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ORIGINAL RESEARCH

# Cost-effectiveness of High-Intensity Interval Training (HIIT) vs Moderate Intensity Steady-State (MISS) Training in UK Cardiac Rehabilitation



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## Abstract

**Objective:** To perform a cost-effectiveness analysis of high-intensity interval training (HIIT) compared with moderate intensity steady-state (MISS) training in people with coronary artery disease (CAD) attending cardiac rehabilitation (CR).

**Design:** Secondary cost-effectiveness analysis of a prospective, assessor-blind, parallel group, multi-center RCT.

**Setting:** Six outpatient National Health Service cardiac rehabilitation centers in England and Wales, UK.

**Participants:** 382 participants with CAD (N=382).

**Interventions:** Participants were randomized to twice-weekly usual care (n=195) or HIIT (n=187) for 8 weeks. Usual care was moderate intensity continuous exercise (60%-80% maximum capacity, MISS), while HIIT consisted of 10 × 1-minute intervals of vigorous exercise (>85% maximum capacity) interspersed with 1-minute periods of recovery.

**Main Outcome Measures:** We conducted a cost-effectiveness analysis of the HIIT or MISS UK trial. Health related quality of life was measured with the EQ-5D-5L to estimate quality-adjusted life years (QALYs). Costs were estimated with health service resource use and intervention delivery costs. Cost-utility analysis measured the incremental cost-effectiveness ratio (ICER). Bootstrapping assessed the probability of HIIT being cost-effective according to the UK National Institute for Health and Care Excellence (NICE) threshold value (£20,000 per QALY). Missing data were imputed. Uncertainty was estimated using probabilistic sensitivity analysis. Assumptions were tested using univariate/1-way sensitivity analysis.

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Trial Registration: ClinicalTrials.gov: [NCT02784873](https://clinicaltrials.gov/ct2/show/NCT02784873). <https://clinicaltrials.gov/ct2/show/NCT02784873>.

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\* McGregor and Edwards contributed equally to this work.

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**Results:** 124 (HIIT, n=59; MISS, n=65) participants completed questionnaires at baseline, 8 weeks, and 12 months. Mean combined health care use and delivery cost was £676 per participant for HIIT, and £653 for MISS. QALY changes were 0.003 and -0.013, respectively. For complete cases, the ICER was £1448 per QALY for HIIT compared with MISS. At a willingness-to-pay threshold of £20,000 per QALY, the probability of HIIT being cost-effective was 96% (95% CI, 0.90 to 0.95).

**Conclusion:** For people with CAD attending CR, HIIT was cost-effective compared with MISS. These findings are important to policy makers, commissioners, and service providers across the health care sector.

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Although mortality rates from coronary artery disease (CAD) have decreased in the industrialized world since the 1960s, 1.8 million people across Europe die as a result of CAD every year,<sup>1</sup> and the decline in cardiovascular disease (CVD) may have slowed.<sup>2</sup> In the UK, 7.6 million people are living with CVD, and 76,000 acute myocardial infarctions are recorded each year. The annual financial effect of CVD on the UK health care system is £9 billion, and £19 billion on the UK economy as a whole.<sup>3</sup>

Secondary prevention aims to attenuate the effect of CAD, maximize quality of life, and restore people to the highest possible level of functional ability.<sup>4</sup> Cardiac rehabilitation (CR) is offered to people with diagnosed CAD and includes components of risk factor modification, behavior change, cardiovascular risk reduction, and exercise training. There is evidence that CR may reduce cardiovascular mortality, morbidity, and unplanned hospital admissions in addition to improving physical fitness and health-related quality of life (HRQoL).<sup>5–7</sup> As a result, CR is recommended in international guidelines for the management of CVD.<sup>8</sup>

Exercise training is considered an essential component of CR, but there is considerable variation in service provision, and in the exercise modality, intensity, and duration adopted around the world.<sup>9,10</sup> Conventionally, CR in the UK is mostly delivered as supervised programs in hospitals, clinics, gyms, or community centers, once to twice weekly over 2–3 months,<sup>11</sup> starting 2–4 weeks after myocardial infarction, or within 6 weeks of cardiac surgery.<sup>12</sup> Cardiovascular prevention and rehabilitation programs are usually delivered by specialist nurses, clinical exercise physiologists, or physiotherapists, overseen by an experienced clinician with a special interest in CR.<sup>13</sup>

As an alternative to traditional moderate-intensity steady-state (MISS) exercise training in CR, high-intensity interval training (HIIT) has been proposed. HIIT involves alternating short bursts of high intensity exercise with short periods of recovery, and commonly results in equivalent or superior improvements in cardiorespiratory fitness (peak oxygen uptake,  $\dot{V}O_{2\text{ peak}}$ ) in clinical populations. The main benefit compared with MISS is the ability to attain a higher overall exercise intensity resulting in an enhanced physiological stimulus, and thus a superior improvement in maximal aerobic capacity.<sup>14</sup>

#### List of abbreviations:

<b>AUC</b>	<b>area under the curve</b>
<b>CAD</b>	<b>coronary artery disease</b>
<b>CR</b>	<b>cardiac rehabilitation</b>
<b>CVD</b>	<b>cardiovascular disease</b>
<b>HIIT</b>	<b>high-intensity interval exercise training</b>
<b>HRQoL</b>	<b>health-related quality of life</b>
<b>MISS</b>	<b>moderate intensity steady state</b>
<b>QALY</b>	<b>quality-adjusted life year</b>
<b>RCT</b>	<b>randomized controlled trial</b>
<b>WTP</b>	<b>willingness-to-pay</b>

Although CR has been recommended as an effective strategy for the long-term management of CAD, published studies on the economic analysis of CR programs are relatively rare. A number of randomized controlled trials (RCTs) and systematic reviews have reported the cost-effectiveness of CR compared with no CR<sup>7,15</sup> and home based compared with center-based CR.<sup>16</sup> In general, evidence suggests that CR is cost-effective, but data are limited and heterogeneous. There are no cost-effectiveness studies comparing HIIT and MISS training programs in CR.

As NHS resources are limited, decisions on implementing CR interventions are determined not only by health outcomes, but also by the costs incurred (ie, cost-effectiveness).<sup>17–19</sup> Cost-effectiveness analysis is an important tool for the evaluation of competing health care interventions, and guides health care professionals and stakeholders in resource allocation.<sup>18</sup>

In a secondary analysis of data from the HIIT or MISS UK multi-center RCT,<sup>14,20</sup> this study aimed to evaluate the cost-effectiveness of HIIT compared with MISS exercise training over a 12-month period.

## Methods

### Study design and population

HIIT or MISS UK was a pragmatic, parallel group, assessor-blind RCT assessing the effectiveness and cost-effectiveness of low-volume HIIT compared with MISS in 6 UK CR centers.<sup>20</sup> Recruitment started in July 2016 and completed in March 2020. The study was approved by the NHS Health Research Authority, East Midlands—Leicester South Research Ethics Committee (16/EM/0079) and prospectively registered with [ClinicalTrials.gov: NCT02784873](https://clinicaltrials.gov/NCT02784873). The eligibility criteria and CR exercise programs have been described in detail previously.<sup>20</sup>

### Cardiac rehabilitation intervention

The CR exercise programs have been described in detail previously.<sup>20</sup> Briefly, each session began with a 10–15 minute cardiovascular and mobility warm-up and ended with a 10-minute cool-down. HIIT and MISS participants performed similar exercise programs in duration and frequency, but the programs varied in intensity and modality. HIIT was performed on a cycle ergometer (Wattbike Trainer, Wattbike, Nottingham, UK) and consisted of 1-minute short bursts of high intensity exercise (>85% heart rate maximum), interspersed with 1-minute periods of lower intensity exercise, at a 1:1 work-to-recovery ratio, totaling 20 minutes. MISS comprised 20–40 minutes of continuous moderate intensity exercise (40%–70% heart rate reserve) using treadmill, cycle

ergometer, rowing ergometer, and cross-trainer. Both programs were modified during the 8-week period to suit the level of progression of each participant.<sup>14</sup>

Participants in both groups performed a muscular strength and endurance training program using resistance machines and free weights, and a group education program that was aligned with UK standards.<sup>21</sup> During the 8-week HIIT or MISS program, clinical exercise staff employed behavioral motivational counselling strategies, designed to help participants overcome potential barriers to ongoing exercise and facilitate long-term behavior change.

## Economic evaluation

As recommended by the National Institute for Health and Care Excellence (NICE, 2022), we performed a cost-utility analysis from a UK National Health Service (NHS) and Personal Social Services perspective, and used quality-adjusted life years (QALYs) as the primary economic outcome. Cost-utility analysis was conducted with outcome and cost data collected at 3 time points (baseline, 8 weeks, and 12 months). Costs were compared with changes in HRQoL between HIIT and MISS participants.

The incremental cost-effectiveness ratio (ICER, a measure of the additional cost per additional unit of health gain conferred by 1 intervention compared with another)<sup>22</sup> was calculated directly from HRQoL outcomes and expressed in terms of cost per QALY. Thus, the cost-effectiveness of HIIT compared with MISS is presented as an ICER, which is the difference in mean costs divided by the difference in mean QALYs over the 12-month period, expressed as the cost per QALY. If the ICER was less than £20,000 per QALY, then the HIIT intervention was considered cost-effective from the perspective of NICE.<sup>22</sup>

Multiple imputation was used to deal with missing data.<sup>23</sup> Outcomes were assessed with complete case data. Analytical uncertainty was quantified through probabilistic sensitivity analysis and univariate/1-way sensitivity and multi-way sensitivity analysis. Sensitivity analysis was conducted on participants who completed questionnaires at baseline, 8 weeks, and 12 months follow-up.

At each time-point, a modified client service receipt inventory (CSRI) was used to record participant health and social care service use. The primary cost-utility outcome was the change in HRQoL<sup>24</sup> at the 3 time-points. QALYs were measured using the EQ-5D-5L.<sup>25</sup>

## Cost measures

A bottom-up approach was used to estimate the costs of HIIT and MISS by recording the actual use of resources during the trial. Costs were estimated from the perspective of the Personal Social Services, as recommended by the Consolidated Health Economic Evaluation Reporting Standards statement.<sup>26</sup> Data from participant health service use was used to calculate an exact cost per patient. All costs were reported in UK sterling (£) at 2019/2020 financial year prices. Costs were not discounted due to participant time from baseline to follow-up not exceeding 1 year.

## Intervention costs

Intervention costs were categorized as either clinical exercise staff, or equipment costs.

## Clinical exercise staff costs

HIIT and MISS programs included 16 sessions led by clinical exercise physiologists or physiotherapists, accompanied by physiologist assistants or specialist nurses. The cost of staff at each site was based on the contact time multiplied by the hourly unit cost. At 1 site, for example, 36 participants in the HIIT group received an average of 880 minutes of contact time and attended an average of 16 sessions at a mean cost of £208 per participant. A detailed breakdown of clinical exercise staff costs for the HIIT and MISS groups is provided in [supplemental table S1](#) (available online only at <http://www.archives-pmr.org/>).

## Equipment costs

A detailed breakdown of equipment costs for the HIIT and MISS programs is available in [supplemental table S2](#) (available online only at <http://www.archives-pmr.org/>). All equipment was costed from correspondence with the principal investigator and clinical exercise staff.<sup>27</sup> A 10-year life cycle costing method was applied to assess the cost per participant of exercise equipment.

## Health service resource use costs

Both primary and secondary health service resource use costs were measured ([supplemental table S3](#), available online only at <http://www.archives-pmr.org/>). Primary costs included the number of contacts participants reported with health care professionals (ie, primary care practice professionals). Secondary costs included the number of visits to specialized hospital services (ie, inpatient stays, outpatient visits, accident and emergency services, and hospital occupational therapy).

## Outcome measures (QALYs)

The EuroQol EQ-5D-5L was used to calculate overall HRQoL, measuring health status across 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 possible levels of perceived problems (no problem, slight problems, moderate problems, severe problems, or unable to/extreme problems). The EQ-5D-5L health states were converted into utilities using the UK general population preference-based tariffs that enable comparisons between EQ-5D-5L index scores and population norms and other medical conditions.<sup>25</sup> An area under the curve (AUC) methodology with baseline adjustment was used to measure changes in QALY gain/loss accrued for each participant at 8 weeks and 12 months ([supplemental table S4](#), available online only at <http://www.archives-pmr.org/>).

## Statistical analysis

### Imputation of missing data

Missing data for the EQ-5D-5L and health service resource questionnaires use were imputed to maximize the use of available data under the assumption that the data were missing at random.<sup>14</sup> Multiple imputation with predictive mean matching was used to impute missing data.<sup>28</sup> The imputation model was specified according to White et al.<sup>29</sup> Baseline data for age, sex, body mass, height, and BMI were used as predictors. Twenty different data sets were created. Pooled estimates were calculated using Rubin's rules. We assumed that the relation between adjacent recorded data were linear to avoid situations where a participant had missing data between 2 points on the timeline.

## Sensitivity analysis

A univariate/1-way sensitivity analysis was applied to explore the uncertainty of cost estimates and to identify the effect of key parameters on cost-effectiveness. This was performed by varying the clinical exercise staff costs, price of equipment, health service resource use costs, number of training sessions, and training duration (min/session). A multi-way sensitivity analysis was performed by varying the number of training sessions and the duration of sessions (minute/session). The input (variable) included in the analysis ranged between  $\pm 30\%$ .

A non-parametric bootstrapping method was used to evaluate the results by resampling with replacement from the original RCT data. The probabilistic sensitivity analysis was applied to quantify the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs. The 1000 bootstrapped incremental cost and outcome estimates were graphed on a cost-effectiveness plane. The cost-effectiveness analysis curve for various willingness-to-pay (WTP) thresholds was developed using values from the ICER iterations. The cost-effectiveness analysis curve represents the probability that the HIIT program was more cost effective than MISS at various payer WTP thresholds for an additional QALY gain. Finally, the sensitivity analyses included an imputed data scenario, which considered incomplete cost and EQ-5D-5L questionnaire data at all 3 time-points (baseline, 8 weeks, and 12 months). Statistical analyses were performed using Stata software<sup>a</sup> and IBM SPSS statistic 27.<sup>b</sup>

## Results

### Complete case analysis

Initially, 382 participants (HIIT,  $n=187$ ; MISS,  $n=195$ ) were recruited. Most were men ( $n=356$ , 93%) with a mean age of 59 (standard deviation, SD, 9.6) years. Because of COVID-19 lock-down restrictions, 51 participants in the HIIT group did not complete the 8-week follow-up and 77 participants the 12-month follow-up, resulting in 59 complete cases. In the MISS group, 41 participants did not complete the 8-week follow-up, and 89 participants the 12-month follow-up, resulting in 65 complete cases. Of the 124 complete cases, most were men ( $n=114$ , 92%) with a mean age of 61 (SD, 10.3) years. Baseline characteristics for

complete cases of HIIT and MISS participants were similar (table 1). Data for the included sample were all collected prior to COVID-19 lock-down restrictions.

For complete cases, the baseline EQ-5D-5L mean score for the HIIT arm was 0.85 (SD, 0.12), compared with 0.87 (SD, 0.11) for MISS. The Mann-Whitney U test indicated that QALY data were not significantly different between the 2 groups ( $P=.84$ ).

Because of COVID-19 lock-down restrictions, some cost and QALY data were missing (67.5% at 12 months). However, when missing cost and QALY data were estimated, no differences between the 2 groups were detected ( $P=.27$ ). Missing data were imputed using a multiple regression method. The area under receiver-operating characteristic curve was used to test how acceptable the predicted probabilities discriminate between the 2 groups. The AUC result showed a weak discrimination between the 2 groups (AUC=0.59) because of the large amount of missing data (supplemental fig S1, available online only at <http://www.archives-pmr.org/>) suggesting that model variables were not significantly different from random chance.

### Total costs

Total costs included equipment, primary and secondary health service resource use, and clinical exercise staff. During the 8-week CR program, HIIT sessions were on average 7-13 minutes shorter than MISS sessions. As a result, the cost of delivering CR (ie, equipment costs plus clinical exercise staff costs) was £318 per participant for HIIT compared with £346 for MISS. Although delivery costs were less for HIIT, health service resource use costs were higher for HIIT participants at 8 weeks (£211) compared with MISS (£151), but lower at 12 months for HIIT (£147) compared with for MISS (£157). Between the 8-week and 12-month follow-up, the HIIT group showed a substantial reduction in health service resource use, a £64 per participant decrease compared with a £6 increase for MISS participants (table 2).

### Cost-effectiveness

The HIIT intervention had a higher mean cost of £676 compared with £653 for MISS, resulting in an incremental cost loss of £23 (table 3). However, the HIIT program had a higher QALY change (0.003) compared with MISS (-0.013) resulting in an incremental QALY gain for HIIT of 0.016. The ICER was £1448 per QALY. For imputed data, the ICER was £8753 per QALY. For complete and imputed data, the ICERs were well below the NICE threshold of £20,000 per QALY, suggesting that HIIT was cost-effective<sup>22</sup> (table 3).

### Sensitivity analysis

Variation of the key parameter cost  $\pm 30\%$  in the intervention group showed the health service resource use cost and clinical exercise staff cost as the parameters that had the greatest effect on the ICER. Compared with these findings, the variation in number of training sessions had noticeably less effect on the results (fig 1).

The results also showed that HIIT would be dominant if (1) the clinical exercise staff costs were reduced from £207 to £167 or less per HIIT participant; (2) equipment costs were reduced from £111 to £85 or less per HIIT participant; or (3) health service resource use costs were reduced from £358 to £321 or less per HIIT participant (supplemental table S5, available online only at <http://www.archives-pmr.org/>).

**Table 1** Baseline characteristics

	HIIT (n=59)	MISS (n=65)
Mean age, years, mean (standard deviation, SD)	61.5 (10.2)	61.1 (10.3)
Men, n (%)	54 (92.3)	60 (91.5)
Ethnicity, n (%)		
White British	56 (86.2)	52 (88.1)
Other	9 (13.8)	8 (11.9)
Height, centimeters, mean $\pm$ SD	172.8 (7.3)	173.7 (6.7)
Body mass, mean $\pm$ SD (kg/m <sup>2</sup> )	86.7 (14.5)	86.4 (14.7)
Body mass index (BMI), mean $\pm$ SD	29.0 (4.5)	28.5 (4)
Number of sessions, mean $\pm$ SD	16 (1)	16 (1)
<b>EQ-5D-5L, mean <math>\pm</math> SD</b>		
Baseline	0.85 (0.12)	0.87 (0.11)
8-week follow-up	0.90 (0.12)	0.92 (0.1)
12-month follow-up	0.90 (0.1)	0.88 (0.1)



**Table 2** Health service use and intervention delivery costs (per participant)

	8-week Follow-up		12-month Follow-up	
	HIIT (n=59)	MISS (n=65)	HIIT (n=59)	MISS (n=65)
	£ Mean ± SD	£ Mean ± SD	£ Mean ± SD	£ Mean ± SD
<b>Clinical exercise staff costs</b>				
Physiotherapist (Band 6)	24 (38)	23 (41)	0 (0)	0 (0)
Physiotherapist (Band 7)	8 (23)	9 (29)	0 (0)	0 (0)
Exercise Physiologist (Band 5)	40 (26)	50 (29)	0 (0)	0 (0)
Exercise Physiologist (Band 6)	67 (24)	82 (26)	0 (0)	0 (0)
Physiotherapy assistant (Band 4)	16 (25)	15 (26)	0 (0)	0 (0)
Specialist Nursing (Band 6)	52 (34)	66 (38)	0 (0)	0 (0)
<b>Total clinical exercise staff costs</b>	<b>207 (9)</b>	<b>245 (1)</b>	<b>0 (0)</b>	<b>0 (0)</b>
<b>Total equipment costs</b>	<b>111 (0)</b>	<b>101 (0)</b>	<b>0 (0)</b>	<b>0 (0)</b>
<b>Primary health service resource use costs</b>				
GP surgery	34 (42)	31 (36)	37 (51)	46 (65)
GP nurse	13 (29)	13 (39)	22 (55)	14 (31)
<b>Secondary health service resource use costs</b>				
Inpatient	64 (225)	8 (67)	46 (151)	17 (94)
Outpatient	85 (140)	84 (146)	39 (68)	67 (111)
Accident and emergency services	6 (26)	2 (15)	2 (15)	4 (21)
Day hospital	7 (51)	12 (98)	0 (0)	6 (49)
Hospital occupational therapist	2 (11)	1 (7)	1 (7)	1 (7)
<b>Total health service resource use cost</b>	<b>211 (266)</b>	<b>151 (195)</b>	<b>147 (203)</b>	<b>157 (210)</b>
<b>Total costs</b>	<b>529 (268)</b>	<b>497 (194)</b>	<b>147 (203)</b>	<b>157 (210)</b>

Abbreviation: GP, general practitioner.

In the cost-effectiveness plane, the 1000 simulations showed a higher density on the east quadrants of the plot, meaning that HIIT was generally more effective than MISS (fig 2). If all iterations had fallen in the south-east quadrant, the HIIT intervention would have been identified as dominant (more effective and less costly). The results show that 62% of the simulation distribution fell in the north-east quadrant (more effective and more costly) and 35% fell in the south-east quadrant (fig 2).

At a WTP threshold of £0 per QALY, the HIIT intervention had a 0.36 (36%) probability of being cost-effective. At a higher WTP threshold of £20,000 per QALY, the probability increased to 0.96 (96%). The HIIT intervention was cost-effective below the UK NICE threshold of £20,000. A flattening of the curve was noted at a WTP value of £17,000 per QALY, meaning that the probability of being cost effective at £17,000 and the NICE threshold of £20,000 are nearly equal (fig 3).

## Discussion

We examined the costs and outcomes associated with HIIT compared with MISS exercise training for people with CAD attending CR programs in the UK. Using complete and imputed case

analysis to account for a large amount of missing data due to COVID-19 lockdown restrictions, HIIT had a 96% and 74% probability, respectively, of being cost-effective compared with MISS at the NICE threshold of £20,000 per QALY. The ICERs (a measure of the additional cost per additional unit of health gain conferred by 1 intervention compared with another) were £1448 for complete cases and £8753 for imputed cases, both well below the NICE WTP threshold of £20,000, indicating that HIIT was a cost-effective intervention compared with MISS.

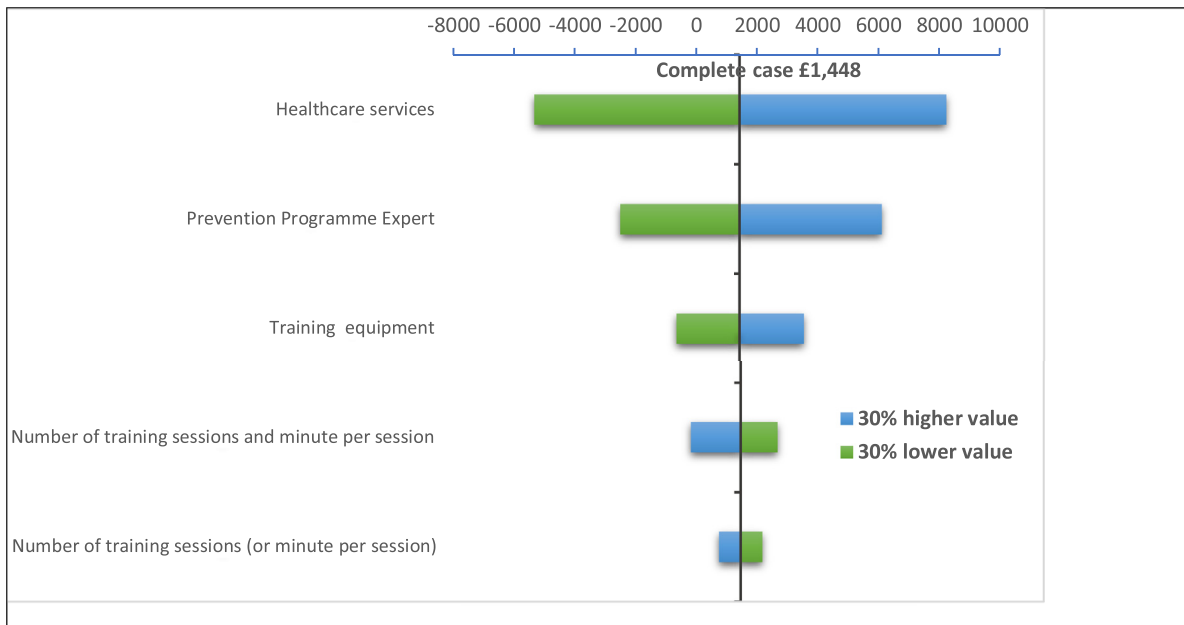
Data on the cost-effectiveness of exercise-based CR are very limited, and there are no data comparing HIIT with MISS. A 2018 systematic review reported a range of CR interventions (psychological, physical, behavioral, tele-health), to be cost-effective compared with no CR, with ICERs ranging from US\$1065 to US\$71,755 per QALY.<sup>15</sup> However, uncertainty in the data were high in relation to the cost-effectiveness of CR exercise training programs.

More recently, a systematic review<sup>7</sup> reported acceptable ICERs in favor of exercise-based CR in 2 contemporary RCTs (US\$42,535<sup>30</sup> and €15,247,<sup>31</sup> respectively), while another identified that home-based CR was likely to be cost-effective in addition to, or as an alternative to, center-based CR.<sup>16</sup> In the latter, however, considerable heterogeneity in CR interventions and

**Table 3** Complete and imputed case incremental cost effectiveness ratios for HIIT vs MISS

	Complete Case Scenario					Imputed Case Scenario						
	Mean Cost	QALYs	Incremental		ICER	CE	Mean Cost	QALYs	Incremental		ICER	CE
			Cost	QALYs					Cost	QALYs		
<b>HIIT</b>	£676	0.003	£22.83	0.016	£1448	96.5%	£761	0.017	£47.36	0.005	£8753	74%
<b>MISS</b>	£653	-0.013					£713	0.012				

Abbreviations: CE, probability of being cost-effective at λ =£20,000 per QALY; ICER, incremental cost effectiveness ratio.



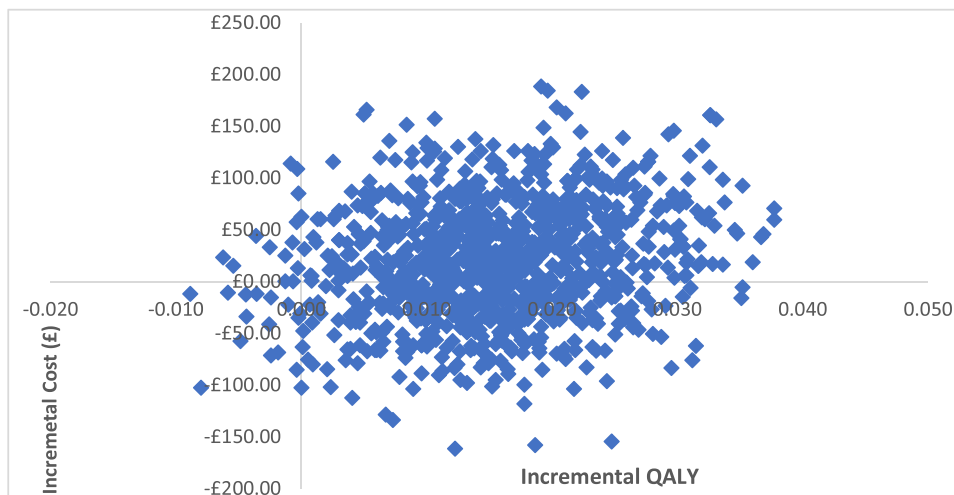
**Fig 1** ICER tornado diagram (HIIT versus MISS). The width of the bars represents the range of the results when the cost of the variables was changed  $\pm 30\%$ .

cost-effectiveness analyses, and the small number of studies included (n=9), meant that generalizability was very limited.

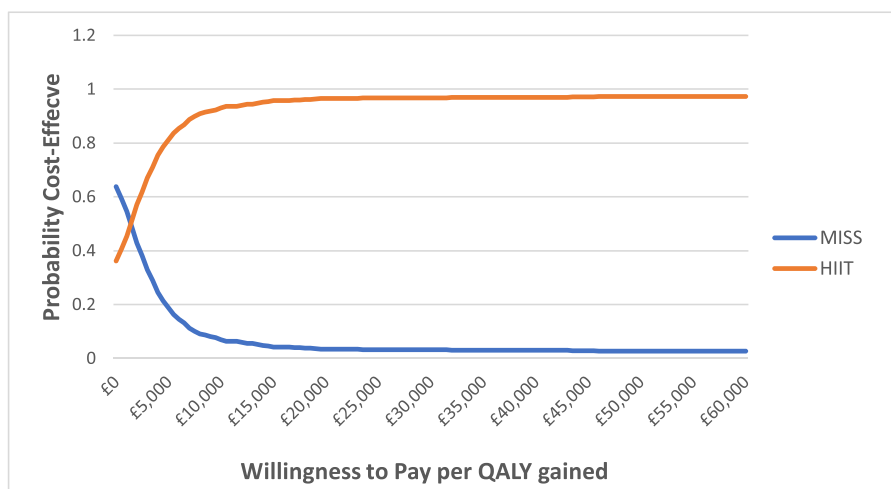
In the only RCT (n=44) comparing the cost-effectiveness of HIIT and low-intensity conventional therapy, the cost-effectiveness of HIIT for people with sub-acute stroke was probable at an ICER of US\$6180. While personnel costs were higher for the provision of HIIT, between group differences in QALYs favored HIIT. In general, our data support these findings, albeit in a different clinical population, but overall, there is a lack of definitive evidence to which we can compare our results.

In our study, CR session delivery costs were lower for HIIT compared with MISS due to slightly lower staff costs as a result of shorter sessions. However, health service resource use for HIIT was higher by £60 per participant at 8 weeks. This is unlikely to be related specifically to the nature of HIIT as we have previously

reported HIIT to be very safe.<sup>14</sup> The data show that this increased cost was driven almost exclusively by inpatient care costs as a result of a small number of individuals with repeated in-patient admission due to illness completely unrelated to the intervention or trial. At 12 months, health service resource use decreased substantially in the HIIT group, while MISS costs remained relatively constant overall. Evidence suggests that low-volume HIIT can elicit higher enjoyment than moderate intensity continuous training,<sup>32</sup> indicating that HIIT could be an effective strategy for developing a regular exercise habit. This was corroborated by comparing HRQoL scores at 8 weeks and 12 months. From baseline to 8 weeks, HIIT participants increased their HRQoL by 0.049 compared with 0.046 for MISS participants. At 12 months, however, HIIT participants reported a 0.047 increase from baseline compared with a much smaller increase of 0.006 for MISS participants, suggesting that HIIT



**Fig 2** Cost-effectiveness plane. A higher density on the east quadrants of the plot indicates that HIIT was generally more effective than MISS.



**Fig 3** Cost-effectiveness acceptability curve. HIIT intervention was cost-effective below the UK NICE threshold of £20,000. Flattening of the curve at a WTP value of £17,000 per QALY, indicates the probability of being cost effective at £17,000 and £20,000 are nearly equal.

participants may have potentially engaged more often in regular exercise after the 8-week intervention.

### Study limitations

Although the cost-effectiveness results for HIIT are promising, there are several limitations, primarily the significant amount of missing data (67.5%) at 12 months because of COVID-19 lockdown restrictions. Because of the missing data, the area under ROC curve showed a lack of differentiation between the 2 arms, indicating a level of uncertainty in the data analysis. To address this, we used multiple imputations to make the most of available data under the assumption that data were missing at random. While the use of multiple imputation allowed data from all included participants to be analyzed, multiple imputation does not completely rule out the possibility of selection bias. In addition to the missing data, recall bias may have affected participants who completed CSRI forms for health service resource use at 8 weeks and 12 months. The second recall period at 12 months required participants to record health service resource use during the previous 10 months, which may have resulted in participants omitting some information. Our trial population was predominantly men, which reduces confidence in generalizing the data. However, the general CR population in the UK is 71% men<sup>11</sup> and it is common for exercise intervention trials in CR to be men dominated.

### Conclusion

This is the first economic evaluation comparing HIIT with MISS in CR. Cost-utility analysis indicated that HIIT had a high likelihood of being cost-effective compared with MISS exercise training. Despite slightly higher health service use costs at 12 months, HIIT participants reported greater gains in HRQoL than MISS participants. In people with CAD attending CR, the HIIT or MISS UK trial showed that HIIT is safe and more clinically effective than MISS for improving cardiorespiratory fitness. The addition of our data supporting the cost-effectiveness of HIIT relative to MISS provides additional evidence for policy makers, commissioners, and service providers to consider when allocating health care resource.

### Suppliers

- Stata software v17.0; Stata Corp
- SPSS statistic 27; IBM

### Keywords

Coronary artery disease; Exercise training; Health economics; Health utility; National Health Service; Rehabilitation

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### References

- Wilkins E, Wilson L, Wickramasinghe K, et al. *European Cardiovascular Disease Statistics 2017*. Brussels, Belgium: European Heart Network; 2017.
- Lopez AD, Adair T. Is the long-term decline in cardiovascular-disease mortality in high-income countries over? Evidence from national vital statistics. *Int J Epidemiol* 2019;48:1815–23.
- Cheema KM, Dicks E, Pearson J, et al. Long-term trends in the epidemiology of cardiovascular diseases in the UK: insights from the British Heart Foundation statistical compendium. *Cardiovasc Res* 2022;118:2267–80.
- Liu L. *Heart Failure: Epidemiology and Research Methods*. The Netherlands: Elsevier; 2017.
- McGregor G, Powell R, Kimani P, et al. Does contemporary exercise-based cardiac rehabilitation improve quality of life for people with



- coronary artery disease? A systematic review and meta-analysis. *BMJ Open* 2020;10:e036089.
6. Powell R, McGregor G, Ennis S, et al. Is exercise-based cardiac rehabilitation effective? A systematic review and meta-analysis to re-examine the evidence. *BMJ Open* 2018;8:e019656.
  7. Dibben GO, Faulkner J, Oldridge N, et al. Exercise-based cardiac rehabilitation for coronary heart disease: a meta-analysis. *Eur Heart J* 2023;44:452–69.
  8. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407–77.
  9. Price KJ, Gordon BA, Bird SR, et al. A review of guidelines for cardiac rehabilitation exercise programmes: is there an international consensus? *Eur J Prev Cardiol* 2016;23:1715–33.
  10. Nichols S, McGregor G, Breckon J, et al. Current insights into exercise-based cardiac rehabilitation in patients with coronary heart disease and chronic heart failure. *Int J Sports Med* 2021;42:19–26.
  11. British Heart Foundation. The National Audit for Cardiac Rehabilitation Quality and Outcomes Report. Available at: <https://www.bhf.org.uk/>. London, England, 2019.
  12. Ennis S, Loble G, Worrall S, et al. Effectiveness and safety of early initiation of poststernotomy cardiac rehabilitation exercise training: the SCAR Randomized Clinical Trial. *JAMA Cardiol* 2022;7:817–24.
  13. Cowie A, Buckley J, Doherty P, et al. Standards and core components for cardiovascular disease prevention and rehabilitation. *Heart* 2019;105:510–5.
  14. McGregor G, Powell R, Begg B, et al. High-intensity interval training in cardiac rehabilitation (HIIT or MISS UK): a multi-centre randomised controlled trial. *Eur J Prev Cardiol* 2023;30:745–55.
  15. Shields GE, Wells A, Doherty P, et al. Cost-effectiveness of cardiac rehabilitation: a systematic review. *Heart* 2018;104:1403.
  16. Shields GE, Rowlandson A, Dalal G, et al. Cost-effectiveness of home-based cardiac rehabilitation: a systematic review. *Heart* 2023;109:913–20.
  17. Bambha K, Kim WR. Cost-effectiveness analysis and incremental cost-effectiveness ratios: uses and pitfalls. *Eur J Gastroenterol Hepatol* 2004;16:519–26.
  18. Rabarison KM, Bish CL, Massoudi MS, et al. Economic evaluation enhances public health decision making. *Front Public Health* 2015;3:164.
  19. Oldridge N, Furlong W, Feeny D, et al. Economic evaluation of cardiac rehabilitation soon after acute myocardial infarction. *Am J Cardiol* 1993;72:154–61.
  20. McGregor G, Nichols S, Hamborg T, et al. High-intensity interval training versus moderate-intensity steady-state training in UK cardiac rehabilitation programmes (HIIT or MISS UK): study protocol for a multicentre randomised controlled trial and economic evaluation. *BMJ Open* 2016;6:e012843.
  21. ACPICR. Standards for physical activity and exercise in the cardiac population. Available at: <http://acpicr.com>, 2015.
  22. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold. *Pharmacoeconomics* 2008;26:733–44.
  23. Schafer JL. Multiple imputation: a primer. *Stat Meth Med Res* 1999;8:3–15.
  24. Jones K, Burns A. Unit Costs of Health and Social Care 2021. Kent, UK: Personal Social Services Research Unit; 2021.
  25. Devlin NJ, Shah KK, Feng Y, et al. Valuing health-related quality of life: an EQ-5D-5L value set for England. *Health Econ* 2018;27:7–22.
  26. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *BMJ* 2022;376:e067975.
  27. McGregor G. Cost effectiveness analysis. In: Hartfiel N, 2021.
  28. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Meth Med Res* 2007;16:199–218.
  29. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377–99.
  30. Briffa TG, Eckermann SD, Griffiths AD, et al. Cost-effectiveness of rehabilitation after an acute coronary event: a randomised controlled trial. *Med J Aust* 2005;183:450–5.
  31. Maddison R, Pfaeffli L, Whittaker R, et al. A mobile phone intervention increases physical activity in people with cardiovascular disease: results from the HEART randomized controlled trial. *Eur J Prev Cardiol* 2015;22:701–9.
  32. Thum JS, Parsons G, Whittle T, et al. High-intensity interval training elicits higher enjoyment than moderate intensity continuous exercise. *PLoS One* 2017;12:e0166299.