

Perioperative care in adults

Appendix 1: Cost-effectiveness analysis: cardiac output monitoring versus conventional clinical assessment during surgery

NICE guideline

Economic analysis report

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*This guideline was developed by the
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1 Cost-effectiveness analysis: cardiac output monitoring versus conventional clinical assessment during surgery

5 1.1 Introduction

6 Cardiac output monitoring is used to guide fluid replacement and pharmacological treatment
7 during surgery. This can optimise the patient's haemodynamic status which helps maintain
8 adequate tissue perfusion. As a result, monitoring can reduce complications and length of
9 stay. However, cardiac output monitoring devices are expensive, and also have an added
10 cost per patient from the additional cost of a probe. There is variation in current practice
11 regarding whether the monitors are used during surgery, therefore if the monitors were
12 recommended there would be a large resource impact. A previous medical technologies
13 guidance on the CardioQ-ODM oesophageal Doppler monitor (MTG3)¹⁰ recommended the
14 use of CardioQ-ODM monitors for patients during surgery, on the basis that it reduced
15 postoperative complications, did not increase the rate of readmissions and reduced length of
16 stay, compared to conventional clinical assessment.

17 Since the publication of MTG3 in 2011, there have been improvements in other areas of the
18 standard perioperative care pathway, which have resulted in a reduction in complications and
19 overall length of stay. As the recommendations in MTG3 were driven by the cost-savings due
20 to reduced length of stay, these savings may not be as significant as previously
21 demonstrated, potentially affecting the cost effectiveness of cardiac output monitoring.

22 There were six economic evaluations included for this question, which were all in agreement
23 that cardiac output monitoring is likely to be cost effective. However the committee
24 considered there to still be uncertainty about the cost effectiveness of cardiac output
25 monitoring versus conventional clinical assessment in the current NHS setting. Reasons for
26 this uncertainty included: the studies relevant to the UK NHS were out of date, or based on
27 only a few studies for treatment effect. Also, the time horizons of most of the studies were
28 short. In addition, some of the published evidence was in a specific population, or only
29 looked at one type of monitor. The committee agreed it was useful to analyse all of the
30 clinical data together for all surgeries and all monitors combined, and use this up to date
31 pooled data in a model, to see if cardiac output monitoring was still considered cost effective.

32 As a result of the trade-off between costs and benefits needing to be explored further, this
33 area was prioritised for new economic analysis.

34

35 1.2 Methods

36 1.2.1 Model overview

37 A cost-utility analysis was undertaken with lifetime quality-adjusted life years (QALYs) and
38 costs from a current UK NHS and personal social services perspective. Both costs and
39 QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological
40 guidance. An incremental analysis was undertaken.

1 1.2.2 Comparators

2 The comparators included in the model were:

- 3 • Cardiac output monitoring (COM)
- 4 • Conventional clinical assessment (CCA)

5 Cardiac output monitoring (also known as goal-directed therapy) can include different types
6 of monitoring. The clinical review included studies which undertook oesophageal Doppler
7 monitoring and pulse contour analysis (also known as pulse pressure waveform analysis).
8 These different types of monitoring were combined for the purpose of the clinical review and
9 this analysis, as there was no heterogeneity to imply that treatment effects might be different
10 by the type of monitor.

11 Conventional clinical assessment can involve non-invasive assessment of various clinical
12 outputs during surgery. These can include heart rate, blood pressure and urinary output.

13 1.2.3 Population

14 The population included adults having major or complex or high risk surgery, and high risk
15 patients undergoing any surgery.

16 The committee discussed how using data from the general population, for baseline data such
17 as mortality (which is typically done in Markov models) may not be appropriate for this model.
18 This is because the population having surgery would typically have worse health than the
19 general population. The committee agreed that a large proportion of major surgery in
20 England is for treating people with cancer, therefore adults with bowel cancer was chosen as
21 the base case population.

22 The baseline age in the model is 60 years. Hospital Episode Statistics¹² indicated that the
23 average age of patients undergoing an intervention in the NHS was 57 years and the
24 average of patients included in the studies in the clinical review was 67. Due to the average
25 age of interventions in the UK and in the studies from the clinical review ranging from 57 to
26 67, the committee agreed that 60 was a suitable base case age for the model. A sensitivity
27 analysis was carried out using a start age of 67.

28 1.2.4 Approach to modelling

29

30 The clinical review found that during the hospital period, COM reduced complications and
31 also led to a small reduction in mortality.

32 The model consisted of a short term decision tree, using the clinical review data for the
33 effectiveness of COM versus CCA, followed by a lifetime Markov model, to capture the
34 lifetime implications of differences in short-term mortality and morbidity between
35 comparators.

36 1.2.4.1 Model structure

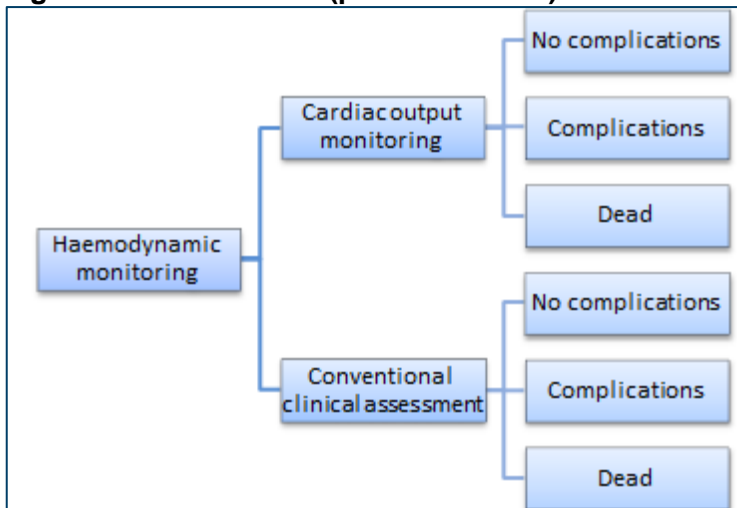
37 The first part of the model structure was a 30-day decision tree to model the probability of
38 experiencing complications or death up to 30 days post-surgery (see Figure 1). The
39 probabilities used in the decision tree were obtained from the clinical review. The studies
40 included in the clinical review recorded mortality up to 90 days post-surgery and
41 complications up to 45 days post-surgery. However, the decision tree used a 30-day time
42 horizon because the majority of the studies reported outcomes at 30 days or at discharge
43 from hospital and this was considered appropriate by the committee. The decision tree
44 applied a different cost and utility to those that experienced complications. The clinical review
45 reported an overall probability of complications which was applied to each arm, but in order
46 to more appropriately capture the cost of complications which can vary: those experiencing

1 complications were further broken down into those having minor complications (grade 1 and
 2 2 Clavien-Dindo complications) and those having major complications (grade 3 and 4
 3 Clavien-Dindo complications).

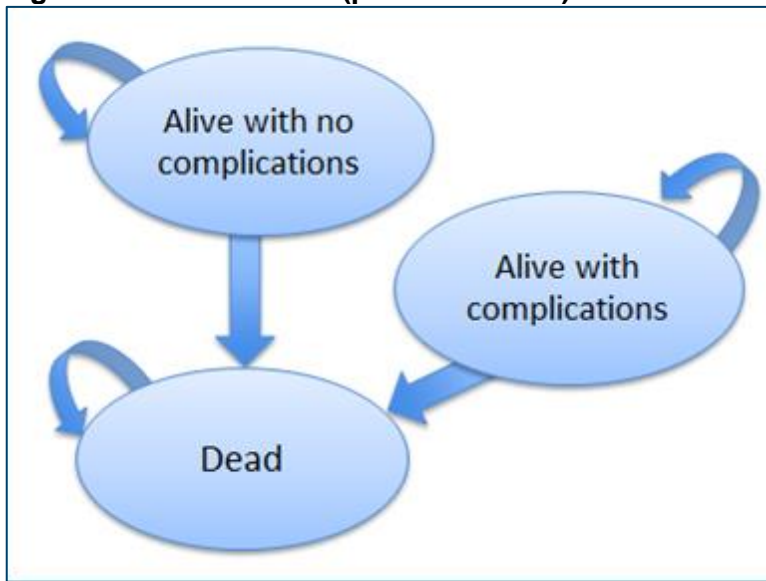
4 The second part of the model structure was a Markov model to capture costs and outcomes
 5 over a lifetime. In a Markov model a set of mutually exclusive health states are defined that
 6 describe what can happen to the population of interest over time. People in the model can
 7 only exist in one of these health states at a time. Possible transitions are defined between
 8 each of the health states and the probability of each transition occurring within a defined
 9 period of time (a cycle) is assigned to each possible transition.

10 Adults alive at the end of the 30 day decision tree entered the Markov model. The Markov
 11 model was made up of 3 health states: 'alive with no complications', 'alive with complications'
 12 and 'dead'. A one year cycle length was used. Adults could only move from the 'alive'
 13 health states to the 'dead' health state, which was determined by transition probabilities based on
 14 mortality rates. Dead is an absorbing health state. Figure 2 illustrates the Markov model
 15 structure and the possible transitions between health states.

Figure 1: Decision tree (part 1 of model)



16 People that experienced no complications in the decision tree entered the 'Alive with no
 17 complications' health state. Also, it was agreed that people that experienced minor
 18 complications in the decision tree would generally have their minor complication dealt with by
 19 the end of 30 days and therefore they would return to the same health as those who did not
 20 experience complications. As a result, they also entered the Markov model in the 'Alive with
 21 no complications' health state. Adults that experienced major complications in the decision
 22 tree entered the 'alive with complications' health state, as it was believed that they would
 23 experience long-term health implications which result in a higher mortality and lower quality
 24 of life, compared to those alive with no complications.

Figure 2: Markov model (part 2 of model)

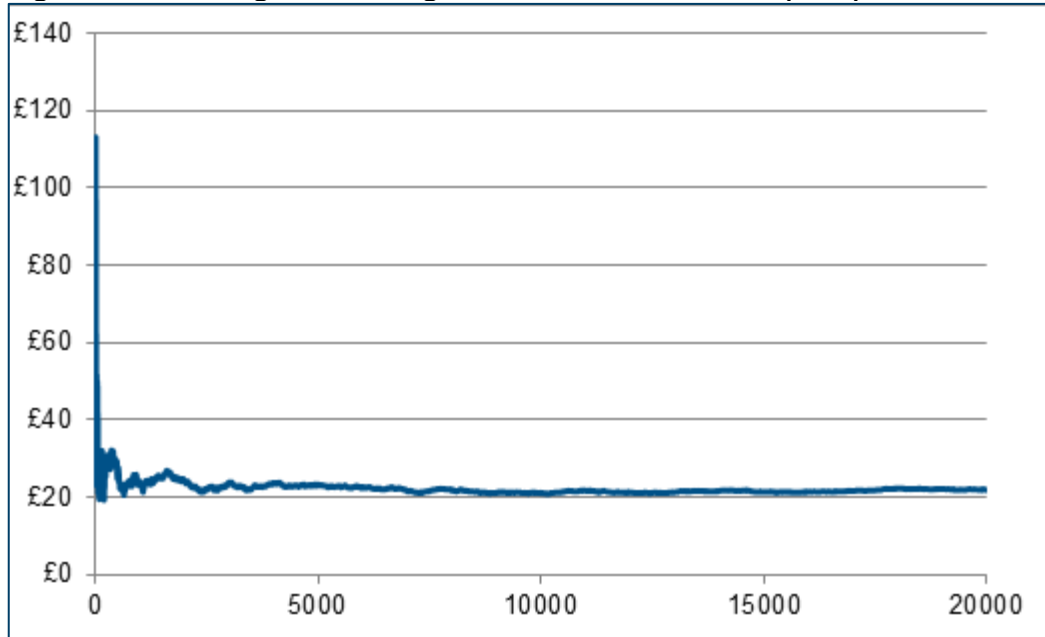
1 The Markov model was run for repeated cycles for both comparators, for 40 years, by which
2 time most people would have died. The time spent alive for both the CCA and COM arm was
3 calculated. The probabilities of transitioning to the dead health state (mortality rates) varied
4 by state but not by comparator. The only thing that varied by comparator was the number of
5 people entering the Markov model and the number of people in each health state, which was
6 based on the data in the decision tree that utilised the effectiveness data from the clinical
7 review.

8 **1.2.4.2 Uncertainty**

9 The model was built probabilistically to take account of the uncertainty around input
10 parameter point estimates. A probability distribution was defined for some model input
11 parameters. When the model was run, a value for each input was randomly selected
12 simultaneously from its respective probability distribution; mean costs and mean QALYs
13 were calculated using these values. The model was run repeatedly – 20,000 times for the
14 base case and for each probabilistic sensitivity analysis – and results were summarised in
15 terms of mean costs and QALYs, and the percentage of times COM was the most cost-
16 effective strategy at a threshold of £20,000.

17 When running the probabilistic analysis, multiple runs are required to take into account
18 random variation in sampling. To ensure the number of model runs were sufficient in the
19 probabilistic analysis, we checked for convergence in the incremental costs and QALYs and
20 net monetary benefit at a threshold of £20,000 per QALY gained for COM versus CCA by
21 plotting the number of runs against the mean outcome at that point (see example in Figure 3)
22 for the base-case analysis. Convergence was assessed visually. All had converged before
23 20,000 runs.

Figure 3: Checking for convergence: incremental costs (total)



1 The way in which distributions are defined reflects the nature of the data, so for example
 2 utilities were given a beta distribution, which is bounded by 0 and 1, reflecting that a quality
 3 of life weighting will not be outside this range. All of the variables that were probabilistic in the
 4 model and their distributional parameters are detailed in Table 1. Probability distributions in
 5 the analysis were parameterised using error estimates from data sources.

6 **Table 1: Description of the type and properties of distributions used in the**
 7 **probabilistic sensitivity analysis**

Parameter	Type of distribution	Properties of distribution
Utility	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: Alpha = $\text{mean}^2 \times [(1-\text{mean})/\text{SE}^2] - \text{mean}$ Beta = $\text{Alpha} \times [(1-\text{mean})/\text{mean}]$
Utility decrements	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and Beta values were calculated as follows: Alpha = $(\text{mean}/\text{SE})^2$ Beta = SE^2/Mean
Risk ratios Hazard ratios	Lognormal	The natural log of the mean was calculated as follows: Mean = $\ln(\text{mean cost}) - \text{SE}^2/2$ Where the natural log of the standard error was calculated by: SE = $[\ln(\text{upper } 95\% \text{ CI}) - \ln(\text{lower } 95\% \text{ CI})]/(1.96 \times 2)$ $\sqrt{\ln \frac{\text{SE}^2 + \text{mean}^2}{\text{mean}^2}}$

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),
- health state costs (based on national average costs from UK national sources)
- device costs (based on list prices provided by manufacturer's/published sources)
- mortality probabilities for general population and cancer (based on UK national sources)
- proportion of people experiencing major or minor complications (based on UK national sources)

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

1.2.5 Model inputs

1.2.5.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources or committee assumptions as required. Model inputs were validated with clinical members of the guideline committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 2 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 2: Summary of base-case model inputs

Input	Data	Source
Comparators	Conventional clinical assessment Cardiac output monitoring	
Population	Adults undergoing major surgery and high risk adults undergoing any surgery	
Age (entering model)	60	
Gender	Male: 57% Female: 43%	Systematic review of RCTs undertaken as part of guideline development
Perspective	UK NHS and PSS	NICE reference case ⁸
Time horizon	Lifetime	NICE reference case ⁸
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case ⁸
Baseline risk with CCA for decision tree		
Probability of mortality at 30 days	2.2%	Systematic review of RCTs undertaken as part of guideline development
Probability of complications at 30 days	44%	Systematic review of RCTs undertaken as part of guideline development
All-cause mortality	Age and gender dependent	Office for National Statistics 2018 ¹⁵
Bowel cancer mortality	Time since diagnosis and gender dependent. Applied only for first 10 years in	Cancer Research UK 2014 ¹

Input	Data	Source
	Markov model.	
Distribution between minor and major complications	Minor: 89% Major: 11%	PQIP 2018 ¹⁴
Relative treatment effects compared to CCA for decision tree (risk ratios; 95% CI)		
Complications at 30 days	0.78 (0.70 – 0.88)	Systematic review of RCTs undertaken as part of guideline development
Mortality at 30 days	0.88 (0.53 – 1.48)	Systematic review of RCTs undertaken as part of guideline development
Hazard ratios applied in Markov model		
Hazard ratio for mortality with major complications – years 0-1	3.51 (2.28 – 5.42)	Moonesinghe 2014 ⁷
Hazard ratio for mortality with major complications – years 1-3	2.44 (1.62 – 3.65)	Moonesinghe 2014 ⁷
Quality of life (utilities)		
General population	0.79 – 0.83 (age dependent)	Health Survey for England 2014 ¹²
Bowel cancer	0.67	Sullivan 2011 ¹⁹
Minor complication (chest infection utility decrement)	0.092	Oppong 2013 ¹⁶
Major complication (ICU survivor utility decrement)	0.16	Cuthbertson 2010 ³
Costs in decision tree		
Cardiac output monitor	£127 (weighted average)	Direct contact with NHS Supply Chain and NICE MTG3 ¹⁰
Minor complication (chest infection)	£2,178	NHS reference costs 2017/18 ¹³
Major complication (ICU stay)	£1,350 (per day)	NHS reference costs 2017/18 ⁴
Health state costs		
Alive with complications – year 0-1	£2,520	Lone 2016 ⁶
Alive with complications – year 1-2	£1,306	
Alive with complications – year 2-3	£1,414	
Costs associated with bowel cancer population		
Bowel cancer costs years 0 – 1	£15,961	Laudicella 2016 ⁵
Bowel cancer costs years 1 – 2	£4,069	
Bowel cancer costs years 2 – 3	£3,411	
Bowel cancer costs years 3 – 4	£2,923	
Bowel cancer costs years 4 – 5	£2,959	
Bowel cancer costs years 5 – 6	£2,985	
Bowel cancer costs years 6 – 7	£2,759	
Bowel cancer costs years 7 – 8	£3,003	
Bowel cancer costs years 8 – 9	£2,592	

1.2.5.2 Initial cohort settings

The analysis was run for adults aged 60 years, as noted above. The percentage of adults that were male was obtained from the studies in the clinical review, which was 57%.

1.2.5.3 Probabilities of events for decision tree

The clinical review on cardiac output monitoring identified twenty-three studies comparing COM to CCA. A summary of the mortality and complications data is summarised in Table 3. Note that not all studies included in the clinical review reported mortality and complications.

Table 3: Short term mortality and complication outcomes

Outcomes	N (studies) Follow-up	CCA probability	Relative effect of COM	COM probability
Mortality	1915 (12 studies) <90 days	2.2%	RR 0.87 (0.53 to 1.43)	1.9%
Complications	1853 (12 studies) <45 days	44%	RR 0.77 (0.69 to 0.87)	34%

Abbreviations: 95% CI = 95% confidence interval; N = total number of participants in studies; RR = risk ratio

The clinical review included studies that reported mortality up to 90 days and complications up to 45 days. However, for the purpose of modelling a time frame of 30 days was chosen. This was because the majority of studies recorded outcomes at either 30 days or until discharge from hospital. In most cases the average time until discharge was below 30, therefore the committee agreed that 30 days was an appropriate time frame to use.

The committee discussed concerns around the systematic review pooling studies from different populations, for example colorectal surgery and cardiac surgery. Despite this concern there was no heterogeneity in the meta-analysis. There was also concern around the fact that some of the older studies included central venous pressure as part of their conventional clinical assessment. Central venous pressure is no longer used in current practice, due to advances in other conventional techniques and there being additional risks associated with it. However, sensitivity analyses around the relative treatment effects were conducted and are discussed in further detail in section 1.2.6.

Those experiencing complications in the decision tree were further broken down in to minor and major complications. Minor and major surgical complications are usually graded using the Clavien-Dindo classification system. A minor complication is a grade 1 and 2 complication and a major complication is a grade 3 and 4 complication. The split between minor and major complications in the decision tree was based on the Perioperative Quality Improvement Programme (PQIP) 2018 annual report¹⁴ which reported that 11% of patients undergoing elective major surgery in the NHS in England developed a serious complication (Clavien-Dindo grade 3 or above). As a result, 11% of those experiencing complications had a major complication and the remaining 89% had a minor complication (Clavien-Dindo grade 2 and below).

1.2.5.4 Mortality rates for Markov model**1.2.5.4.1 General population mortality**

All-cause mortality was based on the Office for National Statistics (ONS)¹⁵ life tables for England 2015-2017.

However, all-cause mortality was adjusted to reflect a higher risk population as the committee agreed that it was not appropriate to use general population mortality rates as the

1 population undergoing surgery would typically have a higher probability of death compared to
2 the general population. See more on this in section 1.2.5.4.2.

3 **1.2.5.4.2 Bowel cancer mortality (proxy for high risk population)**

4 The mortality of the population that undergoes major surgery or are considered high risk
5 adults is higher than the general population. This is because they are more likely to have
6 comorbidities that could have led to the conditions they are having surgery for. It was agreed
7 that a large proportion of adults undergoing high risk surgery would have cancer, and
8 therefore this population was more reflective of the population considered. Some of the
9 studies included in the clinical review were for adults undergoing major surgery for cancer
10 and were bowel or gastrointestinal related, therefore bowel cancer mortality was used in the
11 model as a proxy for a high-risk surgical population. Cancer Research UK¹ publishes ten
12 year bowel cancer survival statistics for England, and these were used to obtain yearly
13 mortality probabilities, which are demonstrated in Table 4.

14 **Table 4: Net Survival and probability of death up to Ten Years after Diagnosis, Adults**
15 **(Aged 15-99), England and Wales**

Years after diagnosis	Net Survival %		Absolute change each year		Probability of death	
	Men	Women	Men	Women	Men	Women
0	100.0	100.0				
1	77.4	73.9	22.6	26.1	0.226	0.261
2	69.5	66.3	7.9	7.6	0.102	0.103
3	64.5	61.9	5.0	4.4	0.072	0.066
4	61.2	59.5	3.3	2.4	0.051	0.039
5	59.2	58.2	2.0	1.3	0.033	0.022
6	58.0	57.5	1.2	0.7	0.020	0.012
7	57.2	57.1	0.8	0.4	0.014	0.007
8	56.6	57.0	0.6	0.1	0.010	0.002
9	56.3	57.1	0.3	0.0	0.005	0.000
10	56.0	57.2	0.3	0.0	0.005	0.000

16 Source: Cancer Research UK 2014¹

17 Net survival estimates the number of people who survive their cancer, excluding death from
18 other causes. Notes accompanying the statistics state that bowel cancer survival falls only
19 slightly beyond 5 years, which means most patients can be considered cured by that time.¹
20 Table 4 shows that net survival does not change in the last two years, meaning that excess
21 survival is not affected and that people have returned to general population mortality. The
22 committee also agreed that adults who survive cancer beyond eight years will no longer have
23 excess mortality and return to the general population mortality rate.

24 In order to apply the bowel cancer related mortality to the general population mortality, bowel
25 cancer related deaths were removed from the general population mortality. Mortality by
26 cause was obtained from the ONS¹⁵. The percentage of deaths that were non-bowel cancer
27 related were calculated and shown in Table 5.

28 **Table 5: Mortality statistics for England 2017 including bowel cancer mortality**

Age	Total deaths		Bowel cancer related deaths		Non-bowel cancer related deaths (%)	
	Male	Female	Male	Female	Male	Female
60 – 64	13,351	9,002	616	347	95.39%	96.15%
65 – 69	19,995	13,863	847	543	95.76%	96.08%

Age	Total deaths		Bowel cancer related deaths		Non-bowel cancer related deaths (%)	
	Male	Female	Male	Female	Male	Female
70 – 74	27,983	20,215	1,109	730	96.04%	96.39%
75 – 79	33,129	26,883	1,135	872	96.57%	96.76%
80 – 84	41,271	38,885	1,338	1,112	96.76%	97.14%
85 – 89	41,307	50,871	1,030	1,078	97.51%	97.88%
90 and over	36,245	73,029	613	863	98.31%	98.82%

Source: ONS 2018¹⁵.

The probability of bowel cancer deaths per year from Table 4 were converted to rates using the formula below in Table 6. These were summed with the mortality rate per year of age from general population data, and the total values converted back to probabilities to be applied as transition probabilities in the model.

Table 6: Formulas for converting between probabilities and rates

$Selected\ rate\ (r) = \frac{-\ln(1 - P)}{t}$	Where P=probability of event over time t t=time over which probability occurs (1 year)
$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where r=selected rate t=cycle length (1 year)

1.2.5.4.3 Hazard ratios for mortality following complications

Those that experienced major complications in the decision tree went on to have a higher mortality rate in the Markov model compared to those that did not experience major complications. Moonesinghe 2014⁷ conducted a cohort study in England and showed that people experiencing complications up to 15 days after surgery have a higher probability of death for 3 years, which then returns to baseline (see Table 7).

Table 7: Hazard ratios for mortality following complications

Years	HR
0 – 1	3.51 (2.28 – 5.42)
1 – 3	2.44 (1.62 – 3.65)

Source: Moonesinghe 2014⁷

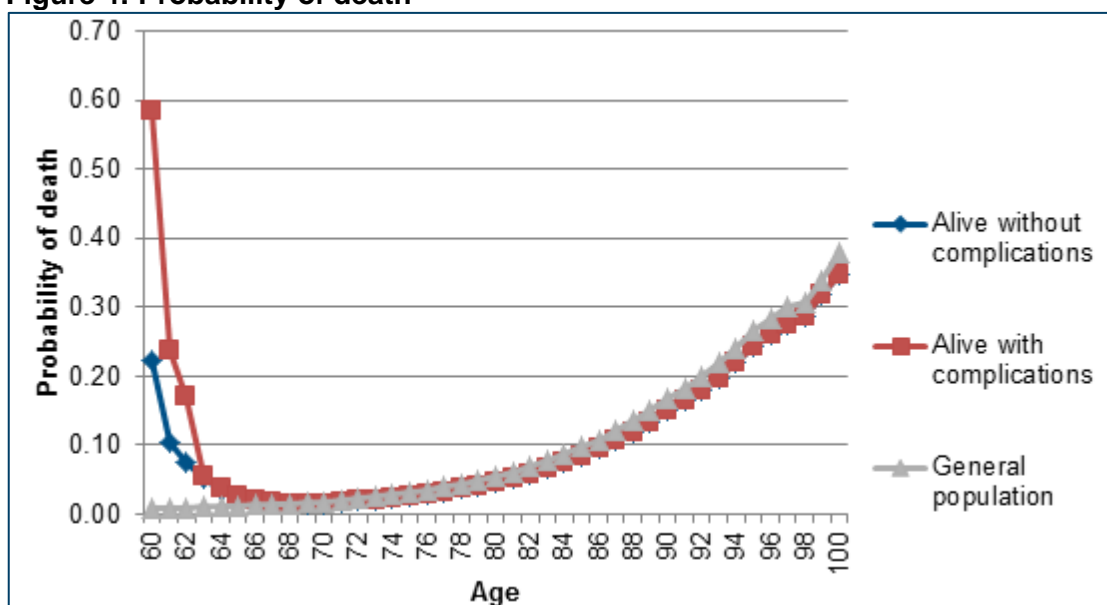
The hazard ratios from this study were used to model the excess risk of death for 3 years in the Markov model. It was highlighted that as the baseline mortality used in the model was for bowel cancer, these statistics would include adults that experienced complications and therefore applying the hazard ratio to this mortality would be overestimating mortality for this population. Therefore, a calibration technique was used to separate the cancer mortality rates into those with and without major complications by using the hazard ratios above. The following formula was used to separate those with and without complications using the hazard ratios:

$$\frac{mx * (no.without complications + no.with complications)}{(no.without complications + HR * no.with complications)}^a$$

^a mx is rate of death
HR is hazard ratio

The probability of death for those with complications, without complications and for the general population is demonstrated graphically in Figure 4.

Figure 4: Probability of death



1

2 **1.2.5.5 Utilities**

3 Quality of life weights (utilities) were applied to adults in the model based on general
 4 population estimates stratified by age. These were taken from an analysis of the Health
 5 Survey for England 2014 dataset.¹¹ These are listed below in Table 8.

6 **Table 8: General population utility estimates**

Age	Mean	Std. Err
60-69	0.829	0.007
70-79	0.821	0.006
80-89	0.792	0.007

7 General population utilities were incorporated into the probabilistic analysis using beta
 8 distributions. This is bounded by 0 and 1.

9 As the committee agreed that the population being modelled had worse health than the
 10 general population, utilities were derived to reflect this population. For those who were alive
 11 and did not experience complications, the utility of having bowel cancer was used (see Table
 12 9). This was because the mortality data used in the model was based on bowel cancer and it
 13 was felt appropriate to use the quality of life associated with having bowel cancer. It was
 14 applied in the decision tree and also in the Markov model for 10 years, in order to correspond
 15 with the length of time that the bowel cancer mortality data was used. After 10 years, the
 16 general population quality of life was used as it was assumed that adults would return to the
 17 health of general population.

18 **Table 9: Utility values from published sources**

Condition	Mean	Std. Err	Source
Bowel cancer	0.67	0.03	Sullivan 2011 ¹⁹
Chest infection	0.74	0.02	Oppong 2013 ¹⁶
ICU survivor	0.67	0.02	Cuthbertson 2010 ³

Adults that experienced complications in the decision tree had lower quality of life compared to those experiencing no complications. As these complications were broken down in to minor and major complications, different utilities were obtained for each of these states. For the purposes of simplification, a typical minor and major complication was chosen by the committee to facilitate obtaining inputs associated with these complications. The committee felt that minor complications would vary from person to person and also between surgery, but a common complication would be a chest infection. For major complications the committee agreed that ICU admission would be a reasonable example as many major complications would require being admitted to ICU. For minor complications, the utility of a chest infection was obtained from published sources. For those experiencing major complications, the utility associated with ICU survivors in the UK was obtained. These utilities are shown in Table 9. The minor and major complications utilities were applied using decrements by working out the difference in utility between these health states and the utility of the general population of someone aged 60 (row 1 in Table 8). The values used in the model are shown in Table 10.

Table 10: Utility values used in the model

Health state	Utility value
Alive with no complications	0.67
Minor complication ^(a)	0.09
Major complication ^(b)	0.16

(a) 0.829-0.74

(b) 0.829-0.67

Adults that experienced minor complications had the utility decrement associated with having a chest infection applied for the full 30 days in the decision tree. After this, they went on to have the same quality of life as those that did not experience any complications. Those experiencing major complications had the utility decrement associated with ICU survival applied in the decision tree and in the Markov model for 3 years. This was to correspond with the length of time that they experienced higher mortality. After 3 years they had the baseline utility applied.

The utility for the baseline value (alive with no complications) was varied probabilistically using a beta distribution. As the minor and major complication utilities were calculated using decrements they were varied using a gamma distribution. All utilities used in the model were obtained using the EQ-5D-3L.

1.2.5.6 Resource use and costs

1.2.5.6.1 Monitor costs

As the clinical review pooled together different types of monitors used for cardiac output monitoring, the costs of the most commonly used monitors in the UK were obtained. A recent survey sent to anaesthetists in the UK reported the usage of the different types of cardiac output monitors used in intensive care units in hospitals.¹⁷ Although this is not specific to surgery, the committee noted that hospitals tend to use the same type of monitors in surgery as they would in ICU. The study reported the percentage of hospitals that have CardioQ-ODM, LiDCO rapid or PiCCO monitor. These figures were used to calculate a weighted average of the cost of the monitors.

The costs of the PiCCO and LiDCO monitors were obtained from correspondence with the NHS supply chain. They also provided information from the manufacturers on the useful life years, and the number of uses per year. Up to date costs of CardioQ-ODM was not obtainable, therefore the costs used in the manufacturer submission for NICE MTG3¹⁰ was used and is shown in Table 11. The up to date list prices of LiDCO and PiCCO were classified as confidential by the manufacturer and therefore not reported. The committee

1 thought that the manufacturer estimates for the useful life years and number of uses per year
 2 looked high compared to their knowledge of how often the machines are used in practice and
 3 how often they would be replaced. The committee made assumptions about useful life years
 4 and number of uses per year and these were used in the base case, which is demonstrated
 5 in Table 12, with these being varied as well as the manufacturer estimates being used in the
 6 sensitivity analysis.

7 **Table 11: Costs of CardioQ-ODM**

Cost	Annual maintenance costs	Cost of disposables (per person)	Useful life years	Number of uses per year
£11,000	£750	£67	7 years	300

8 *Source: NICE Medical Technologies Guidance 3 (MTG3) 2011¹⁰*

9 Although staff time is required to check the monitors during surgery, this was considered to
 10 be done by staff already in the operating theatre and therefore only the cost of the monitor
 11 was applied.

12 **Table 12: Weighted average cardiac output monitor cost used in the base case**

Monitor	Useful life years	Number of uses per year	Cost per use
LiDCO	10	150	Confidential ^(a)
PiCCO	10	150	Confidential ^(a)
CardioQ-ODM	10	150	£81
Weighted average			£127

13 *(a) Costs of individual monitors cannot be reported due to confidentiality.*

14 **1.2.5.6.2 Complication costs**

15 *1.2.5.6.2.1 Decision tree costs*

16 The committee agreed that although minor complications can vary between the type of
 17 surgery and the adult, a chest infection is a typical complication and was used as an example
 18 for modelling purposes. The cost of treating a chest infection in hospital was based on a
 19 weighted average cost of all unspecified acute lower respiratory infections from NHS
 20 reference costs 2017/18⁴ demonstrated in Table 13. The cost was applied in the decision
 21 tree part of the model as a one off cost.

22 **Table 13: Minor adverse event cost**

Currency code	Currency description	Number of FCEs	National average unit cost
DZ22K	Unspecified Acute Lower Respiratory Infection with Interventions, with CC Score 9+	22	£12,033
DZ22L	Unspecified Acute Lower Respiratory Infection with Interventions, with CC Score 0-8	64	£4,882
DZ22M	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 13+	30	£1,847
DZ22N	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 9-12	135	£3,239
DZ22P	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 5-8	356	£2,085
DZ22Q	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 0-4	495	£1,188
Weighted average			£2,178

1 (a) Source: NHS reference costs 2017/18⁴

2 The cost of experiencing a major complication was based on being admitted to ICU after
3 surgery. The cost of ICU from the NHS reference costs is based on a cost per day; therefore
4 a typical number of days in ICU had to be used. The committee agreed that it was
5 appropriate to use the average length of stay in critical care from the Case Mix Analysis 2016
6 of 4.8 days, which was rounded up to 5 days in the model. The average cost per day is
7 demonstrated in Table 14. This was applied to those experiencing major complications in the
8 decision tree.

9 No cost was attributed to adults who did not experience any complications in the decision
10 tree, as everyone entering the model had surgery and the only difference in costs was for
11 complications.

12 **Table 14: Major adverse event cost**

Service code	Service description	Activity	National average unit cost per day
CCU02	Surgical adult patients (unspecified specialty); 0 to 6 or more organs supported	91,009	£1,258
CCU06	Cardiac surgical adult patients predominate; 0 to 6 or more organs supported	179,446	£1,449
CCU07	Thoracic surgical adult patients predominate; 0 to 6 or more organs supported	33,837	£1,242
CCU91	Non-standard location using the operating department; 0 to 3 organs supported	7,654	£613
Weighted average			£1,350
Total cost for 5 days			£6,752

13 (a) Source NHS reference costs 2017/18⁴

14

15 1.2.5.6.2.2 Markov model costs

16 Adults who entered the Markov model in the 'alive with complications' health state had long-
17 term health implications that were assumed to result in ongoing costs. A study conducted
18 across intensive care units in Scotland compared the long-term NHS costs of people who
19 were admitted to ICU to a matched control who were not admitted to ICU.⁶ The difference
20 between the ICU cohort and matched control was calculated and used in the model by
21 applying it to those in the alive with complications health state. These costs are presented in
22 Table 15. It was agreed that the costs would apply for 3 years in the base case analysis as
23 this was the duration that the mortality hazard ratio was applied. Costs were applied for 5
24 years in a sensitivity analysis.

25 **Table 15: Long-term costs associated with ICU admission**

Years	ICU cohort	Matched control	Difference
1	£6,435	£3,915	£2,520
2	£4,142	£2,836	£1,306
3	£3,936	£2,522	£1,414
4	£3,736	£2,254	£1,482
5	£3,283	£2,069	£1,214

26 Source: Lone 2016⁶

27 The long-term costs associated with ICU admission were inflated from 2014 to 2017/18 costs
28 using the Hospital & Community Health Services (HCHS) Pay & Prices Index.²

1 All of the costs listed above were not incorporated probabilistically into the analysis as they
2 were obtained from reliable national sources.

3 **1.2.5.6.3 Disease specific costs**

4 The NICE reference case states that costs specific to the disease of interest should be
5 included. Because a proxy population of bowel cancer was used to reflect the major surgery
6 population in the model, costs related to cancer were also included in the model. Costs
7 associated with having bowel cancer were identified from a study which reported costs
8 associated with the overall bowel cancer population as well as separately for bowel cancer
9 stages 1 to 2 and stages 3 to 4.⁵ Because the type of cancer likely to be operable is less
10 severe, the costs for stages 1 and 2 bowel cancer were applied which are shown in Table 16.
11 The study reported that 60% of those with stages 1 and 2 had surgery whereas only 47% of
12 those with stages 3 and 4 had surgery therefore it was considered appropriate to use costs
13 for stages 1 and 2. These costs were inflated from 2010 to 2017/18 costs using the Hospital
14 & Community Health Services (HCHS) Pay & Prices Index.² Disease specific costs were
15 applied for 9 years to everyone alive in the model, because this was the maximum amount of
16 time the paper reported data for. Also, this is in line with the assumption made in the model
17 that if you survive cancer for around 10 years you are considered cancer free and your
18 health returns to that of the general population, therefore cancer related costs would no
19 longer apply.

20 **Table 16: Bowel cancer specific costs**

Year	Cost
0 – 1	£15,961
1 – 2	£4,069
2 – 3	£3,411
3 – 4	£2,923
4 – 5	£2,959
5 – 6	£2,985
6 – 7	£2,759
7 – 8	£3,003
8 – 9	£2,592

21 *Source: Laudicella 2016⁵*

22 **1.2.6 Sensitivity analyses**

23 **1.2.6.1 SA1 – 3: Using alternative probabilities in the decision tree (probabilistic)**

24 The base case analysis used data from the clinical review for the probabilities in the decision
25 tree. The studies were conducted in different countries; therefore an alternative scenario was
26 used where the baseline and treatment effects were taken from a meta-analysis of studies
27 conducted in the UK (SA1).

28 Another scenario using baseline and treatment effects from a meta-analysis excluding the
29 studies conducted before the publication of MTG3 was conducted. As a decision was made
30 to update MTG3 on the basis that practice had changed and improved since it was
31 published, it was felt appropriate to conduct an analysis which excluded the studies that were
32 included in that analysis (SA2).

33 A scenario using baseline and treatment effects from a meta-analysis excluding studies that
34 were cardiac and emergency surgery was conducted (SA3). The committee felt that although
35 these were in the minority, they were different to the other studies included in the analysis as
36 the other studies were conducted on elective patients and patients typically undergoing

1 bowel or gastrointestinal surgery. The probabilities used in the model from these alternative
2 meta-analyses are in Table 17.

3 **Table 17: Clinical evidence for alternative scenarios**

Input	CCA probability	Relative effect of CoM	Source
UK only studies (SA1)			
Mortality	2.7%	0.94 (0.51 – 1.72)	Systematic review of RCTs undertaken as part of guideline development
Complications	51%	0.80 (0.70 – 0.93)	
Excluded pre-MTG3 studies (SA2)			
Mortality	1.0%	1.20 (0.40 – 3.54)	Systematic review of RCTs undertaken as part of guideline development
Complications	16%	0.63 (0.43 – 0.92)	
Excluded cardiac and emergency surgery (SA3)			
Mortality	1.5%	1.05 (0.58 – 1.92)	Systematic review of RCTs undertaken as part of guideline development
Complications	44%	0.77 (0.68 – 0.87)	

4 **1.2.6.2 SA4 – 5: General population (probabilistic)**

5 The committee agreed that the general population mortality was not appropriate to use in the
6 base case analysis as adults undergoing major surgery would typically have a higher
7 mortality rate than the general population. Therefore, as described in section 1.2.5.4, bowel
8 cancer mortality rates were used instead. Although the committee felt that the cancer
9 mortality rates were more representative of the population being modelled, there was
10 concern it was overestimating mortality for some people as this is a broad area covering a
11 large population, some of which will have major surgery but not have as high mortality as a
12 cancer population. It was therefore agreed that an analysis using the general population
13 mortality instead of cancer mortality was conducted to test if it changed the conclusion of the
14 results. Where the term general population is used, this involves using the general population
15 mortality rates, general population quality of life and removing the disease specific bowel
16 cancer costs (SA4). Another analysis was conducted using the general population
17 assumptions as well as applying age-related NHS costs shown in Table 18 (SA5).

18 **Table 18: Average age-specific NHS spending**

Age	Male	Female	Male and Female combined ^(a)	Source
60-64	£2,628	£2,838	£2,718	Robineau 2016 ¹⁸
65-69	£3,889	£3,784	£3,844	
70-74	£4,520	£4,310	£4,430	
75-79	£5,991	£5,676	£5,856	
80-84	£6,938	£6,412	£6,712	
85+	£8,322	£7,646	£8,031	

19 *(a) These were combined based on the percentage of males and females entering the model.*

20 **1.2.6.3 SA6: Mortality hazard ratio applied for 5 years (probabilistic)**

21 Those that experienced major complications had higher mortality in the long-term compared
22 to those that did not experience complications or those experiencing minor complications.
23 This was modelled using the hazard ratios obtained from Moonesignhe 2014.⁷ The
24 committee noted that there is some data to suggest that surgical complications have a longer

1 impact on mortality. Therefore, an analysis was conducted where the mortality hazard ratio
2 was applied for 5 years instead of 3. Also, the costs of care after ICU admission from the
3 Lone 2016 study were applied for 5 years instead of 3 years as well as the utility decrement.

4 **1.2.6.4 SA7: Discount rate set to 1.5% (probabilistic)**

5 In-line with NICE methodological guidance a sensitivity analysis was undertaken where the
6 discount rate was set to 1.5% for costs and outcomes instead of 3.5% to explore whether
7 results were sensitive to the discount rate used.

8 **1.2.6.5 SA8 – 11: Cardiac output monitoring costs (deterministic)**

9 In the base case analysis the costs of the monitors were determined based on the number of
10 uses and number of years the monitors would be used. The committee agreed that an
11 average number of uses would be 150 per year and that a monitor would have a lifetime of
12 10 years in the NHS. In different scenarios the number of uses per year was varied for each
13 monitor as shown in Table 19. . For each monitor, the manufacturer's suggested figures were
14 higher for the number of uses and lower for useful life years.

15 **Table 19: Alternative number of uses for monitors**

Analysis	Useful life years	Number of uses per year
Low usage (SA8)	10	50
High usage (SA9)	10	250
Manufacturer submitted (SA10)	<i>Confidential^(a)</i>	<i>Confidential^(a)</i>

16 (a) *Manufacturer's suggested uses cannot be reported due to confidentiality.*
17

18 As we did not obtain up to date list prices for CardioQ-ODM+, a sensitivity analysis was
19 conducted where the cost of the monitor was reduced by 50% to reflect that costs might have
20 decreased over time which resulted in the monitor costing £5,500 instead of £11,000 (SA11).
21

22 **1.2.6.6 SA12: Proportion experiencing minor and major complications (deterministic)**

23 When adults experienced a complication in the decision tree, they were further broken down
24 in to minor and major complications. The base case analysis used figures reported in the
25 PQIP 2018¹⁴ report as this was reflective of what is seen across hospitals in England. An
26 alternative scenario was conducted where the estimates from some of the studies included in
27 the clinical review were used. These were not used in the base case because the committee
28 felt the number of major complications was too high and some of the reporting of
29 complications was too vague to categorise as either major or minor. However, it was
30 considered appropriate to run an analysis utilising the data from the clinical review which is
31 reported in Table 20.

32 **Table 20: Alternative distribution of major and minor complications**

Complication	Distribution	Source
Minor (Clavien-Dindo grades 1 & 2)	45.3%	Systematic review of RCTs undertaken as part of guideline development
Major (Clavien-Dindo grades 3 & 4)	54.7%	

33 **1.2.6.7 SA13 – 16: Varying costs in decision tree (deterministic)**

34 Scenarios exploring what effect the costs of major and minor complications had on the
35 results were conducted, in ways that would be more conservative towards COM. One
36 scenario involved excluding the costs associated with minor complications (SA13). This was
37 conducted to be more conservative towards COM because more people in the CCA arm had

1 complications at 30 days and therefore higher costs associated with complications. As a
2 result, excluding some of the complication costs would lead to a larger incremental cost
3 between COM and CCA.

4 Another scenario involved reducing the cost of ICU by shortening the length of stay in ICU
5 from 5 days to 3 days (SA14). This was because the committee indicated that the average
6 length of stay in ICU from the Case Mix Analysis may be influenced by people who have not
7 undergone surgery and are more unwell. It was indicated that there is huge variation in
8 practice but that people typically spend 1 to 3 days in ICU following surgery. Therefore a
9 further analysis involved reducing the length of stay to 1 day (SA15) in order to further test
10 whether the ICU length of stay impacted results.

11 Another analysis was conducted which involved excluding minor complication costs and
12 reducing the length of stay in ICU to 3 days (SA16). This was to further explore the impact of
13 complication costs as the CCA arm had more complications.

14 **1.2.6.8 SA17 – 19: Varying costs in Markov model (deterministic)**

15 Long-term bowel cancer related costs were applied in the model to account for disease
16 related costs associated with those alive. However, these were varied to test whether they
17 impacted conclusions. Firstly, general population age-related NHS costs were added to
18 these costs to account for costs beyond 10 years and also account for any other costs that
19 people might incur (SA17). These costs are demonstrated in the Table 18.

20 Due to costs associated with cancer being very high and not everyone having major surgery
21 will have cancer, the long-term costs of bowel cancer were halved (SA18) and also
22 completely removed (SA19) to test whether they had an impact on the conclusion of results.

23 **1.2.6.9 SA20 – 30: No 30 day mortality impact (deterministic)**

24 Although the clinical review demonstrated a slight mortality difference between COM and
25 CCA, the committee were uncertain that the intervention would affect mortality. Therefore a
26 sensitivity analysis was run assuming no 30 day mortality difference between both the CCA
27 and COM arms (SA20). This would also be more conservative to COM. An analysis was also
28 undertaken where there was assumed to be no 30 day mortality difference between
29 comparators and also using the general population assumptions (SA21). Alternatively an
30 analysis was conducted which was the same as SA21 but also added age-related NHS costs
31 in the Markov model (SA22).

32 Another analysis assuming no difference in mortality at 30 days was conducted using the
33 upper confidence interval value for the complications treatment effect (SA23) and lower
34 confidence interval value for complications relative treatment effect (SA24).

35 As the committee highlighted the importance of the analysis excluding studies conducted
36 prior to MTG3, an analysis was conducted using these treatment effects but assuming no
37 difference in mortality at 30 days (SA25). As above, there was assumed to be no 30 day
38 mortality difference as well as using the lower confidence interval value (SA26) and upper
39 confidence interval value (SA27) from the data excluding studies prior to MTG3.

40 Three more analyses were conducted using the general population assumptions and varying
41 some of the other inputs simultaneously by making them extreme in order to test the
42 robustness of the results. These included:

- 43 • Assuming no difference in 30 day mortality, using the general population, setting the
44 ICU length of stay to 3 days and applying no minor complication costs (SA28)
- 45 • Assuming no difference in 30 day mortality, using the general population, setting the
46 ICU length of stay to 3 days, applying no minor complication costs and using the
47 lower confidence interval value for the complications relative treatment effect(SA29)

- Assuming no difference in 30 day mortality, using the general population, setting the ICU length of stay to 3 days, applying no minor complication costs and using the upper confidence interval value for the complications relative treatment effect (SA30)

1.2.6.10 SA31 – 32: Varying the start age (deterministic)

The start age in the model was agreed by the committee to be 60 years of age. In order to assess whether this impacted results an alternative start age was used, based on the average age of patients obtained from the clinical review, which was 67 years. The first analysis was conducted using all base case inputs and only changing the start age to 67 years (SA31). The second analysis used the general population and a start age of 67 years (SA32).

1.2.6.11 Threshold analyses

Threshold analyses were undertaken to explore the difference in complications treatment effect required for a change in conclusions regarding cost-effectiveness (based on an ICER of £20,000). This was conducted for the base case analysis, and when it was assumed that there was no difference in mortality at 30 days.

1.2.7 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for mortality. Baseline utility was also time dependent and was conditional on the age of the cohort.

Patients entered the decision tree which lasted for 30 days. At the end of 30 days they entered the Markov model in cycle 0 in the health state determined by the decision tree. Patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities. General population rates were combined with the bowel cancer rates and then converted into transition probabilities to be used in the Markov model. Where hazard ratios were used for those with major complications, they were calibrated with the mortality rates and then converted to probabilities.

To calculate QALYs in the decision tree, the time spent in the health state (30 days) was weighted by a utility value. In the Markov model, life years for the cohort were computed for each cycle. To calculate QALYs for each cycle, life years were weighted by a utility value. A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle were calculated in the same way as QALYs. For the decision tree the intervention costs were applied as well as the costs associated with complications. In the Markov model in the base case, bowel cancer costs were applied for 9 years and major complication costs were applied for only 3 cycles. In an alternative scenario the major complication costs were applied up to 5 cycles. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discounting formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: r =discount rate per annum n =time (years)
--	---

In the deterministic and probabilistic analyses, the total number of QALYs and costs accrued for each comparison was recorded. The costs from the decision tree were added to the costs accrued in the Markov model. The total cost and QALYs accrued by the cohort were divided

1 by the number of patients in the population to calculate an average cost per patient, and
2 average cost per QALY.

3 **1.2.8 Model validation**

4 The model was developed in consultation with the committee; model structure, inputs and
5 results were presented to and discussed with the committee for clinical validation and
6 interpretation.

7 The model was systematically checked by the health economist undertaking the analysis;
8 this included inputting null and extreme values and checking that results were plausible given
9 inputs. The model was peer reviewed by a second experienced health economist from the
10 NGC; this included systematic checking of the model calculations.

11 **1.2.9 Estimation of cost effectiveness**

12 The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER).
13 This is calculated by dividing the difference in costs associated with 2 alternatives by the
14 difference in QALYs. The decision rule then applied is that if the ICER falls below a given
15 cost per QALY threshold the result is considered to be cost effective. If both costs are lower
16 and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Cost effective if:
• ICER < Threshold

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

17 Results are also presented graphically where total costs and total QALYs for each strategy
18 are shown.

19 **1.2.10 Interpreting Results**

20 NICE's report 'Social value judgements: principles for the development of NICE guidance'⁹
21 sets out the principles that committees should consider when judging whether an intervention
22 offers good value for money. In general, an intervention was considered to be cost effective if
23 either of the following criteria applied (given that the estimate was considered plausible):

- 24 • The intervention dominated other relevant strategies (that is, it was both less costly in
25 terms of resource use and more clinically effective compared with all the other relevant
26 alternative strategies), or
- 27 • The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained
28 compared with the next best strategy.

29

1 1.3 Results

2 1.3.1 Base case

3 The base case results are presented in Table 21 and graphically in Figure 5.

4 COM was associated with higher QALYs and additional costs in the base case analysis with
 5 an incremental cost-effectiveness ratio of £286 per QALY gained. This means that COM is
 6 considered cost-effective as the ICER is below the NICE threshold of £20,000 per QALY
 7 gained. There was little uncertainty in this conclusion in the probabilistic analysis as 97% of
 8 simulations were cost-effective at the £20,000 threshold. Results from the 30-day decision
 9 tree are also presented in Table 22. These showed that COM was dominant at 30 days,
 10 resulting in additional QALYs and lower costs.

11 **Table 21: Probabilistic base case results for lifetime analysis (average per person,**
 12 **discounted)**

	Total cost	Total QALYs	ICER	Probability COM CE at £20k
CCA	£27,748	7.07		
COM	£27,768	7.14		
Incremental (COM vs CCA)	£20	0.07	£285	97%

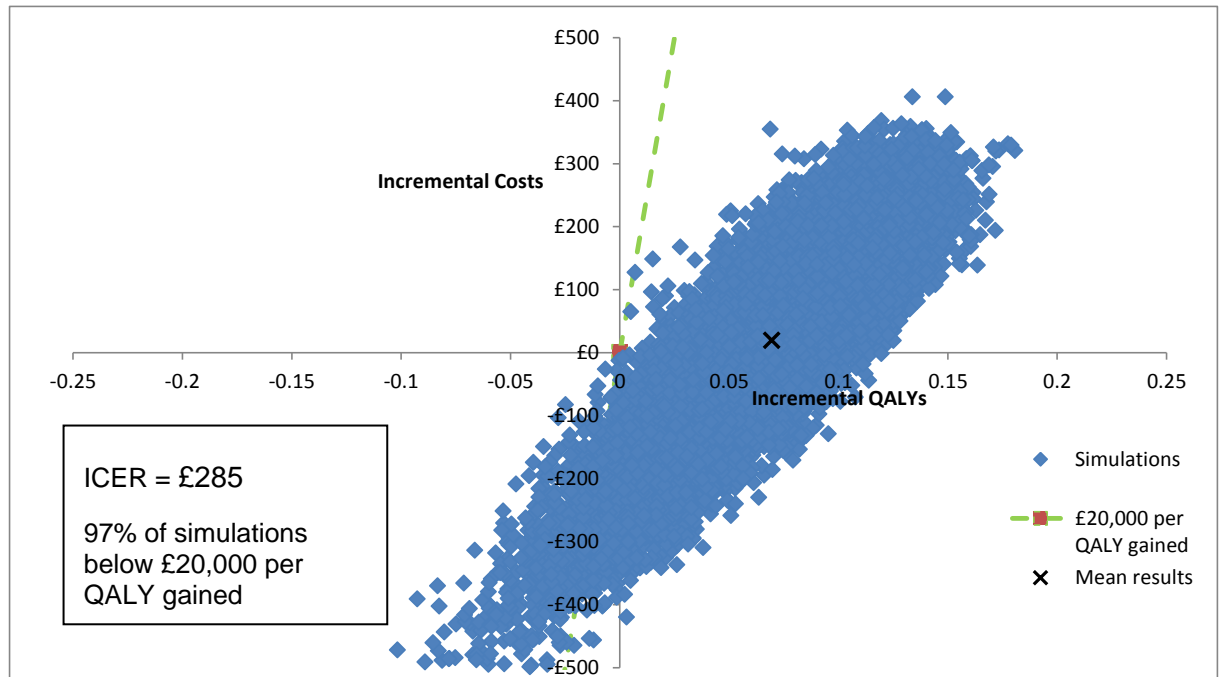
13 Abbreviations: CE = cost-effective; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life
 14 years

15 **Table 22: Probabilistic base case results at 30 days (average per person)**

	Total cost	Total QALYs	ICER
CCA	£1,177	0.050	
COM	£1,033	0.051	
Incremental	-£144	0.001	COM dominant

16 Abbreviations: ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

17
 18
 19

1
2**Figure 5: Results: incremental cost and QALY pairs scatter plot for base case analysis (per person, probabilistic analysis)**3
4

5 1.3.2 Sensitivity analyses

6 The results of the sensitivity analyses undertaken are presented in Table 23. All of the results
7 from the sensitivity analyses did not impact the base case conclusions, with COM remaining
8 cost effective (either below £20,000 per QALY or dominant).

9 Sensitivity analyses conducted to make the model as conservative as possible toward COM
10 by varying different parameters at once showed that COM remained cost-effective, with the
11 highest ICER being £16,881. This was for the sensitivity analysis where the treatment effects
12 excluded pre-MTG3 studies, there was no mortality difference and the upper confidence
13 interval for complications was used. The reason the ICER increased was due to the upper
14 confidence interval of the complications relative risk being only slightly lower than 1, which
15 resulted in a smaller difference in QALYs compared to the base case analysis. However this
16 showed that the costs of even a small number of events avoided offsets the costs of the
17 intervention and increased QALYs.

18 The sensitivity analyses demonstrate how specific inputs affect the results. Firstly, the
19 mortality rates used in the Markov model affect the QALYs per person. When using the
20 general population mortality rather than adjusting it with cancer mortality, the difference in
21 QALYs is smaller. This is because people are dying more slowly in the model when smaller
22 mortality rates are applied. Although there is not a big difference in the number of people
23 alive, those in the CCA arm have more major complications, which leads to a higher mortality
24 risk, and therefore the mortality probability is much higher, resulting in fewer QALYs in the
25 CCA arm.

26 The model results were also impacted by the treatment effects. Sensitivity analysis 2 resulted
27 in a smaller QALY difference compared to the base case. Although this analysis showed
28 complications were lower in the COM arm compared to the base case analysis, this was due
29 to there being slightly worse mortality in the COM arm than the CCA arm. So the benefit of
30 reduced complications from COM is being balanced against a higher risk of mortality, leading
31 to a smaller difference in QALYs.

1 Using bowel cancer costs as well as age-related NHS costs (SA17) in the Markov model
 2 resulted in a greater difference in costs compared to the base case analysis because the
 3 COM arm had more people alive and therefore incurring more costs. However, this still
 4 resulted in an ICER of £6,055 per QALY gained.

5 The costs of complications also had some impact on results, as using lower complication
 6 costs also resulted in increasing the incremental cost. Making complications cheaper
 7 adversely affects the intervention because the same reduction in events leads to a smaller
 8 saving. However, this still showed that the increase in QALYs and downstream costs offset
 9 the cost of the intervention.

10 **Table 23: Results from sensitivity analyses**

Analysis	Mean difference (COM-CCA)		ICER (COM vs CCA)	Prob COM % CE at 20K
	Cost	QALY		
Base case	£20	0.069	£285	97%
Probabilistic sensitivity analyses				
<i>Using alternative probabilities in the decision tree</i>				
SA1: Excluded non UK studies	-£17	0.061	COM Dominant	88%
SA2: Excluded pre-MTG3 studies	-£32	0.014	COM Dominant	73%
SA3: Excluded emergency + cardiac surgery studies	-£80	0.042	COM Dominant	91%
<i>Testing different baseline population</i>				
SA4: General population	-£199	0.048	COM Dominant	84%
SA5: General population, and age-related NHS costs	£22	0.047	£456	85%
<i>Extending duration of impact for major complications</i>				
SA6: HR for major complications applied for 5 years	£18	0.074	£246	97%
<i>Discount rate</i>				
SA7: Discount rate set to 1.5%	£28	0.086	£324	97%
Deterministic sensitivity analyses				
<i>Cardiac output monitoring costs</i>				
SA8: Low usage costs for monitors	£51	0.070	£732	n/a
SA9: High usage costs for monitors	£17	0.070	£237	n/a
SA10: Manufacturer usage costs for monitors	£17	0.070	£249	n/a
SA11: Reduce list price of CardioQ-ODM by 50%	£21	0.070	£295	n/a
<i>Proportion experiencing minor and major complications</i>				
SA12: Proportion experiencing minor and major complications	£82	0.249	£332	n/a
<i>- Varying costs in decision tree</i>				
SA13: No minor complication costs	£218	0.070	£3,112	n/a
SA14: ICU stay 3 days	£52	0.070	£748	n/a
SA15: ICU stay 1 day	£82	0.070	£1,176	n/a
SA16: ICU stay 3 days and no minor complication cost	£248	0.070	£3,540	n/a

Analysis	Mean difference (COM-CCA)		ICER (COM vs CCA)	Prob COM % CE at 20K
	Cost	QALY		
<i>Varying costs in Markov model</i>				
SA17: Including general population age related NHS costs	£424	0.070	£6,055	n/a
SA18: Bowel cancer costs halved	-£75	0.070	COM Dominant	n/a
SA19: No bowel cancer costs applied	-£173	0.070	COM Dominant	n/a
<i>No 30 day mortality impact</i>				
SA20: No 30 day mortality difference	-£56	0.049	COM Dominant	n/a
SA21: No 30 day mortality difference and general population	-£199	0.011	COM Dominant	n/a
SA22: No 30 day mortality difference, general population and age-related NHS costs	-£168	0.011	COM Dominant	n/a
SA23: No 30 day mortality difference and upper CI for complications RR	£23	0.028	£839	n/a
SA24: No 30 day mortality difference and lower CI for complications	-£120	0.066	COM Dominant	n/a
SA25: No 30 day mortality difference and excluded pre-MTG studies	£23	0.029	£790	n/a
SA26: No 30 day mortality difference, excluded pre-MTG studies and lower CI for complications RR	-£34	0.044	COM Dominant	n/a
SA27: No 30 day mortality difference, excluded pre-MTG studies and upper CI for complications RR	£104	0.006	£16,881	n/a
SA28: No 30 day mortality difference, general population and lower complication costs	£27	0.011	£2,317	n/a
SA29: No 30 day mortality difference, general population, lower costs and lower CI for complications RR	-£8	0.015	COM Dominant	n/a
SA30: No 30 day mortality difference, general population, lower costs and upper CI for complications RR	£70	0.006	£10,793	n/a
<i>Varying start age</i>				
SA31: Start age set to 67	£21	0.058	£360	n/a
SA32: General population and start age set to 67	-£198	0.043	COM Dominant	n/a

1 Abbreviations: CI = confidence interval; ICU = intensive care unit; RR = relative risk

2 The results from the threshold analyses are shown in Table 24. These indicated that the
3 treatment effect for complications would only have to go slightly above 1 to increase the

1 ICER to £20,000. This is because there is still a slight mortality benefit in the COM arm.
 2 When assuming there is no 30 day mortality, the complications relative risk would have to be
 3 just below 1 to increase the ICER to £20,000. This shows that a small complications benefit
 4 would still result in COM being cost-effective.

5 **Table 24: Results from threshold analyses**

Analysis	Input varied	Result
Base case analysis	Complications relative risk	1.04
No 30-day mortality	Complications relative risk	0.97

6

7 **1.4 Discussion**

8 **1.4.1 Summary of results**

9 The analysis found that COM was associated with higher costs and higher QALYs than CCA
 10 with a lifetime horizon. Using NICE reference case methods, the incremental cost-
 11 effectiveness ratio was £286 per QALY gained. This would be considered cost-effective
 12 using NICE decision-making criteria and there was little uncertainty in this conclusion in the
 13 probabilistic analysis. The 30-day analysis found that COM had lower costs and higher
 14 QALYs meaning that COM was dominant.

15 Various sensitivity analyses were conducted, and the results remained robust. When
 16 changing the base case population to the general population (and removing long-term cancer
 17 costs and only including age-related NHS costs) the ICER increased but still remained below
 18 the threshold at £771. When it was assumed that there was no 30-day mortality difference,
 19 COM was dominant as it resulted in less costs and more QALYs. Sensitivity analyses were
 20 also conducted to test the robustness of the results by varying different inputs
 21 simultaneously, to make the model inputs as conservative as possible towards COM. This
 22 did not impact results as the incremental cost-effectiveness ratios remained below the NICE
 23 threshold of £20,000 per QALY gained. However, the ICER did increase to £16,880 for the
 24 analysis where there was no 30-day mortality difference and the treatment effect for
 25 complications was based on the upper confidence interval of the excluded pre-MTG3
 26 studies. This was due to the relative risk being higher and closer to 1, therefore resulting in a
 27 smaller number of people avoiding complications from COM compared to the base case
 28 analysis.

29 Although varying the treatment effects did not impact conclusions, the threshold analysis
 30 showed that when assuming no mortality difference at 30 days the ICER would increase to
 31 £20,000 if the complications relative risk is 1.04.

32 The model was most sensitive to the mortality rates used in the Markov model and the
 33 treatment effects, as varying these usually resulted in the QALY difference being lower and
 34 therefore the ICER increasing. Also, varying the costs increased the difference in costs and
 35 also increased the ICER in comparison to the base case analysis. Although the model was
 36 sensitive to some of the inputs, COM still remained cost-effective in all of the analyses.

37 **1.4.2 Limitations and interpretation**

38 The population of interest was very broad as it was all adults undergoing major or complex
 39 surgery. The committee felt that as the review question on COM was specifically around
 40 people undergoing high risk surgery or high risk people, then these are people who would be
 41 at higher risk of mortality than the general population both pre and post-surgery. As a result,
 42 a proxy population was used and this was adults with bowel cancer. This was because a
 43 large proportion of major surgery in England is cancer related, and the majority of the studies

1 included in the clinical review were bowel or gastrointestinal related. Mortality data used in
2 the analysis was based on bowel cancer data. Although it was felt that cancer surgery would
3 make up a large proportion of major surgery in England, this was still a very specific
4 population to use and therefore could be overestimating the mortality in the model. Also, not
5 everyone included in this mortality data would have undergone surgery. Approximately 70%
6 of adults with cancer will have surgery, but the remaining adults are usually too unwell to
7 undergo surgery and may only receive chemotherapy. As a result, the mortality rates may be
8 overestimated for a surgical population. The quality of life for the base case analysis was
9 specific to bowel cancer and was applied for 10 years in the model. This could have been too
10 low for a population of adults undergoing major surgery. Also, the costs specific to living with
11 bowel cancer were applied in the model for 9 years to capture disease related costs as per
12 the NICE reference case. Costs associated with cancer treatment are typically very high
13 compared to other conditions and this could be overestimating the costs in the model.
14 However, sensitivity analyses using general population mortality and quality of life was
15 conducted as well as reducing the long-term costs. These analyses did not impact
16 conclusions.

17 The mortality and complications treatment effect with COM compared to CCA was based on
18 the systematic review and meta-analysis undertaken as part of guideline development. There
19 were some uncertainties in the clinical evidence used to inform the model. Firstly, some of
20 the studies in the CCA arm included central venous pressure. The committee highlighted this
21 was no longer considered part of current practice and therefore not relevant. However, the
22 sensitivity analysis which used treatment effects after the publication of MTG3 was more
23 relevant to current practice and addressed this concern. Another limitation was that there had
24 been a limited number of studies published since MTG3 and current practice has evolved
25 since a lot of the RCTs were conducted. For example, CCA has improved and is considered
26 more effective compared to 10 years ago and central venous pressure measurement is no
27 longer conducted. Also, the introduction of enhanced recovery programmes has improved
28 surgery outcomes and surgical techniques have developed and as a result, complications
29 after surgery have reduced. There has also been a trend towards administering less fluids
30 during surgery. Although there was evidence that COM reduced complications from the
31 clinical review, the committee did not have a lot of confidence in this data.

32 There was also uncertainty around whether mortality would be impacted by whether you use
33 COM or CCA. The committee noted that some years ago there may have been mortality
34 benefits from using COM instead of CCA. However in current practice it would be unusual to
35 see a mortality difference based on whether you used COM or not as mortality post-surgery
36 is now very low. Sensitivity analyses were conducted around some of these uncertainties
37 and did not impact conclusions.

38 The cost and utility data used in the model for minor complications was specific to a chest
39 infection. In reality adults undergoing surgery are at risk of many different minor
40 complications, ranging from wound infections to urinary tract infections. All types of minor
41 complications have different costs associated with them as they require different levels of
42 treatment. Also, minor complications can vary largely based on the type of surgery, for
43 example, anastomotic leaks commonly occur during colorectal surgery. Although the cost of
44 a chest infection was used, sensitivity analysis around this was conducted by removing the
45 cost and this did not impact conclusions.

46 The costs and quality of life of major complications was based on being admitted to ICU and
47 also incurred long-term costs associated with ICU survivors. Although this is more applicable
48 to a range of adults, there is still variability across the different types of major complications
49 and how long they impact someone's life. Some scenarios may involve higher costs such as
50 requiring further surgery or even having a life changing event such as a stroke. Also, some
51 people that experience major complications may not incur higher costs for such a long
52 duration of time as it was applied in the model. Other models in this area have used ICU

1 costs and quality of life to model major complications therefore this was considered
2 appropriate.

3 It was assumed that those with major complications had a higher mortality and lower quality
4 of life for 3 years post-surgery and also applied higher costs during this period. This was
5 based on the Moonesinghe 2014 study which showed that adults have a higher mortality risk
6 for 3 years if they experience complications up to day 15 post-surgery.⁷ There were some
7 limitations of this study as it was conducted on a small number of people and practice may
8 have improved since it was conducted. The committee acknowledged that there is variation
9 among adults regarding how long major complications would impact mortality and quality of
10 life and also acknowledged that this area has limited research. However, as the
11 Moonesinghe 2014 study was conducted in the UK and was based on different types of
12 major surgery it was the best available data source. Sensitivity analyses were conducted to
13 address these uncertainties and did not impact conclusions.

14 **1.4.3 Generalisability to other populations or settings**

15 Although the analysis was conducted for all adults undergoing major or high-risk surgery, the
16 baseline population used was bowel cancer. Limitations of using this population were tested
17 in sensitivity analyses by using data from the general population. The treatment effects used
18 in this model were obtained from the meta-analysis of RCTs. Although the RCTs were on
19 various different surgeries, the majority of them were abdominal and bowel procedures. As a
20 result, it is hard to determine how applicable this analysis is for all types of major or high-risk
21 surgery.

22 **1.4.4 Comparisons with published studies**

23 The economic literature review results are detailed in full in Evidence report J. Six published
24 economic evaluations were included that compared cardiac output monitoring to
25 conventional clinical assessment.

26 One of the published economic evaluations was the manufacturer submission for the NICE
27 medical technologies guidance 3 (MTG3). This was a cost-comparison that compared six
28 interventions in adults undergoing complex, major or high-risk surgery. The comparisons
29 included oesophageal Doppler monitoring (ODM) in addition to conventional clinical
30 assessment (CCA) with: CCA alone, central venous pressure (CVP) + CCA, pulse pressure
31 waveform analysis (PPWA) + CCA, CVP + ODM + CCA, and CVP + PPWA + CCA. The
32 results of this analysis showed that ODM with CCA was cost-saving when compared to all
33 other interventions. This analysis adopted a short time horizon which was the length of
34 hospital stay. A meta-analysis of previously conducted RCTs and Hospital Episode Statistics
35 were used to make assumptions on the estimates in reduction of hospital length of stay and
36 applied a reduction of 1.92 days. The committee highlighted that there were issues with this
37 assumption in reduction in length of stay as the RCTs used to inform this were old and based
38 on various countries, which is not reflective of current UK practice. Deterministic analyses
39 showed that there was uncertainty in the results as ODM did not remain cost-saving in some
40 scenarios.

41 Mowatt 2009 conducted a cost-utility analysis for high risk surgical adults from a UK NHS
42 perspective. This analysis compared ODM + CCA to CCA alone as well as another
43 analysis comparing ODM + CVP + CCA compared to CVP + CCA. A meta-analysis was
44 conducted and the outcomes that fed in to the model were mortality and length of stay. The
45 committee highlighted that some of the RCTs included in this analysis used starch boluses,
46 which were excluded from our analysis. Also, the model assumed that adults survived on
47 average 5 years post-surgery, which was not considered a reflection of what happens in
48 current practice. This study did not give a breakdown of the costs or QALYs for each
49 intervention but concluded that ODM was cost-effective at a threshold of £30,000 per QALY.
50 No results were presented for a threshold of £20,000 per QALY.

1 Sadique 2015 conducted a cost-utility analysis from a UK NHS perspective comparing a
2 specific type of COM (pulse contour analysis using the LiDCO rapid machine) to
3 conventional clinical assessment. This was a within-trial analysis with modelled post-trial
4 extrapolation. The population was adults 50 years and over undergoing major
5 gastrointestinal surgery. The analysis found that COM was dominant with an 87% probability
6 of being cost-effective at a £20,000 threshold. Different subgroup analyses were undertaken
7 which generally did not affect the results.

8 Legrand 2015 conducted a cost-effectiveness analysis from a French healthcare perspective.
9 The analysis was conducted on adults undergoing intermediate and high-risk abdominal
10 surgery. The outcomes they considered were cost per major complication avoided and death
11 avoided and had a follow-up time until hospital discharge. They compared different types of
12 COM (ODM and PCA) to each other and to CCA. The time horizon was until hospital
13 discharge which was considered too short to fully capture costs and outcomes and some of
14 the RCTs included in the meta-analysis used starch boluses. The results showed that both
15 ODM and PCA were dominant when they were compared to CCA alone, as they resulted in
16 less costs and additional health benefits (by reducing deaths and complications). Although
17 the analysis compared ODM and PCA this is not relevant to our question as we combined all
18 types of COM for this analysis.

19 Maeso 2011 conducted a cost-effectiveness analysis for adults undergoing colorectal
20 resection from a Spanish healthcare perspective. A cost-utility analysis was also conducted
21 as a secondary analysis. ODM + CCA was compared to CCA alone and another analysis
22 compared ODM + CVP + CCA to CVP + CCA. A meta-analysis informed the treatment
23 effects and identified 3 RCTs, of which 1 included starch boluses. The study concluded that
24 ODM increased health benefits (in terms of survival rate and reduction in complications) and
25 reduced costs, which made it dominant.

26 Bartha 2011 conducted a cost utility analysis from a Swedish healthcare perspective, and
27 looked at COM compared to CCA in adults over 80 years old undergoing surgery for a hip
28 fracture. A 5-year time horizon was used to model longer term impacts of complications such
29 as cardiac complications and stroke. Treatment effects that informed the analysis were
30 obtained from RCTs, and some were not relevant to the population being modelled. Cardiac
31 output monitoring resulted in less costs and additional QALYs over the 5-year time horizon.

32 This original cost-utility analysis found that COM was cost-effective compared to CCA with
33 an incremental cost-effectiveness ratio of £286 per QALY gained. This analysis differed from
34 the previously published analyses as a lifetime horizon was used, whereas shorter time
35 horizons were previously adopted, such as until hospital discharge or for 5 years. Also, most
36 of the studies used a specific type of cardiac output monitoring whereas this analysis
37 combined all types. The previously published studies are generally more favourable towards
38 COM, as the majority resulted in COM being dominant.

39 **1.4.5 Conclusions**

40 This analysis found that COM was cost-effective compared to CCA with an incremental cost-
41 effectiveness ratio of £286 per QALY gained. Conclusions were not sensitive to varying
42 inputs as all sensitivity analyses resulted in COM being cost-effective.

43 **1.4.6 Implications for future research**

44 Although there has been a considerable amount of research in to this area, there still
45 remains a need for further research. Conducting more RCTs in this area, specifically in a UK
46 context, may be useful due to current practice changing and surgical techniques improving
47 which has produced uncertainty over the relevance of these machines during surgery.
48 Further research looking in to what subgroups might benefit from having COM would also be
49 beneficial.

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