ORIGINAL RESEARCH

Development of a Resource Impact Model for Clinics Treating Pre-Operative Iron Deficiency Anemia in Ireland

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ABSTRACT

Introduction: Intravenous (IV) iron is typically the preferred treatment for patients with iron deficiency anemia (IDA) who cannot tolerate or absorb oral iron, or who require fast replenishment of iron stores pre-operatively. Several IV iron formulations are available with different dosing characteristics affecting infusion speed and maximum dose. The aim was to develop a resource impact model to calculate the cost of establishing an IV iron clinic and model resource impact of different IV irons to inform clinicians and service providers implementing innovative pre-operative IV iron services in Ireland.

Methods: A resource impact tool was developed to model resource utilization and IDA treatment costs. Two fast-administration, high-dose formulations of IV iron are available in Ireland: iron isomaltoside 1000/ferric derisomaltose (IIM) and ferric carboxymaltose (FCM). The tool modeled clinic throughput based on their different dosing characteristics in a specific IDA population, capturing fixed overheads, variable costs, clinic income from private and publicly-funded patients, and savings associated with IV iron.

Results: Based on a 70:30 split between public and private patients in a new pre-operative service with capacity for 12 infusion slots weekly, IIM would facilitate correction of iron deficits in 474 patients annually, resulting in a net annual clinic balance of €42,736 on income of €159,887 and net costs of €117,151. FCM would facilitate treatment of 353 patients, resulting in a net annual clinic balance of €36,327 on income of €116,050 and costs of €79,722, a difference of €6408 and 121 patients treated in favor of using IIM over FCM.

Conclusion: Based on this provider-perspective analysis, IIM would maximize clinic throughput relative to other IV iron formulations, allowing clinicians in Ireland to optimize their current service provision and expenditure, and model the impact of introducing IV iron clinics for pre-operative patients with IDA.

Keywords: Administration; Costs and cost analysis; Health economics; Hematology;

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INTRODUCTION

Anemia is defined by the World Health Organization as hemoglobin levels < 13 g/dL in men older than 15 years, < 12 g/dL in non-pregnant women older than 15 years, and < 11 g/dL in pregnant women [1]. Iron deficiency is the top-ranking cause of anemia worldwide, and iron deficiency anemia (IDA) is the combination of anemia and depressed total body iron, with the latter typically confirmed by low (< 30 μg/L) serum ferritin levels [2]. In Ireland in 2013, Kassebaum et al. estimated that there were 464,893 patients with mild anemia, 352,789 patients with moderate anemia, and 23,470 patients with severe anemia, with IDA comprising 62.6% of all cases of anemia globally [3].

Anemia has multiple etiologies, including a wide range of conditions that cause diminished iron uptake, increased iron demand or increased iron loss, with gastrointestinal or gynecological involvement being among the most common causes [4]. For a variety of pathophysiological reasons including inflammatory processes, nutritional deficiencies, and iatrogenic causes, anemia is also extremely common in patients admitted to hospital, including those undergoing elective surgery [5]. For instance, in a cohort of 232,450 adult patients hospitalized in the Cleveland Clinic Health System between January 2009 and August 2011, 43,741 (19%) presented with anemia upon admission, and 60% of those who were not anemic upon presentation developed hospital-acquired anemia [6].

In patients undergoing surgery, the prevalence of anemia varies by the nature of the disease in the patient population; for instance, around one-third of patients undergoing non-cardiac surgery have pre-operative anemia [7, 8], while studies in colorectal surgery have shown even higher rates, with 57.6% of patients with right-sided colon cancer having anemia prior to surgical resection [9]. Anemia is considered to be a symptom of the underlying condition requiring surgery, but several large studies have recently established that pre-operative anemia is also an independent risk factor for increased perioperative morbidity, mortality, and prolonged length of hospital stay [7, 10–12]. Pre-operative anemia increases the likelihood of perioperative allogeneic blood transfusion and the associated risks of wound problems, systemic sepsis, and prolonged length of post-operative hospital stay [5, 13–15].

Correction of pre-operative anemia can therefore play an important role in reducing the risk of these perioperative complications

(including mortality), shortening the length of hospital stay, reducing red blood cell (RBC) transfusion rates and improving quality of life. This has been demonstrated in smaller randomized clinical trials, in real-world data from large cohorts of patients, and in meta-analyses [16, 17]. Randomized controlled trials (RCTs) have further illustrated the benefits of using intravenous (IV) iron prior to surgery. In 2016, an RCT in 72 patients published by Froessler and colleagues showed a 60% reduction in the transfusion rate of allogeneic RBCs (12.5% vs. 31.25%), a greater increase in hemoglobin levels ($+ 0.8$ g/dL vs. $+ 0.1$ g/dL), and a shorter length of hospital stay (7.0 days vs. 9.7 days) in patients treated with IV iron relative to those receiving usual care [18]. Spahn et al. also recently reported the findings of an RCT in patients with IDA prior to cardiac surgery, in which 20 mg/kg of IV iron, 40,000 U of subcutaneous erythropoietin alpha, 1 mg subcutaneous vitamin B12, and 5 mg oral folic acid were compared with placebo [19]. The study showed a significant reduction in the median number of red blood cell units transfused from 1 to 0, with a corresponding increase in hemoglobin concentration, reticulocyte count, and a reticulocyte hemoglobin content [19]. Similarly, a 2018 study by Biboulet and colleagues demonstrated the superior efficacy of IV iron in combination with erythropoietin relative to oral iron in patients undergoing major orthopedic surgery, showing a 0.7-g/dl larger increase in preoperative hemoglobin ($p < 0.001$) [20].

Reductions in RBC transfusion rates associated with correction of pre-operative anemia mean that IV iron infusion plays a central role in patient blood management (PBM) programs. In 2015, this role was codified in UK guidance from the National Institute for Health and Care Excellence (NICE). The guidance focused on reducing unnecessary blood transfusions, with IV iron being recommended as an alternative to blood, especially in patients with IDA requiring rapid iron replenishment, intolerant of oral iron, or with functional iron deficiency [21]. In Ireland, PBM initiatives, such as improving blood stock management and increasing monitoring of RBC usage indicators, have resulted in remarkable reductions in RBC issuance [22].

Increasing the use of IV iron in the correction of pre-operative anemia therefore represents an additional initiative that has the potential to still further improve the outcomes of the PBM program in Ireland.

More recently, a randomized trial in patients with colorectal cancer was published by Keeler et al., demonstrating that ferric carboxymaltose (FCM; Ferinject®; Vifor France, Paris, France) administered 2 weeks prior to surgery significantly increased hemoglobin levels on the day of surgery and 3 months after surgery, and significantly improved quality of life relative to oral iron. No difference in complications, transfusion or length of stay was demonstrated, which may be due to sample size, and/or the patients having non-metastatic cancer, with a relatively good condition and a low risk profile (ASA score). However, the group receiving intravenous iron needed a dose of 1500–2000 mg of intravenous iron in 82 of the cases, meaning that two hospital visits were required to receive the full dose, since only 1000 mg of FCM can be given in a single infusion [23, 24].

Further to this research, the ITACS and PREVENTT double-blind RCTs are currently ongoing [25–27]. The primary endpoint of ITACS is the number of days alive and out of hospital in the first 30 days after surgery in patients receiving placebo versus those receiving 1000 mg of IV iron [25, 26]. Secondary endpoints include the proportion of patients experiencing correction of anemia, number of allogeneic blood units transfused, intensive care and hospital stay duration, quality of life, and cost-effectiveness [25]. Similarly, PREVENTT is investigating the risk of blood transfusion or death, and the blood transfusion rate in patients with anemia prior to undergoing elective major (> 1 h) open abdominal surgery [27]. Patients ($n = 487$) were randomly assigned to receive either placebo or IV iron prior to surgery. Once completed, PREVENTT will represent the largest RCT ever conducted on the efficacy of correcting pre-operative anemia.

Two fast-administration, high-dose IV iron formulations are currently available in Ireland: FCM and iron isomaltoside 1000/ferric derisomaltose (IIM; Monover®; Pharmacosmos,

Holbæk, Denmark). Both iron formulations are colloidal, consisting of iron (III) hydroxide complexed with different carbohydrates. The drugs differ in their approved posology: IIM can be dosed up to 20 mg per kg body weight with no other dose limitations, while FCM can only be dosed up to a maximum of 1000 mg and 20 mg per kg body weight per infusion.

While the benefits of pre-operative IV iron infusion have been demonstrated in the Froessler et al. RCT [18], the economic and logistical aspects of pre-operative iron infusion have not been evaluated. In the present study, we therefore sought to develop a model to evaluate the resource use and cost implications associated with establishing an iron infusion clinic for the treatment of pre-operative IDA in Ireland, with the secondary objective of quantifying how the use of different IV iron formulations affects resource use and costs in the clinic setting.

METHODS

Resource Impact Model

A resource impact model was developed in Microsoft Excel (Microsoft, Redmond, WA, USA) to model resource utilization and pre-operative IDA treatment costs based on a combination of infusion costing data from the finance department at Cork University Hospital, previously-published models of IDA treatment, and the posological characteristics of modern IV iron formulations [28]. A multidisciplinary team was involved in establishing key aspects of the financial flows and resource utilization in an iron infusion clinic in Ireland, including fixed overhead costs, variable costs (i.e., costs incurred with each infusion), clinic income from private and publicly-funded patients, and savings associated with the correction of pre-operative anemia (Fig. 1; Table 1).

The resource impact model simulated clinic throughput based on an assumed number of available infusion slots per year, with a model input to govern the allocation of infusion slots to privately- and publicly-funded patients, and elective versus non-elective procedures. The
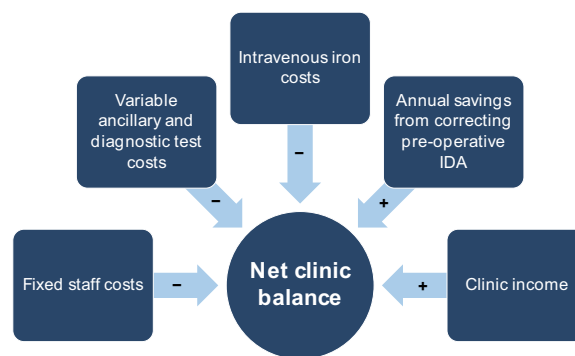

Fig. 1 Costs, savings and income driving the calculation of the net clinic balance

clinic throughput assumptions were combined with a model of IV iron dosing characteristics and iron deficits in a specific population with pre-operative IDA to establish the number of patients whose iron deficiency could be corrected in the clinic per year.

Iron deficits in the modeled cohort were based on the simplified tables of iron need found in the summaries of product characteristics (SPCs) for the respective IV iron products [29, 30]. The simplified tables of iron need were used in preference to the alternative iron deficit calculation approach of the Ganzoni equation, on the grounds that the European Crohn's and Colitis Organisation guidelines recommend the use of this calculation method [31].

The use of the Ganzoni formula as the basis of the iron deficit model was explored in a sensitivity analysis:

$$\begin{aligned} \text{Iron deficit (mg)} = \ & \text{Weight (kg)} \\ & \times [15 - \text{Hb(g/dL)}] \times 2.4 \\ & + 500 \end{aligned}$$

In addition to modeling IIM and FCM, resource use and costs associated with two other IV iron products were also modeled: iron sucrose (IS; Venofer®; Vifor France), which can be dosed up to 200 mg per infusion, and low molecular weight iron dextran (LMWID; CosmoFer®; Pharmacosmos), which can be infused intravenously over 4–6 h at up to 20 mg/kg.

Table 1 Income, costs and savings captured in the resource impact model

Cost category	Cost components
Annual fixed staff costs	Medical admin staff
	Consultant
	Staff nurse
Annual variable ancillary and diagnostic test costs	Full blood count
	Renal function
	Transferrin saturation
	Serum ferritin
	C-reactive protein
	Giving set/cannula/dressing
IV iron costs	IV iron (FCM, IIM, IS, or LMWID)
Annual savings arising from correction of pre-operative anemia	Reduction in ICU stay
	Reduction in ward stay (elective admissions)
	Reduction in ward stay (non-elective admissions)
	Potential blood saving per patient (standard red cells)
	Annual savings via reduced hospital readmission rate (within 30 days)
Clinic income	Public patient day case admission
	Private patient day case admission
	Private patient IV iron charge
	Private patient billing for materials and laboratory costs
	Private patient billing for consultant costs

FCM ferric carboxymaltose, *IIM* iron isomaltoside 1000, *ICU* intensive care unit, *IS* iron sucrose, *IV* intravenous, *LMWID* low molecular weight iron dextran

Base Case Analysis

In the base case analysis, it was assumed that the clinic would operate for half a day (4 h) a week with 12 infusion slots per half-day, corresponding to 624 infusion slots per annum. The assumption of 12 infusion slots was based on an assumption of one nurse being capable of administering and monitoring three infusions per hour. For each half-day of clinic operation, a nurse was assumed to be present 100% of the time along with a member of medical admin staff, with a consultant also present 60% of the time (2.4 h per half day). The analysis was conducted over a 1-year time horizon from the perspective of an infusion clinic in Ireland.

Clinic running costs were taken from a variety of sources specific to the Irish setting (Table 2). Staff costs and costs associated with diagnostic tests, cannulas, dressings, and giving sets were provided by Cork University Hospital, while costs of IV iron were based on list prices from MIMS Ireland in January 2019.

Cost savings arising from the correction of pre-operative anemia with IV iron were based

Table 2 Unit costs and resource use assumptions employed in the base case clinic costing analysis

Fixed cost item	Cost (€)	Resource use
Medical admin staff day rate	128.69	1 FTE
Consultant day rate	770.30	0.6 FTE
Staff nurse day rate	159.77	1 FTE

Variable cost item	Cost (€)	Resource use
Laboratory test panel (full blood count, renal function, transferrin saturation, serum ferritin, and C-reactive protein)	60.00	1 per patient
Giving set/cannula/dressing	3.37	1 per patient
Iron isomaltoside (5 × 1 ml at 100 mg/ml; 500 mg total)	147.06	Average 1493 mg
Ferric carboxymaltose (1 × 20 ml at 50 mg/ml; 1 g total)	270.75	Average 1493 mg

FTE full-time equivalent

Table 3 Annual savings and clinic income

Annual savings arising from IV iron	Savings per patient (€)
Reduction in ICU stay	1780
Reduction in ward stay	810
Reduction in ward stay (non-elective admissions)	810
Potential blood saving per patient (standard RBC transfusion)	295
Annual savings from reduced hospital readmission (within 30 days)	1620

Clinic income	Income per patient (€)
Day case admission	80.00
Private patient day case admission	407.00
Private patient IV iron charge (IIM)	441.18
Private patient IV iron charge (FCM)	406.13
Private patient IV iron charge (IS)	155.10
Private patient IV iron charge (LMWID)	181.29
Private billing for materials lab costs	63.37

Clinic income	Portion covered by private payers (€)
Private billing for consultant costs	12,016.62

FCM ferric carboxymaltose, *IIM* iron isomaltoside 1000, *ICU* intensive care unit, *IS* iron sucrose, *LMWID* low molecular weight iron dextran, *RBC* red blood cell

on unit cost estimates from Cork University Hospital (Table 3). In the absence of resource use data specific to Ireland, Irish unit costs associated with reduced ward or intensive care unit (ICU) stays were combined with Hospital Episode Statistics (HES) from NHS Digital based on data from all NHS hospitals in England [32]. Savings arising from a reduction in the need for RBC transfusions were based on the difference in the number of units transfused intra- and post-operatively in patients receiving pre-operative iron (8 units in 40 patients) versus those receiving usual care (25 units in 32 patients) in the Froessler et al. RCT [18].

Estimates of clinic income for publicly-funded day case admissions, private day case admissions, private IV iron pass-through costs, and private billing for materials and diagnostic test costs were provided by Cork University Hospital. For the base case analysis, a public:private split of 70:30 was assumed based on consultation with Cork University Hospital, and an elective:non-elective split of 77.4:22.6 was assumed based on the NHS HES data [32].

The characteristics of the specific IDA population were based on a weighted average of mean baseline hemoglobin and bodyweight from seven studies included in a recent review of IDA [33]. Mean baseline hemoglobin was taken to be 9.99 g/dL with a standard deviation of 1.03 g/dL, and bodyweight was assumed to be 82.36 kg with a standard deviation of 22.5 kg. The modeled cohort was distributed across lognormal distributions of hemoglobin and bodyweight to reflect the right-skewed distributions typically observed of both bodyweight and hemoglobin at a population level (Fig. 2) [34, 35]. To avoid capturing patients for whom no specific dose recommendations are made in the dosing tables in the SPCs, the lower end of the bodyweight distribution was truncated at 50 kg by mirroring the probability density function around the minimum weight of 50 kg, as described previously [28]. Note that the analysis was based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.
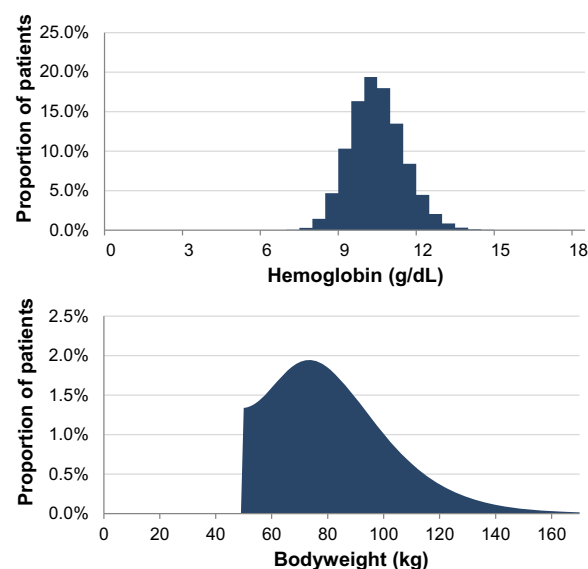

Fig. 2 The modeled hemoglobin and bodyweight distributions in the reference case analysis

Sensitivity Analyses

A series of one-way sensitivity analyses were conducted around key model inputs to establish the effect of individual parameters on top-line outputs. Analyses were conducted in which 100% of procedures were modeled as being elective and 100% being non-elective; the assumed clinic throughput was varied from 3 infusions per hour in the base case analysis to 2 and 4 infusions per hour; the bodyweight and hemoglobin levels of the population with IDA were adjusted to match the baseline characteristics in the Froessler et al. RCT [18]; the Ganzoni equation was used to model iron need; the assumptions of reduced ward stay and hospital readmission in the base case were abolished; and the proportion of total infusion time overseen by a consultant was increased from 60% in the base case to 100%.

RESULTS

Based on the assumptions employed in the base case analysis, the resource impact model reported the number of privately- and publicly-funded patients whose pre-operative IDA would be corrected given a fixed annual clinic
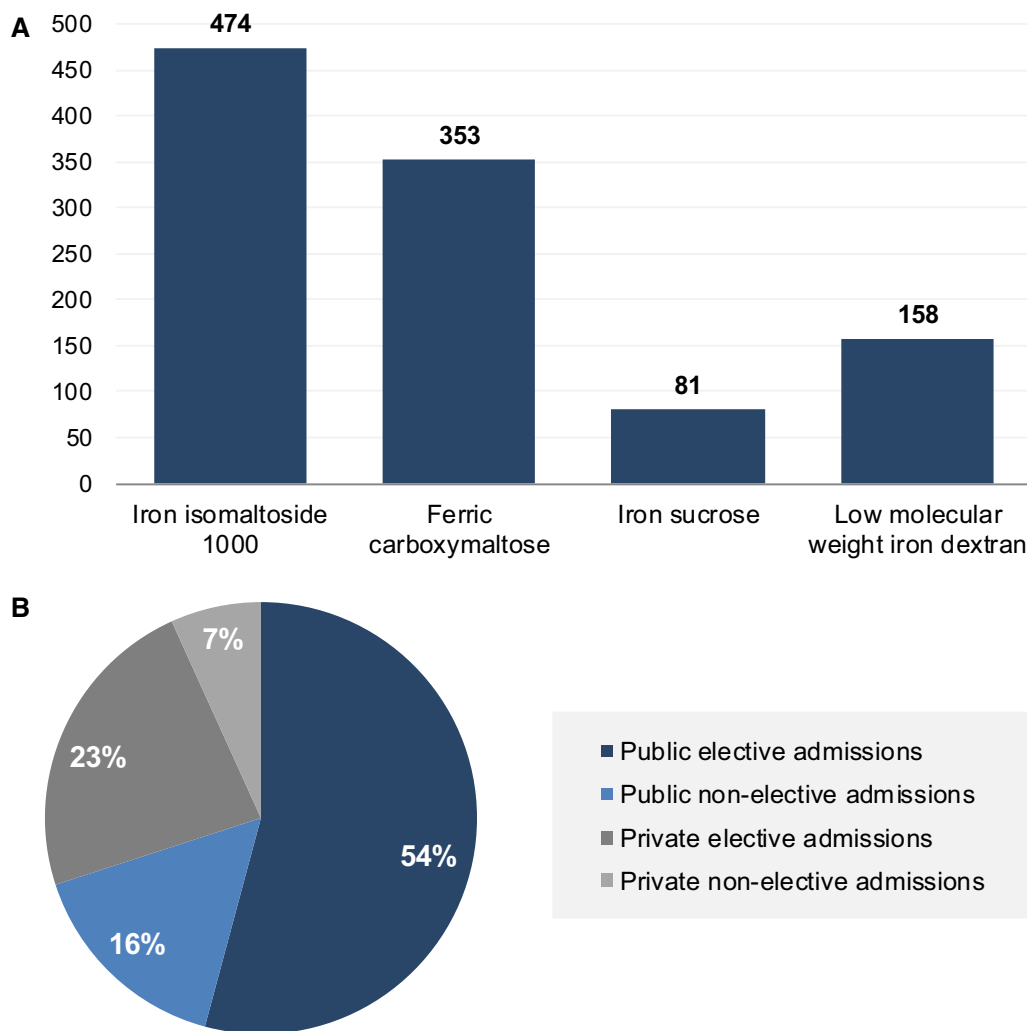
A

B

- Public elective admissions
- Public non-elective admissions
- Private elective admissions
- Private non-elective admissions

Fig. 3 **a** Patients with pre-operative iron deficiency anemia treatable annually with 12 infusion slots per week (624 per year) based on simplified dosing tables and assuming lognormal distributions of hemoglobin and bodyweight, and **b** proportions of publicly- versus privately-funded patients and proportions treated as elective versus non-elective

throughput in terms of the number of iron infusions. The model also reported the fixed and variable clinic running costs, the cost savings arising from correcting pre-operative anemia, and the clinic income from conducting a mix of privately- and publicly-funded day cases.

Based on the simplified tables of iron need in a new pre-operative service with capacity for 624 infusions annually, IIM would facilitate correction of iron deficits in 474 patients, compared with 353 for FCM, 81 for IS, and 158 for LMWID (Fig. 3a). Based on a 70:30 split between public and private patients and a 77.4:22.6 split between elective and non-elective iron replacement, the majority (54%) of patients underwent publicly-funded elective iron replacement, with 23% undergoing elective privately-funded replacement, and 16% and 7% undergoing non-elective iron replacement with public and private funding, respectively (Fig. 3b).

The use of IIM resulted in the treatment of 474 patients and a net annual clinic balance of €42,736 on income of €159,887, costs of
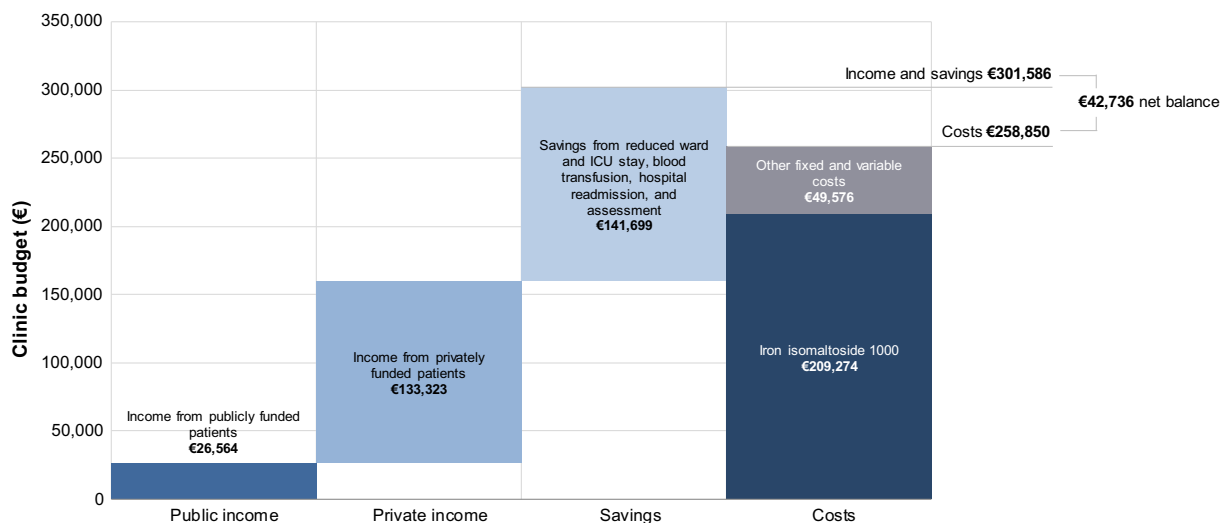
Fig. 4 Modeled clinic income, costs and savings arising from correction of pre-operative anemia using iron isomaltoside 1000, based on a 30:70 split between privately- and publicly-funded patients

€258,850 and savings of €141,699 relative to not addressing pre-operative anemia (Fig. 4). FCM would facilitate treatment of 353 patients, resulting in a net annual clinic balance of €36,327 on income of €116,050, costs of €185,036 and savings of €105,314 relative to not correcting pre-operative anemia. Relative to FCM, IIM would therefore result in an additional surplus balance of €6408 over 1 year and 121 (34.2%) additional patients treated with IV iron. The low throughput with IS resulted in lower income, variable costs, savings and net clinic balance; income was projected to be €23,242, with costs of €37,125, and annual savings relative to not correcting pre-operative anemia of €24,077, resulting in a net clinic balance of €10,194. The slower rate of infusion of LMWID similarly resulted in lower throughput with income of €43,371, costs of €58,201, and savings of €47,233 resulting in a net clinic balance of €32,403.

One-way sensitivity analyses showed that the net clinic balance was most sensitive to the number of infusion slots available per half-day; higher throughputs resulted in an increased net balance as fixed clinic running costs per procedure decreased while clinic income increased (Table 4). Changing the iron need calculation approach to the Ganzoni equation resulted in the largest change in the difference in net clinic

balance and patient throughput between the iron formulations, with the difference between IIM and FCM increasing from €6408 (and an additional 121 patients) in the base case to €15,963 (and an additional 191 patients) using the Ganzoni equation. Changing the baseline cohort characteristics to match those from the Froessler et al. study [18] also had a notable effect on the difference between formulations, increasing the difference in net clinic balance between IIM and FCM to €12,217 and increasing the difference in patient throughput to 169 patients (520 vs. 352) from 121 in the base case.

DISCUSSION

The present analysis showed that, in an iron infusion clinic with a fixed annual throughput, IIM would result in more patients with IDA receiving treatment to correct their iron deficiency. In addition to the increased throughput, the use of IIM was projected to result in a higher net clinic balance relative to FCM, IS and LMWID. The analysis represents the first attempt to characterize the costs of running an IV iron clinic in the Irish setting. One previous study, by Radia and colleagues, was identified in the literature that evaluated the selection of IV iron in an IV iron service in the United

Table 4 One-way sensitivity analysis results showing the net clinic balance (higher is better) and the change in the net clinic balance arising from the use of other iron formulations relative to iron isomaltoside 1000

Analysis	IIM	FCM		IS		LMWID	
	Net balance (€)	Net balance (€)	Δ from IIM (€)	Net balance (€)	Δ from IIM (€)	Net balance (€)	Δ from IIM (€)
Base case	42,736	36,327	− 6408	10,194	− 32,542	32,403	− 10,333
100% elective procedures	39,028	33,572	−5456	9564	−29,464	31,167	−7861
100% non-elective procedures	55,434	45,765	−9669	12,352	−43,083	36,636	−18,799
8 infusion slots per half day	23,187	18,914	−4272	1492	−21,694	16,298	−6889
16 infusion slots per half day	62,285	53,740	−8544	18,896	−43,389	48,507	−13,777
Full consultant oversight	37,128	30,720	−6408	4586	−32,542	26,795	−10,333
No ward stay reduction with pre-operative iron	35,270	30,779	−4491	8926	−26,344	29,914	−5356
No reduction in hospital readmission with pre-operative iron	38,156	32,924	−5232	9416	−28,740	30,876	−7280
Ganzoni equation-based iron need calculation	46,332	30,369	−15,963	10,504	−35,828	35,365	−10,967
Froessler et al. baseline characteristics	48,390	36,173	−12,217	10,608	−37,723	37,085	−11,329

€ 2019 Euros, *FCM* ferric carboxymaltose, *IIM* iron isomaltoside 1000, *ICU* intensive care unit, *IS* iron sucrose, *LMWID* low molecular weight iron dextran

Kingdom, but the selection of IV iron was based on contraindications for IIM which have since been removed from the IIM SPC, and did not factor in the special warnings and precautions now contained in the FCM SPC pertaining to hypophosphatemia and hepatic or renal impairment [36]. Other studies have previously modeled costs of performing infusions in other healthcare settings and indications, focusing on the administration of biological agents, such as infliximab in patients with inflammatory bowel disease and rheumatoid arthritis, alongside other biologic disease-modifying antirheumatic drugs such as rituximab and abatacept [37, 38].

The comparative analysis of the modern IV iron formulations was driven primarily by posological differences between the iron formulations. Using the simplified tables of iron need, all patients weighing ≥ 70 kg and all patients with hemoglobin levels < 10 g/dL

cannot be infused with a sufficiently high dose (i.e. 1,500 mg or 2000 mg) of FCM to provide the recommended amount of iron to correct the iron deficit in a single infusion. The weight-dependent maximum dosing of IIM means a single infusion of IIM is sufficient to administer the recommended dose (1500 mg) in all patients with hemoglobin ≥ 10 g/dL weighing 75 kg or more. The limitations of dosing with FCM in the PBM context were borne out in the Keeler et al. trial in patients with pre-operative anaemia, in which 82% of patients required two iron infusions prior to surgery for colorectal cancer [23]. Conversely, recent real-world data from the UK suggests that, where a majority of patients require > 1000 mg of iron, IIM enables administration in a single dose [39].

The relative efficacy of the two IV iron formulations should also be considered when interpreting the findings of the analysis. A

recent network meta-analysis conducted by Aksan et al. reported that "concerning efficacy, no statistically significant difference was found when comparing FCM, [IIM] and IS", specifically with regard to the proportion of patients showing hematopoietic response, defined as normalization of hemoglobin levels or an increase in Hb of ≥ 2 g/dL in patients with IBD [40]. While the authors subsequently noted that "[t]hese types of analyses are more exploratory-pragmatic or 'observational' rather than confirmatory" [41], the finding of no significant difference in the proportion of responders is aligned with a recent indirect treatment comparison (ITC) of IIM and FCM using a common comparator of IS. The ITC reported no significant difference in the proportion of patients achieving a clinically-relevant response with IIM and FCM, but did report a significantly larger mean increase in hemoglobin from baseline with IIM relative to FCM [42].

Notably, the average modeled dose of 1493 mg in the present study is high relative to real-world studies such as the non-interventional Monofer (NIMO) study, which reported a mean administered iron dose of 1100 mg in 185 patients with anemia [43]. As reported in the study, however, the mean iron need was calculated to be 1481 mg according to the simplified table of iron need and 1324 mg according to the Ganzoni formula. The NIMO study authors acknowledged the shortfall of iron administered in clinical practice in their discussion, but did not investigate or speculate on the underlying reason [43]. Regardless of the reason, the shortfall was not without consequence: of the patients enrolled in the NIMO study with anemia at baseline, 37% were still anemic following the first iron treatment, suggesting that the administered dose was indeed insufficient [41]. Notably, patients in NIMO receiving doses of IIM over 1000 mg experienced a 65% lower probability of needing retreatment versus patients receiving exactly 1000 mg, illustrating a dose–response relationship that would justify administering higher initial doses to reduce the need for retreatment [41].

High doses of IIM have been shown to be both well tolerated and effective in the PROMISE trial, in which 21 patients with IBD

patients and IDA were treated with single doses of up to 2000 mg, and cumulative doses of between 1500 and 3000 mg of IV iron [44]. In PROMISE, no serious adverse drug reactions were observed, and no patients experienced severe hypophosphatemia (s-phosphate level < 1 mg/dL) [44]. While the sample size in PROMISE was small, the absence of serious adverse drug reactions suggests that there should be no additional concern associated with administering > 1000 mg versus administering 1000 mg or less. Recent evidence has also shown that the risk of hypophosphatemia appears to be significantly greater with FCM relative to IIM, with a pooled analysis of 245 patients in the two PHOSPHARE RCTs showing severe hypophosphatemia occurring in 11.3% of patients treated with FCM versus 0.0% of patients treated with IIM ($p < 0.0001$), and hypophosphatemia < 2 mg/dL occurring in 74.4% of patients treated with FCM versus 8.0% treated with IIM ($p < 0.0001$) [45].

Finally, it is worth considering the limitations of the present study when interpreting the findings. The first notable limitation is that the clinic running costs were not exhaustive; for instance, some overhead costs such as depreciation, ground rent or space charges, maintenance costs, and utility bills were not included. A second important limitation was the exclusion of any clinical discretion on the administered iron doses. For instance, the simplified tables of iron need for both IIM and FCM recommend that a patient weighing 72 kg with a hemoglobin level of 10 g/dL would require 1500 mg. In the case of IIM, such a patient would receive one dose of 1440 mg in a first infusion (the maximum permissible dose based on 20 mg/kg) and then 60 mg in a second infusion. In practice, the clinician may decide that the first infusion would be sufficient to address the iron deficit and that no subsequent infusion would be required. However, this modeling assumption results in a conservative estimate of the net clinic balance by reducing patient throughput for a given number of infusion slots, and was adopted for all iron formulations. Given the more fine-grained body-weight-based dosing increments with IIM relative to FCM (and therefore the increased

frequency with which this assumption would affect IIM), the assumption may have also underestimated the benefit of IIM versus FCM. One final potential limitation is the generalizability of the model and findings. The study deliberately adopted the perspective of a pre-operative infusion clinic in Ireland to address our specific research question. The clinic perspective, focusing on the net clinic balance, is notably distinct from national payer perspectives where diagnosis-related groups, healthcare resource groups, or reference costs are commonly used to establish the size of payments to service providers. Nevertheless, the modeling approach employed should be applicable to infusion clinics in other geographies and payer settings with only minimal changes.

CONCLUSIONS

Treating IDA before surgery is a cornerstone of PBM as recommended by NICE, and has been shown to improve patient outcomes and save costs at a large scale. The development of a robust resource impact model in the present analysis allows decision-makers in Ireland to model the impact of introducing IV iron clinics for the treatment of pre-operative patients with IDA.

Based on clinic throughput modeling using data from an existing IV iron clinic in Ireland, and the posological characteristics of the IV iron formulations as specified in the SPCs, IIM was shown to result in substantially higher patient throughput than other IV iron formulations, while also driving favorable economic outcomes from the clinic perspective. IIM should therefore be considered as the IV iron formulation of choice in the establishment of IV iron infusion clinics for the treatment of pre-operative anemia in Ireland.

ACKNOWLEDGEMENTS

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