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Quality of life measured by EQ-5D at different treatment time points for coronary artery disease: Protocol for a systematic review and meta-analysis

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3 1 Title page
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5 2 Quality of life measured by EQ-5D at different treatment time points
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7 3 for coronary artery disease: Protocol for a systematic review and
8
9 4 meta-analysis
10

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57 37 Word count: 3013
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2
3 39 **ABSTRACT**

4
5 40 **Introduction**

6
7 41 Cardiovascular disease is estimated to affect 423 million people globally. It caused 18 million deaths
8 42 in 2017 and is projected to cost USD\$1 trillion by 2030 worldwide. Coronary artery disease (CAD) is
9 43 the most common type of cardiovascular disease; CAD treatments can affect patients' quality of life.
10 44 Valuations of quality of life or health utilities are important for economic evaluations to ascertain
11 45 relative health benefit when comparing treatments, and can be expected to change for individuals
12 46 over time. The purpose of this systematic review is to estimate the quality of life of CAD patients
13 47 reported through the EuroQol EQ-5D questionnaire, from short to longer-term time points following
14 48 different treatments.
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19 50 **Methods and analysis**

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21 51 PubMed, Embase, Web of Science, the Cochrane Database of Systematic Reviews, and the EuroQol
22 52 website will be systematically searched from 2003 to 2020. Published, peer-reviewed, English
23 53 language studies assessing quality of life of CAD patients using the EQ-5D will be included. One
24 54 researcher will conduct the search; two researchers will independently screen titles and abstracts for
25 55 potential inclusion. Full texts of potentially eligible studies will be retrieved for a second round of
26 56 independent screening against inclusion and exclusion criteria by two researchers. The final list of
27 57 included studies will be assessed for risk of bias using the Rob 2 and ROBINS-I tools for randomized
28 58 and non-randomized studies, respectively. Data extraction will be done by one researcher, with data
29 59 extraction for a random 10% of included studies checked by a second researcher. Mean utility
30 60 weights for individual studies will be combined using random effects model meta-analyses. A model
31 61 will be run separately for each time point and treatment. Treatment time points of interest include
32 62 baseline, 30 days, 6 months, 12-24 months, and more than 24 months. Subgroup analysis of patients
33 63 with diabetes who received interventional treatments — coronary artery bypass graft or
34 64 percutaneous coronary intervention with or without stents, will be conducted for the same selected
35 65 time points.
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43 67 **Ethics and dissemination:** Ethics approval is not required for systematic reviews. Results of the
44 68 review will be disseminated via publication in a peer-reviewed journal.
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47 69
48 70 **PROSPERO registration number:** Pending
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51 71
52 72 **Key words:**

53 73 Coronary artery disease; quality of life; EQ-5D; coronary artery bypass graft; percutaneous coronary
54 74 intervention.
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78 **ARTICLE SUMMARY****Strengths and limitations of this study**

- The search strategy is designed to be comprehensive and aligned with the Peer Review of Electronic Search Strategies (PRESS) guidelines.(1)
- We will use PubMed as one of the databases instead of Medline to capture articles not yet indexed with MeSH terms and those released ahead of print.
- A final search will be run just before data synthesis begins to find any new articles that should be included in the analysis, since the search.
- The systematic review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines.(2)
- Inclusion of studies that are available as full text and in English only may lead to language bias.

79

80 **INTRODUCTION**

81 Cardiovascular disease affects 423 million people globally(3) and causes 31% of deaths annually with
 82 18 million deaths in 2017.(4) Cardiovascular disease is projected to cost USD\$1 trillion by 2030 in
 83 direct healthcare costs, lost productivity due to disability or premature death, and time lost from
 84 work.(5) Coronary artery disease (CAD) is the most common type of cardiovascular disease.(6)
 85 Patients with CAD are treated with long-term medications, lifestyle modifications, and/or
 86 interventional procedures.(7) Commonly used interventional procedures include coronary artery
 87 bypass graft (CABG) and percutaneous coronary intervention (PCI) with or without stents.(7)

88 Individuals living with CAD experience changes in their quality of life.(8-11) CAD treatments can
 89 affect quality of life in either a positive or negative direction; and this can be expected to change
 90 over a period of time, particularly in the immediate vs. longer-term period post-CABG or PCI.(8, 9)
 91 Quality of life estimates as measured by health utilities are important for economic evaluations to
 92 determine relative health benefit when comparing treatments.(12) Health utilities are the numerical
 93 value reflecting the strength of an individual's preference for specific health-related outcomes,
 94 where 0 represents death and 1 represents full health.(12) Together with length of life, health
 95 utilities are used to calculate quality-adjusted life years (QALYs).(12) QALYs are used in cost-
 96 effectiveness studies to enable direct comparisons between treatment options.(12)

97 For chronic illnesses such as coronary artery disease, health utilities over time are particularly
 98 important so as not to bias estimates of cost-effectiveness toward treatments that show early but
 99 unsustained health benefits, and against those which may only show health benefits in the longer-
 100 term.(8) However, health utilities over various time points can be logistically challenging and
 101 expensive to collect; and estimates need to be as robust as possible given their use in informing
 102 medical decision-making and health-related policies. Hence, to reduce research waste and to
 103 increase the robustness of utility estimates, systematic reviews and meta-analyses of health utilities
 104 from single studies are conducted.

105 Previous reviews and meta-analyses of health utilities in cardiovascular diseases focused on either
 106 summarising preference weights of various health-related quality of life instruments(13) or in

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3 107 synthesising the evidence on the validity and reliability of the EQ-5D.(14) Although the 2010 review
4 108 by Dyer et al. summarised utility scores of the EQ-5D,(14) a number of important studies such as the
5 109 ORBITA trial have since been published.(15) We will focus on studies that used the EQ-5D to
6 110 measure health-related quality of life, as it is the most widely used generic preference-based
7 111 instrument.(16) The EQ-5D is also the preferred instrument for Health Technology Assessments by
8 112 the UK National Institute for Health and Care Excellence (NICE), and the Zorginstituut Nederland
9 113 (ZIN).(16, 17)

12 114 The aim of this study is to estimate the quality of life of people with CAD quantified by the EQ-5D at
13 115 selected time points (short-, mid- and longer-term) following the initiation of different treatments.
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Box 1. Definitions

- Coronary artery disease: Any one of the following conditions — coronary atherosclerosis, angina, acute coronary syndromes i.e. unstable angina, myocardial infarction (STEMI or NSTEMI).
- Optimal medical therapy: A combination of medications (pharmacological) to treat disease progression and symptoms, along with lifestyle modifications (non-pharmacological).
- Interventional procedures: Coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI) with — bare metal stent (PCI-BMS), drug-eluting stent (PCI-DES), absorbable stent (PCI-AS) or without stents (balloon angioplasty), carried out in addition to optimal medical therapy.
- Tariff: Preference weight which reflects the preference on different health states of a particular population.

34 117

36 118 METHODS AND ANALYSIS

38 119 Study design

39 120 The study protocol has been developed based on the Preferred Reporting Items for Systematic
40 121 Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines.(2)
41
42

43 122

44 123 Search strategy

46 124 Databases

47 125 The following databases and sources will be searched: PubMed, Embase (Ovid), Web of Science, the
48 126 Cochrane Database of Systematic Reviews, and the EuroQol website.

49 127 A previous study demonstrated that to optimize the search when conducting systematic reviews, the
50 128 following four electronic databases should be searched as a minimum: Medline, Embase, Web of
51 129 Science, and Google Scholar.(18) We selected PubMed as it has a larger repository than Medline,
52 130 including additional life sciences journals, citations that are “ahead of print” and those not yet
53 131 indexed with MeSH terms.(19) We did not select Google Scholar as the search may not be replicable.
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3 134 *Timeframe*
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5 135 The search will encompass the following period: 1 January 2003 to the date of the first search in
6 136 2020. Where the search functions of particular databases do not allow day/month/year to be
7 137 specified, we will use the month and year e.g. January 2003 to March 2020.

9 138 The lower date limit of January 2003 was selected as the first commercially available drug-eluting
10 139 stent was approved by the US Food and Drug Administration in that year.(20) The upper date limit
11 140 will be the date of the first search conducted (within the second search in the three-step strategy
12 141 below); and will subsequently be used as the upper date limit when searching the remaining
13 142 databases. This strategy ensures that the date range for searches is consistent across all databases.

16 143 *Search strategy*
17

18 144 The search aims to find both published and “ahead of print” publications. A three-step strategy will
19 145 be used.

- 21 146 1. First search (EL): Initial search limited to PubMed only, followed by analysis of text words in
22 147 the (a) titles and abstracts of retrieved papers (keywords); and (b) index terms used to
23 148 describe the articles (metadata, tags). Keywords for the initial search: coronary artery
24 149 disease; EQ-5D; EQ-5D-3L; EQ-5D-5L; EuroQoL; treatment. Output: The search string for the
25 150 systematic review will be constructed.
- 28 151 2. Second search (EL): PubMed, Embase (Ovid), Web of Science, the Cochrane Database of
29 152 Systematic Reviews, and the EuroQol website will then be searched using the search string
30 153 constructed from the previous step. The yield from this step will be subjected to title and
31 154 abstract screening for potential inclusion (first screening), followed by retrieval of full text
32 155 articles, and screening of full text articles for inclusion (second screening).
- 35 156 3. Third search (EL): The reference list of included articles will be manually examined to identify
36 157 additional studies for inclusion in the systematic review.

38 158 Finally, as per good practice, searches will be re-run just before data synthesis to identify any
39 159 new studies that should be retrieved for inclusion.

41 160 The following is a preliminary example of a search strategy for PubMed which will be
42 161 refined/confirmed after the first search outlined above:

44 162 (((((((((((coronary artery disease) OR (coronary heart disease)) OR (coronary atherosclerosis)) OR
45 163 (myocardial infarction)) OR (acute coronary syndrome)) OR (angina)))) AND ((EQ-5D) OR
46 164 (EuroQol)))) NOT ((editorial)) OR (conference proceeding))

48 165 The final search strategy will be provided to PROSPERO once the review has been completed.
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52 167 **Types of studies to be included**
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54 168 All types of studies will be included so long as inclusion criteria are met. Systematic reviews
55 169 identified from the search will be examined for relevant studies for inclusion.
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3 172 *Inclusion criteria*
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- 5 173 • Studies which report on quality of life post-treatment for coronary artery disease —
6 174 coronary atherosclerosis, angina, acute coronary syndromes i.e. unstable angina, myocardial
7 175 infarction (STEMI or NSTEMI)
8
9 176 • Treatments may be pharmacological, non-pharmacological (e.g. lifestyle modifications), or
10 177 interventional procedures (e.g. coronary artery bypass graft, percutaneous coronary
11 178 intervention with or without stents)
12
13
14 179 • Preference based utility values for quality of life using EQ-5D
15
16 180 • Studies reported in English
17
18 181

19 182 *Exclusion criteria*
20

- 21 183 • Editorials, letters, and conference proceedings
22
23 184 • Study protocols or studies-in-progress e.g. clinical trial registrations
24
25 185 • Studies which reported only EQ-5D Visual Analogue Scale outcomes
26
27 186 • Studies which reported EQ-5D values derived from mapping other measures of health
28 187 outcomes
29
30 188 • Studies which reported quality of life from other studies, without contributing new data
31
32 189 • Studies which reported on subgroups of a previously reported dataset
33
34 190 • Highly specific patient groups e.g. studies examining coronary artery disease in people with
35 191 depression
36
37 192 • For post-treatment estimates, treatment was not specified e.g. did not report the type of
38 193 stent used
39
40 194 • Studies on enhanced external counter pulsation (EECP) therapy
41
42 195 • Full text article not available
43
44 196

45 197 **Condition or domain being studied**
46

47 198 Quality of life (health utilities) at various treatment time points for coronary artery disease.
48
49 199

50 200 **Participants/population**
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52 201 Inclusion: Adults (18 years old and above) diagnosed with coronary artery disease using criteria such
53 202 as the International Classification of Diseases and Related Health Problems (ICD-10).

55 203 Exclusion: People under 18 years old. Highly specific patient groups e.g. studies examining coronary
56 204 artery disease in people with depression
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3 **207 Interventions**

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5 208 Pharmacological, non-pharmacological, and interventional procedures.

6
7 209 Pharmacological interventions are medications used to manage or treat coronary artery disease
8 210 and/or prevent secondary cardiovascular events, and may include cholesterol-modifying
9 211 medications, antiplatelets, beta blockers, calcium channel blockers, ranolazine, nitrates, angiotensin-
10 212 converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB).

11
12 213 Non-pharmacological interventions include lifestyle modifications such as smoking cessation,
13 214 choosing healthy foods, engaging in regular physical activity/exercise, removing excess weight, and
14 215 reducing stress.

15
16 216 Interventional procedures: Coronary artery bypass graft (CABG) or percutaneous coronary
17 217 intervention (PCI) with or without stents (e.g. balloon angioplasty). Stents used in PCI may be bare
18 218 metal stents, drug-eluting stents, absorbable stents, or absorbable drug-eluting stents.

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23 **220 Comparator/ Control**

24
25 221 The review will compare health utilities reported from patients receiving the treatments listed above
26 222 at selected treatment time points.

27
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30 **224 Context**

31 225 Any setting — inpatient, outpatient, community.

32
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35 **227 Main outcome**

36 228 Quality of life health utilities i.e. EQ-5D-3L and EQ-5D-5L at selected treatment time points.

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38 229 *Timing and effect measures*

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40 230 Baseline, 30 days, 6 months (short term), 12-24 months (mid-term), more than 24 months (long
41 231 term).

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45 **233 Study screening**

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47 234 Yields from searches will be exported into the reference manager software EndNote x9
48 235 (www.endnote.com). Duplicates will be removed. Two copies of the EndNote library will be made for
49 236 two researchers (EL, VM) to independently screen study titles and abstracts against inclusion and
50 237 exclusion criteria. Any discrepancies will be resolved via discussion; a third researcher (NG) will
51 238 moderate if consensus is not reached.

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53
54 239 Full text records of the included papers from the first round of screening are then retrieved. Studies
55 240 will be excluded if full text is not available at this stage or not in English.

56
57 241 Next, all full text records retrieved will be independently assessed against the same inclusion and
58 242 exclusion criteria by two researchers (EL, VM). Reasons for exclusion will be documented. Any
59
60

243 discrepancies will be resolved via discussion; a third researcher (NG) will moderate if consensus is
244 not reached. Study selection will be illustrated as a PRISMA flow diagram.

245

246 **Risk of bias (quality) assessment**

247 For included studies, we will use the RoB 2 tool to assess risk of bias at the study level in randomised
248 trials and the ROBINS-I tool for non-randomised studies.(21, 22) The RoB 2 tool prompts judgements
249 regarding biases in five domains: bias arising from the randomisation process, those due to
250 derivations from intended interventions, missing outcome data, measurement of the outcome, and
251 selection of the reported result.(21) The ROBINS-I tool covers seven domains: bias due to
252 confounding, participant selection, classification of interventions, deviations from intended
253 interventions, missing data, measurement of outcomes, and selection of the reported results.(22)

254 One researcher (EL) will complete the risk of bias/quality appraisal; a second researcher (VM) will
255 check the assessment for ten percent of the included studies. Any discrepancies will be resolved via
256 discussion; a third researcher (NG) will moderate if consensus is not reached. All studies will be
257 included in the data synthesis; in addition, studies with low risk of bias will also be analysed
258 separately.

259

260 **Data extraction**

261 Data extraction will be conducted on all studies that are included. We will take the following
262 approaches to data extraction to ensure published estimates are not counted more than once.

- 263 • Where there are multiple analyses for the same dataset, we will use only one estimate per
264 subgroup per time point
- 265 • We will use the broadest grouping available for each dataset. For example, if a study reports
266 on all patients with bypass surgery and another reports on subgroups of patients with
267 bypass surgery by their obesity status from the same dataset, we will include only the overall
268 bypass surgery utility weights, not the obesity subgroups
- 269 • Where a paper provides updated findings (e.g. for a later time point) from a previous
270 published study of the same quality of life data collection, we will only include data for the
271 later time point from the updated analysis

272 For baseline or time zero utility measurements, we will note when the EQ-5D questionnaire was
273 given to patients.

274 For each included study, the following data will be extracted:

- 275 • Authors
- 276 • Publication date
- 277 • Country/countries where study was done
- 278 • Baseline presentation of patients
- 279 • Treatment received e.g. coronary artery bypass graft, percutaneous coronary intervention
280 and type of stent used
- 281 • Survey instrument (e.g. EQ-5D, EQ-5D-5L)

- 282 • Location of participants (e.g. hospital – inpatient, hospital – outpatient, home)
- 283 • Administration mode of survey (e.g. interviewer, self-completion)
- 284 • Respondent identity (e.g. self, proxy)
- 285 • Language of survey
- 286 • Tariff (preference weights) used to generate utility weights from the EQ-5D results
- 287 • Mean utility weights reported for each treatment and time point combination
- 288 • Standard error or relevant statistics to enable calculation of the standard error i.e. standard
- 289 deviation and sample size
- 290 • Number of participants in the group, mean age, percentage of men and women in the group
- 291 • Percentage of participants with diabetes
- 292 • Percentage of participants who currently smoke tobacco

293 Data extraction will be piloted by one researcher (EL) with five studies randomly selected from the
 294 included papers. A second researcher (VM) will check the pilot data extraction. Discrepancies will be
 295 resolved via discussion. A third researcher (NG) will moderate if discrepancies are not resolved.
 296 Subsequently, one researcher will complete data extraction of the remaining studies (EL). A second
 297 researcher will check the data extracted for a random ten percent of included papers (VM). Similarly,
 298 discrepancies will be resolved via discussion; a third researcher (NG) will moderate if any
 299 discrepancies are unresolved.

300 An Excel spreadsheet will be set up for data extraction.

302 **Strategy for data synthesis**

303 Mean utility weights for individual studies will be combined using random effects model meta-
 304 analyses. We will use the R package, metafor,(23) to do this. A model will be run separately for each
 305 time point and treatment.

306 For utility weights following interventional treatments, we will include all studies related to that
 307 particular treatment. Each type of interventional procedure will be analysed separately e.g. CABG,
 308 PCI without stent (balloon angioplasty), PCI with bare metal stent (PCI-BMS), PCI with drug-eluting
 309 stent (PCI-DES), PCI with absorbable stent (PCI-AS).

310 For re-hospitalisations for acute coronary artery disease, we will use estimates only from studies
 311 related to acute presentations. For other re-hospitalisations we will use estimates only from studies
 312 not related to acute presentations.

314 **Analysis of subgroups or subsets**

315 Subgroup analysis of patients with diabetes who received CABG, balloon angioplasty, PCI-BMS, PCI-
 316 DES, PCI-AS (if any) will be conducted for the same selected time points regarding the EuroQoL EQ-
 317 5D. Previous studies have demonstrated increased morbidity and/or mortality among people with
 318 diabetes who received coronary revascularisation procedures compared to those without
 319 diabetes.(24, 25) Hence, the utility value of the quality of life may differ between patients with
 320 diabetes and those without.

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3 322 **Type and method of review**
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5 323 Systematic review, Meta-analysis.
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8 325 **Anticipated or actual start date**
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10 326 27 February 2020.
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12 327

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14 328 **Anticipated completion date**

15 329 30 June 2020.
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19 331 **Patient and public involvement**
20

21 332 No patient or public involvement.
22
23 333

24 334 **Ethics and dissemination**

25
26 335 Ethical approval is not required for systematic review protocols. Results of the review will be
27 336 disseminated via publication in a peer-reviewed journal. In addition, should the findings of the
28 337 review warrant a re-examination of current clinical practice, a brief will be prepared and sent to
29 338 relevant lead agencies in Australia and Singapore e.g. Ministry of Health (Singapore), Department of
30 339 Health (Australia), Deeble Institute (Australia).
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35 341 **Data deposition and curation**

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37 342 Data extraction tables will be deposited in an open data repository such as the Open Science
38 343 Framework (<https://osf.io/>).
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42 345 **Amendments**

43 346 All amendments to the protocol will be dated, described, accompanied by a rationale, and
44 347 documented in PROSPERO post-registration.
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49 349 **DISCUSSION**

50 350 To date, there is only one systematic review of patient reported quality of life focussed on EQ-5D
51 351 which was published in 2010 by Dyer et al.(14) Given that important clinical studies in the
52 352 cardiovascular field have since been published, another review is timely.

53
54
55 353 Our findings will be useful for economic evaluations to determine relative health benefit when
56 354 comparing treatments. Knowing the health utilities at various treatment time points following
57 355 different CAD treatments will facilitate cost-effective policy-making, inform clinical guidelines and
58 356 practice changes. This study will also be useful to other researchers and decision-makers who wish
59 357 to work on cost-effectiveness analyses for cardiology. In Singapore where this study is being

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3 358 undertaken, the health utilities estimated by this study will add value to the national longitudinal
4 359 database of cardiology patients — SingCLOUD,(26) and other disease registries here and elsewhere
5
6 360 that have not collected EQ-5D data.

7
8 361 Limitations are that non-English language articles and studies that use other health-related quality of
9 362 life instruments will be excluded. We chose to focus on EQ-5D generated health utilities as it is the
10 363 most widely used generic preference-based measure due to its robustness, reliability, and
11 364 responsiveness across many health conditions and countries.(16) Health utilities derived from
12 365 different instruments are not interchangeable with the EQ-5D and there are no straightforward
13 366 methods for translation.(27)

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17 368 **AUTHOR CONTRIBUTIONS**

19 369 The systematic review was conceptualised by all authors. EL drafted the protocol, which was
20 370 critically reviewed by VM, NL and NG. All protocol authors read, provided feedback, and approved
21 371 the final manuscript. Database searches will be completed by EL; articles will be screened for
22 372 inclusion and exclusion by EL and VM; data extraction will be led by EL. Data analyses will be done by
23 373 EL and VM, and reviewed by NL and NG. The guarantor of the review is NG.

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27 375 **FUNDING STATEMENT**

28
29 376 This research received no specific grant from any funding agency in the public, commercial or not-
30 377 for-profit sectors.

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32
33 378

34 379 **COMPETING INTERESTS STATEMENT**

35 380 No competing interests to declare.

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39 382 **REFERENCES**

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

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	Reporting Item	Page Number
Title		
Identification	#1a Identify the report as a protocol of a systematic review	1, Title
Update	#1b If the protocol is for an update of a previous systematic review, identify as such	n/a, not an update

Title

	Reporting Item	Page Number
Identification	#1a Identify the report as a protocol of a systematic review	1, Title

Update	#1b If the protocol is for an update of a previous systematic review, identify as such	n/a, not an update
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1 **Registration**
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4 [#2](#) If registered, provide the name of the registry 2, pending PROSPERO
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6 (such as PROSPERO) and registration registration
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11 **Authors**
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15 **Contact**

16 [#3a](#) Provide name, institutional affiliation, e-mail 1
17 address of all protocol authors; provide
18 physical mailing address of corresponding
19 author
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24 **Contribution**

25 [#3b](#) Describe contributions of protocol authors 11, Author Contributions
26 and identify the guarantor of the review
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30 **Amendments**
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33 [#4](#) If the protocol represents an amendment of 10, Amendments
34 a previously completed or published
35 protocol, identify as such and list changes;
36 otherwise, state plan for documenting
37 important protocol amendments
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45 **Support**
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48 **Sources**

49 [#5a](#) Indicate sources of financial or other support 11, Funding Statement
50 for the review
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54 **Sponsor**

55 [#5b](#) Provide name for the review funder and / or n/a, no funder or
56 sponsor sponsor
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1	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and /	n/a, no funder or
2			or institution(s), if any, in developing the	sponsor
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17	Objectives	#7	Provide an explicit statement of the	4, Introduction
18			question(s) the review will address with	
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20			comparators, and outcomes (PICO)	
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30	Eligibility criteria	#8	Specify the study characteristics (such as	4, Study design
31			PICO, study design, setting, time frame) and	5, Timeframe of
32			report characteristics (such as years	searches
33			considered, language, publication status) to	6-7, PICO; Context
34			be used as criteria for eligibility for the	(setting)
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48	Information	#9	Describe all intended information sources	4, Databases
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50	sources		study authors, trial registers or other grey	searches (dates of
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1	Search strategy	#10	Present draft of search strategy to be used	5, Search strategy
2			for at least one electronic database,	
3			including planned limits, such that it could be	
4			repeated	
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6	Study records -	#11a	Describe the mechanism(s) that will be used	7, Study screening
7	data management		to manage records and data throughout the	8-9, Data extraction
8			review	
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11	Study records -	#11b	State the process that will be used for	7, Study screening
12	selection process		selecting studies (such as two independent	
13			reviewers) through each phase of the review	
14			(that is, screening, eligibility and inclusion in	
15			meta-analysis)	
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19	Study records -	#11c	Describe planned method of extracting data	8-9, Data extraction
20	data collection		from reports (such as piloting forms, done	
21	process		independently, in duplicate), any processes	
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31	Data items	#12	List and define all variables for which data	7, Interventions
32			will be sought (such as PICO items, funding	7, Main outcome –
33			sources), any pre-planned data assumptions	Timing
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43	Outcomes and	#13	List and define all outcomes for which data	7, Main outcome (3,
44	prioritization		will be sought, including prioritization of main	rationale in Introduction)
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13 14 15 16 17 18	Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9, Strategy for data synthesis
19 20 21 22 23 24 25 26 27 28 29 30 31 32	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's τ)	9, Strategy for data synthesis
33 34 35 36 37 38 39 40	Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9, Analysis of subgroups
41 42 43 44 45	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a – quantitative synthesis is applicable
46 47 48 49 50 51 52 53	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8, Risk of bias assessment
54 55 56 57 58 59 60	Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8, Risk of bias assessment

1 evidence

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3 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution
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BMJ Open

Quality of life measured by EQ-5D at different treatment time points for coronary artery disease: Protocol for a systematic review and meta-analysis

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11 5 Elaine Lum^{1,2}, Victoria McCreanor^{3,4}, Nan Luo⁵, Nicholas Graves¹
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ABSTRACT**Introduction**

Cardiovascular disease is estimated to affect 423 million people globally. It caused 18 million deaths in 2017 and is projected to cost USD\$1 trillion by 2030 worldwide. Coronary artery disease (CAD) is the most common type of cardiovascular disease; CAD treatments can affect patients' quality of life. Valuations of quality of life or health utilities are important for economic evaluations to ascertain relative health benefit when comparing treatments, and can be expected to change for individuals over time. The purpose of this systematic review is to estimate the quality of life of CAD patients reported through the EuroQol EQ-5D questionnaire, from short to longer-term time points following different treatments.

Methods and analysis

PubMed, Embase, Web of Science, the Cochrane Database of Systematic Reviews, and the EuroQol website will be systematically searched from January 2003 to March 2020. Published, peer-reviewed, English language studies assessing quality of life of CAD patients using the EQ-5D will be included. One researcher will conduct the search; two researchers will independently screen titles and abstracts for potential inclusion. Full texts of potentially eligible studies will be retrieved for a second round of independent screening against inclusion and exclusion criteria by two researchers. The final list of included studies will be assessed for risk of bias using the Rob 2 and ROBINS-I tools for randomized and non-randomized studies, respectively. Data extraction will be done by one researcher, with data extraction for a random 10% of included studies checked by a second researcher. Mean utility weights for individual studies will be combined using random effects model meta-analyses. A model will be run separately for each time point and treatment. Treatment time points of interest include baseline, 30 days, 6 months, 12-24 months, and more than 24 months. Subgroup analysis of patients with diabetes who received interventional treatments — coronary artery bypass graft or percutaneous coronary intervention with or without stents, will be conducted for the same selected time points.

Ethics and dissemination: Ethics approval is not required for systematic reviews. Results of the review will be disseminated via publication in a peer-reviewed journal.

PROSPERO registration number: Pending

Key words:

Coronary artery disease; quality of life; EQ-5D; coronary artery bypass graft; percutaneous coronary intervention.

78 **ARTICLE SUMMARY****Strengths and limitations of this study**

- The search strategy is designed to be comprehensive and aligned with the Peer Review of Electronic Search Strategies (PRESS) guidelines.
- We will use PubMed as one of the databases instead of Medline to capture articles not yet indexed with MeSH terms and those released ahead of print.
- A final search will be run just before data synthesis begins to find any new articles that should be included in the analysis, since the search.
- The systematic review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines.
- Inclusion of studies that are available as full text and in English only may lead to language bias.

79

80 **INTRODUCTION**

81 Cardiovascular disease affects 423 million people globally(1) and causes 31% of deaths annually with
 82 18 million deaths in 2017.(2) Cardiovascular disease is projected to cost USD\$1 trillion by 2030 in
 83 direct healthcare costs, lost productivity due to disability or premature death, and time lost from
 84 work.(3) Coronary artery disease (CAD) is the most common type of cardiovascular disease.(4)
 85 Patients with CAD are treated with long-term medications, lifestyle modifications, and/or
 86 interventional procedures.(5) Commonly used interventional procedures include coronary artery
 87 bypass graft (CABG) and percutaneous coronary intervention (PCI) with or without stents.(5)

88 Individuals living with CAD experience changes in their quality of life.(6-9) CAD treatments can affect
 89 quality of life in either a positive or negative direction; and this can be expected to change over a
 90 period of time, particularly in the immediate vs. longer-term period post-CABG or PCI.(6, 7) Quality
 91 of life estimates as measured by health utilities are important for economic evaluations to
 92 determine relative health benefit when comparing treatments.(10) Health utilities are the numerical
 93 value reflecting the strength of an individual's preference for specific health-related outcomes,
 94 where 0 represents death and 1 represents full health.(10) Together with length of life, health
 95 utilities are used to calculate quality-adjusted life years (QALYs).(10) QALYs are used in cost-
 96 effectiveness studies to enable direct comparisons between treatment options.(10)

97 For chronic illnesses such as coronary artery disease, health utilities over time are particularly
 98 important so as not to bias estimates of cost-effectiveness toward treatments that show early but
 99 unsustained health benefits, and against those which may only show health benefits in the longer-
 100 term.(6) However, health utilities over various time points can be logistically challenging and
 101 expensive to collect; and estimates need to be as robust as possible given their use in informing
 102 medical decision-making and health-related policies. Hence, to reduce research waste and to
 103 increase the robustness of utility estimates, systematic reviews and meta-analyses of health utilities
 104 from single studies are conducted.

105 Previous reviews and meta-analyses of health utilities in cardiovascular diseases focussed on either
 106 summarising preference weights of various health-related quality of life instruments(11) or in

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3 107 synthesising the evidence on the validity and reliability of the EQ-5D.(12) Although the 2010 review
4 108 by Dyer et al. summarised utility scores of the EQ-5D,(12) a number of important studies such as the
5 109 ORBITA trial have since been published.(13) We will focus on studies that used the EQ-5D to
6 110 measure health-related quality of life, as it is the most widely used generic preference-based
7 111 instrument.(14) The EQ-5D is also the preferred instrument for Health Technology Assessments by
8 112 the UK National Institute for Health and Care Excellence (NICE), and the Zorginstituut Nederland
9 113 (ZIN).(14, 15)

12 114 The aim of this study is to estimate the quality of life of people with CAD quantified by the EQ-5D at
13 115 selected time points (short-, mid- and longer-term) following the initiation of different treatments.
14 116 Definitions of terms used are in Box 1.
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Box 1. Definitions

- Coronary artery disease: Any one of the following conditions — coronary atherosclerosis, angina, ischaemia and no obstructive coronary artery disease (INOCA); acute coronary syndromes i.e. unstable angina, myocardial infarction (STEMI or NSTEMI), myocardial infarction and no obstructive coronary artery disease (MINOCA); silent ischaemia.
- Optimal medical therapy: A combination of evidence-based treatments recommended by clinical guidelines e.g. medications (pharmacological) to treat disease progression and symptoms, along with lifestyle modifications (non-pharmacological).
- Interventional procedures: Coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI) with — bare metal stent (PCI-BMS), drug-eluting stent (PCI-DES), absorbable stent (PCI-AS) or without stents (balloon angioplasty), carried out in addition to optimal medical therapy.
- Tariff: Preference weight which reflects the preference on different health states of a particular population.

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39 119 METHODS AND ANALYSIS

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43 121 The study protocol has been developed based on the Preferred Reporting Items for Systematic
44 122 Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines.(16)
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48 124 Search strategy

49 125 Databases

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52 126 The following databases and sources will be searched: PubMed, Embase (Ovid), Web of Science, the
53 127 Cochrane Database of Systematic Reviews, and the EuroQol website.
54

55 128 A previous study demonstrated that to optimize the search when conducting systematic reviews, the
56 129 following four electronic databases should be searched as a minimum: Medline, Embase, Web of
57 130 Science, and Google Scholar.(17) We selected PubMed as it has a larger repository than Medline,
58 131 including additional life sciences journals, citations that are “ahead of print” and those not yet
59 132 indexed with MeSH terms.(18) We did not select Google Scholar as the search may not be replicable.

133 *Timeframe*

134 The search will encompass the following period: 1 January 2003 to the date of the first search in
135 2020. Where the search functions of particular databases do not allow day/month/year to be
136 specified, we will use the month and year e.g. January 2003 to March 2020.

137 The lower date limit of January 2003 was selected as the first commercially available drug-eluting
138 stent was approved by the US Food and Drug Administration in that year.⁽¹⁹⁾ The upper date limit
139 will be the date of the first search conducted (within the second search in the three-step strategy
140 below); and will subsequently be used as the upper date limit when searching the remaining
141 databases. This strategy ensures that the date range for searches is consistent across all databases.

142 *Search strategy*

143 The search aims to find both published and “ahead of print” publications. A three-step strategy will
144 be used.

- 145 1. First search (EL): Initial search limited to PubMed only, followed by analysis of text words in
146 the (a) titles and abstracts of retrieved papers (keywords); and (b) index terms used to
147 describe the articles (metadata, tags). Keywords for the initial search: coronary artery
148 disease; EQ-5D; EQ-5D-3L; EQ-5D-5L; EuroQol; treatment. Output: The search string for the
149 systematic review will be constructed (see Supplementary File).
- 150 2. Second search (EL): PubMed, Embase (Ovid), Web of Science, the Cochrane Database of
151 Systematic Reviews, and the EuroQol website will then be searched using the search string
152 constructed from the previous step. The yield from this step will be subjected to title and
153 abstract screening for potential inclusion (first screening), followed by retrieval of full text
154 articles, and screening of full text articles for inclusion (second screening).
- 155 3. Third search (EL): The reference list of included articles will be manually examined to identify
156 additional studies for inclusion in the systematic review.

157 Finally, as per good practice, searches will be re-run just before data synthesis to identify any
158 new studies that should be retrieved for inclusion.

159

160 **Types of studies to be included**

161 All types of studies will be included so long as inclusion criteria are met. Systematic reviews
162 identified from the search will be examined for relevant studies for inclusion.

163

164 *Inclusion criteria*

- 165 • Studies which report on quality of life post-treatment for coronary artery disease —
166 coronary atherosclerosis, angina, ischaemia and no obstructive coronary artery disease
167 (INOCA); acute coronary syndromes i.e. unstable angina, myocardial infarction (STEMI or
168 NSTEMI), myocardial infarction and no obstructive coronary artery disease (MINOCA); silent
169 ischaemia

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170 • Treatments may be pharmacological, non-pharmacological (e.g. lifestyle modifications), or
171 interventional procedures (e.g. coronary artery bypass graft, percutaneous coronary
172 intervention with or without stents)

173 • Preference based utility values for quality of life using EQ-5D

174 • Studies reported in English

175

176 *Exclusion criteria*

177 • Editorials, letters, and conference proceedings

178 • Study protocols or studies-in-progress e.g. clinical trial registrations

179 • Studies which reported only EQ-5D Visual Analogue Scale outcomes

180 • Studies which reported EQ-5D values derived from mapping other measures of health
181 outcomes

182 • Studies which reported quality of life from other studies, without contributing new data

183 • Studies which reported on subgroups of a previously reported dataset

184 • Specific patient groups known to have highly impaired quality of life (to avoid skewing
185 estimates) e.g. studies examining coronary artery disease in people with depression

186 • For post-treatment estimates, treatment was not specified e.g. did not report the type of
187 stent used

188 • Studies on enhanced external counter pulsation (EECP) therapy

189 • Full text article not available

190

191 **Condition or domain being studied**

192 Quality of life (health utilities) at various treatment time points for coronary artery disease.

193

194 **Participants/population**

195 Inclusion: Adults (18 years old and above) diagnosed with coronary artery disease using criteria such
196 as the International Classification of Diseases and Related Health Problems (ICD-10).

197 Exclusion: People under 18 years old. Highly specific patient groups e.g. studies examining coronary
198 artery disease in people with depression

199

200 **Interventions**

201 Pharmacological, non-pharmacological, and interventional procedures.

202 Pharmacological interventions are medications used to manage or treat coronary artery disease
203 and/or prevent secondary cardiovascular events, and may include cholesterol-modifying
204 medications (e.g. statins, ezetimibe and PCSK9 inhibitors), antiplatelets, beta blockers, calcium

205 channel blockers, ranolazine, nitrates, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II
206 receptor blockers (ARB).

207 Non-pharmacological interventions include lifestyle modifications such as smoking cessation,
208 choosing healthy foods, engaging in regular physical activity/exercise, removing excess weight, and
209 reducing stress.

210 Interventional procedures: Coronary artery bypass graft (CABG) or percutaneous coronary
211 intervention (PCI) with or without stents (e.g. balloon angioplasty). Stents used in PCI may be bare
212 metal stents, drug-eluting stents, absorbable stents, or absorbable drug-eluting stents. Implantable
213 cardioverter defibrillators (ICD) will not be included.

214

215 **Comparator/ Control**

216 The review will compare health utilities reported from patients receiving the treatments listed above
217 at selected treatment time points.

218

219 **Context**

220 Any setting — inpatient, outpatient, community.

221

222 **Main outcome**

223 Quality of life health utilities i.e. EQ-5D-3L and EQ-5D-5L at selected treatment time points.

224 *Timing and effect measures*

225 Baseline, 30 days, 6 months (short term), 12-24 months (mid-term), more than 24 months (long
226 term).

227

228 **Study screening**

229 Yields from searches will be exported into the reference manager software EndNote x9
230 (www.endnote.com). Duplicates will be removed. Two copies of the EndNote library will be made for
231 two researchers (EL, VM) to independently screen study titles and abstracts against inclusion and
232 exclusion criteria. Any discrepancies will be resolved via discussion; a third researcher (NG) will
233 moderate if consensus is not reached.

234 Full text records of the included papers from the first round of screening are then retrieved. Studies
235 will be excluded if full text is not available at this stage or not in English.

236 Next, all full text records retrieved will be independently assessed against the same inclusion and
237 exclusion criteria by two researchers (EL, VM). Reasons for exclusion will be documented. Any
238 discrepancies will be resolved via discussion; a third researcher (NG) will moderate if consensus is
239 not reached. Study selection will be illustrated as a PRISMA flow diagram.

240

241

242 Risk of bias (quality) assessment

243 For included studies, we will use the RoB 2 tool to assess risk of bias at the study level in randomised
244 trials and the ROBINS-I tool for non-randomised studies.(20, 21) The RoB 2 tool prompts judgements
245 regarding biases in five domains: bias arising from the randomisation process, those due to
246 derivations from intended interventions, missing outcome data, measurement of the outcome, and
247 selection of the reported result.(20) The ROBINS-I tool covers seven domains: bias due to
248 confounding, participant selection, classification of interventions, deviations from intended
249 interventions, missing data, measurement of outcomes, and selection of the reported results.(21)

250 One researcher (EL) will complete the risk of bias/quality appraisal; a second researcher (VM) will
251 check the assessment for ten percent of the included studies. Any discrepancies will be resolved via
252 discussion; a third researcher (NG) will moderate if consensus is not reached. All studies will be
253 included in the data synthesis; in addition, studies with low risk of bias will also be analysed
254 separately. The risk of bias assessment for all included studies will be reported in a table format
255 showing the overall judgment for each study (Rob 2: low/ high/ some concerns; ROBINS-I: low/
256 moderate/ serious/ critical).

257

258 Data extraction

259 Data extraction will be conducted on all studies that are included. We will take the following
260 approaches to data extraction to ensure published estimates are not counted more than once.

- 261 • Where there are multiple analyses for the same dataset, we will use only one estimate per
262 subgroup per time point
- 263 • We will use the broadest grouping available for each dataset. For example, if a study reports
264 on all patients with bypass surgery and another reports on subgroups of patients with
265 bypass surgery by their obesity status from the same dataset, we will include only the overall
266 bypass surgery utility weights, not the obesity subgroups
- 267 • Where a paper provides updated findings (e.g. for a later time point) from a previous
268 published study of the same quality of life data collection, we will only include data for the
269 later time point from the updated analysis

270 For baseline or time zero utility measurements, we will note when the EQ-5D questionnaire was
271 given to patients.

272 For each included study, the following data will be extracted:

- 273 • Authors
- 274 • Publication date
- 275 • Country/countries where study was done
- 276 • Baseline presentation of patients
- 277 • Treatment received e.g. coronary artery bypass graft, percutaneous coronary intervention
278 and type of stent used
- 279 • Survey instrument (e.g. EQ-5D, EQ-5D-3L, EQ-5D-5L)
- 280 • Location of participants (e.g. hospital – inpatient, hospital – outpatient, home)
- 281 • Administration mode of survey (e.g. interviewer, self-completion)

- 282 • Respondent identity (e.g. self, proxy)
- 283 • Language of survey
- 284 • Tariff (preference weights) used to generate utility weights from the EQ-5D results
- 285 • Mean utility weights reported for each treatment and time point combination
- 286 • Standard error or relevant statistics to enable calculation of the standard error i.e. standard deviation and sample size
- 287
- 288 • Number of participants in the group, mean age, percentage of men and women in the group
- 289 • Percentage of participants with diabetes
- 290 • Percentage of participants who currently smoke tobacco

291 Data extraction will be piloted by one researcher (EL) with five studies randomly selected from the
292 included papers. A second researcher (VM) will check the pilot data extraction. Discrepancies will be
293 resolved via discussion. A third researcher (NG) will moderate if discrepancies are not resolved.
294 Subsequently, one researcher will complete data extraction of the remaining studies (EL). A second
295 researcher will check the data extracted for a random ten percent of included papers (VM). Similarly,
296 discrepancies will be resolved via discussion; a third researcher (NG) will moderate if any
297 discrepancies are unresolved.

298 An Excel spreadsheet will be set up for data extraction.

299

300 **Strategy for data synthesis**

301 Mean utility weights for individual studies will be combined using random effects model meta-
302 analyses. We will use the R package, metafor,(22) to do this. A model will be run separately for each
303 time point and treatment.

304 For utility weights following interventional treatments, we will include all studies related to that
305 particular treatment. Each type of interventional procedure will be analysed separately e.g. CABG,
306 PCI without stent (balloon angioplasty), PCI with bare metal stent (PCI-BMS), PCI with drug-eluting
307 stent (PCI-DES), PCI with absorbable stent (PCI-AS).

308 For re-hospitalisations for acute coronary artery disease, we will use estimates only from studies
309 related to acute presentations. For other re-hospitalisations we will use estimates only from studies
310 not related to acute presentations.

311

312 **Analysis of subgroups or subsets**

313 Subgroup analysis of patients with diabetes who received CABG, balloon angioplasty, PCI-BMS, PCI-
314 DES, PCI-AS (if any) will be conducted for the same selected time points regarding the EuroQoL EQ-
315 5D. Previous studies have demonstrated increased morbidity and/or mortality among people with
316 diabetes who received coronary revascularisation procedures compared to those without
317 diabetes.(23, 24) Hence, the utility value of the quality of life may differ between patients with
318 diabetes and those without.

319 We will also conduct subgroup analysis of patients with acute coronary syndromes (ACS) vs stable
320 CAD /stable coronary syndromes (SCS). ACS includes unstable angina, NSTEMI, STEMI, myocardial

1
2
3 321 infarction with no obstructive coronary artery disease (MINOCA); and stable CAD includes
4 322 obstructive CAD and ischaemia with no obstructive coronary artery disease (INOCA).(25)
5
6 323
7

8 324 **Type and method of review**

9
10 325 Systematic review, Meta-analysis.
11
12 326

13 327 **Anticipated or actual start date**

14
15 328 27 February 2020.
16
17 329

18
19 330 **Anticipated completion date**

20 331 31 August 2020.
21
22 332

23
24 333 **Patient and public involvement**

25
26 334 No patient or public involvement.
27
28 335

29 336 **Ethics and dissemination**

30
31 337 Ethical approval is not required for systematic review protocols. Results of the review will be
32 338 disseminated via publication in a peer-reviewed journal. In addition, should the findings of the
33 339 review warrant a re-examination of current clinical practice, a brief will be prepared and sent to
34 340 relevant lead agencies in Australia and Singapore e.g. Ministry of Health (Singapore), Department of
35 341 Health (Australia), Deeble Institute (Australia).
36
37 342

38
39
40 343 **Data deposition and curation**

41 344 Data extraction tables will be deposited in an open data repository such as the Open Science
42 345 Framework (<https://osf.io/>).
43
44 346

45
46 347 **Amendments**

47
48 348 All amendments to the protocol will be dated, described, accompanied by a rationale, and
49 349 documented in PROSPERO post-registration.
50
51 350

52
53 351 **DISCUSSION**

54
55 352 To date, there is only one systematic review of patient reported quality of life focussed on EQ-5D
56 353 which was published in 2010 by Dyer et al.(12) Given that important clinical studies in the
57 354 cardiovascular field have since been published, another review is timely.
58
59
60

Our findings will be useful for economic evaluations to determine relative health benefit when comparing treatments. Knowing the health utilities at various treatment time points following different CAD treatments will facilitate cost-effective policy-making, inform clinical guidelines and practice changes. This study will also be useful to other researchers and decision-makers who wish to work on cost-effectiveness analyses for cardiology. In Singapore where this study is being undertaken, the health utilities estimated by this study will add value to the national longitudinal database of cardiology patients — SingCLOUD,(26) and other disease registries here and elsewhere that have not collected EQ-5D data.

Limitations are that non-English language articles and studies that use other health-related quality of life instruments will be excluded. We chose to focus on EQ-5D generated health utilities as it is the most widely used generic preference-based measure due to its robustness, reliability, and responsiveness across many health conditions and countries.(14) Health utilities derived from different instruments are not interchangeable with the EQ-5D and there are no straightforward methods for translation.(27)

369

370 **AUTHOR CONTRIBUTIONS**

The systematic review was conceptualised by all authors. EL drafted the protocol, which was critically reviewed by VM, NL and NG. All protocol authors read, provided feedback, and approved the final manuscript. Database searches will be completed by EL; articles will be screened for inclusion and exclusion by EL and VM; data extraction will be led by EL. Data analyses will be done by EL and VM, and reviewed by NL and NG. The guarantor of the review is NG.

376

377 **FUNDING STATEMENT**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

380

381 **COMPETING INTERESTS STATEMENT**

No competing interests to declare.

383

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For peer review only

Supplementary File. PubMed search strategy

#1	((((((((((((coronary artery disease) OR (coronary heart disease)) OR (coronary artery stenosis)) OR (cardiovascular disease)) OR (myocardial ischemia)) OR (myocardial infarction)) OR (acute coronary syndrome)) OR (angina)) OR (angina pectoris)) OR (chest pain)) OR (silent ischemia)) OR (myocardial ischemia[MeSH Terms]))
#2	((((((((((((EQ-5D) OR (EQ-5D-3L)) OR (EQ-5D-5L)) OR (EuroQOL)) OR (European Quality of Life - 5 Dimensions)) OR (European QOL - 5 Dimensions)) OR (EuroQOL five-dimensional questionnaire)) OR (EuroQOL 5D)) OR (Quality of life[MeSH Terms])) OR (Quality-adjusted life years[MeSH Terms])) OR (Cost-benefit analysis[MeSH Terms]))
#3	((((((((((((((((((((((optimal medical treatment) OR (best medical therapy)) OR (coronary revascularization)) OR (myocardial revascularization)) OR (coronary angiography)) OR (coronary artery bypass graft)) OR (CABG)) OR (percutaneous coronary intervention)) OR (PCI)) OR (drug-eluting stent)) OR (Paclitaxel-eluting stent)) OR (Sirolimus-eluting stent)) OR (Everolimus-eluting stent)) OR (bare metal stent)) OR (angioplasty)) OR (myocardial ischemia/drug therapy[MeSH Terms])) OR (myocardial ischemia/surgery[MeSH Terms])) OR (myocardial revascularization[MeSH Terms])) OR (percutaneous coronary intervention[MeSH Terms])) OR (drug-eluting stent[MeSH Terms]))
#4	((#1) AND (#2)) AND (#3)
#5	((((#4) NOT (stroke[MeSH Terms])) NOT (peripheral arterial disease[MeSH Terms])) NOT (venous insufficiency[MeSH Terms])) NOT (atherectomy[MeSH Terms]))
#6	((((#5) NOT (editorial[Publication Type])) NOT (clinical conference[Publication Type])) NOT (letter[Publication Type]))
#7	(#6) AND (English[Language])
#8	(#7) AND (("2003/01/01"[Date - Entry] : "2020/03/09"[Date - Entry]))

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

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

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

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

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

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

	Reporting Item	Page Number
Title		
Identification	#1a Identify the report as a protocol of a systematic review	1, Title
Update	#1b If the protocol is for an update of a previous systematic review, identify as such	n/a, not an update

Title

	Reporting Item	Page Number
Identification	#1a Identify the report as a protocol of a systematic review	1, Title

Update	#1b If the protocol is for an update of a previous systematic review, identify as such	n/a, not an update
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1 **Registration**
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3

4 [#2](#) If registered, provide the name of the registry 2, pending PROSPERO
5
6 (such as PROSPERO) and registration registration
7
8 number
9
10

11 **Authors**
12
13
14

15 **Contact**

16 [#3a](#) Provide name, institutional affiliation, e-mail 1
17 address of all protocol authors; provide
18 physical mailing address of corresponding
19 author
20
21
22
23
24

25 **Contribution**

26 [#3b](#) Describe contributions of protocol authors 11, Author Contributions
27 and identify the guarantor of the review
28
29

30 **Amendments**
31
32

33 [#4](#) If the protocol represents an amendment of 10, Amendments
34 a previously completed or published
35 protocol, identify as such and list changes;
36 otherwise, state plan for documenting
37 important protocol amendments
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45 **Support**
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48 **Sources**

49 [#5a](#) Indicate sources of financial or other support 11, Funding Statement
50 for the review
51
52
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54 **Sponsor**

55 [#5b](#) Provide name for the review funder and / or n/a, no funder or
56 sponsor sponsor
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1	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and /	n/a, no funder or
2	funder		or institution(s), if any, in developing the	sponsor
3			protocol	
4				
5				
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8				
9	Introduction			
10				
11				
12	Rationale	#6	Describe the rationale for the review in the	3-4, Introduction
13			context of what is already known	
14				
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16				
17	Objectives	#7	Provide an explicit statement of the	4, Introduction
18			question(s) the review will address with	
19			reference to participants, interventions,	
20			comparators, and outcomes (PICO)	
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27	Methods			
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30	Eligibility criteria	#8	Specify the study characteristics (such as	4, Study design
31			PICO, study design, setting, time frame) and	5, Timeframe of
32			report characteristics (such as years	searches
33			considered, language, publication status) to	6-7, PICO; Context
34			be used as criteria for eligibility for the	(setting)
35			review	5-6, Types of studies;
36				Inclusion and Exclusion
37				criteria
38				
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48	Information	#9	Describe all intended information sources	4, Databases
49	sources		(such as electronic databases, contact with	5, Timeframe of
50			study authors, trial registers or other grey	searches (dates of
51			literature sources) with planned dates of	coverage)
52			coverage	
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1	Search strategy	#10	Present draft of search strategy to be used	5, Search strategy and
2			for at least one electronic database,	Supplementary File
3			including planned limits, such that it could be	
4			repeated	
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11	Study records -	#11a	Describe the mechanism(s) that will be used	7, Study screening
12	data management		to manage records and data throughout the	8-9, Data extraction
13			review	
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18	Study records -	#11b	State the process that will be used for	7, Study screening
19	selection process		selecting studies (such as two independent	
20			reviewers) through each phase of the review	
21			(that is, screening, eligibility and inclusion in	
22			meta-analysis)	
23				
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31	Study records -	#11c	Describe planned method of extracting data	8-9, Data extraction
32	data collection		from reports (such as piloting forms, done	
33			independently, in duplicate), any processes	
34			for obtaining and confirming data from	
35			investigators	
36				
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43	Data items	#12	List and define all variables for which data	6-7, Interventions
44			will be sought (such as PICO items, funding	7, Main outcome –
45			sources), any pre-planned data assumptions	Timing
46			and simplifications	8-9, Data extraction
47				
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53	Outcomes and	#13	List and define all outcomes for which data	7, Main outcome (3,
54	prioritization		will be sought, including prioritization of main	rationale in Introduction)
55			and additional outcomes, with rationale	
56				
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1	Risk of bias in	#14	Describe anticipated methods for assessing	8, Risk of bias
2				
3	individual studies		risk of bias of individual studies, including	assessment
4				
5			whether this will be done at the outcome or	
6			study level, or both; state how this	
7				
8			information will be used in data synthesis	
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13	Data synthesis	#15a	Describe criteria under which study data will	9, Strategy for data
14			be quantitatively synthesised	synthesis
15				
16				
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18	Data synthesis	#15b	If data are appropriate for quantitative	9, Strategy for data
19			synthesis, describe planned summary	synthesis
20			measures, methods of handling data and	
21			methods of combining data from studies,	
22			including any planned exploration of	
23			consistency (such as I ² , Kendall's τ)	
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33	Data synthesis	#15c	Describe any proposed additional analyses	9, Analysis of subgroups
34			(such as sensitivity or subgroup analyses,	
35			meta-regression)	
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41	Data synthesis	#15d	If quantitative synthesis is not appropriate,	n/a – quantitative
42			describe the type of summary planned	synthesis is applicable
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46	Meta-bias(es)	#16	Specify any planned assessment of meta-	8, Risk of bias
47			bias(es) (such as publication bias across	assessment
48			studies, selective reporting within studies)	
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54	Confidence in	#17	Describe how the strength of the body of	8, Risk of bias
55			evidence will be assessed (such as GRADE)	assessment
56	cumulative			
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1 evidence

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8 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

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