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### Cost-effectiveness modelling of telehealth for patients with raised cardiovascular disease risk: Evidence from a cohort simulation conducted alongside the Healthlines randomised controlled trial

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- 1 Cost-effectiveness modelling of telehealth for patients with
- 2 raised cardiovascular disease risk: Evidence from a cohort
- **3** simulation conducted alongside the Healthlines randomised
- 4 controlled trial
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- 12 Short title: Lifetime cost-effectiveness modelling of telehealth in CVD

### 13 Abstract

1	35	Conclusions: The intervention was likely to be cost-effective under a lifetime
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3	36	perspective.
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6	37	Trial registration: ISRCTN27508731, prospectively registered 05/07/2012
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		<sup>3</sup> For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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2 3	39	Strengths and limitations	
4 5	40	<ul> <li>The Healthlines trial was one of the largest RCTs designed to evaluate a</li> </ul>	
6 7	41	telehealth-based complex intervention for the management of cardiovascular	
8 9 10	42	disease risk.	
11 12 13	43	<ul> <li>This study complements and extends the findings of a within-trial evaluation</li> </ul>	
14 15	44	carried out on outcomes at 12 months from randomisation by evaluating the	
16 17	45	cost-effectiveness of the telehealth intervention over the lifetime of trial	
18 19 20	46	participants using a cohort simulation model	
21 22 23	47	<ul> <li>The intervention is likely to be cost-effective from a health system</li> </ul>	
23 24 25	48	perspective, but we cannot identify the most plausible duration of	
26 27	49	intervention effect	
28 29 30	50	Introduction	
31	51		
32 33	52	Cardiovascular disease (CVD) is a prevalent long-term condition associated with	
34 35	53	substantial morbidity and mortality. <sup>1</sup> Effective care for patients with raised CVD risk	
36 37	54	requires attention to, and management of, underlying risk factors such as high blood	
38 39 40	55	pressure and obesity. <sup>2</sup> A challenge in estimating the cost-effectiveness of	
41 42	56	interventions intended to reduce CVD risk is that randomised controlled trials (RCTs)	
43 44	57	may have follow-up periods that are shorter than the period over which an	
45 46	58	intervention may affect CVD risk. This is in spite of the impact that interventions to	
47 48	59	reduce CVD risk – such as blood pressure management and weight management	
49 50 51	60	programmes – might have in reducing the future occurrence of debilitating events	
52 53 54	61	such as acute myocardial infarction and stroke.	
55 56	62	Telehealth is one form of condition management that may be relevant to long-term	
57 58 59	63	conditions in general and to CVD in particular. <sup>3</sup> However, there is a lack of high-	
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quality evidence regarding the cost-effectiveness of telehealth. <sup>4 5 6 7</sup> To estimate the
clinical and cost-effectiveness of a de novo telehealth intervention, the Healthlines
CVD risk RCT individually randomised 641 participants to receive either usual care or
a theory-based telehealth intervention that encouraged participants to engage in
beneficial behaviour change. The primary clinical outcome of the trial was 10-year
CVD risk, measured using the QRISK2 risk prediction algorithm<sup>8</sup>, at the end of 12months of follow-up.

In the absence of data from long-term follow-up, there is no means of assessing the enduring impact on cost-effectiveness of the changes in modifiable risk factors that the intervention may have wrought. For example, it is plausible that some patients who managed to reduce their blood pressure (BP), body mass index (BMI) or whose medication adherence was improved as a result of the intervention may continue with newly acquired beneficial behaviours after the end of the 12 months of trial follow-up. Indeed, it is implausible that all trial participants would immediately revert to their pre-intervention BP or BMI immediately on trial completion. 

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This paper describes the development and analysis of a state transition cohort simulation cost-effectiveness model intended to estimate the expected net benefits of the Healthlines telehealth intervention over the lifetime of trial participants. This approach is consistent with the principles of economic evaluation,<sup>9</sup> guidance from the National Institute for Health and Care Excellence (NICE)<sup>10</sup>, and ISPOR guidelines<sup>11</sup> which recommend that cost-effectiveness analyses be undertaken over a time period that reflects differences in cost and effect attributable to an intervention or treatment. The long-term cost-effectiveness analysis complements the analysis of costeffectiveness of the intervention at 12 months post-randomisation published in a companion paper.<sup>12</sup> 

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The Healthlines RCT The trial protocol, methods, results and cost-effectiveness analyses have been reported elsewhere.<sup>3</sup> Briefly, patients aged between 40 and 74 with ten-year CVD risk ≥20% (measured by the QRISK2 algorithm) and at least one modifiable risk factor (for example, weight management or smoking) were recruited from 42 GP practices in England. Individuals were not considered if they had a confirmed diagnosis of CVD, were pregnant, did not have access to the internet and telephones or were unable to communicate verbally. More detail on these and other exclusion criteria is available in Salisbury et al.<sup>3</sup> In total, 641 patients were randomised, and received either unmodified usual care (n=316), or a telehealth intervention in addition to usual care (n=325), for a follow-up period of 12 months. Participants in the intervention arm could receive up to 13 responsive, tailored telehealth encounters with trained Health Information Advisors (HIAs). Participants were encouraged to access and use online material and apps related to CVD risk. Participants with systolic blood pressure ≥140 mmHg and without atrial fibrillation were offered a blood pressure monitor to use at home, and could upload readings to a portal to monitor progress. Telephone calls focused on goal setting, stimulus control and the management of CVD risk in a way that was relevant to the circumstances of each individual participant and which was in line with NICE guidelines. This included ensuring that patients were taking appropriate drug treatment, and addressing problems with medication adherence. The within-trial economic evaluation at the end of 12 months of follow-up adopted an NHS perspective. The cost-effectiveness of the intervention was estimated against NICE thresholds using NHS cost data collected from medical records and questionnaires during the trial, and using data on quality-adjusted life years (QALYs)

estimated from responses to the EQ-5D-5L<sup>13</sup> generic quality-of-life measure at

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baseline, and six and 12 months from randomisation. Mean incremental NHS costs in 2012/13 prices were estimated to be £138 per patient (i.e. the intervention was more expensive), and mean incremental QALY gains were estimated to be 0.012. The estimated ICER was £10,859, and the estimated net benefit at a threshold of £20,000 was estimated to be £116 (95% confidence interval: -£58 to £291). The probability that the intervention was cost-effective at this threshold value was 0.77.

#### Methods

Model structure 

Cohorts of 1,000 patients were simulated. These cohorts were based on the characteristics of the 641 trial participants. Cohorts differed according to age at randomisation, sex and trial allocation of the patient groups modelled. A set of discrete, mutually exclusive states were created and defined by the presence (or absence) of a CVD-related condition, or with death (Figure 1). Sequences of states experienced by the simulated cohort members defined clinical pathways in which QALYs (associated with utilities and mortality) and costs were accumulated. Cost-effectiveness, as measured by the averages of costs and QALYs in each arm, was the primary outcome. These averages were calculated and allowed for the construction of net benefit statistics. Costs were expressed in 2012/13 sterling prices. The model is based on adapted updated versions of models used in previous health technology assessments in the area of CVD risk.<sup>14 15</sup> A National Health System perspective was adopted. The model cycled annually. Both costs and outcomes were subject to a half-cycle correction.<sup>16</sup> Consistent with the inclusion criteria of the trial, and the construction of the QRISK2 algorithm,<sup>8</sup> patients were assumed to be free of CVD when they entered the model – this corresponds to the 'event free' state. Subsequent states correspond to the occurrence of the events used in the QRISK2 

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140	algorithm – acute myocardial infarction (AMI), angina, transient ischaemic attack
141	(TIA) and stroke – and to post-event states, e.g. a 'post-stroke' state (Figure 1).
142	Patients cycled the model until death, or age 100, at which point they were assumed
143	to die. A total of 1,000 iterations of the model were simulated, in which values of input
144	parameters were varied simultaneously. Each iteration used a value drawn from
145	probability distributions assigned to particular input parameters of the model as
146	described below, in the supplementary material and in Salisbury et al. <sup>3</sup> Probabilistic
147	sensitivity analysis was used to quantify uncertainty around point estimates of net
148	benefit. The model was implemented in Excel 2013 (Microsoft: Redmond,
149	Washington).
150	Probability of transitioning to primary and secondary states
151	The probability of entering a particular state is determined by CVD risk. Initial risk
152	scores of patients at the beginning of the model, corresponding to the event-free
153	state, were based on information collected in the RCT (Table 1). CVD risk in the
154	initial year (year 0) is thus average participant baseline QRISK2 score. Change in
155	CVD risk at the end of this year/start of the next year (year 1) is measured by
156	QRISK2 score calculated at 12-month follow-up and adjusted for baseline risk,
157	details of which are provided in Salisbury et al. <sup>3</sup> CVD risk in subsequent years was
158	obtained by adding percentage increases obtained from growth rates in annual risk in
159	males when all input values to the QRISK2 algorithm other than age were held
160	constant.
161	Growth rates from males were used because the level of CVD risk is higher for males
162	than for females at all ages, other variables being constant. Using the relatively more
163	rapid growth rates observed in female risk levels as a basis for extrapolation would

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2 3 4 5 6 7 8 9 10 11 2 3 4 5 6 7 8 9 10 11 2 3 4 5 6 7 8 9 10	164	have meant that at some ages female risk was much higher than male risk. The use
	165	of male risk growth rates constrains female risk levels to be below male levels at all
	166	ages, ensures that risk does not rise above 100%, better reflects estimated
	167	prevalence of risk in males and females, and more generally ensures that the cost-
	168	effectiveness results are based on plausible risk profiles. <sup>3</sup>
	169	The QRISK2 algorithm is not validated for ages beyond 84. Risk for patients
16 17 18	170	surviving to 85 and above was obtained by extrapolating 10-year risk by 1% per
19 20	171	annum, which corresponds to the coefficient obtained from an ordinary least squares
21 22	172	regression of QRISK2 scores on age.
23 24	170	To a user wink as we are used at the are arrayed wink of a put available to we first the
25 26	173	Ten-year risk scores were converted into an annual risk of any event to reflect the
27 28	174	annual cycles of the model. Annual risk scores of any defined CVD event were then
20 29 30 31 32 33 34 35 36 37 38 39 40 41 42	175	disaggregated into the risk of a <i>specific</i> event – AMI, angina, TIA and stroke – using
	176	data on the incidence of these conditions by age and sex. The sources for these data
	177	and the input values used are described in the online supplementary material.
	178	Further detail on their calculation is available in Salisbury et al. <sup>3</sup>
	179	These incidence rates establish the probability of moving from the event-free state to
	180	a specific CVD-related event state; that is, they establish the risk of a primary event.
43 44	181	Transitions to secondary events (any event after the primary event) are determined
45 46	182	by the age and sex-specific transition probabilities given in Ara et al, <sup>14</sup> who describe
47 48	183	in detail the data sources and methods used in their construction. Permitted
49 50 51	184	transitions between states are listed in the online supplementary material (Table A1).
52 53 54	185	The probability of death due to causes not related to CVD risk was based on
55 56	186	standardised mortality ratios calculated from the most recently available (2012) Office
57 58 59	187	of National Statistics Interim Life Tables. <sup>17</sup> This mortality ratio excluded CVD-related
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ICD-10 codes (I20-I25 and I60-I69). The risks of mortality used in each iteration of the model were based on draws from a univariate normal distribution. Simulated participants were constrained to experience no more than three CVD events, an assumption that reflected data availability and model tractability. The same assumption was used in Ara et al.<sup>14</sup> However, few of the 1,000 simulated participants approached experiencing three events, and therefore the assumption is unlikely to have influenced cost-effectiveness conclusions. Duration of effect of intervention The duration of the effect of the Healthlines intervention on CVD risk beyond the end of trial follow-up is unknown, but the modelling thereof is the principal motivation for undertaking the simulation modelling described here. Four different scenarios based on different durations of effect were modelled, and their implications for costeffectiveness compared. This is similar to the approach of Mistry et al.<sup>18</sup> The scenarios modelled are of durations of intervention effect of one, two, and five 

years from baseline, and for remaining lifetime. If, for example, the duration effect is two years, then participants in the intervention arm receive the benefit of lower risk for two years, after which they are modelled as having the same sex- and age-adjusted risk as participants in the control arm. Similar logic applies to the other scenarios. In the case of a lifetime duration of effect, risk is permanently lower in the intervention arm. To avoid sudden 'jumps' in risk at the point at which the intervention ends, the model uses a smoothing adjustment which calculates the average score of intervention arm risk and usual care risk for the year after which the modelled duration of effect expires. 

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### 11 Data on utility

QALYs in year zero of the model were obtained from participant responses to the
EQ-5D-5L measure at baseline, six and 12 months of RCT follow-up, and were
'cross-walked' to UK EQ-5D-3L instrument and valued using the Euroqol UK value
set.<sup>19</sup> QALYs were adjusted to account for between-arm differences observed at the
end of trial follow-up. For other years of the model, age- and sex-adjusted population
EQ-5D norms were estimated from Ara and Brazier<sup>20</sup> to provide baseline utility
scores that applied to the event-free state. These EQ-5D data were used to calculate
QALYs.

Multiplicative adjustments, which assume a constant proportional effect on baseline utility,<sup>20</sup> were made to reflect the decremental impact of experiencing CVD-related health states. Ara and Brazier<sup>20</sup> was used as the source of state-specific utilities other than TIA, which were drawn from Luengo-Fernandez et al,<sup>21</sup> and for unstable angina. It was assumed that the utility estimates for angina in Ara and Brazier related to stable angina; it was further assumed that utility associated with the unstable angina health state would be 90% of the stable angina values, as in Ara et al.<sup>14</sup>

Condition-specific utility values were drawn from univariate normal distributions, as
recommended by Ara and Wailoo,<sup>22</sup> to reflect uncertainty in mean values. Utilities
corresponding to post-event states were never lower than for the event state itself.
This means, for example, that utilities of the "post-stroke" event state were higher
than or equal to the "stroke" state, implying that experiencing a stroke had a greater
negative impact on average on patient utility than did experiencing the "post-stroke"

It was assumed that the second and third events (such as second and third non-fatal
 strokes) had the same impact on utility as the first event. This rules out multiplicative
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impacts of events on quality of life. The utility values associated with different statesare presented in the online supplementary material (Table A2).

### 238 Data on cost

A health-system perspective was adopted for the analysis, and hence only NHS costs were considered. This excluded consideration of any personal or societal costs associated with, for example, incapacity and exit from the labour force connected with a debilitating but non-fatal stroke

The costs of health states were based, in most cases, on Ward et al<sup>23</sup> and Ara et al.<sup>14</sup>
The first year of the model also included costs of the intervention, and NHS costs
incurred in each arm. The costs of each health state is described in the online
supplementary material.

The cost estimates in Ward et al<sup>23</sup> and Ara et al<sup>14</sup>, derived from systematic reviews, were updated where appropriate and possible with new data, as described in more detail in Salisbury et al.<sup>3</sup> Mean costs enter the simulation model at each iteration as draws from a gamma distribution.

### 251 Cost effectiveness analysis

The simulation model uses information on the NHS costs and QALYs observed during the 12-months of trial follow-up in the initial year (year 0). All subsequent costs and QALYs are simulated by the model as a function of QRISK2 scores using the methods described above. Costs and outcomes were both discounted at 3.5% per year, in line with NICE recommendations.<sup>10</sup> Cumulative costs and QALYs were obtained for the lifetime of cohort members by calculating probability-weighted averages of the number of patients in each state, the length of time patients have

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2 3 4	259	been in particular states, and the costs, mortality and quality of life associated with
5 6 7	260	each state.
8 9	261	Results
9 10 11 12 13 14 15 16	262	The mean age of males (females) in the trial was 67 (69), and males comprised $80\%$
	263	of trial participants. Table 1 contains baseline and adjusted 12 month QRISK2 scores
	264	<ul> <li>higher scores indicate higher CVD risk.</li> </ul>
17 18	265	Table 2 provides the results of the cost-effectiveness analysis for different durations
19 20	266	of intervention effect. The longer the assumed duration of effect, the more likely it is
21 22 23	267	that the intervention is cost-effective at cost effectiveness thresholds conventionally
23 24 25	268	employed (i.e. £20,000 per QALY). It is notable that, even if the beneficial effects of
26 27 28 29 30 31	269	the intervention on CVD risk last only one year, the intervention is likely to be cost-
	270	effective. This is also apparent in the cost-effectiveness acceptability curves, where a
	271	monotonic relationship between duration of the probability of cost-effectiveness is
32 33 34	272	evident (Figure 2).
35 36 37 38 39	273	The small QRISK2 difference between arms means that the control and intervention
	274	groups have very similar risk profiles once the assumed duration of effect expires.
40 41	275	The lifetime cost-effectiveness results are therefore influenced, especially at short
42 43 276		durations of effect, by the inclusion of costs and QALYs observed during the 12-
44 45 46	277	month period of trial follow-up. The between-arm cost and QALY differences in the
46 47 48	278	initial 12 months are propagated forward over the remaining lifetime of trial
49 50	279	participants, and are more influential than the subsequent minor differences in costs
51 52	280	and QALYs associated with different levels of simulated QRISK2. Nevertheless, the
53 54	281	differences in QRISK2 are consequential at longer durations of effect, since they are
55 56 57 58	282	associated with fewer CVD events in the intervention arm.

## Discussion

Cost-effectiveness over the lifetime of participants in the Healthlines telehealth trial was estimated using a cohort simulation model. The probability of cost-effectiveness increased with longer durations of effect, but even with the shortest duration of effect the intervention was estimated to be cost-effective. These results reflect the costeffectiveness analysis at 12 months: because of the small difference in QRISK2 between arms, the QALY difference observed at the end of trial follow-up has a major influence on lifetime cost-effectiveness.

The model is subject to a number of limitations. The quality of the output reflects the assumptions and data used to construct and populate the model. The QRISK2 algorithm is not validated for ages beyond 84, and we made an assumption as to growth in risk for the small number of simulated trial participants who lived to 85 and beyond.

As in all modelling exercises of this type, the results may be sensitive to structural assumptions, such as the number of health states modelled.<sup>11</sup> We cannot eliminate the possibility that alternative representations of clinical pathways may produce different conclusions. However, we have relied on a representation of health states that is consistent with the QRISK2 algorithm, the defined events (e.g. stroke) of which are represented as distinct states in the model.

The model understates uncertainty associated with QRISK2 because the variance structures underlying the algorithm are not published or otherwise available, and the consequence of this is to narrow confidence intervals around net monetary benefit statistics. This may have implications, in particular, for the probability of costeffectiveness.

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2 3 4	307	We have not accounted for non-health service costs, which may have consequences
4 5 6 7 8 9 10	308	for carers and the wider economy for some of the conditions modelled, such as
	309	stroke. <sup>24</sup> However, it is not clear if accounting for these costs would necessarily alter
	310	the between-arm comparison of cost-effectiveness, since slightly fewer fatal and non-
11 12 13	311	fatal strokes would be experienced in the intervention arm.
14 15 16	312	Finally, the analysis does not identify the most plausible duration of effect. Evidence
10 17 18	313	from long-term follow-up is necessary to conclusively answer this question, although
19 20	314	synthesis of evidence from similar trials and relevant observational studies may also
21 22	315	offer a useful complementary approach to long-term follow-up.
23 24 25 26	316	Comparison with other literature
27 28	317	Comparison of the findings of this study with other literature assessing the long-term
29 30	318	cost-effectiveness of interventions directed at managing CVD risk is complicated by
31 32 33	319	differences in the study design used to inform the modelling, patient profiles, and the
34 35	320	nature of the interventions examined. However, the approach of using different
36 37	321	assumed durations of effect, or different effect sizes, is encountered in similar
38 39	322	studies.
40 41		
42 43	323	For example, the evaluations of CVD interventions from a long-term perspective
44 45	324	undertaken by Mistry et al <sup>18</sup> , Asaria et al <sup>25</sup> and Penaloza-Ramos et al <sup>26</sup> are all
46 47	325	sensitive to some degree to assumptions made concerning the duration of
48 49	326	intervention effect. This is in spite of differences between these studies in population
50 51 52	327	characteristics, CVD risk equation used and interventions studied, which preclude a
52 53 54	328	comparison of the findings of the present study and these other analyses.
55 56 57	329	Studies also differ in the study design used to inform long-term cost-effectiveness
58 59	330	modelling. The effect estimates used as the basis of modelling in our study are those
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of the 'intention to treat' analysis of the Healthlines RCT. This is a source of difference between the present paper and, for example, the economic modelling undertaken in support of the routine use of "health checks" in the NHS in England.<sup>27</sup> The economic model developed to analyse the consequences of these health checks was based on a much more extensive simulation involving synthesis of various model parameters, compliance rates and effect estimates from a variety of sources. Ultimately, although modelling and evidence synthesis will continue to be important sources of evidence in this area, definitive evidence on the long-term consequences for CVD risk of Healthlines (and similar interventions) will require RCTs with longterm follow-up. CONCLUSION The Healthlines telehealth service is likely to be cost-effective for individuals with raised CVD risk when a lifetime perspective is adopted. Results are somewhat sensitive to the assumed duration of intervention effect. When considering the deployment of large scale telehealth programmes in this area, decision makers may need to consider the longevity of the behavioural and other changes rendered by the type of telehealth service studied in the Healthlines RCT, alongside other evidence concerning the long-term cost effectiveness of similar interventions for CVD risk. 

**Tables and figures** 

351 Table 1 QRISK2 scores at baseline and after 12-months of follow-up

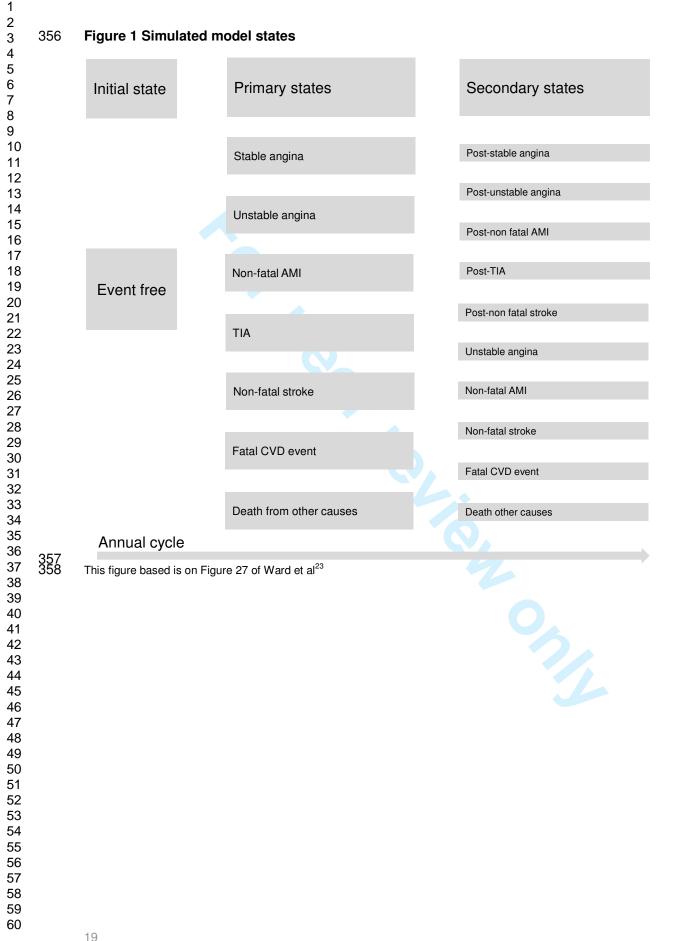
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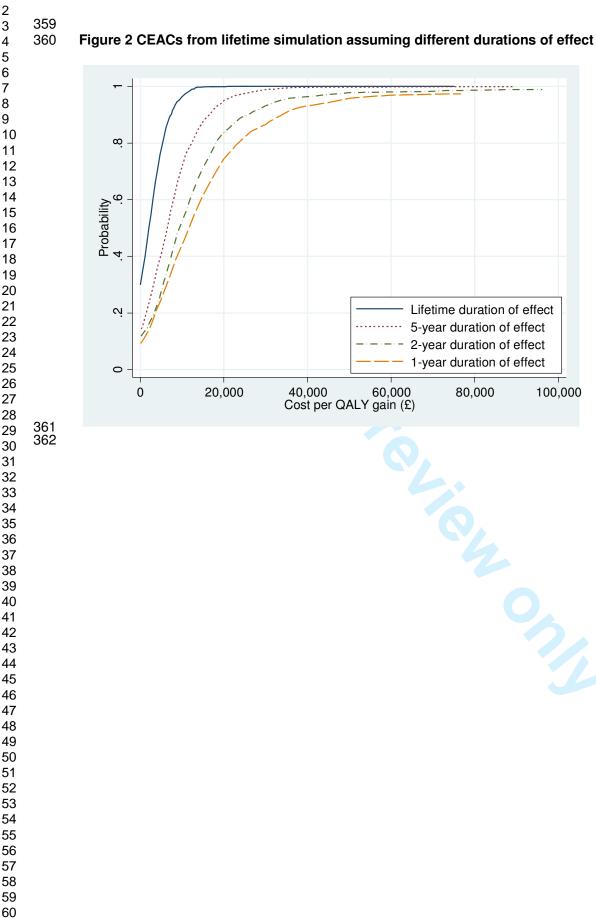
	Control arm	Intervention arm			
	Baseline	12 month follow-up, adjusted for baseline	Baseline	12 month follow-up, adjusted for baseline	
QRISK2 score for males	31.59	32.00	31.83	31.60	
QRISK2 score for females	27.73	28.24	27.86	27.84	

Note: The data are presented as levels of QRISK2 as it is the level of risk that determines the probability of events such as stroke or acute myocardial infarction.

These data are based on imputed QRISK2 scores – multiply imputed data are used in the base case economic evaluation at 12 months from randomisation.<sup>3</sup> These data are based on CVD risk of all of those randomised (n=641) in the RCT. The methods used for multiple imputation are described in further detail in the companion 12 month economic evaluation paper.<sup>12</sup>

Control arm NHS costs	1 voor	Modelled du	ation of effect	
	1 year	2 years	5 years	Lifetime (permanent) effect
Intervention arm NHS costs	£6,595	£6,617	£6,608	£6,602
	£6,726	£6,741	£6,714	£6,657
Control arm QALYs	8.573	8.573	8.573	8.572
Intervention arm QALYs	8.584	8.586	8.589	8.598
Incremental costs (95% CI)	£131 (£125 to 138)	£124 (£118 to 130)	£107 (101 to 112)	£55 (49 to 61)
Incremental QALYs (95% CI)	0.011 (0 .011 to 0 .011)	0.013 (0 .012 to 0 .013)	0.016 (0.016 to 0.017)	0.026 (0.026 to 0.027)
ICER	£11,776	£9,886	£6,477	£2,091
Probability cost effective at £20,000 threshold	0.74	0.84	0.95	0.99
Probability cost effective at £30,000 threshold	0.87	0.93	0.99	1.00
NMB at threshold of £20,000 (95% CI)	£92 (-172 to 352)	£127 (-144 to 382)	£223 (-153 to 468)	£472 (197 to 728)





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1 2		
2 3 4	363	Contributorship statemement: PD and SH: Conducted economic analysis. RA: Led
5 6	364	development of original simulation model, which was updated and modified by PD for
7 8	365	the Healthlines study. Provided advice on model development and adaptation. LE:
9 10	366	Acted as trial manager. Undertook participant recruitment and follow-up, data
11 12	367	collection and data entry. AF: Participant recruitment and follow-up, data collection
13 14 15	368	and data entry for the RCT. CS: Led protocol development and the funding
16 16 17	369	application for the programme grant, acted as chief investigator with overall
18 19	370	responsibility for conduct of the RCT. All authors had a role in interpreting the data.
20 21	371	PD wrote the first draft of this article, and all authors contributed to subsequent
22 23 24	372	revisions. All authors approved the final version for submission.
24 25 26	373	<b>Conflict of interest statement:</b> The authors declare no conflicts of interest.
27 28	575	Connict of interest statement. The authors declare no connicts of interest.
29 30	374	Funding statement: This report summarises independent research funded by the
31 32	375	National Institute for Health Research (NIHR) under its Programme Grant for Applied
33 34 25	376	Research (Grant Reference Number RP-PG-0108-10011). The views and opinions
35 36 37	377	expressed in this report are those of the authors and do not necessarily reflect those
38 39	378	of the National Institute for Health Research (NIHR), the NHS or the Department of
40 41	379	Health. The funder had no role in the conduct of the study, the writing of the
42 43	380	manuscript or the decision to submit it for publication.
44 45 46 47	381	Data sharing: No additional data available
48 49	382	Acknowledgements: We are very grateful to all patients, health care professionals,
50 51	383	Health Information Advisors and other NHS Direct staff who contributed time and
52 53 54	384	effort to make the Healthlines trial possible. We are grateful to administrative staff at
55 56	385	trial sites for support with participant recruitment, data entry and trial administration.
57 58 59	386	The Healthlines Study was designed and delivered in collaboration with Bristol
60		21

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Randomised Trials Collaboration (BRTC), a UKCRC Registered Clinical Trials Unit in 

- receipt of National Institute for Health Research CTU support funding.
- <text> Ethics: The Healthlines trial was approved by the National Research Ethics Service
- Committee South West - Frenchay (Reference 12/SW/0009). All participants
- provided informed consent to take part in the trial.

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## Appendix – online supplementary information

### A1 Permitted transitions in simulation model

### Event free state to primary states

Event free to Primary Stable Angina (SA)

Event free to Primary Unstable Angina (USA)

Event free to Primary AMI

Event free to Primary TIA

Event free to Primary Stroke

Event free to Fatal CVD event (FCVD)

Event free to Death other causes (DOC)

Primary states to subsequent states

PRIMARY\_SA to SECONDARY\_(USA or 1st AMI or 1st Stroke or FCVD or DOC) else post SA PRIMARY\_USA to SECONDARY\_(1st AMI or 1st Stroke or FCVD or DOC) else post USA PRIMARY\_AMI to SECONDARY\_(1st AMI or 1st Stroke or FCVD or DOC) else post AMI PRIMARY\_TIA to SECONDARY\_(1st AMI or 1st Stroke or FCVD or DOC) else post TIA PRIMARY\_Stroke to SECONDARY\_(1st Stroke or FCVD or DOC) else post TIA PRIMARY\_Stroke to SECONDARY\_(1st Stroke or FCVD or DOC) else post Stroke **Post-primary states to subsequent states** 

Post PRIMARY\_SA to SECONDARY\_(USA or 1st AMI or 1st Stroke or FCVD or DOC) else post SA Post PRIMARY\_USA to SECONDARY\_(1st AMI or 1st Stroke or FCVD or DOC) else post USA Post PRIMARY\_AMI to SECONDARY\_(1st AMI or 1st Stroke or FCVD or DOC) else post AMI Post PRIMARY\_TIA to SECONDARY\_(1st AMI or 1st Stroke or FCVD or DOC) else post TIA Post PRIMARY\_Stroke to SECONDARY\_(1st Stroke or FCVD or DOC) else post Stroke

### Secondary state transitions

SECONDARY\_SA to SECONDARY\_( (USA or 2nd AMI or 2nd Stroke or FCVD or DOC) else post SA SECONDARY\_USA to SECONDARY\_( (2nd AMI or 2nd Stroke or FCVD or DOC) else post USA SECONDARY\_AMI to SECONDARY\_( (2nd AMI or 2nd Stroke or FCVD or DOC) else post AMI SECONDARY\_TIA to SECONDARY\_( (2nd AMI or 2nd Stroke or FCVD or DOC) else post TIA SECONDARY\_Stroke to SECONDARY\_( (2nd Stroke or FCVD or DOC) else post Stroke Post SECONDARY\_SA to SECONDARY\_(USA or 2nd AMI or 2nd Stroke or FCVD or DOC) else post SA Post SECONDARY\_USA to SECONDARY\_(2nd AMI or 2nd Stroke or FCVD or DOC) else post USA Post SECONDARY\_AMI to SECONDARY\_(2nd AMI or 2nd Stroke or FCVD or DOC) else post AMI Post SECONDARY\_AMI to SECONDARY\_(2nd AMI or 2nd Stroke or FCVD or DOC) else post AMI Post SECONDARY\_TIA to SECONDARY\_(2nd AMI or 2nd Stroke or FCVD or DOC) else post TIA Post SECONDARY\_TIA to SECONDARY\_(2nd AMI or 2nd Stroke or FCVD or DOC) else post TIA

Notes to A1: SA = Stable angina; USA = Unstable angina; AMI = Acute myocardial infarction; TIA = Transient ischaemic attack; FCVD = Fatal cardiovascular disease event; DOC = Death other causes This is the same list of permitted transitions described as in Ara et al <sup>1</sup> and Ara et al <sup>2</sup>. A1 contains the same information as Table 82 in Ara et al <sup>1</sup>.

# INPUT VALUES, REFERENCES AND PROBABILITY DISTRIBUTIONS FOR MODEL PARAMETERS

Table A2 provides a map to the various model parameters, input values, and associated probability distributions from which input values for specific model runs were drawn, and which are presented in more detail where applicable.

### A2 Key input parameters and associated probability distributions

Parameter	Input values	Probability distribution	Comments
Health state utility	Various; listed in Table	Normal	Ara and Wailoo <sup>3</sup>
values	A3		recommend the use of
			normal distributions to
			characterise the
			uncertainty in mean
			utilities
Health state costs	Various, listed in Table	Gamma	A number of sources, eg
	A4		Gray et al <sup>4</sup> , recommend
			using gamma
			distributions in
			characterising
			uncertainty in cost
			variables
Incidence rates for	Various, listed in Table	N/A	We follow Ward et al⁵
primary CVD events	A5 and Table A6		and Ara et al <sup>2</sup> in using
-			the mean values of
			published incidence
			rates in each model run
CVD Risk	Based on age and sex	N/A	The variance structures
	adjusted QRISK2 scores		underlying the QRISK2
	from baseline and 12m		algorithm are not
	follow-up that are		published and hence we

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1				
2 3		presented in Table 1 in		could not characterise
4 5		the main text, and then		uncertainty in this
6		adjusted subsequently		measure. See
7 8		using the QRISK2		Discussion in main
9 10		algorithm		paper.
11 12	Risk of death from	Based on standardised	Normal distribution	We follow Ara et al <sup>2</sup> in
13		mortality ratios		
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### UTILITIES

Ara and Brazier<sup>6</sup> was used as the source of state-specific utilities other than TIA, which are based on Luengo-Fernandez et al<sup>7</sup>. It was assumed that the utility estimates for angina in Ara and Brazier related to stable angina, and that unstable angina health utilities would be 90% of the stable angina values, as in Ara et al.<sup>2</sup>

As further noted in the main text, any 'third' events, i.e. those occurring after a secondary event, have the same utility as the 'second' event.

A3 Health state utility values	
Health state	Mean utility value
Primary stable angina	0.615
Primary unstable angina	0.556
Primary AMI	0.721
Primary TIA	0.760
Primary stroke	0.626
Post-primary angina	0.775
Post-primary unstable angina	0.701
Post-primary AMI	0.742
Post-primary TIA	0.78
Post-primary stroke	0.668
Secondary stable angina	0.541
Secondary unstable angina Secondary AMI Secondary TIA Secondary stroke	0.489
Secondary AMI	0.431
Secondary TIA	0.760
Secondary stroke	0.479
Post-secondary stable angina	0.715
Post-secondary unstable angina	0.647
Post-secondary AMI	0.685
Post-secondary TIA	0.78
Post-secondary stroke	0.641

### Costs

 A detailed discussion of the cost data used to model each state is provided in Salisbury et al.<sup>8</sup> Briefly, the costs of stable and unstable angina, of non-fatal acute myocardial infarction a are based on Ward et al<sup>5</sup> and Ara et al.<sup>2</sup> The cost of fatal

acute myocardial infarction are based on Clarke et al.<sup>9</sup> The costs of non-fatal stroke and of transient ischaemic attack are based on Luengo-Fernadez et al.<sup>7</sup> The cost of fatal stroke is based on Youman et al.<sup>10</sup> In all cases, costs were adjusted to 2012/13 sterling prices as described in Salisbury et al.<sup>8</sup>

A4 Health state costs	
Health state	Mean cost in 2012/13 £ prices
Stable angina	606
Stable angina in subsequent years	356
Unstable angina	4,324
Unstable angina in subsequent years	453
Non-fatal acute myocardial infarction	3,362
Post non-fatal acute myocardial infarction	356
Fatal acute myocardial infarction	1,846
Transient ischaemic attack	3,963
Transient ischaemic attack in subsequent years	1,380
Non-fatal stroke	8,989
Non-fatal stroke in subsequent years	1,976
Fatal stroke	9,493

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### INCIDENCE RATES FOR PRIMARY EVENTS

Incidence rates for primary events are used to calculate the probability of one of stable angina, unstable angina, acute myocardial infarction (AMI), stroke, and transient ischaemic attack (TIA). These incidence rates are then used to disaggregate the risk of any such event, measured by the QRISK2 score, into the risk of a single event.

The data sources and adjustments made to data are described in more detail in Salisbury et al. <sup>8</sup> Here, we briefly describe these sources, and present in A5 and A6 the incidence data used in the simulation model.

The incidence of angina was taken from data for England reported British Heart Foundation Coronary Heart Disease Statistics 2012,<sup>11</sup> using the data reported for England. This was split into incidences of stable and unstable angina using incidences reported in Sutcliffe et al. <sup>12</sup> Incidence of fatal and non-fatal AMI was also taken from British Heart Foundation Coronary Heart Disease Statistics 2012.<sup>11</sup> Incidence of first ever stroke was based on Wang et al, <sup>13</sup> and incidence on mortality from strokes was based on Lee et al. <sup>14</sup>

Incidence of TIA is taken from British Heart Foundation Stroke Statistics 2009.<sup>15</sup>

### A5 Incidence rates of CVD events per 1,000 males per year

Age band	Stable angina	Unstable angina	Non-fatal AMI	Fatal AMI	TIA	Non- fatal stroke	Fatal stroke
55-64	0.84	0.25	0.28	0.04	0.74	0.65	0.08
65-74	1.16	0.35	0.42	0.11	1.45	1.27	0.16
75-84	0.75	0.23	0.73	0.29	3.27	2.73	0.35
85+	0.75	0.23	1.23	0.76	7.94	5.12	0.65

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### A6 Incidence rates of CVD events per 1,000 females per year

Age band	Stable angina	Unstable angina	Non-fatal AMI	Fatal AMI	ΤΙΑ	Non- fatal stroke	Fatal stroke
55-64	0.35	0.11	0.07	0.02	1.05	0.63	0.14
65-74	0.74	0.22	0.18	0.06	2.18	1.23	0.28
75-84	0.57	0.17	0.38	0.22	5.61	2.64	0.6
85+	0.57	0.17	0.75	0.64	9.14	4.95	1.13

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	Item		Reported on page No/
Section/item	No	Recommendation	line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use	Page 1
		more specific terms such as "cost-effectiveness	
		analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives,	Page 3
		perspective, setting, methods (including study design	
		and inputs), results (including base case and	
		uncertainty analyses), and conclusions.	
Introduction			
Background and	3	Provide an explicit statement of the broader context	Lines 60-87
objectives		for the study.	
		Present the study question and its relevance for	Lines 88-97
		health policy or practice decisions.	
Methods			
Target population and	4	Describe characteristics of the base case population	Lines 99-108
subgroups		and subgroups analysed, including why they were	
		chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the	Lines 99-103
	-	decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this	Lines 119-120
	-	to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being	Lines 109-118
comparators		compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and	Lines 88-97
	0	consequences are being evaluated and say why	Liftes 08-57
		appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs	Lines 262-263
Discount rate	5	and outcomes and say why appropriate.	Lines 202-205
Choice of health	10	Describe what outcomes were used as the measure(s)	Line 139-140
outcomes	10	of benefit in the evaluation and their relevance for	Line 139-140
outcomes		the type of analysis performed.	
Measurement of	11a	Single study-based estimates: Describe fully the	Estimates are based on
	114	design features of the single effectiveness study and	effectiveness data from
effectiveness			
		why the single study was a sufficient source of clinical effectiveness data.	the Healthlines RCT (Lines 109-129)
	116		109-129)
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and	Not applicable
		synthesis of clinical effectiveness data.	Not applicable
NA	10	,	Lin 220, 220
Measurement and	12	If applicable, describe the population and methods	Lines 220-226
valuation of preference		used to elicit preferences for outcomes.	
based outcomes	10		
Estimating resources and	13a	Single study-based economic evaluation:Describe	
costs		approaches used to estimate resource use associated	
		with the alternative interventions. Describe primary	Not applicable
		or secondary research methods for valuing each	
		resource item in terms of its unit cost. Describe any	
		adjustments made to approximate to opportunity	
		costs.	
	13b	Model-based economic evaluation: Describe	Lines 246-257 in main
		approaches and data sources used to estimate	text, and page5-6 of

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Section/item	No	Recommendation	line No
		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost.	supplementary materia
		Describe any adjustments made to approximate to	
<u> </u>		opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting	Line 14
		estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into	
		a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to	Lines 132-140 and Figure
		show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Lines 142-202
Analytical methods	17	Describe all analytical methods supporting the	Lines 132-21
· · · · · <b>,</b> · · · · · · · · · · · · · · · · · · ·		evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1 in main text, and Tables A2, A3, A4, A5and A6 in the appendix
Incremental costs and	19	For each intervention, report mean values for the	Table 2 in main tex
outcomes	19	main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Not applicable
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Table 2 and Figure 2 ir the main tex
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Not applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Lines 291 to 34
Other		5	
Source of funding	23	Describe how the study was funded and the role of	Page

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24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical	Page 2
	Journal Editors recommendations.	
	No 24 IEERS states	No       Recommendation         the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support.         24       Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.         IEERS statement checklist format is based on the format of the CON:

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## Cost-effectiveness modelling of telehealth for patients with raised cardiovascular disease risk: Evidence from a cohort simulation conducted alongside the Healthlines randomised controlled trial

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Secondary Subject Heading:	Health services research, Cardiovascular medicine
Keywords:	HEALTH ECONOMICS, STROKE MEDICINE, Myocardial infarction < CARDIOLOGY, Angina

SCHOLARONE<sup>™</sup> Manuscripts

- 1 Cost-effectiveness modelling of telehealth for patients with
- 2 raised cardiovascular disease risk: Evidence from a cohort
- **3** simulation conducted alongside the Healthlines randomised
- 4 controlled trial
- 5 Padraig Dixon<sup>1\*</sup>, Sandra Hollinghurst<sup>1</sup>, Roberta Ara<sup>2</sup>, Louisa Edwards<sup>1</sup>, Alexis
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- 12 Short title: Lifetime cost-effectiveness modelling of telehealth in CVD

## 13 Abstract

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1	35	Conclusions: The intervention was likely to be cost-effective under a lifetime
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3 4	36	perspective.
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6	37	Trial registration: ISRCTN27508731, prospectively registered 05/07/2012
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2 3	39	Strengths and limitations
4 5	40	<ul> <li>The Healthlines trial was one of the largest RCTs designed to evaluate a</li> </ul>
6 7	41	telehealth-based complex intervention for the management of cardiovascular
8 9 10	42	disease risk.
11 12 13	43	<ul> <li>This study complements and extends the findings of a within-trial evaluation</li> </ul>
14 15	44	carried out on outcomes at 12 months from randomisation by evaluating the
16 17	45	cost-effectiveness of the telehealth intervention over the lifetime of trial
18 19 20	46	participants using a cohort simulation model
21 22 22	47	<ul> <li>The intervention is likely to be cost-effective from a health system</li> </ul>
23 24 25	48	perspective, but we cannot identify the most plausible duration of
26 27	49	intervention effect
28 29 30	50	Introduction
31	51	
32 33	52	Cardiovascular disease (CVD) is a prevalent long-term condition associated with
34 35	53	substantial morbidity and mortality. <sup>1</sup> Effective care for patients with raised CVD risk
36 37	54	requires attention to, and management of, underlying risk factors such as high blood
38 39 40	55	pressure and obesity. <sup>2</sup> A challenge in estimating the cost-effectiveness of
40 41 42	56	interventions intended to reduce CVD risk is that randomised controlled trials (RCTs)
43 44	57	may have follow-up periods that are shorter than the period over which an
45 46	58	intervention may affect CVD risk. This is in spite of the impact that interventions to
47 48	59	reduce CVD risk – such as blood pressure management and weight management
49 50	60	programmes – might have in reducing the future occurrence of debilitating events
51 52 53 54	61	such as acute myocardial infarction and stroke.
55 56	62	Telehealth is one form of condition management that may be relevant to long-term
57 58 59	63	conditions in general and to CVD in particular. <sup>3</sup> However, there is a lack of high-
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guality evidence regarding the cost-effectiveness of telehealth.<sup>4567</sup> To estimate the clinical and cost-effectiveness of a de novo telehealth intervention, the Healthlines CVD risk RCT individually randomised 641 participants to receive either usual care or a theory-based telehealth intervention that encouraged participants to engage in beneficial behaviour change. The primary clinical outcome of the trial was 10-year CVD risk, measured using the QRISK2 risk prediction algorithm<sup>8</sup>, at the end of 12-months of follow-up. In the absence of data from long-term follow-up, there is no means of assessing the enduring impact on cost-effectiveness of the changes in modifiable risk factors that the intervention may have wrought. For example, it is plausible that some patients who managed to reduce their blood pressure (BP), body mass index (BMI) or whose medication adherence was improved as a result of the intervention may continue with newly acquired beneficial behaviours after the end of the 12 months of trial follow-up. Indeed, it is implausible that all trial participants would immediately revert to their pre-intervention BP or BMI immediately on trial completion. This paper describes the development and analysis of a state transition cohort simulation cost-effectiveness model intended to estimate the expected net benefits of the Healthlines telehealth intervention over the lifetime of trial participants. This approach is consistent with the principles of economic evaluation,<sup>9</sup> guidance from the National Institute for Health and Care Excellence (NICE)<sup>10</sup>, and ISPOR guidelines <sup>11</sup> which recommend that cost-effectiveness analyses be undertaken over a time period 

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that reflects differences in cost and effect attributable to an intervention or treatment.

86 The long-term cost-effectiveness analysis complements the analysis of cost-

effectiveness of the intervention at 12 months post-randomisation published in a
companion paper.<sup>12</sup>

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52 53 54	111	NHS perspective
54 55 56	112	NICE threshold
57 58	113	questionnaires
59 60	114	estimated from

nes RCT col, methods, results and cost-effectiveness analyses have been here.<sup>3 13</sup> Briefly, patients aged between 40 and 74 with ten-year CVD asured by the QRISK2 algorithm) and at least one modifiable risk nple, weight management or smoking) were recruited from 42 GP gland. Individuals were not considered if they had a confirmed VD, were pregnant, did not have access to the internet and telephones to communicate verbally. More detail on these and other exclusion able in Salisbury et al.<sup>3</sup> In total, 641 patients were randomised, and unmodified usual care (n=316), or a telehealth intervention in addition n=325), for a follow-up period of 12 months. the intervention arm could receive up to 13 responsive, tailored ounters with trained Health Information Advisors (HIAs). Participants ed to access and use online material and apps related to CVD risk. th systolic blood pressure ≥140 mmHg and without atrial fibrillation blood pressure monitor to use at home, and could upload readings to itor progress. Telephone calls focused on goal setting, stimulus management of CVD risk in a way that was relevant to the of each individual participant and which was in line with NICE s included ensuring that patients were taking appropriate drug addressing problems with medication adherence. economic evaluation at the end of 12 months of follow-up adopted an ve. The cost-effectiveness of the intervention was estimated against ds using NHS cost data collected from medical records and during the trial, and using data on quality-adjusted life years (QALYs) responses to the EQ-5D-5L<sup>14</sup> generic quality-of-life measure at 6

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baseline, and six and 12 months from randomisation. Mean incremental NHS costs in 115 2012/13 prices were estimated to be £138 per patient (i.e. the intervention was more 116 117 expensive), and mean incremental QALY gains were estimated to be 0.012. The 118 estimated ICER was £10,859, and the estimated net benefit at a threshold of £20,000 was estimated to be £116 (95% confidence interval: -£58 to £291). The probability 119 120 that the intervention was cost-effective at this threshold value was 0.77.

#### 121 Methods

Model structure 122

Cohorts of 1,000 patients were simulated. These cohorts were based on the 123 characteristics of the 641 trial participants. Cohorts differed according to age at 124 randomisation, sex and trial allocation of the patient groups modelled. A set of 125 126 discrete, mutually exclusive states were created and defined by the presence (or absence) of a CVD-related condition, or with death (Figure 1). Sequences of states 127 128 experienced by the simulated cohort members defined clinical pathways in which 129 QALYs (associated with utilities and mortality) and costs were accumulated. Costeffectiveness, as measured by the averages of costs and QALYs in each arm, was 130 the primary outcome. These averages were calculated and allowed for the 131 132 construction of net benefit statistics. Costs were expressed in 2012/13 sterling prices. 133 The model is based on adapted updated versions of models used in previous health technology assessments in the area of CVD risk.<sup>15 16</sup> A National Health System 134 perspective was adopted. The model cycled annually. Both costs and outcomes were 135 subject to a half-cycle correction.<sup>17</sup> Consistent with the inclusion criteria of the trial, 136 and the construction of the QRISK2 algorithm,<sup>8</sup> patients were assumed to be free of 137 CVD when they entered the model – this corresponds to the 'event free' state. 138 139 Subsequent states correspond to the occurrence of the events used in the QRISK2

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140	algorithm – acute myocardial infarction (AMI), angina, transient ischaemic attack
141	(TIA) and stroke – and to post-event states, e.g. a 'post-stroke' state (Figure 1).
142	Patients cycled the model until death, or age 100, at which point they were assumed
143	to die. A total of 1,000 iterations of the model were simulated, in which values of input
144	parameters were varied simultaneously. Each iteration used a value drawn from
145	probability distributions assigned to particular input parameters of the model as
146	described below, in the supplementary material and in Salisbury et al. <sup>3</sup> Probabilistic
147	sensitivity analysis was used to quantify uncertainty around point estimates of net
148	benefit. The model was implemented in Excel 2013 (Microsoft: Redmond,
149	Washington).
150	Probability of transitioning to primary and secondary states
151	The probability of entering a particular state is determined by CVD risk. Initial risk
152	scores of patients at the beginning of the model, corresponding to the event-free
153	state, were based on information collected in the RCT (Table 1). CVD risk in the
154	initial year (year 0) is thus average participant baseline QRISK2 score. Change in
155	CVD risk at the end of this year/start of the next year (year 1) is measured by
156	QRISK2 score calculated at 12-month follow-up and adjusted for baseline risk,
157	details of which are provided in Salisbury et al. <sup>3</sup> CVD risk in subsequent years was
158	obtained by adding percentage increases obtained from growth rates in annual risk in
159	males when all input values to the QRISK2 algorithm other than age were held
160	constant.
161	Growth rates from males were used because the level of CVD risk is higher for males
162	than for females at all ages, other variables being constant. Using the relatively more
163	rapid growth rates observed in female risk levels as a basis for extrapolation would

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2 3 4	164	have meant that at some ages female risk was much higher than male risk. The use
4 5 6 7 8	165	of male risk growth rates constrains female risk levels to be below male levels at all
	166	ages, ensures that risk does not rise above 100%, better reflects estimated
9 10	167	prevalence of risk in males and females, and more generally ensures that the cost-
11 12 13	168	effectiveness results are based on plausible risk profiles. <sup>3</sup>
14 15 16	169	The QRISK2 algorithm is not validated for ages beyond 84. Risk for patients
17 18	170	surviving to 85 and above was obtained by extrapolating 10-year risk by 1% per
19 20	171	annum, which corresponds to the coefficient obtained from an ordinary least squares
21 22 23	172	regression of QRISK2 scores on age.
24 25	173	Ten-year risk scores were converted into an annual risk of any event to reflect the
26 27	174	annual cycles of the model. Annual risk scores of any defined CVD event were then
28 29 30	175	disaggregated into the risk of a <i>specific</i> event – AMI, angina, TIA and stroke – using
31 32	176	data on the incidence of these conditions by age and sex. The sources for these data
33 34	177	and the input values used are described in the online supplementary material.
35 36 37	178	Further detail on their calculation is available in Salisbury et al. <sup>3</sup>
38 39 40	179	These incidence rates establish the probability of moving from the event-free state to
40 41 42	180	a specific CVD-related event state; that is, they establish the risk of a primary event.
43 44	181	Transitions to secondary events (any event after the primary event) are determined
45 46	182	by the age and sex-specific transition probabilities given in Ara et al, <sup>15</sup> who describe
47 48	183	in detail the data sources and methods used in their construction. Permitted
49 50 51	184	transitions between states are listed in the online supplementary material (Table A1).
52 53 54	185	The probability of death due to causes not related to CVD risk was based on
55 56	186	standardised mortality ratios calculated from the most recently available (2012) Office
57 58 59	187	of National Statistics Interim Life Tables. <sup>18</sup> This mortality ratio excluded CVD-related
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ICD-10 codes (I20-I25 and I60-I69). The risks of mortality used in each iteration of the model were based on draws from a univariate normal distribution. Simulated participants were constrained to experience no more than three CVD events, an assumption that reflected data availability and model tractability. The same assumption was used in Ara et al.<sup>15</sup> However, few of the 1,000 simulated participants approached experiencing three events, and therefore the assumption is unlikely to have influenced cost-effectiveness conclusions. **Duration of effect of intervention** The duration of the effect of the Healthlines intervention on CVD risk beyond the end of trial follow-up is unknown, but the modelling thereof is the principal motivation for undertaking the simulation modelling described here. Four different scenarios based on different durations of effect were modelled, and their implications for costeffectiveness compared. This is similar to the approach of Mistry et al.<sup>19</sup> The scenarios modelled are of durations of intervention effect of one, two, and five 

years from baseline, and for remaining lifetime. If, for example, the duration effect is two years, then participants in the intervention arm receive the benefit of lower risk for two years, after which they are modelled as having the same sex- and age-adjusted risk as participants in the control arm. Similar logic applies to the other scenarios. In the case of a lifetime duration of effect, risk is permanently lower in the intervention arm. To avoid sudden 'jumps' in risk at the point at which the intervention ends, the model uses a smoothing adjustment which calculates the average score of intervention arm risk and usual care risk for the year after which the modelled duration of effect expires. 

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## 1 Data on utility

QALYs in year zero of the model were obtained from participant responses to the
EQ-5D-5L measure at baseline, six and 12 months of RCT follow-up, and were
'cross-walked' to UK EQ-5D-3L instrument and valued using the Euroqol UK value
set.<sup>20</sup> QALYs were adjusted to account for between-arm differences observed at the
end of trial follow-up. For other years of the model, age- and sex-adjusted population
EQ-5D norms were estimated from Ara and Brazier<sup>21</sup> to provide baseline utility
scores that applied to the event-free state. These EQ-5D data were used to calculate
QALYs.

Multiplicative adjustments, which assume a constant proportional effect on baseline utility,<sup>21</sup> were made to reflect the decremental impact of experiencing CVD-related health states. Ara and Brazier<sup>21</sup> was used as the source of state-specific utilities other than TIA, which were drawn from Luengo-Fernandez et al,<sup>22</sup> and for unstable angina. It was assumed that the utility estimates for angina in Ara and Brazier related to stable angina; it was further assumed that utility associated with the unstable angina health state would be 90% of the stable angina values, as in Ara et al.<sup>15</sup>

Condition-specific utility values were drawn from univariate normal distributions, as
recommended by Ara and Wailoo,<sup>23</sup> to reflect uncertainty in mean values. Utilities
corresponding to post-event states were never lower than for the event state itself.
This means, for example, that utilities of the "post-stroke" event state were higher
than or equal to the "stroke" state, implying that experiencing a stroke had a greater
negative impact on average on patient utility than did experiencing the "post-stroke"

It was assumed that the second and third events (such as second and third non-fatal
 strokes) had the same impact on utility as the first event. This rules out multiplicative
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impacts of events on quality of life. The utility values associated with different statesare presented in the online supplementary material (Table A2).

238 Data on cost

A health-system perspective was adopted for the analysis, and hence only NHS costs were considered. This excluded consideration of any personal or societal costs associated with, for example, incapacity and exit from the labour force connected with a debilitating but non-fatal stroke

The costs of health states were based, in most cases, on Ward et al<sup>24</sup> and Ara et al.<sup>15</sup> The first year of the model also included costs of the intervention, and NHS costs incurred in each arm. The costs of each health state is described in the online supplementary material.

The cost estimates in Ward et al<sup>24</sup> and Ara et al<sup>15</sup>, derived from systematic reviews, were updated where appropriate and possible with new data, as described in more detail in Salisbury et al.<sup>3</sup> Mean costs enter the simulation model at each iteration as draws from a gamma distribution.

251 Cost effectiveness analysis

The simulation model uses information on the NHS costs and QALYs observed during the 12-months of trial follow-up in the initial year (year 0). All subsequent costs and QALYs are simulated by the model as a function of QRISK2 scores using the methods described above. Costs and outcomes were both discounted at 3.5% per year, in line with NICE recommendations.<sup>10</sup> Cumulative costs and QALYs were obtained for the lifetime of cohort members by calculating probability-weighted averages of the number of patients in each state, the length of time patients have

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2 3	259	been in particular states, and the costs, mortality and quality of life associated with
4 5 6 7	260	each state.
, 8 9	261	Results
10	262	The mean age of males (females) in the trial was 67 (69), and males comprised 80%
11 12 13	263	of trial participants. Table 1 contains baseline and adjusted 12 month QRISK2 scores
14 15 16	264	<ul> <li>higher scores indicate higher CVD risk.</li> </ul>
17 18	265	Table 2 provides the results of the cost-effectiveness analysis for different durations
19 20	266	of intervention effect. The longer the assumed duration of effect, the more likely it is
21 22 23	267	that the intervention is cost-effective at cost effectiveness thresholds conventionally
23 24 25	268	employed (i.e. $\pounds$ 20,000 per QALY). It is notable that, even if the beneficial effects of
26 27	269	the intervention on CVD risk last only one year, the intervention is likely to be cost-
28 29	270	effective. This is also apparent in the cost-effectiveness acceptability curves, where a
30 31	271	monotonic relationship between duration of the probability of cost-effectiveness is
32 33 34	272	evident (
35 36 37	273	evident (
38 39 40 41	274	
42 43	275	Figure 2). The corresponding cost-effectiveness planes for each scenario illustrate
44 45	276	this point in a different way (Figure 3). At longer durations of effect, almost all of the
46 47	277	1,000 simulated incremental cost/incremental pairs are in the northeast or southeast
48 49 50	278	quadrants. At shorter durations, an increasing but still modest number of these pairs
50 51 52 53	279	are in the northwest or southwest quadrants.
54 55	280	The small QRISK2 difference between arms means that the control and intervention
56 57	281	groups have very similar risk profiles once the assumed duration of effect expires.
58 59	282	The lifetime cost-effectiveness results are therefore influenced, especially at short
60		13

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durations of effect, by the inclusion of costs and QALYs observed during the 12month period of trial follow-up. The between-arm cost and QALY differences in the initial 12 months are propagated forward over the remaining lifetime of trial participants, and are more influential than the subsequent minor differences in costs and QALYs associated with different levels of simulated QRISK2. Nevertheless, the differences in QRISK2 are consequential at longer durations of effect, since they are associated with fewer CVD events in the intervention arm. Discussion Cost-effectiveness over the lifetime of participants in the Healthlines telehealth trial was estimated using a cohort simulation model. The probability of cost-effectiveness increased with longer durations of effect, but even with the shortest duration of effect the intervention was estimated to be cost-effective. These results reflect the cost-effectiveness analysis at 12 months: because of the small difference in QRISK2 between arms, the QALY difference observed at the end of trial follow-up has a major influence on lifetime cost-effectiveness. The model is subject to a number of limitations. The quality of the output reflects the assumptions and data used to construct and populate the model. The QRISK2 algorithm is not validated for ages beyond 84, and we made an assumption as to growth in risk for the small number of simulated trial participants who lived to 85 and beyond. As in all modelling exercises of this type, the results may be sensitive to structural assumptions, such as the number of health states modelled.<sup>11</sup> We cannot eliminate the possibility that alternative representations of clinical pathways may produce different conclusions. However, we have relied on a representation of health states

1		
2 3 4	307	that is consistent with the QRISK2 algorithm, the defined events (e.g. stroke) of
4 5 6 7 8 9	308	which are represented as distinct states in the model.
	309	The model understates uncertainty associated with QRISK2 because the variance
10 11	310	structures underlying the algorithm are not published or otherwise available, and the
12 13	311	consequence of this is to narrow confidence intervals around net monetary benefit
14 15	312	statistics. This may have implications, in particular, for the probability of cost-
16 17 18	313	effectiveness.
19 20 21	314	We have not accounted for non-health service costs, which may have consequences
22 23	315	for carers and the wider economy for some of the conditions modelled, such as
24 25	316	stroke. <sup>25</sup> However, it is not clear if accounting for these costs would necessarily alter
26 27	317	the between-arm comparison of cost-effectiveness, since slightly fewer fatal and non-
28 29 30	318	fatal strokes would be experienced in the intervention arm.
31 32 33	319	Finally, the analysis does not identify the most plausible duration of effect. Evidence
34 35	320	from long-term follow-up is necessary to conclusively answer this question, although
36 37	321	synthesis of evidence from similar trials and relevant observational studies may also
38 39	322	offer a useful complementary approach to long-term follow-up.
40 41 42 43	323	Comparison with other literature
44 45	324	Comparison of the findings of this study with other literature assessing the long-term
46 47	325	cost-effectiveness of interventions directed at managing CVD risk is complicated by
48 49 50	326	differences in the study design used to inform the modelling, patient profiles, and the
50 51 52	327	nature of the interventions examined. However, the approach of using different
53 54	328	assumed durations of effect, or different effect sizes, is encountered in similar
55 56	329	studies.
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330	For example, the evaluations of CVD interventions from a long-term perspective
331	undertaken by Mistry et al <sup>19</sup> , Asaria et al <sup>26</sup> and Penaloza-Ramos et al <sup>27</sup> are all
332	sensitive to some degree to assumptions made concerning the duration of
333	intervention effect. This is in spite of differences between these studies in population
334	characteristics, CVD risk equation used and interventions studied, which preclude a
335	comparison of the findings of the present study and these other analyses.
336	Studies also differ in the study design used to inform long-term cost-effectiveness
337	modelling. The effect estimates used as the basis of modelling in our study are those
338	of the 'intention to treat' analysis of the Healthlines RCT. This is a source of
339	difference between the present paper and, for example, the economic modelling
340	undertaken in support of the routine use of "health checks" in the NHS in England. <sup>28</sup>
341	The economic model developed to analyse the consequences of these health checks
342	was based on a much more extensive simulation involving synthesis of various
343	model parameters, compliance rates and effect estimates from a variety of sources.
344	Ultimately, although modelling and evidence synthesis will continue to be important
345	sources of evidence in this area, definitive evidence on the long-term consequences
346	for CVD risk of Healthlines (and similar interventions) will require RCTs with long-
347	term follow-up.
348 349	<b>CONCLUSION</b> The Healthlines telehealth service is likely to be cost-effective for individuals with
350	raised CVD risk when a lifetime perspective is adopted. Results are somewhat
351	sensitive to the assumed duration of intervention effect. When considering the
250	deployment of large apple teleboolth pregrammes in this area, deploise makers may

- 352 deployment of large scale telehealth programmes in this area, decision makers may
- need to consider the longevity of the behavioural and other changes rendered by the

1 2		
2 3 4	354	type of telehealth service studied in the Healthlines RCT, alongside other evidence
5 6	355	concerning the long-term cost effectiveness of similar interventions for CVD risk.
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### Table 1 QRISK2 scores at baseline and after 12-months of follow-up

9 359 10 11

	Control arm		Intervention	arm
	Baseline	12 month follow-up, adjusted for baseline	Baseline	12 month follow-up, adjusted for baseline
QRISK2 score for males	31.59	32.00	31.83	31.60
QRISK2 score for females	27.73	28.24	27.86	27.84

Note: The data are presented as levels of QRISK2 as it is the level of risk that determines the probability of events such as stroke or acute myocardial infarction.

These data are based on imputed QRISK2 scores – multiply imputed data are used in the base case economic evaluation at 12 months from randomisation.<sup>3</sup> These data are based on CVD risk of all of those randomised (n=641) in the RCT. The methods used for multiple imputation are described in further detail in the companion 12 month economic evaluation paper. <sup>12</sup>

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	Modelled duration of effect			
	1 year	2 years	5 years	Lifetime (permanent) effect
Control arm NHS costs	£6,595	£6,617	£6,608	£6,602
Intervention arm NHS costs	£6,726	£6,741	£6,714	£6,657
Control arm QALYs	8.573	8.573	8.573	8.572
Intervention arm QALYs	8.584	8.586	8.589	8.598
Incremental costs (95% CI)	£131 (£125 to 138)	£124 (£118 to 130)	£107 (101 to 112)	£55 (49 to 61)
Incremental QALYs (95% CI)	0.011 (0 .011 to 0 .011)	0.013 (0 .012 to 0 .013)	0.016 (0.016 to 0.017)	0.026 (0.026 to 0.027)
ICER	£11,776	£9,886	£6,477	£2,091
Probability cost effective at	0.74	0.84	0.95	0.99
£20,000 threshold				
Probability cost effective at	0.87	0.93	0.99	1.00
£30,000 threshold				
NMB at threshold of £20,000	£92 (-172 to 352)	£127 (-144 to 382)	£223 (-153 to 468)	£472 (197 to 728)
(95% CI)				
SD: Standard deviation; CI = Co enefit	nfidence interval; QALYs = Qua	ity-adjusted life years; ICER = Incre	emental cost-effectiveness ratio; CE	E = Cost-effectiveness; NMB = Net moneta
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2 3 4	363	Figure 1 Simulated model states
5	364 365	
6 7	366 367	This figure based is on Figure 27 of Ward et al <sup>24</sup>
8 9	368 369	Figure 2 CEACs from lifetime simulation assuming different durations of effect
10 11	370	
12 13 14	371 372	Figure 3 Cost-effectiveness planes from lifetime simulation assuming different durations of effect
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3 4	374	Contributorship statemement: PD and SH: Conducted economic analysis. RA: Led
5 6 7 8 9 10 11 12 13	375	development of original simulation model, which was updated and modified by PD for
	376	the Healthlines study. Provided advice on model development and adaptation. LE:
	377	Acted as trial manager. Undertook participant recruitment and follow-up, data
	378	collection and data entry. AF: Participant recruitment and follow-up, data collection
13 14 15	379	and data entry for the RCT. CS: Led protocol development and the funding
16 17	380	application for the programme grant, acted as chief investigator with overall
18 19	381	responsibility for conduct of the RCT. All authors had a role in interpreting the data.
20 21	382	PD wrote the first draft of this article, and all authors contributed to subsequent
22 23	383	revisions. All authors approved the final version for submission.
24 25		
26 27	384	Conflict of interest statement: The authors declare no conflicts of interest.
28 29 30 31 32 33 34	385	Funding statement: This report summarises independent research funded by the
	386	National Institute for Health Research (NIHR) under its Programme Grant for Applied
	387	Research (Grant Reference Number RP-PG-0108-10011). The views and opinions
35 36	388	expressed in this report are those of the authors and do not necessarily reflect those
37 38 39 40 41 42 43 44 45 46	389	of the National Institute for Health Research (NIHR), the NHS or the Department of
	390	Health. The funder had no role in the conduct of the study, the writing of the
	391	manuscript or the decision to submit it for publication.
	392	Data sharing: The data used in the paper are based on the sources described in the
47 48	393	main text and supplementary material, also on summarised data from the Healthlines
49 50 51	394	RCT. Requests for the sharing of the patient-level data from the Healthlines RCT that
52 53	395	underlies summarised data presented here may be made to CS. Consent for data
54 55	396	sharing was not obtained but the presented data are anonymised and risk of
56 57 58 59	397	identification is low.
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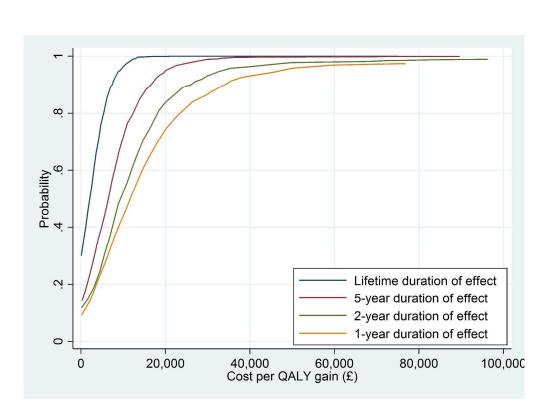
Acknowledgements: We are very grateful to all patients, health care professionals,
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trial sites for support with participant recruitment, data entry and trial administration.
The Healthlines Study was designed and delivered in collaboration with Bristol
Randomised Trials Collaboration (BRTC), a UKCRC Registered Clinical Trials Unit in
receipt of National Institute for Health Research CTU support funding.
Ethics: The Healthlines trial was approved by the National Research Ethics Service
Committee South West – Frenchay (Reference 12/SW/0009). All participants
provided informed consent to take part in the trial.

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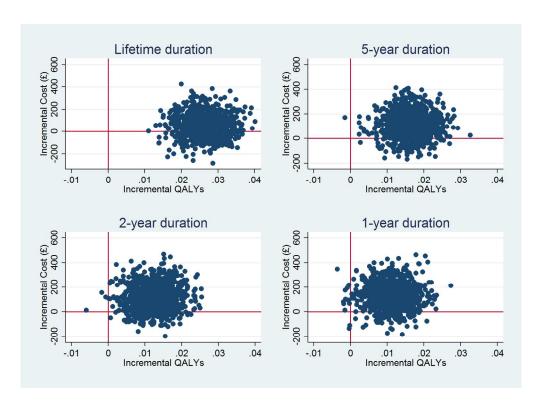
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	Initial state	Primary states	Secondary states
		Stable angina	Post-stable angina
		Unstable angina	Post-unstable angina Post-non fatal AMI
	Event free	Non-fatal AMI	Post-TIA
		TIA	Post-non fatal stroke
		Non-fatal stroke	Unstable angina Non-fatal AMI
		Fatal CVD event	Non-fatal stroke
		Death from other causes	Fatal CVD event Death other causes
	Annual cycle		
Sim	ulated model states	# + # + Note to figure: This fig Figure 1 418x375mm (300 x 3	ure based is on Figure 27 of Ward et al

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CEACs from lifetime simulation assuming different durations of effect Figure 2



Cost-effectiveness planes from lifetime simulation assuming different durations of effect Figure 3 BMJ Open: first published as 10.1136/bmjopen-2016-012355 on 26 September 2016. Downloaded from http://bmjopen.bmj.com/ on May 19, 2025 at Department GEZ-LTA Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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## Appendix – online supplementary information

## A1 Permitted transitions in simulation model

## Event free state to primary states

Event free to Primary Stable Angina (SA)

Event free to Primary Unstable Angina (USA)

Event free to Primary AMI

Event free to Primary TIA

Event free to Primary Stroke

Event free to Fatal CVD event (FCVD) Event free to Death other causes (DOC)

Primary states to subsequent states

PRIMARY SA to SECONDARY (USA or 1st AMI or 1st Stroke or FCVD or DOC) else post SA PRIMARY USA to SECONDARY (1st AMI or 1st Stroke or FCVD or DOC) else post USA PRIMARY\_AMI to SECONDARY\_(1st AMI or 1st Stroke or FCVD or DOC) else post AMI PRIMARY\_TIA to SECONDARY\_(1st AMI or 1st Stroke or FCVD or DOC) else post TIA PRIMARY\_Stroke to SECONDARY\_(1st Stroke or FCVD or DOC) else post Stroke

Post-primary states to subsequent states

Post PRIMARY\_SA to SECONDARY\_(USA or 1st AMI or 1st Stroke or FCVD or DOC) else post SA Post PRIMARY\_USA to SECONDARY\_(1st AMI or 1st Stroke or FCVD or DOC) else post USA Post PRIMARY\_AMI to SECONDARY\_(1st AMI or 1st Stroke or FCVD or DOC) else post AMI Post PRIMARY\_TIA to SECONDARY\_(1st AMI or 1st Stroke or FCVD or DOC) else post TIA Post PRIMARY Stroke to SECONDARY (1st Stroke or FCVD or DOC) else post Stroke

## Secondary state transitions

SECONDARY SA to SECONDARY ( (USA or 2nd AMI or 2nd Stroke or FCVD or DOC) else post SA SECONDARY\_USA to SECONDARY\_( (2nd AMI or 2nd Stroke or FCVD or DOC) else post USA SECONDARY AMI to SECONDARY ( (2nd AMI or 2nd Stroke or FCVD or DOC) else post AMI SECONDARY\_TIA to SECONDARY\_( (2nd AMI or 2nd Stroke or FCVD or DOC) else post TIA SECONDARY Stroke to SECONDARY ( (2nd Stroke or FCVD or DOC) else post Stroke Post SECONDARY\_SA to SECONDARY\_(USA or 2nd AMI or 2nd Stroke or FCVD or DOC) else post SA Post SECONDARY USA to SECONDARY (2nd AMI or 2nd Stroke or FCVD or DOC) else post USA Post SECONDARY\_AMI to SECONDARY\_(2nd AMI or 2nd Stroke or FCVD or DOC) else post AMI Post SECONDARY TIA to SECONDARY (2nd AMI or 2nd Stroke or FCVD or DOC) else post TIA Post SECONDARY\_Stroke to SECONDARY\_(2nd Stroke or FCVD or DOC) else post Stroke

Notes to A1: SA = Stable angina; USA = Unstable angina; AMI = Acute myocardial infarction; TIA = Transient ischaemic attack; FCVD = Fatal cardiovascular disease event; DOC = Death other causes This is the same list of permitted transitions described as in Ara et al <sup>1</sup> and Ara et al <sup>2</sup>. A1 contains the same information as Table 82 in Ara et al <sup>1</sup>. 60

## INPUT VALUES, REFERENCES AND PROBABILITY DISTRIBUTIONS FOR MODEL PARAMETERS

Table A2 provides a map to the various model parameters, input values, and associated probability distributions from which input values for specific model runs were drawn, and which are presented in more detail where applicable.

## A2 Key input parameters and associated probability distributions

Parameter	Input values	Probability distribution	Comments
Health state utility	Various; listed in Table	Normal	Ara and Wailoo <sup>3</sup>
values	A3		recommend the use of
			normal distributions to
			characterise the
			uncertainty in mean
			utilities
Health state costs	Various, listed in Table	Gamma	A number of sources, eg
	A4		Gray et al <sup>4</sup> , recommend
			using gamma
			distributions in
			characterising
			uncertainty in cost
			variables
la cidence andre for	V/ · · · · · · · · · · · · · ·	N1/A	
Incidence rates for	Various, listed in Table	N/A	We follow Ward et al⁵
primary CVD events	A5 and Table A6		and Ara et al <sup>2</sup> in using
			the mean values of
			published incidence
			rates in each model run
CVD Risk	Based on age and sex	N/A	The variance structures
	adjusted QRISK2 scores		underlying the QRISK2
	from baseline and 12m		algorithm are not
	follow-up that are		published and hence we

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1 2				
3		presented in Table 1 in		could not characterise
4 5		the main text, and then		uncertainty in this
6 7		adjusted subsequently		measure. See
8 9		using the QRISK2		Discussion in main
10 11		algorithm		paper.
12 13	Risk of death from	Based on standardised	Normal distribution	We follow Ara et al <sup>2</sup> in
14 15	non-CVD causes	mortality ratios		using a normal
16 17		published by the ONS		distribution for model
18 19 20 21 22		published by the ONS		draws
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## UTILITIES

Ara and Brazier<sup>6</sup> was used as the source of state-specific utilities other than TIA, which are based on Luengo-Fernandez et al<sup>7</sup>. It was assumed that the utility estimates for angina in Ara and Brazier related to stable angina, and that unstable angina health utilities would be 90% of the stable angina values, as in Ara et al.<sup>2</sup>

, ' thir. utility as the As further noted in the main text, any 'third' events, i.e. those occurring after a secondary event, have the same utility as the 'second' event.

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Mean utility value

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A3 Health state utility values	
Health state	

Treattri State	wear utility va
Primary stable angina	0.615
Primary unstable angina	0.556
Primary AMI	0.721
Primary TIA	0.760
Primary stroke	0.626
Post-primary angina	0.775
Post-primary unstable angina	0.701
Post-primary AMI	0.742
Post-primary TIA	0.78
Post-primary stroke	0.668
Secondary stable angina	0.541
Secondary unstable angina	0.489
Secondary AMI	0.431
Secondary TIA	0.760
Secondary stroke	0.479
Post-secondary stable angina	0.715
Post-secondary unstable angina	0.647
Post-secondary AMI	0.685
Post-secondary TIA	0.78
Post-secondary stroke	0.641

## Costs

A detailed discussion of the cost data used to model each state is provided in Salisbury et al.<sup>8</sup> Briefly, the costs of stable and unstable angina, of non-fatal acute myocardial infarction a are based on Ward et al<sup>5</sup> and Ara et al.<sup>2</sup> The cost of fatal

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acute myocardial infarction are based on Clarke et al.<sup>9</sup> The costs of non-fatal stroke and of transient ischaemic attack are based on Luengo-Fernadez et al.<sup>7</sup> The cost of fatal stroke is based on Youman et al.<sup>10</sup> In all cases, costs were adjusted to 2012/13 sterling prices as described in Salisbury et al.<sup>8</sup>

#### A4 Health state costs

Health state	Mean cost in 2012/13 £ prices
Stable angina	606
Stable angina in subsequent years	356
Unstable angina	4,324
Unstable angina in subsequent years	453
Non-fatal acute myocardial infarction	3,362
Post non-fatal acute myocardial infarction	356
Fatal acute myocardial infarction	1,846
Transient ischaemic attack	3,963
Transient ischaemic attack in subsequent years	1,380
Non-fatal stroke	8,989
Non-fatal stroke in subsequent years	1,976
Fatal stroke	9,493

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## INCIDENCE RATES FOR PRIMARY EVENTS

Incidence rates for primary events are used to calculate the probability of one of stable angina, unstable angina, acute myocardial infarction (AMI), stroke, and transient ischaemic attack (TIA). These incidence rates are then used to disaggregate the risk of any such event, measured by the QRISK2 score, into the risk of a single event.

The data sources and adjustments made to data are described in more detail in Salisbury et al. <sup>8</sup> Here, we briefly describe these sources, and present in A5 and A6 the incidence data used in the simulation model.

The incidence of angina was taken from data for England reported British Heart Foundation Coronary Heart Disease Statistics 2012,<sup>11</sup> using the data reported for England. This was split into incidences of stable and unstable angina using incidences reported in Sutcliffe et al. <sup>12</sup> Incidence of fatal and non-fatal AMI was also taken from British Heart Foundation Coronary Heart Disease Statistics 2012.<sup>11</sup> Incidence of first ever stroke was based on Wang et al, <sup>13</sup> and incidence on mortality from strokes was based on Lee et al. <sup>14</sup>

Incidence of TIA is taken from British Heart Foundation Stroke Statistics 2009.<sup>15</sup>

## A5 Incidence rates of CVD events per 1,000 males per year

Age band	Stable angina	Unstable angina	Non-fatal AMI	Fatal AMI	TIA	Non- fatal stroke	Fatal stroke
55-64	0.84	0.25	0.28	0.04	0.74	0.65	0.08
65-74	1.16	0.35	0.42	0.11	1.45	1.27	0.16
75-84	0.75	0.23	0.73	0.29	3.27	2.73	0.35
85+	0.75	0.23	1.23	0.76	7.94	5.12	0.65

Age band	Stable angina	Unstable angina	Non-fatal AMI	Fatal AMI	ΤΙΑ	Non- fatal stroke	Fatal stroke							
55-64	0.35	0.11	0.07	0.02	1.05	0.63	0.14							
65-74	0.74	0.22	0.18	0.06	2.18	1.23	0.28							
75-84	0.57	0.17	0.38	0.22	5.61	2.64	0.6							
85+	0.57	0.17	0.75	0.64	9.14	4.95	1.13							
		Refe	erences											
1 Ara R Tum	ur I, Pandor A, et	al Ezetimihe	for the treat	ment of hype	rcholest	erolaemi	a In <sup>.</sup>							
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•	1-212.					<i>,</i> (	, ,							
		h State Utility	Values in M	odels Explor	ing the C	Cost-								
	-	•		•	-		3. Ara R, Wailoo A. Using Health State Utility Values in Models Exploring the Cost- Effectiveness of Health Technologies, Value Health 2012; <b>15</b> (6):971-74							
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- 14. Lee S, Shafe ACE, Cowie MR. UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database. BMJ Open 2011;1(2).
- 15. Scarborough P., Peto V., Bhatnagar P., et al. British Heart Foundation Stroke statistics 2009, 2009.

# CHEERS checklist—Items to include when reporting economic evaluations of health interventions

	Item		Reported on page No/
Section/item	No	Recommendation	line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use	Page 1
		more specific terms such as "cost-effectiveness	
		analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives,	Page 3
		perspective, setting, methods (including study design	
		and inputs), results (including base case and	
		uncertainty analyses), and conclusions.	
Introduction			
Background and	3	Provide an explicit statement of the broader context	Lines 60-87
objectives		for the study.	
		Present the study question and its relevance for	Lines 88-97
		health policy or practice decisions.	
Methods	•		
Target population and	4	Describe characteristics of the base case population	Lines 99-108
subgroups		and subgroups analysed, including why they were	
		chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the	Lines 99-103
		decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this	Lines 119-120
		to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being	Lines 109-118
·		compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and	Lines 88-97
		consequences are being evaluated and say why	
		appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs	Lines 262-263
		and outcomes and say why appropriate.	
Choice of health	10	Describe what outcomes were used as the	Line 139-140
outcomes		measure(s) of benefit in the evaluation and their	
		relevance for the type of analysis performed.	
Measurement of	11a	Single study-based estimates: Describe fully the	Estimates are based on
effectiveness		design features of the single effectiveness study and	effectiveness data from
		why the single study was a sufficient source of clinical	the Healthlines RCT (Lines
		effectiveness data.	109-129)
	11b	Synthesis-based estimates: Describe fully the	
		methods used for identification of included studies	Not applicable
		and synthesis of clinical effectiveness data.	
Measurement and	12	If applicable, describe the population and methods	Lines 220-226
valuation of preference		used to elicit preferences for outcomes.	
based outcomes		·	
Estimating resources and	13a	Single study-based economic evaluation:Describe	
costs		approaches used to estimate resource use associated	
-		with the alternative interventions. Describe primary	
		or secondary research methods for valuing each	Not applicable
		resource item in terms of its unit cost. Describe any	
		adjustments made to approximate to opportunity	

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53 54 55 56	
57 58 59 60	

	ltem		Reported on page No/
Section/item	No	Recommendation	line No
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to	Lines 246-257 in mair text, and page5-6 o supplementary materia
Currency, price date, and conversion	14	opportunity costs. Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Line 14:
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Lines 132-140 and Figure
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Lines 142-202
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Lines 132-218
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1 in main text, and Tables A2, A3, A4, A5and A6 in the appendix
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 2 in main tex
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Not applicable
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Table 2 and Figure 2 ir the main text
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Not applicable
Discussion		,	
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Lines 291 to 347

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Section/item	No	Recommendation	line No
Other			
Source of funding	23	Describe how the study was funded and the role of	Page
		the funder in the identification, design, conduct, and	
		reporting of the analysis. Describe other non-	
		monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study	Page
		contributors in accordance with journal policy. In the	
		absence of a journal policy, we recommend authors	
		comply with International Committee of Medical	
		Journal Editors recommendations.	
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