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Research Article

Cost-Effectiveness of Intravenous Iron Formulations in Patients with Iron Deficiency Anaemia and Inflammatory Bowel Disease, in a Swedish Regional Setting Using Real-World Tender Prices

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Aims. A widespread complication of inflammatory bowel disease (IBD) is iron deficiency anaemia (IDA), which affects quality of life (QoL) and is associated with frequent hospitalizations. The intravenous iron therapies, ferric carboxymaltose (FCM), ferric derisomaltose (FD), and iron sucrose (IS), have previously been shown to replenish haemoglobin (Hb) levels more effectively than oral iron. However, they differ in both costs and efficacy (response to treatment), leading to differences in acquisition by health-care payers. We investigated the cost-effectiveness of FCM versus FD and IS, in terms of additional cost per additional responder, for the treatment of IBD-associated IDA in multiple Swedish regional settings, using current tender prices. *Methods and Materials.* A microsimulation model estimated the additional cost per patient achieving a response, based on Hb normalization or an increase of ≥2 g/dL in Hb levels. Efficacy estimates were taken from a previously published network meta-analysis. Treatment costs (2021 SEK) included current tender prices in Swedish health-care regions. Resource use depended partly on dosing, which was based on patient characteristics simulated in the model. *Results.* The analysis showed that FCM was associated with the highest number of responders (81%) compared to FD (74%) and IS (75%), while costing less per responder than its comparators, in included regions. *Conclusions.* These results suggest that regional health-care budget holders should consider more than drug prices when choosing which IV formulations to acquire and that they should use all available tools when deciding how to fulfil the needs of their patients.

1. Introduction

The most widespread complication of inflammatory bowel disease (IBD) is anaemia, which is estimated to be prevalent in about 24% of patients with IBD [1]. Iron deficiency anaemia (IDA) is one of the two most common causes of anaemia in patients with IBD, often overlapping with the other common cause, anaemia of chronic disease [2, 3]. IDA in IBD is associated with a reduction in patient's quality of life and further inflammation and can lead to symptoms such as fatigue, decreased performance, nausea, dyspnoea, and headaches [4, 5]. These negative impacts have been shown to result in more frequent hospitalizations than in the normal population [6].

In a 2010 study, Sweden was estimated to have 61,344 living patients with diagnosed IBD, corresponding to a prevalence of 0.65% (95% CI: 0.65-0.66) [7]. The study recognized increasing trends in prevalence within the population over time. The prevalence of anaemia and iron deficiency in patients with IBD was also studied across Scandinavia,

in a study from 2011 [8]. The overall prevalence of anaemia in IBD was estimated at 19% (95% CI: 16-23%), with 68% of anaemic patients with IBD having both IDA and anaemia of chronic disease and 20% having only IDA [8].

The European Crohn's and Colitis Organization (ECCO) established consensus guidelines for the diagnosis, treatment, and prevention of IDA in IBD, in Europe. These treatment guidelines focus on different methods of iron supplementation, depending on disease severity, baseline haemoglobin, and body weight, with a secondary objective of prevention through regular monitoring. The goal of iron supplementation is to revert haemoglobin and iron levels to normal for the given patient. The guidelines recommend that oral iron be used in patients with mild anaemia and clinically inactive IBD, who have not been previously intolerant to oral iron. However, recent studies have found that the use of oral iron negatively affects gut microbiota, thus potentially exacerbating IBD [9, 10]. Intravenous (IV) iron supplementation should be used as a first-line treatment in clinically active patients with IBD, with intolerance to oral iron and low haemoglobin levels (<10 g/dL) [11].

Currently, the treatment landscape in Sweden for patients with IDA in IBD involves both oral and intravenous iron supplementation. Oral supplements include iron(II) and iron(III) formulations with the convenience of home administration resulting in a low cost. However, studies of iron(II) show that they are often associated with limited efficacy, as well as gastrointestinal side effects, which lead to poor adherence [11–13]. A systematic literature review by Kulnigg and Gasche includes several articles that show a connection between unabsorbed iron in the inflamed tissue leading to a worsening of IBD symptoms [14]. IV formulations have been shown to be more effective in terms of iron replenishment compared to oral iron. Due to the absence of gastrointestinal side effects, IV formulations can be used in patients with clinically active IBD [11]. The IV iron therapies available in Sweden are FCM (brand name in Sweden: Ferinject (ferric carboxymaltose), CSL Vifor) (ferric carboxymaltose), FD (brand name in Sweden: Monofer (ferric derisomaltose), Pharmacosmos A/S) (ferric derisomaltose), IS (brand name in Sweden: Venofer (iron sucrose), CSL Vifor) (iron sucrose), and iron dextran (brand name in Sweden: CosmoFer (iron dextran), Pharmacosmos A/S). However, the IV treatments accessible to a patient vary by region, based on regional clinical practice and procurement preferences.

To date, studies comparing the relative efficacy of IV formulations are lacking. A Bayesian network meta-analysis (NMA) of existing randomized controlled trials (RCTs) was performed by Aksan et al. in 2017 [12], comparing the efficacy and tolerability of different IV formulations to treat IDA in IBD. In this study, FCM was the only IV formulation with a higher efficacy that was statistically significant, in terms of response rate, defined by Hb normalization or an increase of ≥2 g/dL, when compared to oral iron. FCM was also shown to have a numerically higher response rate compared to both FD and IS, with an 83% probability of being more effective than its comparators. Table 1 shows the results of the NMA.

Table 1: Treatment efficacy: odds ratio for response rate [12].

	Odds ratio compared with FCM	Lower 95% credible interval	Upper 95% credible interval
FD	0.69	0.34	1.40
IS	0.70	0.48	1.00
Oral iron	0.53	0.32	0.89

Health care in Sweden is decentralized within the state. Each of the twenty-one regions is responsible for the procurement and provision of health care within the respective region, including pharmaceuticals for hospital use. This results in differences in procurement. However, all regions follow the process centrally structured by the state, in accordance with the Public Procurement Act (2016 : 1145) [15].

The individual regions are grouped into regional procurement clusters as follows: Stockholm (which includes Gotland) and Västra Götaland procure for their individual regions. Skåne, Blekinge, and Kronoberg can procure individually or be grouped with Halland into "Södra Sjukvårdsregionen." The remaining regions fall into the following procurement groups: JÖK (Jönköping, Östergötland, and Kalmar county), 3-Klöver (Örebro, Sörmland, and Värmland), 4-Klövern (Uppsala, Västmanland, Dalarna, and Gävle), and Norrland (Norrbotten, Jämtland/Härjedalen, and Västernorrland) [16].

The decentralized procurement process and variation between regions result in disparities in tender prices and the quantities procured. Therefore, making a state-wide assessment of cost-effectiveness between products (let alone, budget impact) would be less impactful for regional decision-making in decentralized systems like Sweden. A regional focus for cost-effectiveness analysis (CEA) allows policy-makers at this level to make informed decisions, based on their regional needs.

The IV iron formulations available in Sweden have a nationally approved price (known as the list price), based on previous price approval procedures and funding decisions. However, since these products are IV formulations and administered in a hospital setting, they are therefore included in the regional procurement process and are usually purchased at tender prices.

IV iron formulations are not interchangeable in terms of efficacy and safety. In addition to the clinical efficacy results from the aforementioned NMA, a study on patients with haemodialysis examining the impact of switching from an original formulation of IV iron (IS) to an iron sucrose similar preparation shows that the switch led to a destabilization in terms of reduction in mean Hb levels and in mean transferrin saturation ratio (TSAT), in a well-controlled population. Additionally, the mean total anaemia drug costs increased after the switch [17]. Another study presented a different scenario, when switching from generic IV iron to original formulation; the switch resulted in lower doses of IV iron required in order to maintain the same mean Hb levels [18]. Some studies looking at the safety of these IV formulations

have found different adverse event (AE) profiles for the respective treatments, as elaborated in their respective summaries of product characteristics (SmPCs) [19–21].

The availability of multiple products in a given region allows for policy-makers and health-care providers to maximize health-care gains despite scarce resource allocation; certain products may be more appropriate for certain patient populations. Thus, if the cost-effectiveness of pharmaceuticals differs between regions, it is important to stratify results to be able to form tailored decisions on a decentralized level.

For the purposes of assessing the value of a new product, many European health technology assessment authorities recommend CEA, often in the form of cost-utility analyses (CUA). In terms of CUAs, the results are presented as an incremental cost-effectiveness ratio (ICER) with an outcome measure, such as the quality adjusted life year (QALY), used to measure relative effectiveness [22]. For patient populations where health-related quality of life (HRQoL) data is missing, it is not possible to perform a cost-utility analysis; this is currently the case with the IDA population within IDB.

When it is not possible to conduct cost-utility analyses, one of the most globally influential HTA agencies, NICE in the UK, has recommended the use of "natural units" (e.g., the number of deaths avoided or mmHg for blood pressure) [23]. For this study, the number of patients who responded to treatment was implemented as a natural unit, using a well-recognized cut-off to define response: Hb normalization or an increase of ≥2 g/dL [11]. Therefore, cost-effectiveness is shown as the cost per responder in an adapted ICER based on formula below.

$$\text{ICER} = \frac{\text{Cost}_{\text{intervention}} - \text{Cost}_{\text{comparator}}}{\text{Number of responders}_{\text{intervention}} - \text{Number of responders}_{\text{comparator}}} \quad (1)$$

Economic comparisons between different iron supplements have been made previously in the European context, with conflicting conclusions. A CEA of FD vs. FCM in the UK found that haematological response was 9% higher in patients treated with FD than with FCM [24]. On the other hand, two separate analyses of FCM vs. FD and IS in Switzerland and the UK estimated that, in terms of cost-effectiveness, FCM was both more effective and less costly for the respective health-care systems [25, 26]. In the Nordic context, a 2018 economic evaluation of FD vs. FCM was conducted in the Danish setting, followed by another economic evaluation in 2021, which used data for patients in Norway, Sweden, and Denmark. However, both studies only looked at the budget impact from a national payer perspective, using DRG codes for costing, without including efficacy [27, 28].

To our knowledge, this is the first Nordic study of the cost-effectiveness of IV iron supplements for IBD-associated IDA that includes results at the regional level, using variations in costs, such as current public tender prices, as well as treatment efficacy. This level of detail can provide regional decision-makers with the tools to tailor their resource allocation to fit the needs of their patient population.

The aim of this article is to calculate the cost-effectiveness of FCM versus FD and IS, in terms of additional cost per additional responder, for the treatment of IBD-associated IDA in Swedish regional settings, using current public tender prices.

2. Materials and Methods

An MS Excel™-based cost-effectiveness model was used to estimate the percentage of patients with IDA in IBD achieving a response and the related costs incurred by those patients, when treated with FCM, FD, or IS. Response was defined according to ECCO guidelines as normalization of haemoglobin levels, or an increase of ≥2 g/dL in Hb levels. In the FCM arm, response rate was based on a weighted average of the two RCTs of FCM captured in the Aksan et al. NMA [12]. Over these two trials, 81% of patients receiving FCM achieved a response. To calculate the percentage of patients achieving a response with FD, IS, the odds ratio for each comparator versus FCM was sampled based on the mean and the 95% credible interval (CI) calculated by Aksan et al. (Table 1).

The model simulated a cohort of 10,000 patients, using variable patient characteristics with defined distributions, replicating varying input values for patients in Sweden. Variation in the simulated population allowed both supplemental iron requirements and costs to differ between patients. Additionally, these differences between simulated patients helped the model represent the uncertainty in the relative efficacies between treatments that were identified by Aksan et al. [12], simulating more realistic response rates. Model projections were limited to a 1-year time horizon, meaning that outcomes were not discounted. The underlying model has previously been published by Aksan et al. for similar calculations of the cost per responder in the Swiss and UK national settings [25, 26] but was restructured to meet the scope of this study, in the Swedish regional setting.

Costs are expressed in 2021 SEK value. Drug costs were based on the current tender prices for each product within the different regional clusters, which were valid during 2021. Table 2 presents the current tender prices, for selected regions. These regions were selected based on the size of the region and the number of IV iron products procured. Regions not represented in the tables below were not included in the analysis, either due to size (Blekinge and Halland) or if that region had only procured either one or none of the IV iron products, making a comparison between products not possible. To address this, population-weighted averages for the price of each product were included in the analysis, using 2020 population estimates for the included regions. These weighted averages provide a pooled estimate of the cost-effectiveness for the included regions, which could then be extrapolated to regions not included in the analysis.

Based on dosing recommendations from the respective SmPCs [19–21], two separate methods were used to calculate supplemental iron dosing for the three treatment arms.

Table 2: Tender prices, by treatment pack and region in Sweden (valid during 2021).

Sweden (SEK)		Stockholm	4-Klövern	3-Klövern	JÖK	Population-weighted average
FCM	2 mL (100 mg)	132.00	132.00	140.00	137.00	134.21
	10 mL (500 mg)	660.00	660.00	700.00	685.00	671.04
	20 mL (1000 mg)	1,320.00	1,320.00	1,400.00	1,370.00	1342.08
	Mean price per mg	1.32	1.32	1.40	1.37	1.34
FD	1 mL (100 mg)	125.00	139.00	134.00	134.00	131.20
	5 mL (500 mg)	625.00	695.00	670.00	670.00	655.98
	10 mL (1000 mg)	1,250.00	1,390.00	1,340.00	1,340.00	1311.96
	Mean price per mg	1.25	1.39	1.34	1.34	1.32
IS	5 mL (100 mg)	38.50	38.40	38.00	38.50	38.40
	Mean price per mg	0.39	0.38	0.38	0.39	0.38

For FCM and FD, a simplified dosing table based on the ECCO anaemia guidelines used body weights and Hb levels to determine the appropriate dosing (see Table 3 for details) [11].

For IS, the Ganzoni formula was implemented (presented below) [29].

$$\text{Iron deficit (mg)} = \text{body weight} * (\text{target Hb} - \text{Hb}) * 2.4 + \text{iron stores} \quad (2)$$

Both methods were explored for all treatments in the scenario analyses. For each simulated patient, body weight (mean: 66.6 kg, SE: 0.7 kg) and Hb levels (mean: 9.6 g/dL, SE: 0.1 g/dL) were sampled based on the distributions of patient characteristics from two well-known RCTs of FCM [30, 31]. The sampled values dictated dosing, and therefore, the number of infusions is required.

To quantify health-care resource use from a hospital perspective, a microcosting approach was used in the base case for each region. This included the sum of the costs of administration (e.g., infusion time at the clinic and supervision time) and consumable resources (e.g., dressings and giving sets) used for a given patient. It was assumed that health-care professionals would try to minimize wastage of treatment vials. Tables 4 and 5 present the time and costs associated with resource use.

Several scenario analyses were explored in addition to the base case. As there were two methods for calculating iron deficiency dosing, scenarios were tested where all treatment doses were calculated using the same method (either the simplified dosing table or the Ganzoni formula). In addition, as an alternative to the microcosting approach for resource use, DRG codes were identified to determine the expected costs for relevant procedures (e.g., the fees for laboratory blood tests and infusion procedures).

To assess the robustness of results, deterministic sensitivity analyses were run in addition to the scenario analyses. Body weight and Hb levels are key factors in estimating the required iron dose. Therefore, mean body weight was adjusted up and down by 10 kg, and Hb level was adjusted up and down by 1 g/dL, respectively. To assess sensitivity of the results to the efficacy estimates from the NMA, the model was run using the estimates of the upper and lower 95% confidence intervals for the odds ratios of achieving a response with the comparator vs. FCM.

Table 3: Simplified dosing table.

Haemoglobin (g/dL)	Body weight (kg)		
	<35	35-70	≥70
<10	500	1,500	2,000
10-14	500	1,000	1,500
≥14	500	500	500

Table 4: Estimates of time required for treatment, based upon SmPC.

	FCM	FD	IS
<500 mg	6 min	—	—
500-1000 mg	15 min	—	—
<1000 mg	—	15 min	—
>1000 mg	—	30 min	—
<50 mg	—	—	8 min
50-100 mg	—	—	15 min
100-200 mg	—	—	30 min
Preparation time (min)	15 min	15 min	15 min
Observation time (min)	30 min	30 min	30 min
Giving sets required	1	1	1
Cannula required	1	1	1
Dressings required	1	1	1

2.1. Ethical Considerations. This article is based on the previously conducted analyses and does not involve any studies with human participants or animals performed by any of the authors.

3. Results

Across the presented procurement regions, FCM was found to be more effective and less costly than FD and IS (Table 6). The procurement region with the highest estimated iron

Table 5: Resource use costs.

Hospital-based health-care professional time	Salary for a nurse 38200 SEK/month
General practice-based health-care professional time	Salary for a nurse 38700 SEK/month
Laboratory blood test	30 SEK
Giving set	5073 SEK infusion in hospital setting

Table 6: Base case results for selected Swedish (SE) regions.

	FCM	FD	IS
Responder rate			
Stockholm	81%	74%	75%
3-Klöver	81%	74%	75%
4-Klövern	81%	74%	75%
JÖK	81%	74%	75%
Average of selected regions	81%	74%	75%
Iron dose			
Stockholm	1,443	1,356	1,365
3-Klöver	1,446	1,358	1,368
4-Klövern	1,443	1,357	1,365
JÖK	1,441	1,351	1,360
Average of selected regions	1,438	1,348	1,358
Number of infusions			
Stockholm	1.7	1.5	7.3
3-Klöver	1.7	1.5	7.3
4-Klövern	1.7	1.5	7.3
JÖK	1.7	1.5	7.3
Average of selected regions	1.7	1.5	7.3
Cost of treatment (SEK)			
Stockholm	SEK 25,335	SEK 25,618	SEK 129,942
3-Klöver	SEK 25,461	SEK 25,701	SEK 130,204
4-Klövern	SEK 25,317	SEK 25,645	SEK 129,935
JÖK	SEK 25,365	SEK 25,478	SEK 129,543
Average of selected regions	SEK 25,274	SEK 25,436	SEK 129,285
ICER		(FCM vs. FD)	(FCM vs. IS)
Stockholm			
3-Klöver			
4-Klövern		FCM more effective and less costly per responder than both FD and IS	
JÖK			
Average of selected regions			

dose requirements, and therefore costs of treatment, was 3-Klöver (comprising Örebro, Sörmland, and Värmland). IS was found to have the highest costs between the three treatments, requiring the highest number of infusions. Although the iron dose and number of infusions were slightly higher for FCM compared to FD, the difference in infusion times made the cost of treatment cheaper for FCM. The population-weighted average ICER for the selected regions also estimated a more effective and less costly treatment with FCM, versus the other treatments.

The scenario analyses included three scenarios: an alternative approach to quantifying treatment costs, as well as using either of two methods for calculating the required iron dose. Table 7 presents the scenario analyses results. In the scenario with DRG costing, FCM remained more effective and less costly vs. IS, but it exhibited a small extra cost per additional responder (i.e., extra efficacy) when compared with FD, over a year of treatment. When the table-based dosing method was used for all three treatments, FCM remained more effective and less costly vs. FD and IS in all

Table 7: Results of scenario analyses, FCM compared to FD and IS.

Incremental cost per responder (SEK)	DRG costing		All table-based dosing		All Ganzoni formula	
Region	vs. FD	vs. IS	vs. FD	vs. IS	vs. FD	vs. IS
Stockholm	16,804	More effective/less costly	More effective/less costly	More effective/less costly	19,550	More effective/less costly
3-Klöver	16,278	More effective/less costly	615	More effective/less costly	20,210	More effective/less costly
4-Klövern	17,051	More effective/less costly	More effective/less costly	More effective/less costly	24,137	More effective/less costly
JÖK	14,762	More effective/less costly	More effective/less costly	More effective/less costly	20,842	More effective/less costly
Average of selected regions	16,326	More effective/less costly	More effective/less costly	More effective/less costly	15,248	More effective/less costly

regions, with the exception of the FD comparison in the 3-Klöver region. On the other hand, the Ganzoni method of calculating dosages resulted in an extra cost per additional responder for FCM, when compared to FD. The population-weighted average of the selected regions followed the same trends as the individual regional clusters, in each scenario.

The deterministic sensitivity analysis tested three variables: odds ratios for the efficacy of treatment, body weight, and haemoglobin. For all scenarios, FCM was more effective and less costly than IS with both the upper and lower bound values (Table 8). The results were more sensitive when comparing FCM to FD, as the cost and efficacy values were estimated to be so close that the random variability inherent in patient simulation influenced the ratio in the ICER.

When testing the odds ratios for treatment efficacy, the estimate for the upper bound of the 95% CI resulted in FCM either being more effective and less costly than FD or estimating a small incremental cost per additional responder. The estimate for the lower bound of the confidence interval resulted in reduced responders with reduced costs, as treatment efficacy of FCM was diminished, compared to FD. Increasing the average body weight resulted in extra cost per additional responder for FCM versus FD. In most of the presented regions, a reduction in the average body weight resulted in FCM being more effective and less costly than FD, with the JÖK regional cluster estimating a slight increase in incremental costs per additional responder. With variation in the average patient Hb levels, FCM was more effective and less costly than FD in most regions, with only the Stockholm region estimating small increases in the cost per additional responder, when haemoglobin was increased.

4. Discussion

This evaluation of the cost-effectiveness of FCM vs. IS and FD is unique in that it presents both the comparative efficacy and costs for the different IV iron supplements, using current public tender prices at the regional level. The base case analyses suggest that in all selected Swedish regions, FCM is more effective and less costly per additional responder than the two comparators. When FCM was compared with FD, similar numbers of infusions resulted in slightly lower costs, explained by reduced infusion time and consequently lower health-care professional cost with FCM (see Table 4 for dosing details). When comparing FCM to IS, the higher number of infusions was the main driver of costs, causing FCM to be more effective and less costly than IS in all regions in the base case. This relationship was also reflected in the scenario analysis and sensitivity analysis.

The ICER results for FCM vs. FD were most dependent on the price for the region in question. This meant that minor changes in the price, or costs, could mean the difference between FCM being more effective and less costly than FD, or being more effective with a smaller extra cost per additional responder. However, differences in the efficacy of treatment and differences in health-care resource use of infusion can mitigate trivial differences in the price that currently exist. Reducing the number of infusions or the time of an infusion required for a patient can free up hospital capacity while also reducing costs.

Therefore, price should not be the sole factor in procurement decision-making. A recent article by Gaspar et al. discusses the absence of coherent standards for evaluations of nonbiological complex drugs, citing the approval of iron sucrose and iron dextran complexes despite differences in the scrutiny of provided evidence and a lack of established classification criteria [32]. These issues highlight the importance of a robust clinical assessment for nonbiological complex drugs before stating therapeutic equivalence, which is often assumed by authorities in charge of procurement, without having conducted a robust assessment. Considering the differences in effect between the different IV supplements can allow payers to allocate resources based on the needs of their patient populations.

Moreover, the respective regions are not static in their procurement methods, so understanding how these treatments compare within multiple regional formats can provide a blueprint for future decision-making. In addition, as not all regions in Sweden were available for inclusion in this comparative analysis, the creation of a population-weighted

Table 8: DSA results; FCM compared to FD and IS.

Stockholm	Bounds	vs. FD	vs. IS
OR +/-	Upper 95%	More effective/less costly	More effective/less costly
	Lower 95%	Reduced responders with reduced costs	More effective/ less costly
Body weight +/-	Increased by 10 kg	7,401 SEK per additional responder	More effective/ less costly
	Decreased by 10 kg	More effective/ less costly	More effective/ less costly
Haemoglobin +/-	Increased by 1 g/dL	2,082 SEK per additional responder	More effective/less costly
	Decreased by 1 g/dL	More effective/ less costly	More effective/less costly
3-Klöver	Bounds	vs. FD	vs. IS
OR +/-	Upper 95%	More effective/ less costly	More effective/ less costly
	Lower 95%	Reduced responders with reduced costs	More effective/ less costly
Body weight +/-	Increased by 10 kg	8,310 SEK per additional responder	More effective/less costly
	Decreased by 10 kg	More effective/less costly	More effective/less costly
Haemoglobin +/-	Increased by 1 g/dL	More effective/ less costly	More effective/ less costly
	Decreased by 1 g/dL	More effective/ less costly	More effective/ less costly
4-Klövern	Bounds	vs. FD	vs. IS
OR +/-	Upper 95%	SEK 24,682 per additional responder	More effective/ less costly
	Lower 95%	Reduced responders with reduced costs	More effective/ less costly
Body weight +/-	Increased by 10 kg	SEK 3,358 per additional responder	More effective/ less costly
	Decreased by 10 kg	More effective/less costly	More effective/less costly
Haemoglobin +/-	Increased by 1 g/dL	More effective/less costly	More effective/less costly
	Decreased by 1 g/dL	More effective/ less costly	More effective/ less costly
JÖK	Bounds	vs. FD	vs. IS
OR +/-	Upper 95%	7.21 SEK per patient	More effective/less costly
	Lower 95%	Reduced responders with reduced costs	More effective/less costly
Body weight +/-	Increased by 10 kg	6,159 SEK per additional responder	More effective/less costly
	Decreased by 10 kg	2,683 SEK per additional responder	More effective/ less costly
Haemoglobin +/-	Increased by 1 g/dL	More effective/less costly	More effective/ less costly
	Decreased by 1 g/dL	More effective/less costly	More effective/ less costly
SE selected regions average	Bounds	vs. FD	vs. IS
OR +/-	Upper 95%	More effective/ less costly	More effective/less costly
	Lower 95%	Reduced responders with reduced costs	More effective/less costly
Body weight +/-	Increased by 10 kg	5,746 SEK per additional responder	More effective/less costly
	Decreased by 10 kg	More effective/less costly	More effective/less costly
Haemoglobin +/-	Increased by 1 g/dL	More effective/less costly	More effective/less costly
	Decreased by 1 g/dL	More effective/less costly	More effective/less costly

average of the available regions provides the missing regions with a general estimate for the cost-effectiveness of the respective iron supplements in their context.

For the CEA, a probabilistic, response-based approach was chosen, as it could provide an intuitive and transparent comparison of these treatments, using a clinical measure of efficacy while allowing simulated patients to vary in required dose, as they would in real life. Since no head-to-head RCT has been conducted that includes all relevant IV formulations for this comparison, the present analysis used patient response rates from an NMA based on current existing RCTs for the included treatments [12]. In addition to the efficacy estimates, Aksan et al. also compared AE rates between treatments. The analysis found low risks for AEs with all IV formulations. A more recent comparison of AEs found similar rates between the relevant treatments, while the most frequent events differed between treatments [33]. As the discussion around AE profiles for different IV formulations was addressed in the NMA by Aksan et al. [12], it was deemed appropriate not to include costs and effects for AE's in this study.

There were certain limitations to the analysis performed in the NMA by Aksan et al., which in turn impact the results of the present analysis. These include the number of trials available for inclusion (5), some heterogeneity between study designs and their respective populations, as well as differences in IV formulation dosing. The NMA used the same ECCO guideline definition for treatment response and found that while FCM was significantly more efficacious than oral iron therapy, FCM did not have a statistically

significant response rate compared with FD and IS. Rank probability assessment found that there was an 83% probability of higher efficacy with FCM, but a 14% probability that FD was more effective.

Furthermore, there were limitations to the scope of this study; the lack of HRQoL data precluded the possibility of a CUA, thereby limiting the comparability of the results to usual willingness-to-pay thresholds and the relative value for money of different interventions across therapeutic areas. However, other cost-effectiveness analyses in different settings have used this cost-per-responder approach and can thus provide context to the results presented here. In addition, AE risks and associated costs were not considered in this study; there are a number of recent publications comparing the safety profiles of IV iron formulations, showing that different treatments are associated with different potential AEs [34–40]. However, the findings in some of the identified studies yielded contradictory results for the relative frequencies of certain AEs. Additionally, a recent and comprehensive Cochrane review of IDA treatments in IBD concluded that no significant differences in the rates of AEs could conclusively be identified between IV iron treatments [41]. Thus, the authors of this study decided that a more cautious approach of not including AE risks in the model was more appropriate while acknowledging that further research needs to be conducted to assess the relative risks.

The results of this study differ from the previous analyses of the costs associated with different IV formulations. However, those studies focused primarily on the budget impact from a state-wide perspective, thus not giving regional decision-makers the entire picture; there are a variety of reasons not to assume therapeutic equivalence between different IV iron formulations. To our knowledge, this is the first study assessing the cost per responder for intravenous iron treatments in IBD, using current public tender prices, and presenting actual results for different regional settings within a state. The regional context provides more meaningful results for decision-makers in a decentralized procurement system like Sweden, allowing them to adapt resource allocation to fit the needs of their respective populations and make informed decisions. In addition, as different IV formulations are associated with different efficacy and potential AE profiles, the inclusion of multiple treatments in each of the discussed regions opens the door for competition, allowing decision-makers to have more bargaining power in their efforts to treat the relevant populations.

This analysis also highlights the need for further research. Cost-effectiveness analyses with a regional focus, like this study, could be performed for other countries that also have a decentralized procurement system. Also, a study providing a robust source of information on how these treatments affect HRQoL would allow for cost-utility analyses, thereby making a comparison of cost-effectiveness results across therapeutic areas possible. With the present study, FCM was projected to be the most cost-effective IV iron therapy in all the selected Swedish regions, increasing the number of responders and leading to potential cost savings in regional health care.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

Conflicts of Interest

Antonio Ramirez de Arellano, Yvonne Thomson, and Dana Enkusson are all employees of CSL Vifor. Mathias Lilja, Linnea Oldsberg, and Nicholas Norton are employees of Quantify Research, which received consulting fees from CSL Vifor to support the preparation of the analysis and development of the manuscript. The authors report no other conflicts of interest in this work.

Authors' Contributions

DE and YT devised the project, approved the outline, and supervised the execution of the adaptation and manuscript. ARDA developed the cost-effectiveness model used in this analysis and supervised the adaptation to the local setting and interpretation of the findings. NN, LO, and ML adapted the model with Swedish inputs and wrote the majority of the manuscript, with support from DE and YT. AA was the chief advisor of the project, having provided the efficacy data for the model through previous published research and helping with high-level input on the manuscript and findings. All authors discussed the results and contributed to the final manuscript. All authors approved the final version of the article, including the authorship list.

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