

ORIGINAL RESEARCH

Budget Impact of Intravenous Iron Therapy with Ferric Carboxymaltose in Patients with Chronic Heart Failure and Iron Deficiency in Romania

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ABSTRACT

Background: Ferric carboxymaltose (FCM) treatment in case of iron deficient (ID) patients with chronic heart failure (CHF) has shown great promise according to the findings of recent studies in improvement of symptoms and quality of life, New York Heart Association (NYHA) classification, and exercise capacity. **Aim of the study:** The purpose of the current study is to assess the budget impact of treating CHF patients with FCM in a sample of Romanian hospitals. **Material and methods:** Calculations have been based on the budget impact model developed by Theidel *et al.* The assumptions and clinical outcomes of the current study were based on a multivariate statistical approach used in the same German study. The predicted outcomes were based on data pooled from four double-blind randomized controlled trials. The time horizon of the model was 1 year. Budget impact calculations were performed from the public payer perspective. Two scenarios have been handled: one without applying the Clawback tax and one with applying the tax to the cost of medication. **Results:** The yearly budget impact of FCM vs. no iron-replacement treatment without applying the tax ranged between €678,383 and €641,588 for 1,000 patients, resulting in €37 of additional costs per patient per year. The yearly budget impact of FCM vs. no iron-replacement treatment with applying the tax ranged between €616,934 and €641,588 for 1,000 patients, resulting in €9 of cost reduction per patient per year. Key cost drivers included the cost of outpatient visits and the cost of hospitalization due to HF worsening. Sensitivity analysis for both scenarios proved the robustness of the results. **Conclusions:** The FCM treatment of CHF patients has a moderate budget impact. Moreover, this budget impact/saving translates into a reduction of the rate and length of hospitalization stay and a better symptomatic profile of the patients.

Keywords: heart failure, iron deficiency, treatment cost, budget impact, ferric carboxymaltose, Romania

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INTRODUCTION

Chronic heart failure (CHF) is a complex, malignant clinical syndrome, resulting in the heart's inability to provide proper output. In spite of the continuous development of new therapies addressed to CHF, the mortality of this disease remains very high, and the episodes of acute decompensation leading to acute pulmonary edema are quite frequent. As a result, the number of hospital readmissions in emergency conditions is increasing, which directly impacts the cost of healthcare in this patient population. The symptoms vary depending on which ventricle is affected. Common signs and symptoms include dyspnea, coughing, wheezing, lower extremity edema, fatigue, nausea, and palpitation.¹ In developed countries, the lifetime risk of chronic heart failure for men and women is 1 in 5, the risks being as high for women as for men.² In order to assess the severity of CHF, it is recommended to use the New York Heart Association (NYHA) functional classification, which is important for the diagnosis and management of the disease, as well as setting a prognosis.³

In Romania, heart failure (HF) can be considered a severe condition, resulting in high mortality and readmission rates. According to the published literature regarding the epidemiological data on CHF in Romania, 4.7% of the population over the age of 35 is diagnosed with the disease. The 1-year mortality for hospitalized CHF patients has been estimated to 6%, and 8.9% of the patients are readmitted.⁴ There is no HF registry in Romania, as there is in other countries; however, there have been several studies assessing the local situation. Recent estimates show an incidence of 0.146% and a prevalence of 1.76% for CHF, with an approximate number of 800,000–900,000 patients.⁵ The incidence of CHF is continually increasing, which may be the result of the aging of the population and the increase of the survival of myocardial infarction patients.⁶

Iron deficiency (ID) is an important comorbidity of CHF. A pooled analysis of 1,506 patients has found that about 50% of CHF patients are iron-deficient, and ID has been found to be connected to the severity of CHF (expressed in NYHA classification).⁷ Similar results were obtained by another study, conducted in the United Kingdom by Cleland *et al.* on 4,456 patients, where 43.2–68.0% of the anemic CHF patients had ID.⁸ Further studies have found that iron homeostasis disorders are correlated with NYHA class, an increased risk of anemia, and the progression of CHF.⁹ Another study of 546 patients has concluded that in case of systolic CHF, ID is quite common, and it represents

a predictor for a negative outcome.¹⁰ The health-related quality of life (HRQoL) of CHF patients is also affected by ID. A study of 552 patients has found that the HRQoL of ID patients is significantly worse compared to non-ID CHF patients, especially because of the negative impact on the physical dimensions of health.¹¹

Various treatment options are accepted in case of ID patients; however, intravenous iron is usually preferred. A meta-analysis of two studies has shown that, when compared to placebo, the intravenous ferric carboxymaltose (FCM) treatment of CHF patients with ID results in the reduction of hospitalizations due to worsening CHF.¹² A study of 459 patients has shown that 50% of the patients treated with FCM reported highly or moderately improved health state per the Patient Global Assessment compared to 28% of the placebo group.¹³ Another randomized clinical trial, with 304 patients, has proven that the FCM treatment of iron-deficient CHF patients results in the improvement of functional capacity, quality of life, and symptoms, and the treatment may also reduce the rate of hospitalizations resulting from the worsening of CHF.¹⁴

At this stage, there is minimal to no information available regarding the budget impact of FCM treatment in Romania. Hence, the main objective of the study is to assess the costs of treating CHF patients with FCM through a budget impact model (BIM).

METHODS

We performed cost measurement analysis in 8 Romanian hospitals, of different size/category and of various geographical locations. Of these 8 public hospitals 3 are town/city hospitals, 3 county/municipal hospitals, and 2 clinical hospitals.

In Romania, the financing of hospitalized patients is covered from various public sources, including the National Health Insurance House (NHIH, DRG and wage subvention), Ministry of Health (through national health programs and the financing of emergency care units), and local authorities (through arrears covering operating expenses), thus a complex public payer stakeholder milieu. The financing rules^{15,16} set forward by the NHIH are not recommended to be used as a basis for any economic evaluation/cost analysis from the public payer perspective, as the inpatient care has other revenue sources as well, such as subsidies covering the increase of salaries and national health programs financing the treatment of specific ailments. All in all, the total sum of financing is covered by the government, so the direct cost measure-

ment is in fact used to closely approximate the public payer perspective.

Patient selection from these hospitals has been based on the ICD-10 diagnosis codes for heart failure, regardless whether the diagnosis of chronic heart failure was primary or secondary. At this stage we did not separate the patients who received FCM during their hospitalization from those who did not, as the volume of drugs administered in the selected hospitals was negligible.

The calculations are based on the actual dosage used in the Romanian medical setting. However, additional calculations were performed to include the study dosage of 1,679 mg FCM.

HOSPITALIZED PATIENT POPULATION

The main scope of the analysis is to assess the total cost of the treatment of CHF patients according to NYHA class. Based on the patient selection criteria, a total number of 8,494 patients have been included in the study. Table 1 represents their distribution according to the treating institution and NYHA class. This patient population was used only for the direct cost measurement in order to adapt the German study to the costs specific to the Romanian healthcare system.

MODEL INPUTS

CLINICAL OUTPUT PARAMETERS

The key clinical parameters were based on the data used by the budget impact model of Theidel *et al.*¹⁷ The key clinical outcomes to feed the BIM are the probabilities for the patients to be in a specific NYHA class (derived from the multivariate statistical analysis), death over time, rate of hospitalization due to the worsening CHF, and average length of stay (ALOS). All these data have been taken from the BIM model of Theidel *et al.*

ECONOMIC PARAMETERS

Cost of FCM treatment and the impact of Clawback

For the budget impact calculations, the wholesaler price of FCM has been used as an input of the model.

As a special situation in case of the financing of the Romanian healthcare system, when it comes to the costs of drugs and medication, there is a special tax that needs to be taken into calculation: the Clawback tax, applied to all drugs and medication. The objective of this tax is to maintain the drugs and medication expenditure of the NHIH at a sustainable level. The expenditure above a specific threshold needs to be paid back by the pharmaceutical companies to the NHIH in the form of this tax. Since this is a more specific case, the budget impact calculations have been performed in two scenarios: both with and without this tax.

In order to calculate the exact cost for the public payer, the price of the medication needs to be reduced by the rate of the Clawback tax of 24.13% for Q1 of 2018, as this is paid back to the public payer by the manufacturer. The mean cumulative dose of FCM measured in Romania has been of 958 mg, which is multiplied by the mean cost per mg (€0.077). On the other hand, if the calculations are performed without considering the Clawback, the mean cost per mg of FCM becomes €0.102.

The dosage of FCM was subject to study, and the exact dose prescribed to Romanian patients has been analyzed based on the official hospital drug consumption reports (reported to the NHIH) of 8 hospitals. According to the conclusions of this study, the average dosage the patients are prescribed is of 958 mg.

Cost of outpatient visit

In order to determine the cost of an outpatient visit, a panel of experts has been interviewed, resulting in a list of services provided per each NYHA class. The following cost elements have been taken into account for the cost

TABLE 1. Patient distribution according to the treating hospital and NYHA class

Hospital type	NYHA class				Number of cases
	I	II	III	IV	
City/town hospital	125	697	485	181	1,488
County/municipal hospital	466	2,784	2,150	507	5,907
Clinical hospital	148	612	289	50	1,099
Total	739	4,093	2,924	738	8,494

calculation: outpatient consultation, electrocardiogram, cardiac echography, laboratory analysis (complete blood count, urea/BUN, serum creatinine, sodium, potassium, aspartate aminotransferase, alanine aminotransferase, NT-pro-BNP, INR, Holter monitoring, cardiac CT scan). The cost of the outpatient visit has been calculated based on actual cost data instead of the reimbursement fee paid by the NHIH, for each cost element.

Cost of home visits

The cost of a home visit has been determined at a value of €7.16, the reimbursement fee of the NHIH for healthcare services of this kind, as no direct cost data was available.

Cost of hospitalization due to CHF worsening

The cost of hospitalization has been calculated based on actual cost data from 8 hospitals (2 clinical level hospitals, 3 county level hospitals, 3 small municipal hospitals). The total hospitalization cost is made up of the following cost components: cost of the hospital stay, cost of ICU stay, cost of diagnostics, and overhead costs. In case of inpatient care, the cost of medication is covered by one of the financing mechanisms (DRG, chronic financing, or national health program). The wages and salaries of the employees in public healthcare units have been measured for the period of the analysis.

Each case of CHF has been identified in these 8 hospitals for the period analyzed, resource use was attributed to these cases, and unit costs were attributed according to the resource use. The NYHA class was known for each case, thus costs could be calculated according to the NYHA class.

The cost of hospitalization also included the cost of one-day hospitalization, which was calculated based on actual hospital costs.

Cost of medication per year

The yearly medication cost of CHF patients has been calculated based on the actual prescriptions for patients, only considering the medication prescribed for the treatment/management of CHF, according to the NYHA class. These costs only include the reimbursement offered by the NHIH, not considering the co-payment paid by the patients. Calculations have been performed in two distinct scenarios: one without considering the Clawback and another, in which the cost of the medication is diminished by the Clawback tax rate for Q1, 2018.

RESULTS

RESULTS OF THE BUDGET IMPACT MODEL USING REAL WORLD DOSAGE DATA

The total cost of the treatment of 1,000 CHF patients without FCM has been €641,588 without the Clawback tax (Table 2) and €625,748 with the Clawback (Table 3).

Due to the improved disease state and lower rate of hospitalization, the introduction of FCM treatment resulted in a net healthcare cost reduction to the value of €484,278, resulting in a total healthcare cost reduction of €157,309.79 when not applying the Clawback, and €156,081.67 after applying the Clawback. This cost reduction was driven by reductions in outpatient visit costs (€91,749.90), hospitalization costs due to CHF worsening (€59,368.76), home visit costs (€1,101.53), and cost of CHF-related medication (€5,089.61 when not applying the Clawback and €3,861.49 after applying the Clawback tax). All these cost savings are reduced by the cost of the FCM treatment, of a grand total of €194,104.54 when calculating with the full price, and €147,267.12 after decreasing the price with the Clawback tax.

When treating 1,000 patients with FCM for a year, without considering the Clawback, the net cost is €36,794.75, compared to no iron treatment, meaning that administering FCM for a year to a patient has an additional cost of €37. If the percentage for the Clawback is also considered, the calculations actually show a net saving of €8,814.55, which translates into approximately €9 of cost saving per each FCM-treated CHF patient.

RESULTS OF THE BUDGET IMPACT MODEL USING STUDY DOSAGE

A scenario analysis has been performed regarding the dosage of FCM. When the study dosage of 1,679 mg is added as an input data to the model, if 1,000 patients are treated with FCM for a year, without considering the Clawback tax, the net cost for FCM patients is €182,879, meaning that administering FCM for a year to a patient has an additional cost of €183. If the percentage for the Clawback is also considered, the calculations show a lower additional cost of €102,020, which translates into approximately €102 of extra cost per each FCM-treated CHF patient.

SENSITIVITY ANALYSIS

Deterministic sensitivity analysis (DSA) has been performed regarding the parameters that have the greatest

TABLE 2. Modelled annual costs (expressed in €) of FCM and non-iron treatment of 1,000 CHF patients in Romania, without applying the Clawback

Treatment cost driver	Non-iron costs (€)					FCM costs (€)					Net budget impact	
	NYHA I	NYHA II	NYHA III	NYHA IV	NYHA V	NYHA I	NYHA II	NYHA III	NYHA IV	NYHA V		
Healthcare resources												
Home visits	51.92	2,359.53	2,662.38	416.70	533.92	298.02	3,106.22	1,157.89	102.78	258.01	-1,101.53	
Outpatient visits	4,118.70	187,182.72	211,208.00	33,057.28	42,356.27	23,377.90	243,663.81	90,829.62	8,062.82	20,238.93	-91,749.90	
Hospitalization due to HF worsening	792.82	36,031.53	40,656.25	6,363.32	8,153.32	1,975.24	20,587.61	7,674.37	681.24	1,710.02	-59,368.76	
CHF-related medications	565.71	25,709.85	29,009.76	4,540.47	5,817.70	3,665.77	38,207.71	14,242.54	1,264.29	3,173.57	-5,089.61	
Total cost of healthcare	5,529.15	251,283.62	283,536.39	44,377.78	56,861.21	29,316.93	305,565.35	113,904.42	10,111.14	25,380.52	-157,309.79	
Total cost of FCM	0.00	0.00	0.00	0.00	0.00	11,750.58	122,474.24	45,654.25	4,052.67	10,172.82	194,104.54	
Total cost	5,529.15	251,283.62	283,536.39	44,377.78	56,861.21	41,067.51	428,039.59	159,558.68	14,163.81	35,553.34	36,794.75	

CHF – chronic heart failure, HF – heart failure, FCM – ferric carboxymaltose

TABLE 3. Modelled annual costs (expressed in €) of FCM and non-iron treatment of 1,000 CHF patients in Romania, after applying the Clawback

Treatment cost driver	Non-iron costs (€)					FCM costs (€)					Net budget impact	
	NYHA I	NYHA II	NYHA III	NYHA IV	NYHA V	NYHA I	NYHA II	NYHA III	NYHA IV	NYHA V		
Healthcare resources												
Home visits	51.92	2,359.53	2,662.38	416.70	533.92	298.02	3,106.22	1,157.89	102.78	258.01	-1,101.53	
Outpatient visits	4,118.70	187,182.72	211,208.00	33,057.28	42,356.27	23,377.90	243,663.81	90,829.62	8,062.82	20,238.93	-91,749.90	
Hospitalization due to HF worsening	792.82	36,031.53	40,656.25	6,363.32	8,153.32	1,975.24	20,587.61	7,674.37	681.24	1,710.02	-59,368.76	
CHF-related medications	429.20	19,506.06	22,009.70	3,444.86	4,413.89	2,781.22	28,988.19	10,805.82	959.22	2,407.78	-3,861.49	
Total cost of healthcare	5,392.65	245,079.84	276,536.34	43,282.16	55,457.40	28,432.38	296,345.83	110,467.70	9,806.07	24,614.74	-156,081.67	
Total cost of FCM	0.00	0.00	0.00	0.00	0.00	8,915.16	92,921.20	34,637.88	3,074.76	7,718.12	147,267.12	
Total cost	5,392.65	245,079.84	276,536.34	43,282.16	55,457.40	37,347.54	389,267.04	145,105.58	12,880.82	32,332.86	-8,814.55	

CHF – chronic heart failure, HF – heart failure, FCM – ferric carboxymaltose

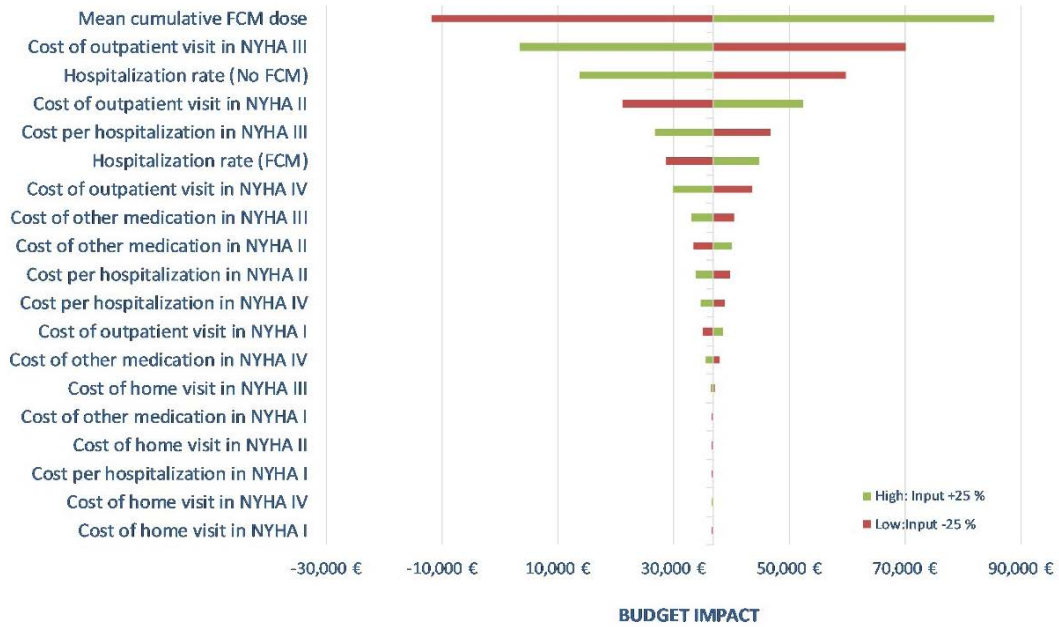


FIGURE 1. Results of the deterministic sensitivity analysis on the influential parameters regarding the budget impact of FCM use in Romania (without applying the Clawback tax)

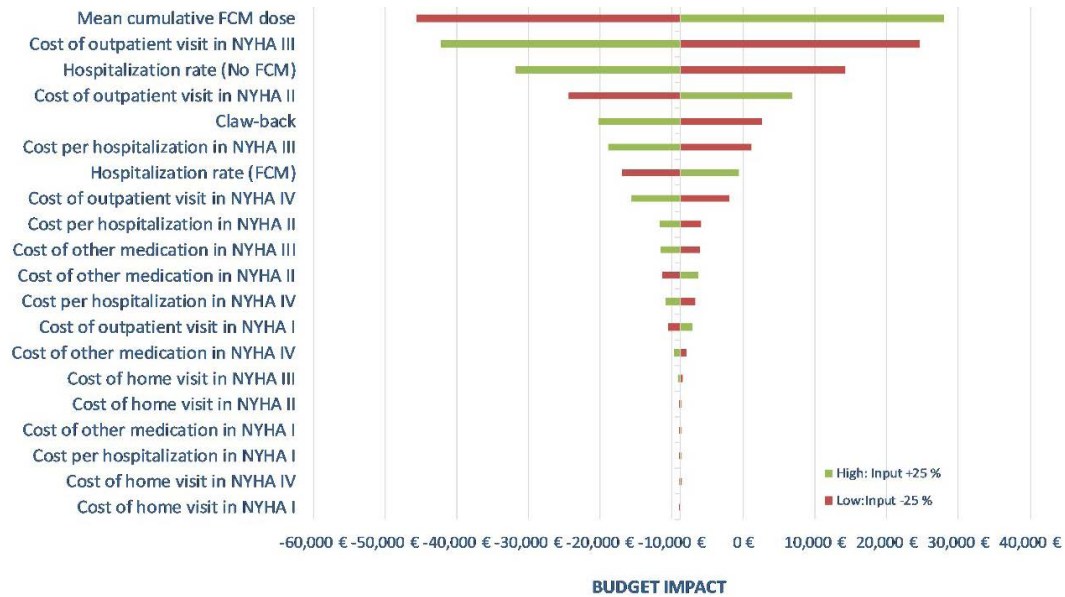


FIGURE 2. Results of the deterministic sensitivity analysis on the influential parameters regarding the budget impact of FCM use in Romania (after applying the Clawback tax)

influence on the financial outcome of the budget impact calculations. This was run for both scenarios, with and without applying the Clawback tax (Figure 1 and Figure 2).

Figure 1: Results of the deterministic sensitivity analysis on the influential parameters regarding the budget impact of FCM use in Romania (without applying the Clawback tax)

According to the results of the DSA for the scenario without the Clawback tax, the mean cumulative dose of FCM administered to the patients has the highest impact on the healthcare budget of the NHIH. Assuming a decrease of the dose by 25%, the budget impact would be reduced by €11,731, while an increase of this parameter by 25% would result in an increase of the budget impact

by €85,321. Other important parameters, but with slightly lower impact are the cost of outpatient visit in NYHA III (+25% €3,386; -25% €70,203) and the hospitalization rate (no FCM) (+25% €13,795; -25% €59,794).

According to the results of the DSA for the scenario with applying the Clawback tax, the mean cumulative dose of FCM administered to the patients has the highest impact on the healthcare budget of the NHIH (just as in case of the scenario without applying the Clawback tax). Assuming a decrease of the dose by 25%, the budget impact would be reduced by €45,631, while an increase of this parameter by 25% would result in an increase of the budget impact by €28,002. Other important parameters, but with slightly lower impact are the cost of outpatient visit in NYHA III (+25% €-42,223; -25% €24,594) and the hospitalization rate (no FCM) (+25% €14,185; -25% €-31,814). The Clawback tax also has great impact on the outcome of the calculations; a 25% increase results in a reduction of the budget impact of €20,217, while a reduction of 25% results in an increase of the budget impact of €2,588.

DISCUSSION

This is the first study to assess the budget impact of the use of FCM on CHF patients in Romania from a public payer perspective and using actual, direct cost measurement data. According to the results of this study, the extra costs associated with prescribing FCM to CHF patients during the first year of treatment are minimal. The findings of this study are consistent with the conclusions of Theidel *et al.*¹⁷ in terms of the total net cost, in case of which the yearly budget impact has been of €40,031 (compared to the Romanian results of €36,795 when not considering the Clawback tax and €8,815 when considering the Clawback tax). Another adaptation of the BIM model has been performed for France as well,¹⁸ which has shown a cost reduction for FCM patients of €5 per patient, using the real-world dose of 925 mg (compared to the Romanian results of €37 when not considering the Clawback tax and €9 when considering the Clawback tax). A similar BIM model has been applied in Austria as well, in case of which there was an overall saving effect of €225,115 in the first year (calculated for 2014).¹⁹

The cost element with the highest contribution to the estimated total costs has been outpatient visits for both the Clawback and no-Clawback scenarios (with a total cost of €477,923 for the no-FCM group and €386,173 for the FCM group) (Table 3). On the other hand, there is also great potential for cost saving for this parameter as well,

of €91,750. Compared to the patients who did not receive FCM treatment, there is an additional cost element of €194,105 of the cost of the medication itself for the no-Clawback scenario and €147,267.12 for the Clawback scenario. Summing up all costs and comparing the costs of the no-FCM arm and the FCM, it results a net cost of €37 for the no-Clawback scenario, and a cost reduction of €9 for the Clawback scenario, per patient during the first year of treatment.

Several cost-effectiveness studies have been performed for FCM as well. According to the one performed for Austria,^{19,20} for a 4-year time horizon, based on the data of the FAIR-HF and CONFIRM-HF pivotal studies, the incremental cost-effectiveness ratio (ICER) of the FCM treatment compared to no treatment has been of €16,921.62, which is below the cost-effectiveness threshold set up by the National Institute for Health and Clinical Excellence (NICE) of €22,200-€33,300. Similar results have been achieved in the UK as well.²¹ The input data of the study has been based on the FAIR-HF trial, and the ICER of the FCM treatment compared with placebo has been of €4,414 per quality-adjusted life-year (QALY). Studies performed in Spain point in the same direction²²; the cost of 1 QALY has been of €6,123.78, again, under the NICE threshold. The time horizon in this case has been of 24 weeks. The same time horizon has been used for a Swedish study as well,²³ based on the FAIR-HF trial. The ICER in case of the Swedish setting has been of €8,194 per QALY, much below the NICE threshold. The cost-effectiveness of FCM compared to no treatment seems to be converging towards similar values all over Europe; the cost-effectiveness study performed in Greece shows similar results.²⁴ The study was based on the FAIR-HF trial for a 24-week time horizon, and the resulting ICER has been of €25,506 per QALY for administration in a day-case unit and €5,368 per QALY for administration in the hospital outpatient department. Compared to the European setting, studies performed in South Korea show a much higher ICER.²⁵ In case of this study with a time horizon of 24 weeks, based on the FAIR-HF trial, the ICER has been of \$22,192, but it is still lower than the NICE threshold. Cost-effectiveness studies are a crucial aspect of decision-making, and such analysis could be performed in Romania based on the findings of the present study.

In comparison with the majority of these studies, the present study follows a period of 52 weeks, based on the CONFIRM-HF study.

Iron deficiency is an important comorbidity in CHF, and according to the current guidelines of the European Society of Cardiology, CHF should be routinely screened

in newly diagnosed patients and properly managed to alleviate symptoms and generate health gain on CHF patients.²⁶

LIMITATIONS

One of the key limitations of the present study is that since in Romania there is no patient registry for CHF, some key parameters of the calculations have been based on the budget impact model developed by Theidel *et al.*, which, in turn, were based on data coming from clinical studies and trials (including the probabilities for the patients to be in a specific NYHA class, death over time, rate of hospitalization due to the worsening CHF, and average length of stay) and may not be in accordance with the real-world treatment patterns or the real-world behavior of the Romanian doctors.

Another limitation of the study is the use of direct reimbursement fees as costs in case of outpatient care, as there is no information regarding the actual costs of this type of care.

CONCLUSIONS

By treating patients with FCM, the signs and symptoms of CHF can be improved, and the duration and frequency of hospitalizations can be reduced. This added clinical benefit can be achieved at a cost of €37 per patient for the no-Clawback scenario and a cost reduction of €9 for the Clawback scenario. Our analysis confirms that the unmet need of CHF patients with ID can be met by the treatment with FCM at a minimal additional cost.

CONFLICT OF INTEREST

None to be declared.

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- [http://www.cnas.ro/casgorj/media/postFiles/Ordin%20397-836_2018%20\(actualizat%20cu%20Ordin%20MS-CNAS%20910-1161_2018\).pdf](http://www.cnas.ro/casgorj/media/postFiles/Ordin%20397-836_2018%20(actualizat%20cu%20Ordin%20MS-CNAS%20910-1161_2018).pdf)
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