Original Article

Screening and treating pre-operative anaemia and suboptimal iron stores in elective colorectal surgery: a cost effectiveness analysis

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Summary
Our study investigated whether pre-operative screening and treatment for anaemia and suboptimal iron stores in a patient blood management clinic is cost effective. We used outcome data from a retrospective cohort study comparing colorectal surgery patients admitted pre- and post-implementation of a pre-operative screening programme. We applied propensity score weighting techniques with multivariable regression models to adjust for differences in baseline characteristics between groups. Episode-level hospitalisation costs were sourced from the health service clinical costing data system; the economic evaluation was conducted from a Western Australia Health System perspective. The primary outcome measure was the incremental cost per unit of red cell transfusion avoided. We compared 441 patients screened in the pre-operative anaemia programme with 239 patients not screened; of the patients screened, 180 (40.8%) received intravenous iron for anaemia and suboptimal iron stores. The estimated mean cost of screening and treating pre-operative anaemia was AU$332 (£183; US$231; €204) per screened patient. In the propensity score weighted analysis, screened patients were transfused 52% less red cell units when compared with those not screened (rate ratio = 0.48, 95%CI 0.36–0.63, $p < 0.001$). The mean difference in total screening, treatment and hospitalisation cost between groups was AU $3776 lower in the group screened (£2080; US$2629; €2325) (95%CI AU$1604–5947, $p < 0.001$). Screening elective patients pre-operatively for anaemia and suboptimal iron stores reduced the number of red cell units transfused. It also resulted in lower total costs than not screening patients, thus demonstrating cost effectiveness.

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Introduction
Anaemia is a global public health issue, affecting nearly one third of the world's population [1]. A systematic analysis for the 2015 Global Burden of Disease Study found that anaemia was the condition that affected most people (2.36 billion) and iron deficiency was the most common cause [2]. Despite the significant disability attributed to anaemia over many years, it has not received as much attention as other diseases associated with lower levels of disability [3, 4].

Although studies show that anaemia rates are higher in low- and middle-income countries, anaemia is also common in high-income countries. For example, one large cohort study found that the rate of pre-operative anaemia was similar in patients from low- to middle-income countries when compared with patients from high-income countries [5]. Other studies investigating pre-operative anaemia demonstrate that anaemia is common and associated with increased mortality and morbidity [6, 7]. This association is also seen in patients with mild anaemia [6].

A number of medical societies and health authorities address the importance of pre-operative anaemia [8–11]. For example, the British Committee for Standards in Haematology Guidelines on the Identification and Management of Pre-Operative Anaemia recommends structuring pathways to ensure that anaemia is screened and corrected before surgery [9]. Patient blood management guidelines from Australia [8] provide recommendations and clinical guidance for identifying, evaluating and managing pre-operative anaemia and suboptimal iron stores. Suboptimal iron stores are defined as ferritin < 100 $\mu g.l^{-1}$ in non-anaemic patients requiring surgery with the risk of substantial blood loss. Notwithstanding these evidence-based recommendations, barriers exist that limit the implementation of pre-operative anaemia screening and suboptimal iron stores treatment clinics. One of these barriers is the view that screening for anaemia and treating pre-operatively is not cost effective [12]. This remains an unresolved issue [13].

If hospital administrators are to fund pre-operative anaemia management clinics, they should know if they are cost effective and, to demonstrate this, a cost-effectiveness analysis is required. This is important because any barriers to implementation also represent barriers to improved patient care. The objective of this study was to conduct a cost-effectiveness analysis of a pre-operative anaemia and suboptimal iron stores screening programme for elective colorectal surgery. Our aim was to answer whether screening for and treating pre-operative anaemia and suboptimal iron stores is cost effective.

Methods

In 2016, a pre-operative clinic was implemented to screen, evaluate and manage suboptimal iron stores and anaemia at Fiona Stanley Hospital, a quaternary hospital serving the state of Western Australia (online Supporting Information, Figure S1). Before 2016, no routine screening was performed, and therefore any decisions made were variable and clinician dependent.

For our analysis, the population of interest was adults booked for elective colorectal surgery, specifically procedures with a potential blood loss of > 500 ml or patients with a high likelihood of pre-operative anaemia. The setting was Fiona Stanley Hospital, a 783-bed metropolitan quaternary hospital, and the study perspective was the Western Australian Health System. We chose this hospital because the state health system is responsible for the management of public hospitals and the majority of funding. As our study aimed to evaluate the financial benefits of pre-operative anaemia clinics, we felt it important the costs were considered from the perspective of the state health system.

The intervention group consisted of patients screened for anaemia and suboptimal iron stores and who were treated appropriately when these conditions were detected. The comparator group were patients admitted for the same elective procedures to the same hospital, but who were not screened for anaemia and suboptimal iron stores. This included patients admitted before implementation of the screening clinic and patients admitted post-implementation who were not screened. The reasons why patients admitted post-implementation were not screened included some who were screened and treated by general practice providers before admission, and others living in regional areas who may have experienced delays in laboratory assessments. The cause of anaemia in the majority of cases was iron deficiency or suboptimal iron stores. Most patients presenting to our hospital for elective colorectal surgery are categorised with a high urgency for surgery (within 30 days). For this reason, intravenous (i.v.) iron was preferred over oral iron for treatment, given the need to replace iron quickly. The i.v. iron formulation used throughout the study was a standardised dose of 1000 mg of ferric carboxymaltose, (Ferinject™; Vifor Pharma, Glattbrugg, Switzerland). Depending on comorbidities and initial laboratory results, patients may have had follow-up tests for thyroid function, folate and vitamin B12 deficiency or soluble transferrin receptor. In the event of other haematinic deficiencies, the clinic routinely recommends oral folate and parenteral B12 to primary care providers.

We analysed categorical variables using the Chi-square test, and normally distributed continuous variables were analysed using the independent samples t-test for mean differences between groups. As our data were not sourced from a randomised trial, differences may have existed between the intervention group and the comparator group. To control for this, we applied propensity score weighting techniques to our regression models. We chose propensity score weighting over propensity score matching as we did not want to exclude any admissions as a result of the matching process. This process involved first applying a logistic regression to determine the probability of receiving the intervention, followed by converting model results into predicted values to be used as weights. All regression models were multivariable, and included a covariate adjustment using the propensity score while adjusting for the following potential confounders: anaemia severity; surgical procedure; age; sex; and comorbidities using the Charlson comorbidity index.

The results of our initial analysis revealed that mean hospital costs per elective colorectal admission decreased over the duration of our study, which was an unexpected finding (online Supporting Information, Table S1). To investigate this, we conducted a post-hoc sensitivity analysis to investigate the impact of time on cost and effect estimates. We did not add year of surgery to our primary propensity score analysis, because in the baseline year it was not possible for patients to be screened by the pre-operative anaemia and suboptimal iron stores clinic. Therefore, our sensitivity analysis excluded the baseline year (2015) and added year of surgery into a propensity score-weighted analysis.

Analyses were performed using R version 3.4.3 (The R Foundation for Statistical Computing), and results reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [14].

The time horizon selected was from the hospital pre-operative assessment through to hospital discharge. This means that the costs associated with the pre-operative outpatient visit (in the intervention group) as well as the elective inpatient admission were included. Given that our time horizon was over a relatively short period, no discounting was applied.

Clinical data were sourced from the Western Australia Patient Blood Management Data System [15]. The primary outcome of interest was units of red blood cells transfused. Our cost effectiveness analysis calculated the difference in hospital costs and the difference in primary outcome (number of red blood cell transfusions avoided) between these two cohorts, with results presented as an incremental cost effectiveness ratio (ICER). The ICER was calculated by dividing the mean difference in costs by the mean difference in red cell units avoided between screened and non-screened patients. The formula is $ICER = (Cost_i - Cost_c)/(Effect_i - Effect_c)$, where 'i' refers to the intervention, and 'c' refers to the control. We applied non-parametric bootstrapping of costs and red cell transfusion units avoided to quantify the underlying variance around the ICER. A thousand bootstrap samples were drawn and plotted on a cost effectiveness plane. Costs were categorised into three broad groups: screening cost, treatment cost and hospitalisation costs.

A breakdown of the cost of screening and treating anaemia and suboptimal iron stores is presented in Table 1. The pre-operative screening clinic is managed by a clinical nurse and a consultant anaesthetist, with support from a senior anaesthesia resident and database manager. The cost of screening for anaemia and suboptimal iron stores is made up of laboratory testing; the salary of clinical staff who review results of patients booked for selected major elective surgical procedures; identifying patients with anaemia and/or suboptimal iron stores; contacting patients; booking appointments through the hospital's patient administration system; and managing the clinic database. Staff costs were calculated by multiplying the mean salary (including on costs) per hour by the number of hours spent on the screening process. These were derived from a log of work activities kept by staff to determine the number of hours per week spent on screening.

The cost of administering the intervention was made up of the cost of staffing time, consumables and the cost of iron product (mainly i.v. iron). Staffing time was calculated by multiplying the salary per hour by the number of hours spent administering the treatment.

Hospitalisation costs were calculated using a bottom-up approach. These data were sourced from the health service clinical costing system, which captures patient-level direct costs. These costs were collected for the relevant elective surgical admissions. The largest cost drivers from this system were hospital length of stay and, where relevant, hours in intensive care and hospital-acquired complications. All costs were referenced to the latest calendar year of admissions (2019) and presented in Australian dollars.

This study was granted ethical approval by the South Metropolitan Health Service Human Research Ethics Committee, who waived the requirement for written informed consent.

Results

Our study included 680 elective admissions that presented for colorectal surgery between 2015 and 2019 (Table 2). These included the following procedures, performed by open or laparoscopic approach: anterior resection of rectum; colectomy; rectosigmoidectomy or proctectomy; and total proctocolectomy. Of these 680, we compared 441 patients screened for iron deficiency with 239 not screened before surgery to assess cost effectiveness (Fig. 1).

Overall, patients presenting for surgery had a mean (SD) age of 62.7 (15.9) years, and 353 (51.9%) were men.

Table 1 Cost of intervention by activity.

Cost component	Cost source	Unit	Cost per unit (AU$)	Cost per patient (AU$)
Stage 1. Screening				
Iron studies	Pathology Provider (PathWest)	Per test	29.30	29.30
Renal function	Pathology Provider (PathWest)	Per test	15.93	15.93
CRP	Pathology Provider (PathWest)	Per test	8.73	8.73
Specimen reporting	Pathology Provider (PathWest)	Per test	10.00	30.00
Registered Nurse	WA Health Nursing Industrial Agreement	Hourly salary (with on cost)	63.65	42.43
Medical Consultant	WA Health Medical Practitioners Industrial Agreement	Hourly salary (with on cost)	212.27	27.60
Senior Anaesthesia Resident	WA Health Medical Practitioners Industrial Agreement	Hourly salary (with on cost)	111.75	3.69
Data Manager	WA Health Services Industrial Agreement	Hourly salary (with on cost)	72.66	18.41
Stage 2. Treatment				
Iron product	Ferric Carboxymaltose	Per 500 mg	142.80	285.60
Iron product	Ferro Gradumet and vitamin C	30 tablets	–	0
Nursing time costs	WA Health Nursing Industrial Agreement	Hourly salary (with on cost)	63.65	79.56
Infusion consumables	Three-port infusion tubing, cannula, dressing, alcohol swab, fluid bag and flush	Per infusion consumable	9.01	18.02

WA, Western Australia; CRP, C-reasctive protein.

Patients screened had comparable presenting haemoglobin levels to patients not screened, 132.5 $g.l^{-1}$ vs. 134.3 $g.l^{-1}$, respectively ($p = 0.214$). Of patients screened for anaemia and suboptimal iron stores, 180 (40.8%) received i.v. iron and 16 (3.6%) received oral iron. Anaemic patients receiving i.v. iron treatment recorded a mean haemoglobin increase of 8.5 $g.l^{-1}$ (mean pre-admission haemoglobin level, 114.3 $g.l^{-1}$; mean post-treatment haemoglobin level, 122.8 $g.l^{-1}$).

Table 1 lists the estimated costs of screening and treating anaemia pre-operatively. The screening costs included the cost of laboratory testing and the salaries of clinical and support staff involved in the screening process. The total screening cost per patient was AU$176 (£97; US $123; €108). The preferred treatment for patients with iron deficiency or suboptimal iron stores was 1000 mg of ferric carboxymaltose. The cost of infusion in the outpatient clinic was AU$383 (£211; US$267; €236). Of the patients screened, 40.8% (n = 180) received i.v. iron, resulting in a mean cost of screening and treatment cost of AU$332 (£183; US$231; €204) per screened patient.

The cost of the subsequent surgical admission was derived from the hospital's clinical costing system. Patients screened had a mean hospitalisation cost of AU$24,204 (£13,333; US$16,850; €14,903), compared with AU$27,510 (£15,154; US$19,152; €16,938) for those not screened. After adjusting for the pre-admission haemoglobin level, the surgical procedure, patient age, sex and comorbidities in a propensity-weighted regression model, the mean difference in hospital cost between groups was AU$4106 (£2262; US$2858; €2528) (95%CI AU$1934–6278, $p < 0.001$) lower in the group screened for anaemia and suboptimal iron stores. Using the same model, the mean difference in total (screening, treatment and hospitalisation) cost between groups was AU$3776 (£2080; US$2629; €2325) (95%CI AU$1604–5947, $p < 0.001$) lower in the group screened for anaemia and suboptimal iron stores pre-operatively.

There was a significant difference between the screened group and the control group in terms of the mean number of red cell units transfused per admission. In the unadjusted analysis, the screened group was transfused 120 units per 1000 admissions compared with 201 for the comparator group ($p = 0.158$). In the propensity score-weighted analysis, screened patients were transfused 52% less red cell units when compared with those not screened (rate ratio = 0.48, 95%CI 0.36–0.63, $p < 0.001$).

Table 3 presents the incremental cost effectiveness ratios from our unadjusted and adjusted analyses. In the propensity score weighted analysis, the pre-operative

Table 2 Characteristics of elective colorectal surgery patients, stratified by the presence of pre-operative screening for anaemia and suboptimal iron stores. Values are number (proportion) or mean (SD).

	Screened for anaemia		
	Yes (n = 441)	No (n = 239)	p value
Received intravenous iron	180 (40.8%)	0	< 0.001
Received oral iron	16 (3.6%)	0	0.007
Pre-operative haemoglobin; g.l^{-1}	132.54 (18.04)	134.33 (17.81)	0.214
Age; years	64.1 (15.3)	60.2 (16.7)	0.002
Sex; male	220 (49.9%)	133 (55.6%)	0.175
Surgical procedure			0.513
Anterior resection of rectum	189 (42.9%)	90 (37.7%)	
Colectomy	187 (42.4%)	111 (46.4%)	
Rectosigmoidectomy or proctectomy	52 (11.8%)	28 (11.7%)	
Total proctocolectomy	13 (2.9%)	10 (4.2%)	
Calendar year			< 0.001
2015	0	97 (40.6%)	
2016	80 (18.1%)	80 (33.5%)	
2017	135 (30.6%)	18 (7.5%)	
2018	124 (28.1%)	18 (7.5%)	
2019	102 (23.1%)	26 (10.9%)	
Charlson comorbidity score			0.422
0	260 (59.0%)	151 (63.2%)	
1	39 (8.8%)	25 (10.5%)	
2	26 (5.9%)	10 (4.2%)	
3+	116 (26.3%)	53 (22.2%)	
Length of stay; days	7.4 (4.6)	8.4 (5.6)	0.011
Received red cell transfusion	26 (5.9%)	21 (8.8%)	0.207
Red cell units transfused; n	0.1 (0.6)	0.2 (0.9)	0.158
Outpatient screening and treatment cost; AU$	332 (189)	0 (0)	<0.001
Hospitalisation cost; AU$	24,204 (11,931)	27,510 (17,423)	0.004
Total cost; AU$	24,536 (11,933)	27,510 (17,423)	0.009

anaemia screening and suboptimal iron stores clinic was less costly and more effective in terms of avoided red blood cell transfusions. Figure 2 demonstrates the bootstrapped mean differences for cost and outcome. Of the 1000 bootstrapped estimates, 96.9% fell into the less costly, more effective quadrant (Quadrant 2), 3.0% of estimates were in the less costly, less effective quadrant (Quadrant 3) and 0.1% of estimates were in the more costly, more effective quadrant (Quadrant 1). These results indicate that pre-operative anaemia and suboptimal iron stores screening and management in elective colorectal surgery is less costly and more effective compared with no intervention.

After removing cases from the pre-implementation year and adjusting for year of surgery, the difference in mean cost comparisons between groups reduced from -AU$3776 to -AU$1078 (AU$+1238 to AU$-3394; p = 0.362). This suggests the cost changes over time had some effect on the outcomes we observed. In addition, in our sensitivity analysis screened patients were transfused 25% less red cell units when compared with those not screened (rate ratio = 0.75, 95%CI 0.55–1.02; p = 0.067). Of 1000 bootstrapped ICER estimates, 59% fell into the less costly, more effective quadrant (Quadrant 2), 16% in the less costly, less effective quadrant (Quadrant 3), 15% in the more costly, more effective quadrant (Quadrant 1) and 10% in the more costly, less effective quadrant (Quadrant 2, online Supporting Information, Figure S2).

Discussion

Our 5-year study demonstrated that the patient blood management pre-operative anaemia and suboptimal iron

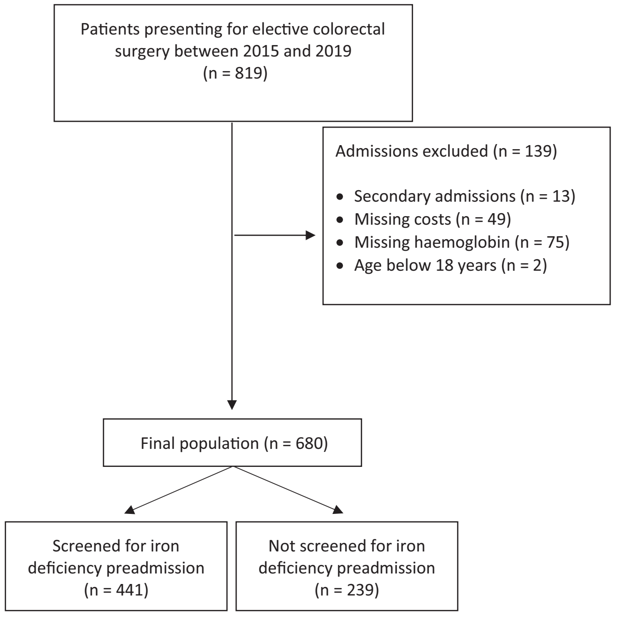

Figure 1 Flow chart of patient identification for the study cohort.

Table 3 Incremental cost and effect.

Analysis type	Group	Mean cost (AU$)	Effect (mean RBC units avoided)	ICER[c]
Unadjusted results	Not screened	27,510	0.799	
	Screened	24,536	0.880	
	Incremental difference	-2974	0.081	-36,716
Multivariable regression model[a]	Not screened	30,826	0.771	
	Screened	27,188	0.888	
	Incremental difference	-3638	0.117	-31,094
Propensity score weighting[b]	Not screened	31,605	0.782	
	Screened	27,829	0.896	
	Incremental difference	-3776	0.114	-33,123

RBC, red blood cells.
[a]Adjusted for admission haemoglobin, procedure, age, sex, comorbidities.
[b]Covariate adjustment using the propensity score weighting in a regression model.
[c]ICER = incremental cost effectiveness ratio. The value represents mean difference in cost divided by the mean difference effect (mean red blood cell units avoided).

stores screening and management programme for elective colorectal surgery was more effective and less costly when compared with no screening. In our primary analysis, the costs incurred by pre-operative anaemia and suboptimal iron stores screening and treatment were outweighed by the savings resulting from the surgical admission, highlighting that screening program returns were greater than the investment. In addition, patients screened by the clinic had significantly lower mean red cell unit transfusions when compared with patients not screened.

In a post-hoc sensitivity analysis, the estimated difference in costs between groups reduced from -AU $3776 to -AU$1078, suggesting the cost changes over time played some role in the outcomes we observed. However, our sensitivity analysis was likely to overestimate the impact of time for two key reasons. First, it excluded important data from the baseline year, resulting in a loss of 40% of our non-screened sample. Second, a number of patients not screened by the hospital clinic may have had anaemia screening and management by their primary care provider. A primary care patient blood management education programme was implemented, and local data indicated that the number of general practitioner clinics performing iron infusions in the metropolitan area

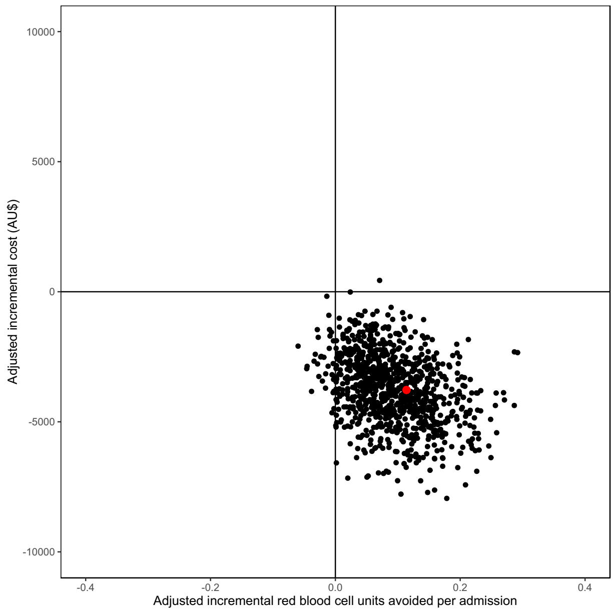

Figure 2 Bootstrapped mean cost and effect differences for a pre-operative anaemia and suboptimal iron stores screening and treatment program compared with no intervention in elective colorectal surgery. The effect represents the mean number of red blood cell unit transfusions avoided.

increased significantly over the study period, likely influencing our results.

Cost effectiveness studies are important given the paucity of published data on the economic outcomes associated with anaemia screening. In 2014, Nosratnejad et al. [16] published a systematic review of the cost effectiveness of anaemia screening in vulnerable groups. Their literature search revealed very little published data on the cost effectiveness of anaemia screening, with no examples pertaining to pre-admission elective surgery. Subsequently, Basora et al. [17] applied a theoretical model to investigate the cost effectiveness of administering i.v. iron pre-operatively to iron deficient anaemic patients undergoing knee replacement surgery. Based on their model they concluded that pre-operative administration of i.v. iron would be cost effective in patients undergoing primary knee replacement. Froessler et al. [18] used a model to report the costs and benefits of anaemia treatment in elective abdominal surgery. Though not a cost effectiveness study, they found peri-operative i.v. iron resulted in cost savings based on reduced transfusions and length of stay. The cost data used in their study were derived from a variety of sources, including peer-reviewed literature and estimates provided by clinicians.

Of interest in our analysis is that hospitals in the Western Australian health system, like most other Australian states, do not pay for blood components. This has led to the misconception that blood transfusions are free, and that in comparison, screening for and treating anaemia and iron deficiency is more costly [12]. Our finding of lower costs in patients screened and treated for not only anaemia but also suboptimal iron stores, addresses these misconceptions and are consistent with the results of other studies. For example, recent studies have suggested that the costs associated with administering a red cell transfusion are several times higher than the cost of product, and have long been underestimated [13, 19, 20]. Additionally, systematic reviews and meta-analyses of observational studies have independently associated both pre-operative anaemia and red cell transfusion with increased mortality and morbidity events, including acute kidney injury, stroke, infection and acute respiratory distress syndrome [7, 8, 21, 22]. In many studies, the risks associated with red cell transfusion are dose dependent [8, 23, 24]. One systematic review and meta-analysis of randomised controlled trials investigated the effect of red cell transfusion strategies on the development of serious hospital-acquired infections [25] and provided Level 1 evidence that liberal transfusion increases the risk of serious hospital-acquired infection. These adverse outcomes are known to significantly increase hospital costs and may explain why total costs were lower in patients screened and treated for pre-operative anaemia in our study.

Our economic evaluation has potential implications for policy. Currently, one barrier to pre-operative anaemia management is the cost of running an anaemia clinic. Given that our evaluation found that a pre-operative anaemia and suboptimal iron stores screening program was more effective and less costly than not screening, our results may encourage hospital administrators to fund anaemia management clinics.

Our study has some limitations. For example, the comparator group was made up of patients admitted before implementation of the screening clinic and patients admitted post-implementation who were not screened. The reasons why patients admitted post-implementation were not screened include some being screened by primary care providers and others living in regional areas who may have experienced delays in laboratory assessments. As our dataset did not collect data on patient rurality or screening provided through a primary care provider, we are unable to include details of their impact on our results. In addition, the design of the screening database did not allow comparison of whether the eventual procedure was laparoscopic or open, and therefore we were unable to explore what impact this may have had on outcomes. However, no significant changes in colorectal surgical practice occurred in our institution over the study period.

In summary, screening elective colorectal surgical patients pre-operatively for anaemia and suboptimal iron stores reduced the number of red cell units transfused at a lower cost than not screening, thus providing health economic evidence of the cost effectiveness of a comprehensive pre-operative anaemia screening clinic.

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Supporting Information

Additional supporting information may be found online via the journal website.

Table S1. Characteristics of elective colorectal surgery patients, stratified by year of surgery.

Figure S1. Pre-operative patient blood management algorithm.

Figure S2. Sensitivity analysis, bootstrapped mean cost and effect differences for a pre-operative anaemia screening and treatment program compared with no intervention in elective colorectal surgery.

