

# Laparoscopic fundoplication compared with medical management for gastro-oesophageal reflux disease: cost effectiveness study

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## ABSTRACT

**Objective** To describe the long term costs, health benefits, and cost effectiveness of laparoscopic surgery compared with those of continued medical management for patients with gastro-oesophageal reflux disease (GORD).

**Design** We estimated resource use and costs for the first year on the basis of data from the REFLUX trial. A Markov model was used to extrapolate cost and health benefit over a lifetime using data collected in the REFLUX trial and other sources.

**Participants** The model compared laparoscopic surgery and continued proton pump inhibitors in male patients aged 45 and stable on GORD medication.

**Intervention** Laparoscopic surgery versus continued medical management.

**Main outcome measures** We estimated quality adjusted life years and GORD related costs to the health service over a lifetime. Sensitivity analyses considered other plausible scenarios, in particular size and duration of treatment effect and the GORD symptoms of patients in whom surgery is unsuccessful.

**Main results** The base case model indicated that surgery is likely to be considered cost effective on average with an incremental cost effectiveness ratio of £2648 (€3110; US \$4385) per quality adjusted life year and that the probability that surgery is cost effective is 0.94 at a threshold incremental cost effectiveness ratio of £20 000. The results were sensitive to some assumptions within the extrapolation modelling.

**Conclusion** Surgery seems to be more cost effective on average than medical management in many of the scenarios examined in this study. Surgery might not be cost effective if the treatment effect does not persist over the long term, if patients who return to medical management have poor health related quality of life, or if proton pump inhibitors were cheaper. Further follow-up of patients from the REFLUX trial may be valuable.

**Trial registration** ISRCTN15517081.

## INTRODUCTION

Around 25% of adults in Western society experience intermittent heartburn, one of the cardinal symptoms

of gastro-oesophageal reflux disease (GORD).<sup>1,2</sup> Once diagnosed with erosive (persistent) GORD, patients often require lifelong pharmacotherapy, usually proton pump inhibitors.<sup>3</sup> Although considered effective, there are concerns about the long term side effects of proton pump inhibitors, and expenditure on these drugs remains considerable, despite recent reductions in prices. In general practice in England expenditure was £233m (€274m; US\$386m) in 2007.<sup>4</sup> Laparoscopic fundoplication is now an alternative way to treat GORD. In addition to potential clinical benefits laparoscopic surgery should lead to the avoidance of continual medication and its associated costs. Several studies have examined economic characteristics of laparoscopic surgery.<sup>5-8</sup> Of those that compared surgery with GORD medication, Bojke<sup>8</sup> found that surgery was cost effective, and Cookson<sup>6</sup> concluded that laparoscopic surgery had similar costs to medical management after eight years and was cost saving thereafter. Arguedas evaluated the strategies in a United States setting and concluded that medical therapy dominated surgery using a 10 year time horizon, assuming a higher rate of symptom recurrence and re-operation after surgery than in the surgery groups in the UK based studies.<sup>5</sup> None of these studies, however, used estimates of health related quality of life derived from a randomised clinical trial comparing laparoscopic fundoplication with medical management, which is of central importance to the evaluation of these treatments. This paper updates the economic study by Bojke<sup>8</sup> to incorporate one year health related quality of life data from the REFLUX trial.<sup>9</sup>

The multicentre REFLUX trial compared a strategy of laparoscopic surgery with one of continued medical management for patients with reasonable symptom control on GORD medications.<sup>9</sup> The clinical and patient assessed outcomes of the trial up to one year after surgery have recently been reported. Although these findings showed clear benefits of surgery at this time in terms of health related quality of life, decision makers are also interested in the costs and cost effectiveness of the two forms of management. GORD is usually a chronic condition and a key issue is the extent

to which benefits are sustained. Surgery is costly in the short term, but these costs may be at least partly offset by reductions in lifetime use of GORD medication. Extrapolation of health benefits and costs are thus needed to provide a meaningful estimate of cost effectiveness.

## METHODS

### Overview

We used a model comparing laparoscopic surgery and continued use of proton pump inhibitors in male patients aged 45 (the median age and predominant sex in the REFLUX trial<sup>9</sup>), and stable on anti-GORD medication. Over a lifetime horizon, health benefits were quantified in terms of quality adjusted life years and costs were assessed from the perspective of the United Kingdom's NHS in 2008/2009 prices. Future costs and health benefits are discounted (adjusted to current values) at 3.5% per year, in accord with UK guidelines for economic evaluation.<sup>10</sup>

### Model structure

Figure 1 shows the model structure. It is a discrete time Markov cohort model with a cycle length of one year. Patients follow a strategy of either early laparoscopic surgery or continuation of medical management (without the option of surgery after failure of medical management).

In the model, surgery may “fail” in one of two ways. Patients may need revision of surgery, either to improve symptom control or because of surgical complications, or they may return to use of long term medical management because of continued symptoms.<sup>11</sup>

This model assumes that patients in the medical management arm are stable on GORD medication. This assumption follows the inclusion criteria for the REFLUX trial. As a result “treatment failure” is not defined as a health state in the model. Annual costs of medical management are estimated using mean consumption of proton pump inhibitors during the REFLUX trial, incorporating any changes to dose or medication, and it is assumed that the estimate of health related quality of life includes, on average, remission or any side effects of medication. The base case assumes that, if surgical patients do not need to return to medical management or need revision of

surgery, the relative difference in health related quality of life of surgery over medical management will be maintained over their lifetime. We used sensitivity analyses to consider other scenarios where the treatment effect (the difference in health related quality of life between medical management and those who do not fail surgery) only lasts for one, two, or five years. In these alternative scenarios, health related quality of life is the same in the surgery group as in the medical management group after the “treatment effect” ends, even in patients who do not return to the use of proton pump inhibitors.

### Evidence used in the model

Costs for the first year in the model were estimated from the REFLUX trial.<sup>9</sup> The trial collected data on use of health service resources up to one year, including inpatient days in hospital wards and high dependency units, diagnostic tests, duration in theatre, outpatient and general practitioner visits, re-admissions, and use of GORD medication. These resources were costed using routine NHS unit costs and prices (table 1).

We calculated rates of return to medical management and revision of surgery using data from the REFLUX trial and studies identified through a literature search.<sup>8,12</sup> The average rate of return to medical management overall was 4.9 per 100 person years and the average rate of revision of surgery was 0.8 per 100 person years, although rates seemed to vary considerably between studies. As we did not find evidence that this variation was related to length of follow-up, we assumed that the annual rate of surgical failure was constant over time. Details of the literature searches and meta-analyses are available in the Health Technology Assessment monograph.<sup>12</sup> Sensitivity analyses were undertaken assuming higher and lower rates of failure.

After the first year, all patients require an annual visit to their general practitioner. It was assumed that patients who fail surgery need an additional visit to their general practitioner and to a hospital specialist. No hospital admissions or outpatient visits for GORD related reasons were included after one year for patients with successful surgery.<sup>13</sup>

Patients can die of other causes,<sup>14</sup> and the model assumed the same age and sex specific risk of mortality as the UK general population. Although no deaths from surgery or revision occurred in the REFLUX trial, a small additional risk of operative mortality was assumed, estimated by a meta-analysis (four deaths in 4000 procedures).<sup>8</sup>

### Estimating quality adjusted life years

The REFLUX trial measured health status using the generic EuroQol EQ-5D instrument.<sup>15</sup> Each of the possible 243 health states was mapped to a preference based value (or “utility”) where zero represents a state equivalent to death and one represents full health.<sup>16</sup> Table 1 shows the mean differences in utility between treatments at one year estimated by the REFLUX

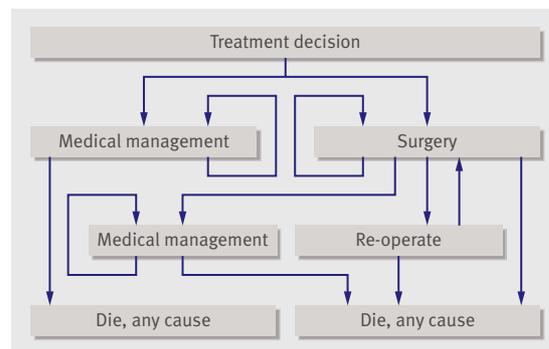


Fig 1 | Model structure

**Table 1** Health related quality of life (HRQOL) estimates and rates of events used in model

Parameter	Mean (SE)*	Distribution for PSA	Source
<b>HRQOL</b>			
HRQOL while on medical management, or return to medical management	0.711 (0.018)	Gamma†	Baseline EQ5D of patients randomised in REFLUX trial <sup>12</sup>
Additional HRQOL after successful laparoscopic surgery compared with medical management			
Adjusted treatment received‡	0.068 (0.038)	Normal	REFLUX <sup>12</sup>
Intention to treat§	0.047 (0.026)	Normal	REFLUX <sup>12</sup>
Per protocol¶	0.076 (0.028)	Normal	REFLUX <sup>12</sup>
<b>HRQOL for general male population</b>			
Aged 45-55	0.84		Kind 1999 <sup>19</sup>
Aged 55-65	0.78		Kind 1999 <sup>19</sup>
Aged 65-75	0.78		Kind 1999 <sup>19</sup>
Aged 75+	0.75		Kind 1999 <sup>19</sup>
<b>Rates of events</b>			
Return to medical management after surgery	460 events, 9389 patient years	Gamma	Meta-analysis <sup>12</sup>
Revision of surgery	53 events, 6720 patient years	Gamma	Meta-analysis <sup>12</sup>
Operative mortality	4 deaths, 3397 patients	Beta	Meta-analysis <sup>8</sup>

SE=standard error, PSA=probabilistic sensitivity analysis.  
 \*Unless otherwise indicated.  
 ‡Adjusted treatment received is estimated by linear model using treatment received indicator variable as a covariable. The residual of regression of treatment received on the randomisation indicator variable is included as another covariable to adjust for confounders.<sup>17</sup> This is the base case used in the model.  
 §Intention to treat is the mean difference between randomised groups adjusting for body mass index, age, sex, and baseline score.  
 ¶Per protocol is the difference between the randomised groups using only participants who received their allocated GORD management adjusting for BMI, age, sex, and baseline score.  
 †The decrement in HRQOL (utility) on medical management compared with the general age-matched population is parameterised in the stochastic model by a gamma distribution with a mean of 1-0.711 and a standard error of 0.018.

trial.<sup>12</sup> No other randomised trials have compared surgery with medication using a preference based measure of health related quality of life.

We assumed that the “adjusted treatment received” analysis of the REFLUX trial<sup>12</sup> was the most appropriate measure of the effect of surgery on health related quality of life to use in the base case model. This approach identifies the efficacy of surgery in patients who are most likely to comply with their clinicians’ recommendations for treatment.<sup>17,18</sup> We also used intention to treat and per protocol estimates in sensitivity analyses.

In the model, we use the term “treatment effect” to refer to the difference in health related quality of life between medical management and those who do not fail surgery. This value differs from the estimates calculated in the trial, which measured the mean difference in health related quality of life between medical management and surgery, whether failed or not. As those who fail surgery would be expected to have lower health related quality of life than those who do not, this approach estimates a lower bound for the benefits of surgery by the model.

We estimated the health related quality of life of the 15 patients in the surgery group of the REFLUX trial who required proton pump inhibitors at one year to be 0.68 (standard error 0.048) using the EQ5D, a decrease of 0.04 from baseline. In view of the small sample of patients and short follow-up, it was assumed in the base case analysis that patients who needed proton pump inhibitors after surgery returned to their baseline

(pre-surgery) health related quality of life, consistent with clinical opinion (Robert Heading, personal communication, 2008) that proton pump inhibitors are just as effective after surgery as before, provided they are being used to treat reflux symptoms. This assumption was varied in sensitivity analysis.

To account for the decline in health related quality of life with age, the mean utility for medical management observed at the end of the REFLUX trial was compared with the average utility for the general population aged 45-55<sup>19</sup> to calculate a proportionate decrement in utility for that health state. It was assumed that this proportionate decrement was constant as the cohort aged (table 1).

### Analysis

We did calculations using Excel. The model estimated mean costs and quality adjusted life years in each treatment cohort. Where one treatment did not dominate the other, the incremental cost effectiveness ratio was calculated as the ratio of the difference in expected costs to the difference in expected quality adjusted life years. A probabilistic sensitivity analysis was done by assigning probability distributions to the model inputs, rather than treating them as point estimates.<sup>20</sup> This analysis calculated the overall uncertainty in the treatment decision as the proportion of simulations where laparoscopic surgery is cost effective, given threshold values for the incremental cost-effectiveness ratio of £20 000 and £30 000 per quality

**Table 2** | Mean use of healthcare resources and costs for GORD related causes in REFLUX trial<sup>12</sup> for patients receiving their randomised treatment per protocol and followed up for one year

	Unit cost (£)	Source*	Unit of measure	Medical (n=155)				Surgery (n=104)			
				Any use (%)	Mean use	Mean cost (£)	SD (£)	Any use (%)	Mean use	Mean cost (£)	SD (£)
Endoscopy	172	a	Tests	—	—	—	—	88	0.88	151	57
pH tests	64	a	Tests	—	—	—	—	70	0.70	45	29
Manometry	61	a	Tests	—	—	—	—	66	0.66	40	29
Operation time	4	a	Minutes	—	—	—	—	100	114.5	420	137
Consumables	825	a	—	—	—	—	—	100	1.00	825	0
Ward	264	b	Days	—	—	—	—	100	2.34	619	354
High dependency	657	b	Days	—	—	—	—	1	0.05	32	322
Total surgery	—	—	—	—	—	—	—	—	—	2132	475
Visit to GP	36	c	Visits	44	1.16	42	71	44	1.14	42	60
Visit from GP	58	c	Visits	1	0.01	1	6	2	0.02	1	8
Outpatient	88	b	Visits	14	0.30	27	76	43	0.54	47	64
Day case	896	b	Admit	10	0.14	127	426	42	0.47	422	572
Inpatient	1259	b	Admit	3	0.03	32	200	4	0.04	48	243
Subsequent costs	—	—	—	—	—	229	632	—	—	560	728
Medication costs	—	d	—	—	—	141	144	—	—	16	52
Total costs	—	—	—	—	—	370	638	—	—	2709	941

\*Sources of unit costs used in the analysis: (a) Mean unit costs of a survey of five participating centres, 2003, updated for inflation,<sup>8</sup> (b) mean hospital costs for England and Wales, 2006/07,<sup>25</sup> (c) Curtis et al, 2008,<sup>26</sup> (d) *British National Formulary*, 2009<sup>24</sup> and REFLUX.<sup>12</sup>

adjusted life year as used by the National Institute of Health and Clinical Excellence.<sup>10</sup>

## RESULTS

Table 2 shows the use of health service resources and cost for GORD related causes during the first year of follow-up in the REFLUX trial,<sup>12</sup> for patients receiving their randomised treatment per protocol. Total costs were £370 per patient in the medical management arm and £2709 in the surgical arm, a difference of £2339 (95% confidence interval 2147 to 2558; calculated with bias corrected accelerated bootstrap).<sup>21</sup>

Under base case assumptions, the model predicts that, for example, by five years 17.7% of surgery patients will have returned to medical management, 2.9% will have undergone a re-operation, and 0.1% will have died during surgery. The average discounted lifetime cost per patient of surgery was £5026, made up of the initial cost of the cost of surgery (£2132), repair of surgery (£746), return to medical management (£1360) and other health care (£788). The discounted lifetime cost of the medical management group was £3411. Therefore, surgery had an additional mean cost of £1616. The mean difference in quality adjusted life years was 0.61, equating to an incremental cost effectiveness ratio of £2648 per quality adjusted life year (table 3, scenario 1). In the base case, the probability that surgery is cost effective at a cost effectiveness threshold of £20 000 is 0.94.

We explored several scenarios regarding the size and duration of treatment effect, GORD symptoms of those who fail surgery and costs (table 3). Use of intention-to-treat and per protocol estimates of effect did not change the conclusion that surgery is cost effective assuming a threshold of £20 000 per quality adjusted life year gained. The probability that surgery

is cost effective decreases to 0.77 if patients who return to proton pump inhibitors have worse GORD symptoms than before surgery (scenario 7). Surgery is unlikely to be cost effective if it is assumed that its benefits (in terms of health related quality of life relative to medical management) are not maintained beyond one year (scenario 4).

Surgery might also not be cost effective in some multivariate sensitivity analyses. For example, the incremental cost effectiveness ratio increases to about £22 000 if proton pump inhibitors can be effectively delivered at half the cost estimated here—perhaps due to greater use of lower cost drugs—and there is no difference in health related quality of life after two years (scenario 16).

## DISCUSSION

### Principal findings

Under base case assumptions, surgery is cost effective on average with an incremental cost-effectiveness ratio of £2648 per quality adjusted life year. The probability of surgery being cost effective is high given a threshold of £20 000 per quality adjusted life year and assuming the treatment effect lasts for at least five years and patients who fail surgery do not have worse symptoms than before surgery.

The results of this analysis are similar to those of Bojke<sup>8</sup> who also found surgery to be cost effective. That model was constructed using baseline utility data from the REFLUX trial but did not include the treatment effect of surgery at one year.

### Strengths and weaknesses of this study

We have compared the cost effectiveness of laparoscopic surgery with that of medical management

**Table 3** Results of base case economic model and sensitivity analyses. Expected costs and QALYs per patient in each scenario were calculated as mean of 1000 simulations using probabilistic model

Scenario	Key input values			Model results				
	Duration of effect	Utility difference for successful surgery	Utility after failure of surgery	QALY difference	Cost difference (£)	ICER (£/QALY)	P (20k)	P (30k)
(1) Base case	20	0.068	0.711	0.61	1616	2648	0.944	0.953
<b>Univariate (one way) sensitivity analyses</b>								
(2) ITT estimate of treatment effect	20	0.047	0.711	0.42	1616	3876	0.918	0.935
(3) Per-protocol estimate of treatment effect	20	0.076	0.711	0.68	1616	2363	0.989	0.992
(4) Treatment effect lasts 1 year	1	0.068	0.711	0.05	1616	32 534	0.204	0.429
(5) Treatment effect lasts 2 years	2	0.068	0.711	0.11	1616	14 807	0.659	0.788
(6) Treatment effect lasts 5 years	5	0.068	0.711	0.26	1616	6232	0.88	0.899
(7) Worse HRQOL after failure of surgery than MM group	20	0.068	0.680	0.37	1616	4405	0.768	0.792
(8) Higher annual probability of return to MM (11.2%) than base case (4.9%)	20	0.068	0.711	0.42	1978	4744	0.899	0.928
(9) Higher annual probability of repair of surgery (4%) than base case (0.8%)	20	0.068	0.711	0.63	3890	6189	0.87	0.905
(10) Higher probability of operative mortality of surgery or repair (1%) than base case (0.1%)	20	0.068	0.711	0.46	1579	3425	0.878	0.888
(11) 100% increase in cost of surgery	20	0.068	0.711	0.61	3927	6437	0.877	0.909
(12) 50% reduction in annual expenditure on PPIs compared with base case	20	0.068	0.711	0.61	2392	3921	0.91	0.931
<b>Multivariate (two-way and three-way) sensitivity analyses</b>								
(13) Duration of treatment effect is for five years and worse HRQOL if fail surgery	5	0.068	0.680	0.02	1616	101 290	0.383	0.428
(14) ITT estimate and duration of treatment effect is for five years	5	0.047	0.711	0.17	1616	9269	0.807	0.859
(15) ITT estimate and duration of treatment effect is for five years and worse HRQOL if fail surgery	5	0.047	0.680	-0.07	1616	Dom	0.213	0.248
(16) 50% reduction in annual expenditure on PPIs and duration of treatment effect is two years	2	0.068	0.711	0.11	2392	21 923	0.455	0.683

Dom=surgery is dominated with higher costs and lower QALYs than MM (and no ICER is calculated); HRQOL=health related quality of life, ICER=incremental cost-effectiveness ratio; ITT=intention to treat analysis; MM=medical management; PPI=proton pump inhibitors; P(20k)=probability surgery is cost effective at a cost-effectiveness threshold of £20 000; P(30k)=probability surgery is cost effective at a cost-effectiveness threshold of £30 000.

using randomised data on the effect of treatment on health related quality of life.

The REFLUX trial was a pragmatic study and the results, in terms of symptom control and health related quality of life, are expected to be generalisable to patients in the UK who are stable on GORD medication and suitable for surgery.<sup>22</sup> Nevertheless, because rates of surgical reintervention and return to medical management in clinical practice might differ from the trial or with longer follow-up,<sup>23</sup> we have used mean rates from a literature review to inform this analysis.

In the base case we used the “adjusted treatment” received estimate of the treatment efficacy. Intention to treat and per protocol estimates were also used in sensitivity analyses. The intention to treat analysis is an unbiased estimate of effectiveness but is diluted by the high proportion (38%) of patients in the REFLUX trial who were randomised to surgery but did not receive it.<sup>12</sup> The most common reason given for non-compliance was patient choice, which was thought to be affected by long waiting times.<sup>12</sup> Given that waiting times vary between centres and over time, the intention to treat estimate in the REFLUX trial might not be generalisable to current practice in the NHS. The per protocol analysis adjusting for baseline age, sex, body mass index, and EQ-5D score is another measure of the efficacy of surgery<sup>12</sup> but using regression to

adjust for observed baseline characteristics may not adequately control for selection bias. Regardless of whether an adjusted treatment received, intention to treat or per protocol analysis is conducted, surgery appears to be cost effective at the thresholds used by NICE (National Institute for Health and Clinical Excellence), if it is assumed that health related quality of life is maintained over the long term.

Costs of medication were calculated using current pack prices<sup>24</sup> applied to the prescribing pattern observed in REFLUX.<sup>12</sup> Some evidence indicates that prescribers have been switching to lower cost proton pump inhibitors such as lansoprazole or omeprazole following sharp reductions in their prices in recent years, and consequently the current cost of medical management may be lower than estimated here.<sup>4</sup> However, surgery remains cost effective even if the annual cost of medication is half that in the base case, other considerations being equal. Nevertheless, in some scenarios surgery is unlikely to be cost effective, particularly where costs of medical management are lower than calculated in the base case and the health related quality of life benefit of surgery is not maintained over the long term.

The duration of the treatment effect is, therefore, an important but uncertain assumption. To inform this question, follow up of REFLUX trial patients has

### WHAT IS ALREADY KNOWN ON THIS TOPIC

Laparoscopic surgery is an efficacious treatment of stable GORD that would otherwise require medical management

Surgery is costly in the short term, but these costs may be at least partly offset by less lifetime use of anti-GORD medication

### WHAT THIS STUDY ADDS

This study compared the cost effectiveness of laparoscopic surgery and medical management using randomised data on the effect of treatment on health related quality of life

The findings indicate that laparoscopic surgery is cost effective provided that clinical benefits are sustained in the medium to long term

been extended to five years. Given the results of the trial so far and the assumptions made in the decision model, extending the follow up of the trial from one year (scenario 4) to five years (scenario 6) would increase the probability that surgery is cost effective at a threshold of £20 000 per quality adjusted life year from 0.20 to 0.88. However, under more pessimistic assumptions about health related quality of life of patients who return to medical management, then even five years of follow-up would still leave considerable uncertainty about the value of surgery.

### Conclusions

Although surgery seems likely to be cost effective in terms of expected (mean) costs and health effects, uncertainty remains about the duration of the treatment effect and the severity of GORD symptoms after failure of surgery. Furthermore, a number of practical issues need to be considered before the NHS could offer surgery to all patients who are currently stable on medical management. In particular, surgical capacity and availability of trained surgeons are potential barriers to implementation that would need to be addressed.

Trial team: Aberdeen—Marion Campbell, Adrian Grant, Craig Ramsay, Samantha Wileman; York—Garry Barton (1999-2002), Laura Bojke, David Epstein, Sue Macran, Mark Sculpher. Trial steering group: Wendy Atkin (independent chair), John Bancewicz, Ara Darzi, Robert Heading, Janusz Jankowski, Zygmunt Krukowski, Richard Lilford, Iain Martin (1997-2000), Ashley Mowat, Ian Russell, Mark Thursz. Data monitoring committee: Jon Nicholl, Chris Hawkey, Iain MacIntyre. Wendy Atkin, Janusz Jankowski, Richard Lilford, Jon Nicholl, Chris Hawkey, and Iain MacIntyre were independent of the trial. Members of the reflux trial group responsible for recruitment in the clinical centres were as follows. Aberdeen Royal Infirmary: A Mowat, Z Krukowski, E El-Omar, P Phull, T Sinclair, L Swan. Belfast Victoria Hospital: B Clements, J Collins, A Kennedy, H Lawther, B Mulvenna. Royal Bournemouth Hospital: D Bennett, N Davies, M McCullen, S Toop, P Winwood. Bristol Royal Infirmary: D Alderson, P Barham, K Green, R Mountford, S Tranter, R Mittal. Princess Royal University Hospital, Bromley: M Asante, L Barr, S El Hasani. Royal Infirmary of Edinburgh: A De Beaux, R Heading, L Meekison, S Paterson-Brown, H Barkell. Royal Surrey County Hospital, Guildford: G Ferns, M Bailey, N Karanjia, TA Rockall, L Skelly, M Smith. Hull Royal Infirmary: M Dakkak, J King, C Royston, P Sedman. Raigmore Hospital, Inverness: K Gordon, I McGauran, LF Potts, C Smith, PL Zentler-Munro, A Munro. General Infirmary at Leeds: A Axon, B Chanley, S Dexter, M McMahon, P Maoyeddi. Leicester Royal Infirmary: DM Lloyd, A Palmer-Jeffrey, B Rathbone. St Mary's Hospital, London: V Loh, M Thursz, A Darzi. Whipps Cross Hospital, London: A Ahmed, R Greaves, A Sawyerr, J Wellwood, T Taylor. Poole Hospital: S Hosking, T Karlowski, S Lowrey, N Sharer, J Snook. Queen Alexandra Hospital,

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**Competing interests:** None declared.

**Ethical approval:** Approval for this study was obtained from the Scottish Multicentre Research Ethics Committee and the appropriate local research ethics committees.

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