitions:</i>	
Cardiovascular outcomes <sup>27</sup>	Myocardial infarction Myocardial injury Cardiac death Non-fatal cardiac arrest Coronary revascularisation Major adverse cardiac event
Pulmonary outcomes <sup>28</sup>	Pneumonia Atelectasis Acute Respiratory Distress Syndrome Pulmonary aspiration
Renal outcomes <sup>29</sup>	Acute Kidney Injury Need for Renal Replacement Therapy
Infection outcomes <sup>30</sup>	Fever Clinical suspicion of infection
Neurological outcomes <sup>31</sup>	Delirium Stroke
Major complications	Sequential Organ Failure Assessment Score
Clinical indicators	Need for unplanned HDU or ICU admission Requirement for new invasive or non-invasive ventilation Length of postoperative critical care and hospital stay Mortality at 30 days
Patient quality of recovery	QoR-15
Patient centred outcomes	EQ-5D-5L WHODAS 2.0 (assessed at 30 days, 3 months, and 12 months postoperatively)
T1-CMR	Pre and postoperative T1-CMR. T1 weighted CMR pre and post intravenous gadolinium to calculate T1 signal and extracellular volume (imaging correlates of myocardial inflammation)

338 NT-proBNP = N-terminal prohormone of brain natriuretic peptide, BNP = brain natriuretic peptide, HsTn =

339 high sensitivity troponin, StEP = Standardised Endpoints, HDU = high dependency unit, ICU = intensive care

340 unit, QoR-15 = quality of recovery-15, EQ-5D-5L = EuroQol-5 Dimension Health Related Quality of Life

341 Questionnaire, WHODAS 2.0 = World Health Organisation Disability Assessment Schedule 2.0, T1-CMR = T1

342 cardiovascular magnetic resonance,

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3 345 **Statistical Considerations**  
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5 346 All statistical analyses will be performed in conjunction with the Robertson Centre for  
6  
7 347 Biostatistics at the University of Glasgow.  
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12 349 **Analysis of co-primary outcomes**

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15 350 Incidence of perioperative RV dysfunction

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17 351 The identified incidence of postoperative RVD will be compared with the null hypothesis that  
18  
19 352 the incidence equals zero using a one-sample binomial test; 95% confidence intervals for the  
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21 353 incidence will be defined using the Clopper-Pearson method. In addition, we will perform  
22  
23 354 sensitivity analyses to identify the incidence of patients that develop new post operative  
24  
25 355 RVD, and identify the incidence of those that have pre-existing RVD maintained through to  
26  
27 356 the postoperative period. Sub-group analyses will estimate the incidence rate of postoperative  
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29 357 LVD and RVD within surgical subgroups and compare the incidence in patients with COPD  
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31 358 vs no COPD, in operations involving mechanical ventilation and no mechanical ventilation  
32  
33 359 (orthopaedic surgery under spinal anaesthesia), one lung ventilation (OLV) vs no OLV, in  
34  
35 360 videoscopic vs open surgeries, and in patients with IHD vs no IHD. Secondary analyses will  
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37 361 explore the association between pre- and postoperative cardiac biomarker levels and  
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39 362 perioperative LVD and RVD.  
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47 364 With a one sample binomial test at a one-sided significance level of 5% with 80% power, 31  
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49 365 patients would be required to confidently identify an incidence of postoperative RVD of 5%  
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51 366 as different from zero in any individual surgical sub-group. As such, recruiting 35 patients  
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53 367 per group provides a 10% margin for loss to follow-up and withdrawals. This results in a total  
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55 368 sample size of 175.  
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3 370 Clinical impact of perioperative RV dysfunction  
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5 371 Assuming the incidence of RVD is proven to be different from zero in any group (highly  
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7 372 likely given our previous findings<sup>8</sup>), then additional analyses will be performed in pooled  
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9  
10 373 data across all surgical groups to assess the clinical impact of postoperative LVD or RVD.  
11  
12 374 Sensitivity analyses will be performed to assess the clinical impact of RVD on patients that  
13  
14 375 develop new postoperative RVD, compared to the clinical impact of pre-existing RVD which  
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16 376 is maintained through to the postoperative period.  
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21 378 DAH<sub>30</sub> postoperatively will be compared between the groups with and without postoperative  
22  
23 379 RVD using negative binomial regression analysis adjusting for age and other known  
24  
25 380 predictors of DAH<sub>30</sub><sup>25,26</sup>. It will also be explored how adjustment for further variables  
26  
27 381 (including cardiac biomarker profile) affects results. We will conduct the same DAH<sub>30</sub>  
28  
29 382 analysis on the sensitivity analysis groups described above.  
30  
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34  
35 384 Performing power analysis for this comparison is challenging given the large number of  
36  
37 385 unknowns in terms of the incidence of RVD, and the potential effect size. As such, an  
38  
39 386 indicative power analysis was performed exploring sample sizes from 50 to 200 patients, an  
40  
41 387 incidence of RVD 15-50% and for a difference in DAH<sub>30</sub> of 2 or 3 days. The anticipated  
42  
43 388 power is in excess of 0.8 in all simulations containing over 125 patients suggesting that in the  
44  
45 389 175-patient sample should have sufficient power in most conceivable scenarios (Figure 2).  
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3 **395 Exploratory outcomes**  
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5 396 LVD will be analysed analogously to RVD as a secondary analysis.  
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10 398 Secondary outcomes from the postoperative period will be used to compare their incidence in  
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12 399 patients with and without the primary outcome (RVD). We will assess for association  
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14 400 between RVD and PMI (via cardiac biomarkers), cardiovascular complications, major  
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16 401 complications, patient recovery, length of ICU and hospital stay. Analysis of intraoperative  
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18 402 data will be used with the aim to identify mechanisms by which RVD may have arisen.  
19

20 403 Where appropriate, multivariate analysis will be used.  
21  
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23 404

24  
25 405 We will use 30-day mortality as our primary survival end point and will assess for association  
26

27 406 with RVD via appropriate survival analyses.  
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30 407

31  
32 408 We will also assess the intermediate and long-term impact of RVD upon patients by assessing  
33

34 409 association between RVD and health related quality of life (via EQ-5D-5L) and functional  
35

36 410 status (via WHODAS 2.0) at 30-day, three months, and one year postoperatively.  
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40 412 Pre- and postoperative T1-CMR will explore for association between imaging correlates of  
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42 413 myocardial inflammation (T1 and extracellular volume) and both RVD and PMI. This sub-  
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44 414 study will also aim to confirm our previous findings of elevated postoperative  
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46 415 T1/extracellular volume in patients after thoracic surgery<sup>15</sup>, and replicate this in other surgical  
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48 416 groups.  
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## 420 **Patient and public Involvement**

421 Our programme of work was presented to the Society of Cardiothoracic Surgeons  
422 ‘RESOLVES’ Patient and Public Involvement (PPI) group with very positive feedback. This  
423 PPI group was unanimously in favour of our research and its obvious benefits to patients.

424

## 425 **Ethics and Dissemination**

426 The study will be conducted in accordance with the ethical principles that have their origin in  
427 the Declaration of Helsinki and to Good Clinical Practice (GCP) Guidelines. The study has  
428 been approved by the Research Ethics Committee (REC reference 22/SC/0442) and will  
429 comply with all applicable UK legislation. All local site Standardised Operating Procedures  
430 (SOPs) will be followed.

431

432 All publications and presentations relating to this study will be authorised by the trial Chief  
433 Investigator (BS). Authorship will be determined according to the international committee of  
434 medical journal editors’ recommendations. The results of the study will be first reported to  
435 study collaborators. Subsequently, we will communicate our results by reporting them to the  
436 funder and presentation at national meetings, with publication in appropriate peer reviewed  
437 journals. Further details about the trial results and final report will be available on request to  
438 the scientific community in a timely manner.

439

## 440 **Authors Contributions**

441 TK and JM wrote the initial draft of the protocol. BS and PM conceived the study and BS is  
442 the grant holder. NG advised on statistical analyses for the study. All authors contributed to  
443 the protocol, and all authors read and approved the final version of the protocol.

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5  
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11  
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13

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15 450

16  
17 **451 Competing Interests**  
18

19 452 No authors have any competing interests to declare.  
20  
21

22 453

23  
24 **454 Acknowledgements**  
25

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31 **457 Word count**  
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3 459 Figure Legends  
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7  
8 461 Figure 1 Overview of IMPRoVE Main Study  
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10 462 Graphical overview of the main IMPRoVE study. One-hundred and seventy-five patients (35  
11  
12 463 from each surgical group) will undergo echocardiography and cardiac biomarker testing pre-  
13  
14 464 and postoperatively. Co-primary outcomes are the incidence of RV dysfunction, diagnosed  
15  
16 465 by RV free wall longitudinal strain, and DAH<sub>30</sub> (shown in red).

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18  
19 466 GI = gastrointestinal, RV = right ventricular, LV = left ventricular, DAH<sub>30</sub> = Days alive and  
20  
21 467 at home at 30 days postoperatively, StEP-COMPAC = Standardised Endpoints and Core  
22  
23 468 Outcome Measures for Perioperative and Anaesthetic Care, WHODAS = WHO Disability  
24  
25 469 Assessment Schedule 2.0, EQ-5D-5L = EuroQol-5 Dimension Health Related Quality of Life  
26  
27 470 Questionnaire, POD = postoperative day  
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31 471

32  
33 472 Figure 2. Simulated power analysis for impact of RVD on days alive and at home at 30 days  
34

35 473 Assuming for 1% of the patients DAH<sub>30</sub> = 0, for the remainder DAH<sub>30</sub> follows a negative  
36  
37 474 binomial distribution with parameters chosen such that the median DAH<sub>30</sub> is 24/25 in one  
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39 475 group and 27 in the other group and the shape of the distribution is similar to that seen in the  
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41 476 validation cohorts. The simulated DAH<sub>30</sub> was then compared between groups using negative  
42  
43 477 binomial regression (repeated) in 1000 samples. The figures show the resulting estimated  
44  
45 478 power for incidences of postoperative RVD from 15-50%<sup>#</sup>, and for a clinical effect size of 2  
46  
47 479 (Fig A) or 3 (Fig B) days difference in DAH<sub>30</sub>\*.

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51 480 *<sup>#</sup>In our previous work the incidence of postoperative RVD was 50% in thoracic surgical*  
52  
53 481 *patients but may be significantly less in, for example, an orthopaedic population.*

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55  
56 482 *\*In Chou et al's study preoperative RV dysfunction prolonged hospital length of stay by over*  
57  
58 483 *50%, but this cohort was a very high-risk vascular surgical population<sup>7</sup>.*  
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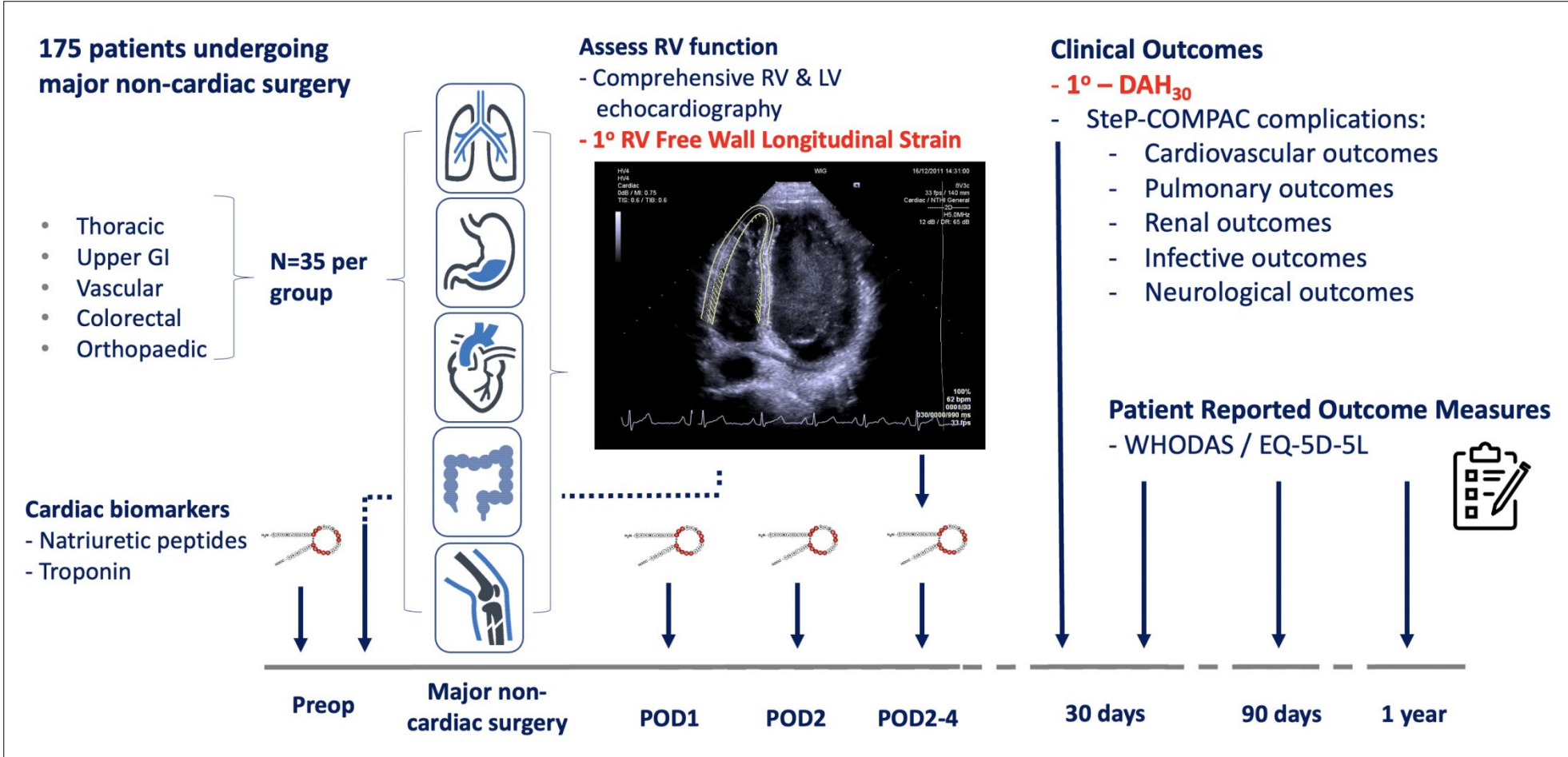
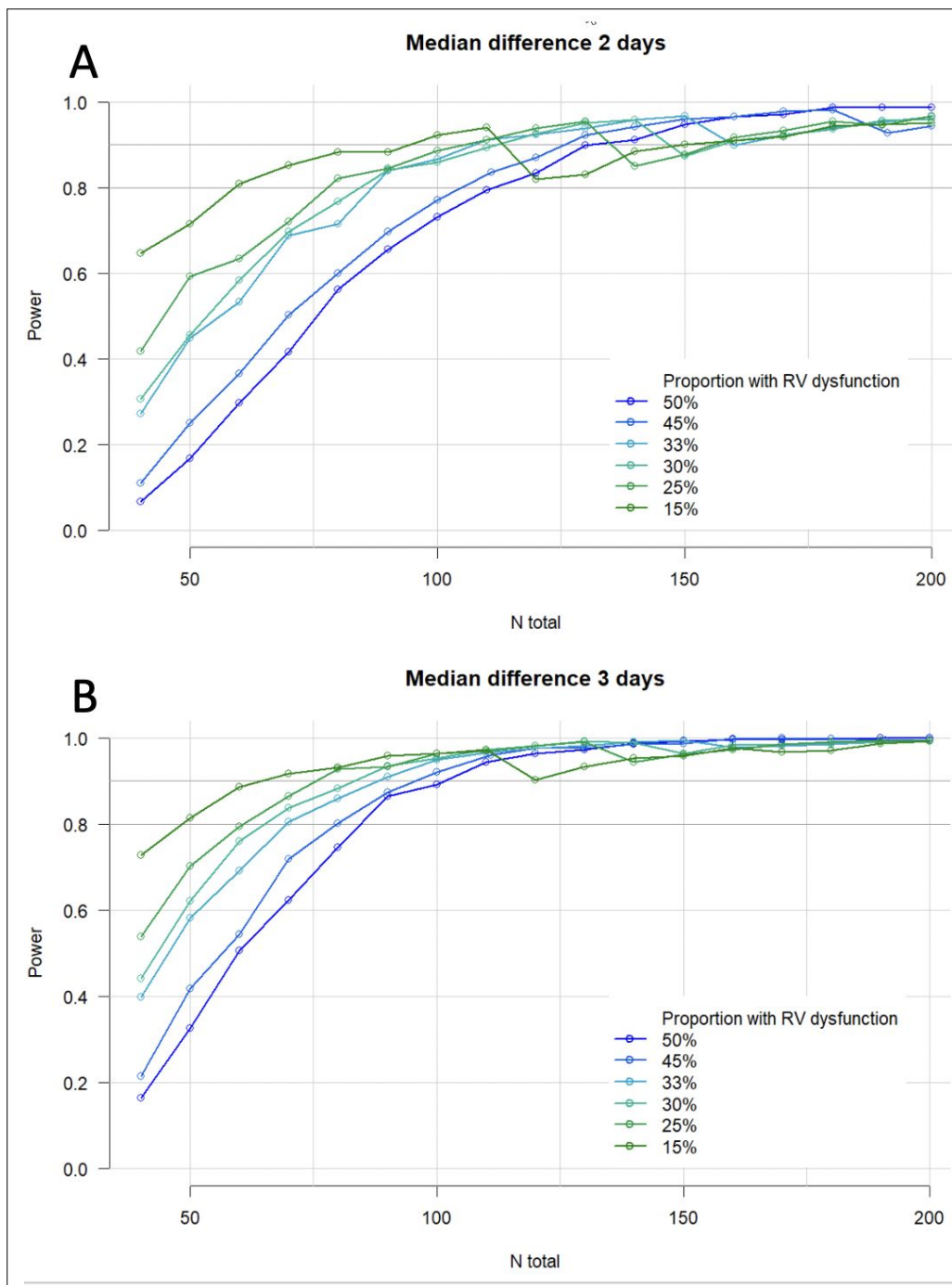


Figure 1 Overview of IMPRoVE Main Study

Graphical overview of the main IMPRoVE study. One-hundred and seventy-five patients (35 from each surgical group) will undergo echocardiography and cardiac biomarker testing pre- and postoperatively. Co-primary outcomes are the incidence of RV dysfunction, diagnosed by RV free wall longitudinal strain, and DAH<sub>30</sub> (shown in red).

GI = gastrointestinal, RV = right ventricular, LV = left ventricular, DAH<sub>30</sub> = Days alive and at home at 30 days postoperatively, StEP-COMPAC = Standardised Endpoints and Core Outcome Measures for Perioperative and Anaesthetic Care, WHODAS = WHO Disability Assessment Schedule 2.0, EQ-5D-5L = EuroQol-5 Dimension Health Related Quality of Life Questionnaire, POD = postoperative day



**Figure 2. Simulated power analysis for impact of RVD on days alive and at home at 30 days**  
 Assuming for 1% of the patients  $DAH_{30} = 0$ , for the remainder  $DAH_{30}$  follows a negative binomial distribution with parameters chosen such that the median  $DAH_{30}$  is 24/25 in one group and 27 in the other group and the shape of the distribution is similar to that seen in the validation cohorts. The simulated  $DAH_{30}$  was then compared between groups using negative binomial regression (repeated) in 1000 samples. The figures show the resulting estimated power for incidences of postoperative RVD from 15-50%<sup>#</sup>, and for a clinical effect size of 2 (Fig A) or 3 (Fig B) days difference in  $DAH_{30}$ \*.  
<sup>#</sup>In our previous work the incidence of postoperative RVD was 50% in thoracic surgical patients but may be significantly less in, for example, an orthopaedic population.  
 \*In Chou et al's study preoperative RV dysfunction prolonged hospital length of stay by over 50%, but this cohort was a very high-risk vascular surgical population<sup>7</sup>.

## Contraindications to Cardiovascular Magnetic Resonance Imaging

Presence of:

- cardiac pacemaker
- artificial heart valve
- neurostimulator
- cochlear implant
- aneurysm clips
- metal injuries to the eye
- loose metal in a part of the body

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1+2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	12+13
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	15+16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	15-17
		(b) Describe any methods used to examine subgroups and interactions	15-17
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
<b>Discussion</b>			N/A
Key results	18	Summarise key results with reference to study objectives	N/A
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Study protocol for IMPROVE: a multicentre prospective observational cohort study of the incidence, impact and mechanisms of perioperative right ventricular dysfunction in non-cardiac surgery

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1 **Title: Study protocol for IMPROVE: a multicentre prospective observational cohort**  
2 **study of the incidence, impact and mechanisms of perioperative right ventricular**  
3 **dysfunction in non-cardiac surgery**

4  
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## 29 Abstract

### 30 Introduction

31 Perioperative myocardial injury evidenced by elevated cardiac biomarkers (both natriuretic  
32 peptides and troponin) is common after major non-cardiac surgery. It is unclear however if  
33 the rise in cardiac biomarkers represents global or more localised cardiac injury. We have  
34 previously shown isolated right ventricular (RV) dysfunction in patients following lung  
35 resection surgery, with no change in left ventricular (LV) function. Given that perioperative  
36 RV dysfunction (RVD) can manifest insidiously, we hypothesise there may be a substantial  
37 burden of covert yet clinically important perioperative RVD in other major non-cardiac  
38 surgical groups. The Incidence, impact and Mechanisms of Perioperative Right Ventricular  
39 dysfunction (IMPRoVE) study has been designed to address this knowledge gap.

### 41 Methods and analysis

42 A multicentre prospective observational cohort study across four centres in the West of  
43 Scotland and London. One-hundred and seventy-five patients will be recruited from five  
44 surgical specialties; thoracic, upper gastrointestinal, vascular, colorectal, and orthopaedic  
45 surgery (35 patients from each group). All patients will undergo pre- and postoperative (day  
46 2-4) echocardiography, with contemporaneous cardiac biomarker testing. Ten patients from  
47 each surgical specialty (50 patients in total) will undergo T1-cardiovascular magnetic  
48 resonance (CMR) imaging preoperatively and postoperatively. The co-primary outcomes are  
49 the incidence of perioperative RVD (diagnosed by RV speckle tracking echocardiography)  
50 and the effect that RVD has on days alive and at home at 30-days postoperatively. Secondary  
51 outcomes include LV dysfunction and clinical outcomes informed by Standardised Endpoints  
52 in Perioperative Medicine (StEP) consensus definitions. T1 CMR will be used to investigate  
53 for imaging correlates of myocardial inflammation as a possible mechanism driving  
54 perioperative RVD.

### 56 Ethics and dissemination

57 Approval was gained from Oxford C Research Ethics Committee (REC reference  
58 22/SC/0442). Findings will be disseminated by various methods including social media,  
59 international presentations, and publication in peer-reviewed journals.

### 61 Trial registration

62 The IMPRoVE study is registered on ClinicalTrials.gov (Identifier NCT05827315).

### 65 Strengths and limitations of this study

66 This is the first study to investigate the incidence of perioperative RVD after major non-  
67 cardiac surgery, and the association between RVD and patient outcomes in this group.

69 T1-CMR sub-study to investigate whether inflammation is a mechanism underlying  
70 perioperative RVD.

72 A large prospective multicentre study with appropriate statistical power analysis.

74 It is difficult to predict the incidence of perioperative RVD in surgical groups other than  
75 lung resection since there is such limited data.

## 77 **Introduction**

78 Perioperative myocardial injury (PMI) is common after major non-cardiac surgery, with a  
79 recent large international observational study demonstrating an elevated postoperative high-  
80 sensitivity troponin (hsTn) level in 19.7% of patients undergoing major non-cardiac  
81 surgery.(1) Perioperative PMI has also been shown to be associated with poor cardiovascular  
82 outcomes in patients undergoing non-cardiac surgery.(2) Similarly, natriuretic peptides  
83 increase following surgery, and this is associated with an increased risk of cardiovascular  
84 complications and mortality.(3) Our group has demonstrated that peak postoperative brain  
85 natriuretic peptide (BNP) is associated with postoperative complications and length of  
86 hospital stay after thoracic surgery.(4) Although an increase in cardiac biomarkers after major  
87 non-cardiac is well described, there has been little research to investigate the location of the  
88 myocardial injury (although it is frequently attributed to injury of the left ventricle with little  
89 evidence to substantiate this assertion). A study in a mixed surgical population requiring  
90 “rescue” echocardiography demonstrated that postoperative right ventricular (RV)  
91 dysfunction was as prevalent as left ventricular (LV) dysfunction, occurring in 24.1% of  
92 patients.(5) Postoperative RV dysfunction (RVD) is difficult to diagnose, manifesting with  
93 subtle clinical signs; it is therefore unsurprising that its importance may have been  
94 overlooked.(6) In addition to postoperative RVD, it has been shown that there may be a  
95 considerable burden of preoperative RVD in patients undergoing non-cardiac surgery. A  
96 study in patients undergoing major vascular surgery found a prevalence of preoperative RVD  
97 of 10%, and this was associated with postoperative major cardiac complications.(7) The  
98 incidence and significance of perioperative RVD in other non-cardiac surgical populations  
99 has been poorly described. We have previously shown that patients undergoing lung resection  
100 experience significant impairment of RV function postoperatively with no change in LV  
101 function.(8) Further research is needed to investigate the incidence and impact of

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3 102 perioperative RVD on patient outcomes in other non-cardiac surgery groups. Additionally,  
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5 103 the mechanisms underlying perioperative RVD require elucidation to allow effective  
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8 104 preventative and treatment strategies to be devised. The IMPRoVE study has been conceived  
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10 105 to address this gap in our understanding of perioperative RVD.

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### 13 14 107 Potential mechanisms of perioperative RV dysfunction

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17 108 The mechanisms of postoperative RVD likely reflect a complex interplay between pre-  
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19 109 existing RVD, patient susceptibility, surgical risk and a multitude of potential perioperative  
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21 110 insults.

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26 112 As described above,(7) RVD may pre-date surgery. In the general population, RVD is more  
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28 113 prevalent in the elderly, and in people with hypertension, diabetes mellitus, ischaemic heart  
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30 114 disease, and lung disease;(9) risk factors which are overrepresented in the surgical  
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32 115 population. As anticipated, in our previous thoracic surgery cohort we found a high  
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34 116 prevalence of pre-existing RV dysfunction of 50%.(8)

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39 118 The perioperative period exposes patients to many insults that may contribute to RVD.

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41 119 Excess pre-load may occur in the form of injudicious IV fluid administration, resulting in RV  
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43 120 distension and tricuspid regurgitation.(6,10) Impaired contractility may occur due to  
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45 121 myocardial ischaemia. RV afterload may increase by many mechanisms, including;

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51 123 - *Pulmonary thromboembolism (PTE)*- occurring sub-clinically in up to 28% of patients  
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53 124 undergoing elective intermediate to high risk noncardiac surgery.(11)

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3 126 - *Lung injury and inflammation*- due to pre-existing lung disease and the combined  
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5 127 deleterious effects of ventilator induced lung injury, systemic inflammation and fluid  
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7  
8 128 overload.(6)  
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10 129  
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12 130 - *Positive-pressure mechanical ventilation*-especially one-lung ventilation.(6)  
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17 132 - *Lung resection*- recently we have demonstrated the pulsatile component of RV  
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19 133 afterload significantly increases after lung resection.(12)  
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### 23 135 Inflammation and Perioperative Myocardial Injury

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26 136 Whilst it is widely hypothesised that PMI results predominantly from ischaemia secondary to  
27  
28 137 myocardial oxygen supply/demand imbalance, this hypothesis remains unproven and is  
29  
30 138 challenged by important observations; in excess of 90% of patients with PMI have no  
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32 139 ischaemic symptoms to support a diagnosis of myocardial infarction,(1) and the extent and  
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34 140 severity of coronary artery disease does not correlate closely with the occurrence of PMI.(13)  
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40 142 The inflammatory response is an important contributor to the myocardial injury seen after  
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42 143 myocardial infarction and cardiac surgery, but the extent to which systemic inflammation is  
43  
44 144 involved in the pathogenesis of PMI after non-cardiac surgery is not known. Ackland et al  
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46 145 recently demonstrated that PMI was associated with an elevated neutrophil-lymphocyte ratio,  
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48 146 suggesting systemic inflammation may predispose patients to PMI.(14) Using T1-weighted  
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50 147 Cardiovascular Magnetic Resonance (T1-CMR) our group has described the presence of  
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52 148 imaging correlates of perioperative RV (but not LV) myocardial inflammation in patients  
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54 149 following lung resection.(15)  
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3 151 In summary, with greater understanding of the incidence, impact and underlying mechanisms  
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5 152 of perioperative RV dysfunction provided through this investigation, preventative  
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7 153 interventions targeted at patients at greatest risk may offer a unique therapeutic opportunity to  
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9 154 provide a personalised approach to perioperative management and improve patient outcomes  
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11 155 across a wide range of surgical populations.  
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### 17 157 **Hypotheses**

18  
19 158 1. Right ventricular dysfunction (RVD) after major non-cardiac surgery is a common covert  
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21 159 contributor to perioperative morbidity.  
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26 161 2. Inflammatory injury to the right ventricle (RV) is a significant contributing factor to  
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28 162 perioperative myocardial injury.  
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### 32 164 **Methods and Analysis**

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35 165 Summary: A multicentre prospective observational cohort study in patients undergoing major  
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37 166 non-cardiac surgery in five surgical specialties. Main study: 175 patients to undergo  
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39 167 transthoracic echocardiography (TTE) pre- and postoperatively (Figure 1). Sub-study: 50  
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41 168 patients to undergo T1-CMR pre- and postoperatively.  
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47 170 Centres: three hospitals in the West of Scotland (Golden Jubilee National Hospital [GJNH],  
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49 171 Queen Elizabeth University Hospital, and Glasgow Royal Infirmary) and one London  
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51 172 hospital (Royal London Hospital).  
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3 174 Study status: Grant funding was secured 12/02/2021, with ethical approval on 12/01/2023  
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5 175 (REC reference 22/SC/0442). Recruitment commenced in May 2023 with an anticipated  
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7  
8 176 study duration of 36 months.  
9

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## 11 178 **Selection of study subjects**

### 12 179 **Inclusion Criteria**

- 13 180 1. Patient aged >18 years
- 14 181 2. Patient undergoing planned elective primary hip or knee joint replacement under spinal
- 15 182 anaesthesia, major colorectal, major vascular surgery, or major surgery requiring one lung
- 16 183 ventilation with or without lung resection
- 17 184 3. Provision of informed consent

18 185

### 19 186 **Main Study Exclusion Criteria**

- 20 187 1. Pregnancy
- 21 188 2. On-going participation in any investigational research which could undermine the
- 22 189 scientific basis of the study
- 23 190 3. Previous major surgery within previous 3 months
- 24 191 4. Previous participation in the IMPRoVE study
- 25 192 5. Inadequate comprehension of English resulting in inability to comply with instructions
- 26 193 while undergoing interventions required for main study and sub-study

27 194

28 195 Risk factors for RVD are likely to be overrepresented in patients presenting for surgery and  
29 196 participants with pre-existing RVD could represent an important population that may face  
30 197 greater consequences of acute perioperative insults to the RV. For this reason, although not a

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3 198 specific inclusion or exclusion criteria, patients with pre-existing RVD, including when  
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5 199 identified on pre-op echocardiography will be included in the study.  
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10 201 **T1-CMR Sub-study Exclusion Criteria**

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12 202 1. Contraindication to T1-CMR (see supplementary material)

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14 203 2. Atrial fibrillation at baseline

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16 204 3. Acute or chronic kidney disease

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18 205 4. Allergy to intravenous contrast

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24 207 **Study Conduct**

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26 208 **Recruitment**

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28 209 Patients will be identified from hospital waiting lists. Patients will be informed of the study,  
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30 210 offered a patient information sheet, and invited to participate at the earliest possible  
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32 211 opportunity after they have been informed of their decision for surgery. Following  
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34 212 appropriate time to consider participation, informed consent will be obtained by a member of  
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36 213 the research team.  
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42 215 **Consent**

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44 216 Written informed consent will be obtained, following a face-to-face discussion about the  
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46 217 study by a member of the study team. Signing of consent form and preoperative blood  
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48 218 sampling and imaging may take place at any time in the 30 days prior to surgery or on the  
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50 219 day of surgery  
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56 221 **Medical Management**  
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222 Medical management will be according to the standard of care at each treating site and is not  
223 influenced by this study protocol.

224

## 225 Study Interventions

226 Table 1 shows the general schedule of assessments/study interventions that patients will  
227 undergo.

228

229 Table 1. Schedule of Assessments

**Table 1. Schedule of assessments for all patients enrolled into IMPRoVE study**

Visit Window	Pre-op	Day of surgery (Day 0)	POD1	POD2	Day of Echo (POD 2-4)	Discharge	30 days	3 months	12 months
Informed consent	x								
Inclusion/exclusion criteria	x								
Baseline demographics and risk scoring	x								
BNP/HsTn	x		x	x	x				
NT-proBNP	x								
Immediate perioperative data		x							
Laboratory Data	x		x	x	x				
Echocardiography	x				x				
T1-CMR <sup>A</sup>	x				x				
QoR-15	x				x				
Organ specific complications (Clavien-Dindo $\geq 2$ )			x	x	x	x	x		
Unplanned ICU Admission			x	x	x	x			
Length of Hospital stay						x			
Length of ICU/HDU stay					x	x			
Mortality					x	x	x	x	x
DAH <sub>30</sub>							x		
Hospital readmission							x		
EQ-5D-5L	x						x	x	x
WHODAS 2.0	x						x	x	x

A= Ten patients from each of the five surgical groups (50 in total)

230 POD = postoperative day, echo = echocardiography, BNP = brain natriuretic peptide, HsTn = high sensitivity

231 troponin, NT-proBNP = N-terminal prohormone of brain natriuretic peptide, T1-CMR = T1 cardiovascular

232 magnetic resonance, QoR-15 = quality of recovery-15 score, ICU = intensive care unit, HDU = high



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3 233 dependency unit, DAH<sub>30</sub> = days alive and at home at 30-days, EQ-5D-5L = EuroQol-5 Dimension Health  
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5 234 Related Quality of Life Questionnaire, WHODAS 2.0 = World Health Organisation Disability Assessment  
6  
7 235 Schedule 2.0.  
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9 236

### 11 237 **Echocardiography Conduct and Analysis**

13 238 Transthoracic echocardiography will be performed on all 175 patients by a British Society of  
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15 239 Echocardiography (BSE) accredited echocardiographers preoperatively and between  
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17 240 postoperative days 2-4. Echocardiography will acquire the minimum BSE image dataset.(16)  
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19 241 In addition to this minimum image dataset, we will acquire a RV focussed apical four  
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21 242 chamber view for RV free-wall peak longitudinal strain (FWLS) analysis (optimising  
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23 243 feasibility as per consensus guidelines(17,18)). All echocardiography study images will be  
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25 244 sent centrally for offline analysis: anonymised images will be transferred via routine clinical  
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27 245 imaging systems to the GJNH.  
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33 247 A full echocardiography data set will be used to assess for RVD (the primary outcome) and  
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35 248 LV dysfunction (LVD). Offline RV and LV 2D speckle tracking strain analysis will be  
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37 249 performed using Tomtec 2D Cardiac Performance Analysis software. Twenty  
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39 250 echocardiography scans will be randomly selected and re-reported by the same reporter a  
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41 251 minimum of two weeks after initial reporting, and reported by a second reporter, to allow  
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43 252 assessment of intra- and inter-observer agreement. Reproducibility will be assessed by  
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45 253 intraclass correlation co-efficient (ICC) using two-way mixed effects with absolute  
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47 254 agreement and Bland–Altman plots.  
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3 **256 T1-CMR Conduct**  
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5 257 A sub-cohort of 50 patients (10 from each surgical group) will undergo T1-CMR  
6  
7 258 preoperatively and on day 2-4 postoperatively. Replicating our previous protocol,(8) CMR  
8  
9 259 will be undertaken on a 1.5 or 3.0 Tesla scanner, by band 7 Health and Care Professions  
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11 260 Council accredited radiographers. T1 weighted scans will be performed pre- and post-  
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13 261 intravenous gadolinium administration. Post-processing will be protocolised and dual  
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15 262 reported by blinded observers.  
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21 **264 Laboratory sampling**  
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24 265 Where possible samples will be drawn contemporaneously with routine clinical blood tests.  
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26 266 Cardiac biomarkers will be batch analysed at University of Glasgow Laboratories.  
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31 **268 DAH<sub>30</sub> Conduct**  
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33 269 Days alive and at home at 30-days postoperatively (DAH<sub>30</sub>) will be assessed by telephone on  
34  
35 270 postoperative day 30 (up to + 5 days). A script will be used to ensure that DAH<sub>30</sub> is reliably  
36  
37 271 and consistently recorded.  
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42 273 Data collection will be performed by the local study team on case report forms (CRFs) which  
43  
44 274 will be filed and securely stored at participating sites. The data will be anonymised at site and  
45  
46 275 a unique numeric study number allocated. Completed CRFs will be entered onto a secure  
47  
48 276 online database in a linked anonymised form. Electronic data will be stored in an encrypted  
49  
50 277 and anonymised format for 15 years following the completion of the trial. At the end of this  
51  
52 278 period, the dataset will be destroyed according to DoD 5220.22-M standards. All data will be  
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54 279 held in accordance with The General Data Protection Regulation (2018).  
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## 281 **Laboratory data**

282 Laboratory data (Full blood count [FBC], Urea and Electrolytes [U+Es] Liver Function Tests  
283 [LFTs] and C-reactive protein [CRP]) will be obtained from the local biochemistry and  
284 haematology laboratory reporting systems perioperatively, on the day of echocardiography  
285 and if clinically indicated, at follow-up.

## 287 **Clinical data**

288 Baseline demographic information will be collected including chronic co-morbidities. We  
289 will specifically gather information on sleep apnoea status and previous COVID-19 infection  
290 since these may affect baseline RV function. Preoperative data will include previous  
291 pulmonary function tests, cardiopulmonary exercise testing, computed tomography (CT)  
292 thorax imaging (for coronary artery calcium scoring), American College of Surgeons  
293 National Surgical Quality Improvement Program risk scoring, and baseline questionnaires  
294 (Duke activity status index [DASI], quality of recovery-15 [QoR-15], EuroQol-5 Dimension  
295 Health Related Quality of Life Questionnaire [EQ-5D-5L], and WHO Disability Assessment  
296 Schedule 2.0 [WHODAS 2.0]). Immediate perioperative data will include the operation  
297 performed, duration of surgery and anaesthesia, duration of one lung ventilation (if  
298 applicable), and use of vasopressor/inotropic support.

## 300 **Study outcomes**

### 301 **Co-primary outcomes**

#### 302 Incidence of postoperative RVD

303 RVD, defined as:

- 304
- 305 • 2D-speckle tracking derived RVFWLS less negative than -20%.(17,19)

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3 3064  
5 307 • Or, (when RVFWLS not available) two of Tricuspid Annular Plane Systolic Excursion6  
7 308 <16mm, S' Wave velocity at the tricuspid annulus <10cm/s or tissue doppler RV index of8  
9 309 myocardial performance >0.55.(20)10  
11 31012  
13 311 Clinical impact of postoperative RVD14  
15 312 Days alive and at home at 30 days postoperatively (DAH<sub>30</sub>). DAH<sub>30</sub> is a continuous number16  
17 313 between 0 and 30 which reflects, out of the 30 days following surgery, the total number of18  
19 314 those days that a patient spends alive and at home. If a patient dies within those 30 days, their20  
21 315 value is set to 0.22  
23 31624  
25 317 **Justification for co-primary outcomes**26  
27 318 Incidence of postoperative RVD28  
29 319 There is currently no consensus on how best to measure RV function in the context of clinical30  
31 320 trials.(21) Recent work however (by our group and others) has demonstrated the superiority32  
33 321 and increased reproducibility of RVFWLS in identifying RVD compared to 'conventional34  
35 322 indices'.(22-24) A recent American Thoracic Society Research Statement has advocated the36  
37 323 use of RVFWLS due to its ability to assess RVD at an early stage and to detect differences38  
39 324 when other traditional measurements fail to do so.(21)40  
41 32542  
43 326 Clinical impact of perioperative RV44  
45 327 Days alive and at home at 30 days postoperatively (DAH<sub>30</sub>) is a novel, well validated clinical46  
47 328 endpoint describing all facets of the perioperative experience and has been recommended as a48  
49 329 patient centred outcome by the Standardising Endpoints in Perioperative (StEP) Medicine50  
51 330 initiative. DAH<sub>30</sub> is sensitive to prolonged stay due to complications, discharge to a

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331 rehabilitation or nursing care facility, readmission to hospital after discharge and mortality

332 thus integrating efficacy, quality, and safety.(25,26)

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For peer review only

334 **Exploratory outcomes**

335 Exploratory outcomes that we will investigate are shown in Table 2.

336

<b>Table 2. Exploratory Outcomes</b>	
Left ventricular dysfunction	Defined by 2D-echocardiography derived biplane ejection fraction
Cardiac biomarkers	NT-proBNP, BNP, hsTn
<i>Clinical outcomes informed by StEP trials consensus definitions:</i>	
Cardiovascular outcomes(27)	Myocardial infarction Myocardial injury Cardiac death Non-fatal cardiac arrest Coronary revascularisation Major adverse cardiac event
Pulmonary outcomes(28)	Pneumonia Atelectasis Acute Respiratory Distress Syndrome Pulmonary aspiration
Renal outcomes(29)	Acute Kidney Injury Need for Renal Replacement Therapy
Infection outcomes(30)	Fever Clinical suspicion of infection
Neurological outcomes(31)	Delirium Stroke
Major complications	Sequential Organ Failure Assessment Score
Clinical indicators	Need for unplanned HDU or ICU admission Requirement for new invasive or non-invasive ventilation Length of postoperative critical care and hospital stay Mortality at 30 days
Patient quality of recovery	QoR-15
Patient centred outcomes	EQ-5D-5L WHODAS 2.0 (assessed at 30 days, 3 months, and 12 months postoperatively)
T1-CMR	Pre and postoperative T1-CMR. T1 weighted CMR pre and post intravenous gadolinium to calculate T1 signal and extracellular volume (imaging correlates of myocardial inflammation)

337 NT-proBNP = N-terminal prohormone of brain natriuretic peptide, BNP = brain natriuretic peptide, HsTn =

338 high sensitivity troponin, StEP = Standardised Endpoints, HDU = high dependency unit, ICU = intensive care

339 unit, QoR-15 = quality of recovery-15, EQ-5D-5L = EuroQol-5 Dimension Health Related Quality of Life

340 Questionnaire, WHODAS 2.0 = World Health Organisation Disability Assessment Schedule 2.0, T1-CMR = T1

341 cardiovascular magnetic resonance,

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3 344 **Statistical Considerations**  
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5 345 All statistical analyses will be performed in conjunction with the Robertson Centre for  
6  
7 346 Biostatistics at the University of Glasgow.  
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12 348 **Analysis of co-primary outcomes**

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15 349 Incidence of perioperative RV dysfunction

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17 350 The identified incidence of postoperative RVD will be compared with the null hypothesis that  
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19 351 the incidence equals zero using a one-sample binomial test; 95% confidence intervals for the  
20  
21 352 incidence will be defined using the Clopper-Pearson method. In addition, we will perform  
22  
23 353 sensitivity analyses to identify the incidence of patients that develop new post operative  
24  
25 354 RVD, and identify the incidence of those that have pre-existing RVD maintained through to  
26  
27 355 the postoperative period. Sub-group analyses will estimate the incidence rate of postoperative  
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29 356 LVD and RVD within surgical subgroups and compare the incidence in patients with COPD  
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31 357 vs no COPD, in operations involving mechanical ventilation and no mechanical ventilation  
32  
33 358 (orthopaedic surgery under spinal anaesthesia), one lung ventilation (OLV) vs no OLV, in  
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35 359 videoscopic vs open surgeries, and in patients with IHD vs no IHD. Secondary analyses will  
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37 360 explore the association between pre- and postoperative cardiac biomarker levels and  
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39 361 perioperative LVD and RVD.  
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47 363 With a one sample binomial test at a one-sided significance level of 5% with 80% power, 31  
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49 364 patients would be required to confidently identify an incidence of postoperative RVD of 5%  
50  
51 365 as different from zero in any individual surgical sub-group. As such, recruiting 35 patients  
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53 366 per group provides a 10% margin for loss to follow-up and withdrawals. This results in a total  
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55 367 sample size of 175.  
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3 369 Clinical impact of perioperative RV dysfunction  
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5 370 Assuming the incidence of RVD is proven to be different from zero in any group (highly  
6  
7 371 likely given our previous findings(8)), then additional analyses will be performed in pooled  
8  
9 372 data across all surgical groups to assess the clinical impact of postoperative LVD or RVD.  
10  
11 373 Sensitivity analyses will be performed to assess the clinical impact of RVD on patients that  
12  
13 374 develop new postoperative RVD, compared to the clinical impact of pre-existing RVD which  
14  
15 375 is maintained through to the postoperative period.  
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21 377 DAH<sub>30</sub> postoperatively will be compared between the groups with and without postoperative  
22  
23 378 RVD using negative binomial regression analysis adjusting for age and other known  
24  
25 379 predictors of DAH<sub>30</sub>.(25,26) It will also be explored how adjustment for further variables  
26  
27 380 (including cardiac biomarker profile) affects results. We will conduct the same DAH<sub>30</sub>  
28  
29 381 analysis on the sensitivity analysis groups described above.  
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33 382

34  
35 383 Performing power analysis for this comparison is challenging given the large number of  
36  
37 384 unknowns in terms of the incidence of RVD, and the potential effect size. As such, an  
38  
39 385 indicative power analysis was performed exploring sample sizes from 50 to 200 patients, an  
40  
41 386 incidence of RVD 15-50% and for a difference in DAH<sub>30</sub> of 2 or 3 days. The anticipated  
42  
43 387 power is in excess of 0.8 in all simulations containing over 125 patients suggesting that in the  
44  
45 388 175-patient sample should have sufficient power in most conceivable scenarios (Figure 2).  
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3 394 **Exploratory outcomes**  
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5 395 LVD will be analysed analogously to RVD as a secondary analysis.  
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10 397 Secondary outcomes from the postoperative period will be used to compare their incidence in  
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12 398 patients with and without the primary outcome (RVD). We will assess for association  
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14 399 between RVD and PMI (via cardiac biomarkers), cardiovascular complications, major  
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16 400 complications, patient recovery, length of ICU and hospital stay. Analysis of intraoperative  
17

18 401 data will be used with the aim to identify mechanisms by which RVD may have arisen.  
19

20 402 Where appropriate, multivariate analysis will be used.  
21  
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23 403

24  
25 404 We will use 30-day mortality as our primary survival end point and will assess for association  
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27 405 with RVD via appropriate survival analyses.  
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31  
32 407 We will also assess the intermediate and long-term impact of RVD upon patients by assessing  
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34 408 association between RVD and health related quality of life (via EQ-5D-5L) and functional  
35

36 409 status (via WHODAS 2.0) at 30-day, three months, and one year postoperatively.  
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41 411 Pre- and postoperative T1-CMR will explore for association between imaging correlates of  
42

43 412 myocardial inflammation (T1 and extracellular volume) and both RVD and PMI. This sub-  
44

45 413 study will also aim to confirm our previous findings of elevated postoperative  
46

47 414 T1/extracellular volume in patients after thoracic surgery,(15) and replicate this in other  
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49 415 surgical groups.  
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## 419 **Patient and public Involvement**

420 Our programme of work was presented to the Society of Cardiothoracic Surgeons  
421 'RESOLVES' Patient and Public Involvement (PPI) group with very positive feedback. This  
422 PPI group was unanimously in favour of our research and its obvious benefits to patients.  
423

## 424 **Ethics and Dissemination**

425 The study will be conducted in accordance with the ethical principles that have their origin in  
426 the Declaration of Helsinki and to Good Clinical Practice (GCP) Guidelines. UK wide ethical  
427 approval was obtained from the South Central- Oxford C Research Ethics Committee (REC  
428 reference 22/SC/0442) and will comply with all applicable UK legislation. Local research and  
429 development approval was obtained from each participating site. All local site Standardised  
430 Operating Procedures (SOPs) will be followed.

431  
432 All publications and presentations relating to this study will be authorised by the trial Chief  
433 Investigator (BS). Authorship will be determined according to the international committee of  
434 medical journal editors' recommendations. The results of the study will be first reported to  
435 study collaborators. Subsequently, we will communicate our results by reporting them to the  
436 funder and presentation at national meetings, with publication in appropriate peer reviewed  
437 journals. Further details about the trial results and final report will be available on request to  
438 the scientific community in a timely manner.

439

## 440 **Authors Contributions**

441 All authors contributed significantly to the submitted work. TK and JM wrote the initial draft  
442 of the protocol. BS and PM conceived the study and BS is the grant holder. CB contributed to  
443 study design and initial funding application. RK and SM are co-principal investigators at

1  
2  
3 444 Glasgow Royal Infirmary and contributed to study design. MW is principal investigator and  
4  
5 445 IR co-investigator at the Queen Elizabeth University Hospital, both contributed to study  
6  
7 446 design. GA is co-investigator at the Royal London Hospital and contributed to study design.  
8  
9 447 KR is a co-investigator and lead interventional cardiologist for the study and was involved in  
10  
11 448 study design. NG advised on statistical analyses for the study. All authors read and  
12  
13 449 approved the final manuscript.  
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450

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28  
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456

### 457 **Competing Interests**

33 458 No authors have any competing interests to declare.  
34  
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459

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### 463 **Word count**

47 464 3170  
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1  
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3 465 Figure Legends  
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6 466

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8 467 Figure 1 Overview of IMPRoVE Main Study  
9

10 468 Graphical overview of the main IMPRoVE study. One-hundred and seventy-five patients (35  
11  
12 469 from each surgical group) will undergo echocardiography and cardiac biomarker testing pre-  
13  
14 470 and postoperatively. Co-primary outcomes are the incidence of RV dysfunction, diagnosed  
15  
16 471 by RV free wall longitudinal strain, and DAH<sub>30</sub> (shown in red).

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18  
19 472 GI = gastrointestinal, RV = right ventricular, LV = left ventricular, DAH<sub>30</sub> = Days alive and  
20  
21 473 at home at 30 days postoperatively, StEP-COMPAC = Standardised Endpoints and Core  
22  
23 474 Outcome Measures for Perioperative and Anaesthetic Care, WHODAS = WHO Disability  
24  
25 475 Assessment Schedule 2.0, EQ-5D-5L = EuroQol-5 Dimension Health Related Quality of Life  
26  
27 476 Questionnaire, POD = postoperative day  
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31 477  
32  
33 478 Figure 2. Simulated power analysis for impact of RVD on days alive and at home at 30 days  
34

35 479 Assuming for 1% of the patients DAH<sub>30</sub> = 0, for the remainder DAH<sub>30</sub> follows a negative  
36  
37 480 binomial distribution with parameters chosen such that the median DAH<sub>30</sub> is 24/25 in one  
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39 481 group and 27 in the other group and the shape of the distribution is similar to that seen in the  
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41 482 validation cohorts. The simulated DAH<sub>30</sub> was then compared between groups using negative  
42  
43 483 binomial regression (repeated) in 1000 samples. The figures show the resulting estimated  
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45 484 power for incidences of postoperative RVD from 15-50%<sup>#</sup>, and for a clinical effect size of 2  
46  
47 485 (Fig A) or 3 (Fig B) days difference in DAH<sub>30</sub>\*.

48 486 *<sup>#</sup>In our previous work the incidence of postoperative RVD was 50% in thoracic surgical  
49  
50 487 patients but may be significantly less in, for example, an orthopaedic population.*

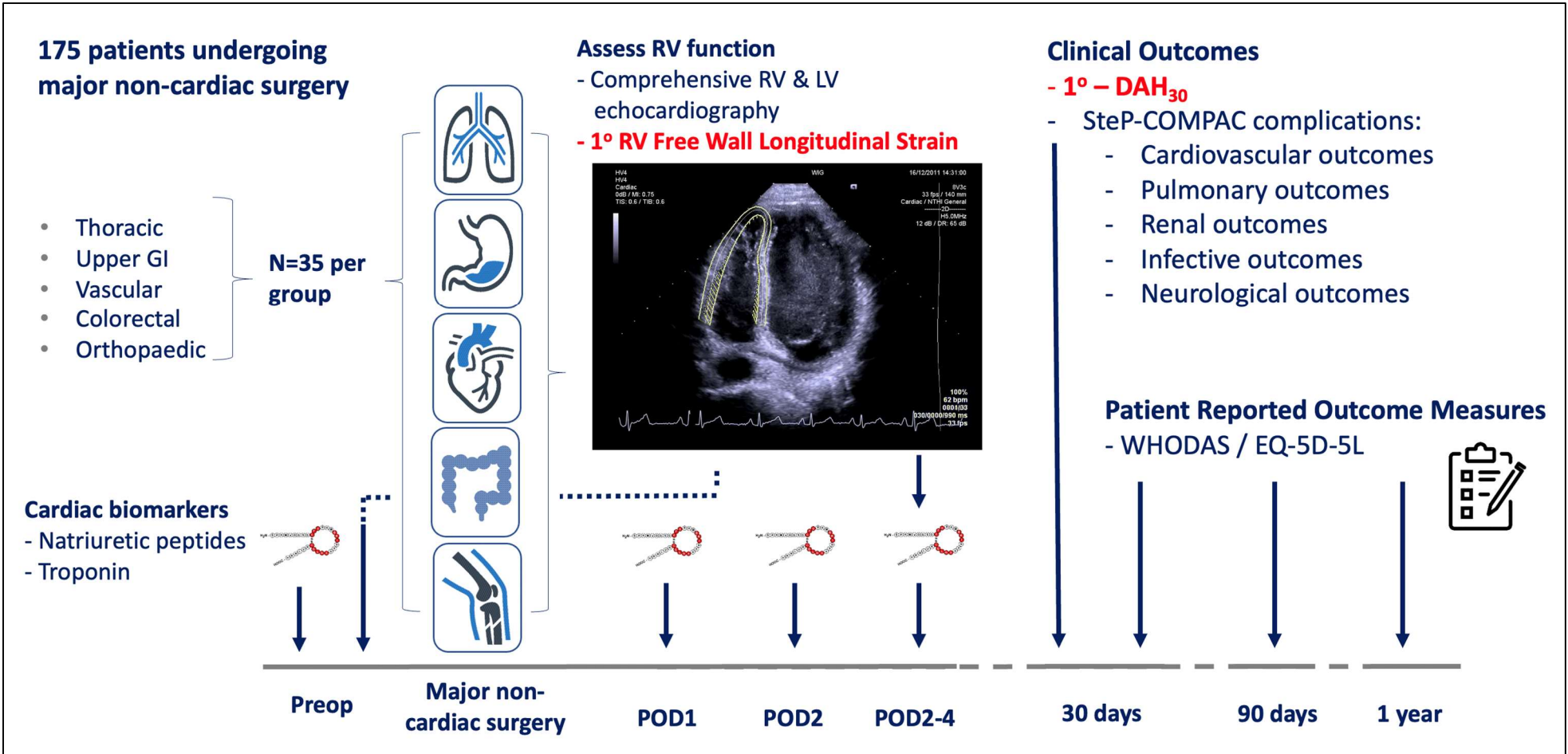
51 488 *\*In Chou et al's study preoperative RV dysfunction prolonged hospital length of stay by over  
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53 489 50%, but this cohort was a very high-risk vascular surgical population.(7)*  
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490 References

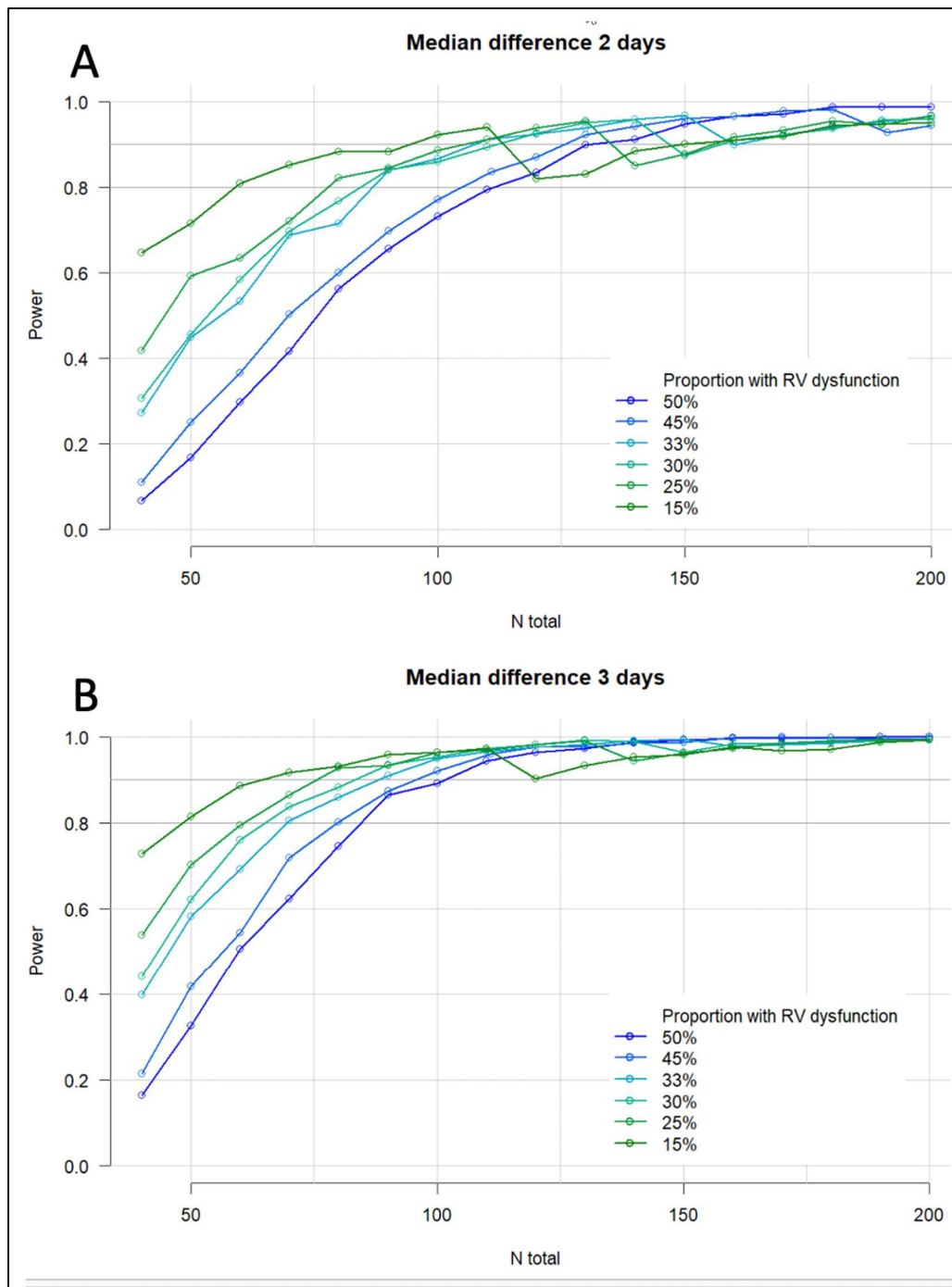
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**Figure 1 Overview of IMPRoVE Main Study**  
 Graphical overview of the main IMPRoVE study. One-hundred and seventy-five patients (35 from each surgical group) will undergo echocardiography and cardiac biomarker testing pre- and postoperatively. Co-primary outcomes are the incidence of RV dysfunction, diagnosed by RV free wall longitudinal strain, and DAH<sub>30</sub> (shown in red).  
 GI = gastrointestinal, RV = right ventricular, LV = left ventricular, DAH<sub>30</sub> = Days alive and at home at 30 days postoperatively, StEP-COMPAC = Standardised Endpoints and Core Outcome Measures for Perioperative and Anaesthetic Care, WHODAS = WHO Disability Assessment Schedule 2.0, EQ-5D-5L = EuroQol-5 Dimension Health Related Quality of Life Questionnaire, POD = postoperative day



**Figure 2. Simulated power analysis for impact of RVD on days alive and at home at 30 days**  
 Assuming for 1% of the patients  $DAH_{30} = 0$ , for the remainder  $DAH_{30}$  follows a negative binomial distribution with parameters chosen such that the median  $DAH_{30}$  is 24/25 in one group and 27 in the other group and the shape of the distribution is similar to that seen in the validation cohorts. The simulated  $DAH_{30}$  was then compared between groups using negative binomial regression (repeated) in 1000 samples. The figures show the resulting estimated power for incidences of postoperative RVD from 15-50%<sup>#</sup>, and for a clinical effect size of 2 (Fig A) or 3 (Fig B) days difference in  $DAH_{30}$ \*.  
<sup>#</sup>In our previous work the incidence of postoperative RVD was 50% in thoracic surgical patients but may be significantly less in, for example, an orthopaedic population.  
 \*In Chou et al's study preoperative RV dysfunction prolonged hospital length of stay by over 50%, but this cohort was a very high-risk vascular surgical population<sup>7</sup>.



## Contraindications to Cardiovascular Magnetic Resonance Imaging

Presence of:

- cardiac pacemaker
- artificial heart valve
- neurostimulator
- cochlear implant
- aneurysm clips
- metal injuries to the eye
- loose metal in a part of the body

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1+2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	12+13
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	15+16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	15-17
		(b) Describe any methods used to examine subgroups and interactions	15-17
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
<b>Discussion</b>			N/A
Key results	18	Summarise key results with reference to study objectives	N/A
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).