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# Economic evaluation of oral versus parenteral iron therapy for iron deficiency without anemia

## Scope

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# 1 Introduction

The *Swiss Federal Office of Public Health* (SFOPH) commissioned a Health Technology Assessment (HTA) regarding iron therapy in symptomatic **patients with iron deficiency without anemia** (iron deficiency no anemia, **IDNA**) to the *Basel Institute for Clinical Epidemiology and Biostatistics* (CEB) and the *Winterthur Institute of Health Economics* (WIG). The scope, which describes the background of the HTA and elucidates the general approach, has been published on the SFOPH homepage.[1]

This HTA followed a step-wise approach. The aim of the **first step** was to assess the **clinical effectiveness** of iron therapy in symptomatic patients with IDNA, and to identify symptomatic populations that benefit from the therapy. In this first step, the clinical effectiveness of iron therapy was assessed in comparison to any other non-iron treatment or placebo, irrespective of the route of iron administration. This step was conducted by CEB, and the results are summarized in chapter 2 of this document.

In the **second step**, which will be conducted by WIG, the **economic evaluation** shall **compare parenteral versus oral iron therapy** for those populations, for which a significant treatment effect of iron therapy (parenteral or oral) versus control could be identified during the first step. Based on the effectiveness results, the scope of the economic evaluation is outlined in chapter 4. Section 4.1 defines the objective of the economic evaluation. Section 4.2 defines the population, the intervention, the comparator, and the outcome (PICO) which will be evaluated. A screening of health economic literature and publicly available HTAs for *economic studies* comparing parenteral with oral iron therapy is presented in section 4.3, and section 4.4 concludes with the outline of the research methodology of the economic evaluation.

[1] https://www.bag.admin.ch/bag/de/home/themen/versicherungen/krankenversicherung/krankenversicherung-bezeichnung-der-leistungen/re-evaluation-hta/scoping-berichte.html

# 2 Summary of effectiveness results

The aim of the clinical effectiveness assessment (first step of the HTA) was to identify high-quality evidence of effectiveness of iron therapy in symptomatic populations with IDNA. Therefore, CEB conducted a systematic review based on RCTs comparing iron therapy (irrespective of the route of administration) with non-iron comparators, placebo or no therapy for multiple indications and endpoints. As a result, **two symptomatic populations with IDNA were identified where iron therapy versus control showed a statistically significant effect**: **women (≥ 18 years) with fatigue** and **adults with restless legs syndrome (RLS)**.

According to the evidence found for the first population (4 RCTs), iron therapy decreased fatigue severity in **women with IDNA and fatigue** (statistically significant effect). Two RCTs compared parenteral iron treatment with placebo [1, 2], and two RCTs compared oral iron treatment with placebo [3, 4]. The outcome of fatigue was measured by the following assessments: A 22-item Piper Scale ranging from 1 (no fatigue) to 10 (very severe fatigue) over a follow-up of eight weeks [1], a brief inventory ranging from 0 (no fatigue) to 10 (maximum imaginable fatigue) with a follow-up of twelve weeks [2], a global fatigue index (MAF, range 0-50) with a follow-up of twelve weeks [3], and a VAS (range 1-10) with a follow-up of four weeks [4]. No RCTs were identified which compared iron therapy to any other active comparator in women with IDNA and fatigue.

For the RLS population, the evidence showed that iron therapy reduced RLS symptom severity (statistically significant effect). Seven RCTs were included in this analysis of adults with **IDNA and RLS**. Five RCTs compared parenteral iron treatment with placebo [5-9], one RCT compared oral iron therapy with placebo [10] and one RCT compared oral iron therapy with pramipexole [11]. All seven RCTs assessed RLS symptom severity on a scale ranging from 0-40[2] and with follow-up periods ranging from two to twelve weeks.

For both populations, potentially different effects of parenteral and oral iron were assessed between subgroups of trials including patients receiving either oral or parenteral iron (test of interaction). However, the number of available RCTs was too limited and no conclusion of differential effects between the two routes of administrations could be drawn, based on formal inspection of difference in effect sizes across these subgroups of trials. The test of interaction for a different effect size in trials of oral versus parental iron therapy was not statistically significant.

[2] Assessments by either the International Restless Legs Syndrome (IRLS) study group severity scale, IRLS severity scale, IRLS group rating scale, ORLS symptoms severity score, or IRLS survey.

As predefined in the scope of the clinical effectiveness assessment (SFOPH[3]), only RCTs with a non-iron comparator were included. Among the included trials, no **RCTs with a head-to-head comparison of oral iron vs. parenteral iron were identified.**

3 https://www.bag.admin.ch/dam/bag/de/dokumente/kuv-leistungen/bezeichnung-der-leistungen/Re-Evaluation-HTA/iron-therapy--iron-deficiency-without-anemia-final-scope-2017 .pdf

# 3 Systematic search for direct comparison oral versus parenteral

It is the primary goal of the economic evaluation to compare cost-effectiveness of oral versus parenteral iron therapy in those populations for which effectiveness has been shown in the first step of the HTA. For such an analysis, results from direct comparisons are desirable. Head-to-head comparison by RCTs represent the most reliable information for such economic evaluation.

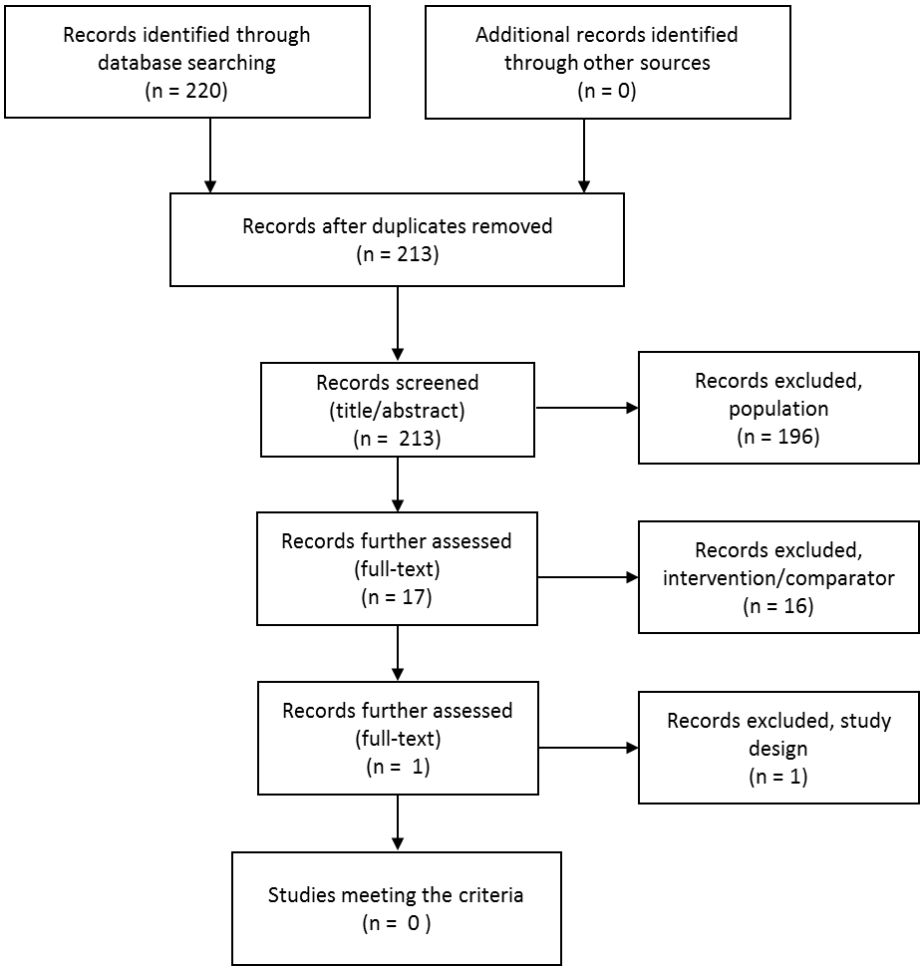
In contrast to the first step of the HTA, in this part of the analysis also RCTs are eligible which did not include a non-iron comparator, as the focus is now on the two populations for which effectiveness of iron therapy has been demonstrated in the first step of the HTA. Therefore, an additional literature search for iron-only head-to-head comparisons of oral versus parenteral iron therapy in IDNA patients with fatigue or restless legs syndrome was conducted. The systematic search was performed in Medline and the Cochrane Central Register of Controlled Trials (CENTRAL) on 30 October 2017. The search strategy was identical to the one used for the clinical effectiveness assessment, except that terms describing the two populations were added. Details about the search strategy are outlined in the Appendix.

After removal of duplicates, 213 records remained for screening of title/abstract. In a next step, the full-text of 17 records were assessed. **None of the 213 records satisfied the inclusion and exclusion criteria** (see Table 1 and Figure 1).

**Table 1: PICO and inclusion and exclusion criteria**

| | |
|---|---|
| **Population** | Inclusion:<br>• 1. Target population: Adult (≥18 years) females with IDNA and fatigue<br>• 2. Target population: Adults (≥18 years) with IDNA and restless legs syndrome<br>• No other cause should have been identified for the symptoms that treatment with iron aims to alleviate<br>Exclusion:<br>• Studies with athletes<br>• Studies including patients who are known to suffer from one of the following underlying diseases:<br>o Chronic heart failure<br>o Renal failure, chronic kidney disease, dialysis<br>o Chronic liver failure<br>o Chronic inflammatory disease in particular inflammatory bowel disease<br>o Achlorhydria, atrophic gastritis, gastric resection<br>o Acute and chronic infections<br>o Malignancy |
| **Intervention / Comparator** | Parenteral versus oral iron therapy |
| **Outcome** | Health and safety outcomes |
| **Study design** | Only randomized controlled trials and quasi-randomized trials in high-income countries were included |
| **Report type** | Poster presentations and conference abstracts were excluded |

### Figure 1: Prisma flow chart




Although none of the studies satisfied the predefined criteria, two RCTs are in our opinion noteworthy. In one RCT conducted by Birgegard et al. (2010), regular blood donors with ID-NA and at least five previous whole blood donations were investigated [12]. A subgroup of 22 donors out of 120 was diagnosed with restless legs syndrome (8 in the parenteral group and 14 in the oral group). Hence, the population in general is not considered symptomatic. The severity was assessed using the International Restless Legs Syndrome Study Group Severity Scale. However, the findings of this study remained inconclusive, and the number of patients was low. In addition, a protocol of an ongoing RCT was found, which directly compares oral with parenteral iron therapy in blood donors with iron deficiency [13]. This RCT, however, has not been published yet.

# 4 Economic evaluation

The clinical effectiveness assessment by CEB identified **two symptomatic IDNA populations** which benefit from iron therapy: **Women with fatigue** and **adults with RLS**. This was concluded based on the clinical evidence provided by RCTs, which compare iron treatment with placebo. The economic evaluation is restricted to these two populations.

During the effectiveness assessment and the additional literature search described in the previous chapter, no data from RCTs with a direct comparison of parenteral and oral iron therapy could be identified. Furthermore, it was considered that no reliable estimation of differential effects can be expected from an indirect comparison of the available RCT data from the first step of this HTA.

Consequently, based on current available indirect evidence from RCTs, there is insufficient evidence for a clinically relevant difference in treatment effects of parenteral versus oral iron therapy. It has therefore been decided in accordance with the SFOPH to restrict the economic evaluation to a **cost-comparison analysis**, rather than a cost-effectiveness analysis.

## 4.1 Objective of the economic evaluation

A **cost-comparison analysis** of parenteral versus oral iron therapy for **IDNA patients with fatigue or RLS** will be conducted. The main objective of the economic evaluation is to quantify the costs of parenteral and oral iron therapy from a health care **payer perspective** (OKP[4], social insurance, including both outpatient and inpatient costs) and to compare them, as well as to perform a budget impact analysis. The following two key research questions will be addressed:

- What are the direct medical costs of oral iron therapy versus parenteral iron therapy in IDNA patients with fatigue or RLS?
- What is the budget impact of different iron treatment strategies in IDNA patients with fatigue or RLS?

As the study will be conducted from a health care payer perspective (OKP, social insurance), indirect costs and additional costs for patients (such as e.g. travel costs) will not be considered.

[4] Obligatorische Krankenpflegeversicherung

## 4.2 PICO

The results of the clinical effectiveness assessment showed statistically significant effects on fatigue severity or RLS symptom severity when iron therapy was compared to placebo in IDNA women with fatigue or IDNA adults with RLS, respectively. Therefore, the economic evaluation will investigate these two symptomatic populations with IDNA and consequently two PICOs are proposed. It will thereby be analyzed whether the cost comparison between parenteral and oral iron therapy yields any different results across the two populations of interest.

PICO 1: Women with fatigue

Population: IDNA women (at least 18 years of age) with fatigue and eligible for oral therapy (i.e. no chronic inflammatory bowel disease)

Intervention: Parenteral therapy with iron

Comparator: Oral therapy with iron with possible switch to parenteral therapy

Outcome: Direct medical costs (drug costs, physician visits, drug administration costs, costs due to management of adverse events both outpatient and inpatient)

PICO 2: Restless legs syndrome

Population: Adults (at least 18 years of age) with IDNA and with RLS and eligible for oral therapy (i.e. no chronic inflammatory bowel disease)

Intervention: Parenteral therapy with iron

Comparator: Oral therapy with iron with possible switch to parenteral therapy

Outcome: Direct medical costs (drug costs, physician visits, drug administration costs, costs due to management of adverse events both outpatient and inpatient)

## 4.3 Results of systematic search of economic literature

The aim of this step was to gain an overview of applied modelling techniques and of previous outcomes of health economic evaluations in the relevant therapeutic area. First, a search for *health economic studies* and *HTAs* of therapies was performed on 19 September 2017 without time restrictions, specifically for patients with IDNA. The search terms and number of hits are listed in Table 2. No search filters were applied.

**Table 2: Literature search for economic studies in patients with IDNA**

| Step | Search terms | PubMed | Cochrane Library | Web of Science |
|---|---|---|---|---|
| 1 | „latent iron deficiency“ | 128 | 15 | 51 |
| 2 | „iron-deficient erythropoiesis“ | 155 | 24 | 145 |
| 3 | ("latent iron deficiency" OR "iron-deficient erythropoiesis") | 280 | 32 | 195 |
| 4 | (("latent iron deficiency" OR "iron-deficient erythropoiesis") AND cost) | 12 | 0 | 8 |
| 5 | (("latent iron deficiency" OR "iron-deficient erythropoiesis") AND ("cost effectiveness" OR "cost-effectiveness")) | 0 | 0 | 0 |
| 6 | (("latent iron deficiency" OR "iron-deficient erythropoiesis") AND "budget impact") | 0 | 0 | 0 |

The number of hits decreased drastically from step three to step four, as economic search terms (costs, cost-effectiveness, budget impact) were added to the medical terms of IDNA. The titles of the 20 hits from step 4 were screened. This lead to the identification of one study that analyzed health insurance claims data to estimate the total costs of outpatient iron therapy, which was conducted from a statutory health insurance perspective in Switzerland for the years 2006 to 2010 [14]. However, this study did not focus on IDNA and did not compare treatment costs on a patient level. Hence, this first step of the literature search did not yield any studies relevant to our HTA. Therefore, the search was widened to a broader definition of iron deficiency in general, also allowing for anemia (Table 3).

**Table 3: Literature search for economic studies in patients with iron deficiency**

| Step | Search terms | PubMed | Cochrane Library | Web of Science |
|---|---|---|---|---|
| 1 | (("iron deficiency" OR "iron-deficiency anemia") AND cost) | 547 | 90 | 497 |
| 2 | (("iron deficiency" OR "iron-deficiency anemia") AND ("cost-effectiveness" OR "cost effectiveness")) | 68 | 1 | 80 |
| 3 | (("iron deficiency" OR "iron-deficiency anemia") AND "budget impact") | 7 | 0 | 5 |

The titles of the 161 hits from steps 2 and 3 were screened. Of 28 studies the abstract was read, leading to six relevant cost-effectiveness studies and three relevant budget impact analyses (Table 4).

Four studies assessed cost-effectiveness of parenteral iron therapy versus placebo in chronic heart failure patients with iron deficiency [15-18]. The time horizon was 24 weeks and the

QALY-gain relatively small (0.037 QALYs in the case of Gutzwiller et al., 2012 [15]). The cost assessment included drug costs, drug administration costs, and chronic heart failure related hospitalization costs. The ICER amounted to 4,414 GBP per QALY [15], 8,194 EUR per QALY [16], 22,192 USD per QALY [17], and 6,123 EUR per QALY [18], respectively (Table 4). Another study conducted a cost comparison analysis comparing three intravenous iron treatments in patients with iron deficiency anemia over one year [19]. This study considered drug costs, drug administration costs, costs due to management of adverse events, patient productivity loss, and patient travelling costs. A further study modelled the cost-effectiveness of parenteral versus oral iron therapy in patients with chronic kidney disease and iron deficiency anemia [20]. This study modelled the cost-effectiveness over the entire lifespan. The QALY-gain was dependent on the age group and ranged from 0.225 QALYs (60-75 year age group) to 0.574 QALYs (18-25 year age group). Costs per QALY gained amounted to 34,660 USD (Table 4).

Three relevant budget impact analyses were identified. One budget impact analysis compared ferric carboxymaltose with iron sucrose in patients receiving parenteral iron therapy in Switzerland, irrespective of the indications [21]. This study was based on prices from the "Spezialitäten Liste", "Mittel- und Gegenstände-Liste" and TARMED positions. Another study compared the budget impact of different parenteral iron therapies in patients with iron deficiency anemia in the UK [22]. The third study analyzed parenteral iron therapy versus no iron therapy in chronic heart failure patients with iron deficiency anemia in Germany [23].

There exists a HTA comparing oral versus parenteral iron therapy in patients with iron deficiency anemia and in patients with symptomatic, severe iron deficiency without anemia conducted by the Swiss Medical Board [24]. However, results were not reported separately for each population, as the analysis does not concern the same research question as the present HTA commissioned by the SFOPH. In this HTA several assumptions were made to compare QALYs using the Karnofsky-Index. Over a time horizon of 1-year, the QALY-gain for parenteral compared to oral iron therapy was 0.025 QALYs. This QALY-gain was based on the assumption that symptoms disappear within 3 weeks with parenteral iron therapy compared to 16 weeks with oral iron therapy[5]. Costs were analyzed from a health care payer perspective and included drug costs (oral and parenteral therapy) and drug administration costs (parenteral therapy). Costs were estimated at CHF 100 per patient and 16-week treatment for the oral therapy (drug costs only), and at CHF 510 per patient and single admin-

[5] In the present HTA commissioned by the SFOPH, the RCTs identified in the effectiveness analysis and the additional search for RCTs directly comparing oral versus intravenous iron therapy do not allow for any distinction of the onset of effect between oral and intravenous iron therapy because time until onset of effect was not reported in any of the identified RCTs.

istration (1'000 mg) for the parenteral therapy (drug costs plus expendable materials, administration, and monitoring). This leads to an ICER of CHF 16'400/QALY.

No study reporting results specifically for the comparison of oral versus parenteral iron therapy in patients with IDNA was found. Furthermore, no model was found that could be adopted to answer the present research question. Consequently, an own model needs to be built specifically for the economic evaluation of this HTA.

**Table 4: Identified cost-effectiveness studies and budget impact analyses for parenteral or oral iron therapy of iron deficiency**

| Ref. | Author | Year | Study design | Intervention/Comparator | Country | Main Results | Remarks |
|---|---|---|---|---|---|---|---|
| **Cost-effectiveness studies** | | | | | | | |
| [15] | Gutzwiller FS, Schwenkglenks M, Blank PR, Braunhofer PG, Mori C, Szucs TD, Ponikowski P, Anker SD | 2012 | C/E analysis based on RCT | Parenteral iron therapy vs. parenteral placebo | United Kingdom | ICER = 4,414 GBP per QALY gained (QoL measured by self-reported EuroQuol), considering direct medical costs in primary care | Chronic heart failure, iron deficiency both with and without anemia, follow-up 24 weeks, very small difference in QALY (intervention vs. control) of 0.037 (bootstrap-based 95% CI 0.017-0.060) |
| [16] | Hofmarcher T, Borg S | 2015 | C/E analysis based on RCT | Parenteral iron therapy vs. parenteral placebo | Sweden | ICER = 75,389 SEK (8,194 EUR) per QALY gained (QoL measured by self-reported EuroQuol), considering direct medical costs in primary care | Use of the same clinical data as Gutzwiller et al. (2012) with the perspective of the Swedish healthcare system; Chronic heart failure, iron deficiency both with and without anemia, follow-up 24 weeks, very small difference in QALY (intervention vs. control) of 0.037 (bootstrap-based 95% CI 0.017-0.060) |
| [17] | Lim EA, Sohn HS, Lee H, Choi SE | 2014 | C/E analysis based on RCT | Parenteral iron therapy vs. parenteral placebo | South Korea | ICER = 22,192 USD per QALY gained (QoL measured by New York Heart Association (NYHA) functional class), considering direct medical costs in primary care | Use of the same clinical data as Gutzwiller et al. (2012) with the perspective of the South Korean healthcare system; Chronic heart failure, iron deficiency both with and without anemia, follow-up 24 weeks, very small difference in QALY (intervention vs. control) of 0.021 (according to NYHA) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| [18] | Comín-Colet J, Rubio-Rodríguez D, Rubio-Terrés C, Enjuanes-Grau C, Gutzwiller FS, Anker SD, Ponikowski P | 2015 | C/E analysis based on RCT | Parenteral iron therapy vs. parenteral placebo | Spain | ICER = 6,123 EUR per QALY gained (QoL measured by self-reported EuroQuol), considering direct medical costs in primary care | Use of the same clinical data as to Gutzwiller et al. (2012) with the perspective of the Spanish healthcare system; Chronic heart failure, iron deficiency both with and without anemia, follow-up 24 weeks, very small difference in QALY (intervention vs. control) of 0.037 (bootstrap-based 95% CI 0.017-0.060) |
| [19] | Fragoulakis V, Kourlaba G, Goumenos D, Konstantoulakis M, Maniadakis N | 2012 | C/M analysis and budget impact analysis | Three different parenteral iron therapies directly compared (no placebo) | Greece | Dominance (costs) of Ferinject over Venofer and CosmoFer; direct medical costs, productivity losses and travel costs for patients are considered | Iron deficiency anemia in inpatient setting (surgical patients or patients hospitalized due to a disease related to chronic or acute blood loss) or in an outpatient setting (non-dialysis chronic kidney disease patients); no evidence of significant difference in clinical effectiveness across the three therapies, therefore C/M analysis is performed |
| [20] | Wong G, Howard K, Hodson E, Irving M, Craig JC | 2013 | C/E analysis based on multiple RCTs | Parenteral iron therapy vs. oral iron therapy | Australia | ICER = 34,660 USD per QALY; With a QALY threshold of 50,000 USD, in 90% of the simulated cases parenteral therapy is cost-effective vs. oral, direct medical costs are considered | Chronic kidney disease patients with iron deficiency anemia, economic evaluation comparing parenteral with oral iron therapy although no clinical trial is available directly comparing the two (clinical trials compare one of the two vs. placebo), difference in clinical effectiveness in favor of parenteral therapy on average but not statistically significant at 95% level |
| **Budget impact studies** | | | | | | | |
| [21] | Brock E, Braunhofer P, Troxler J, Schneider H | 2014 | Budget impact analysis | Parenteral iron therapy with iron sucrose vs. ferric carboxymaltose | Switzerland | Parenteral iron therapy with ferric carboxymaltose was associated with cost savings of 30-44% per patient and treatment cycle, budget impact decreased by 22-31 million CHF across all indications for the year 2009 | Costs calculated for all iron treatments reimbursed by Swiss OKP ("Obligatorische Krankenpflegeversicherung"), hence not restricted to IDNA; based on Swiss TARMED, MiGeL ("Mittel- und Gegenstandsliste") and SL ("Spezialitätenliste") prices, savings mainly due to reduced lab costs |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| [22] | Pollock RF, Muduma G | 2017 | Budget impact analysis | Four different parenteral iron therapies directly compared | United Kingdom | Monofer and Cosmofer (both iron sucrose) are cost saving compared to Ferinject (costs reduced by 143 GBP per patient) and Venofer (costs reduced by 2,149 GBP), requiring fewer infusions; The active agent of Ferinject is iron carboxymaltose and of Venofer it is iron sucrose | Iron deficiency anemia |
| [23] | Theidel U, Väätäinen S, Martikainen J, Soini E, Hardt T, Doehner W | 2017 | Budget impact analysis | Parenteral iron therapy vs. no-iron | Germany | Cost-savings of 40 EUR per patient per year due to reduced and shorter hospitalizations and improved status of patients, direct medical costs are considered | Anemic patients with chronic heart failure |

## 4.4 Method of cost comparison and budget impact analysis

The direct medical costs of the different routes of administration will be modelled with a decision tree. The time horizon of the analysis is one year. Based on the clinical experts involved in this project, a 3 months period is the typical duration of one treatment cycle (medication + re-evaluation) for both oral and parenteral iron application in patients with IDNA and fatigue or RLS in Switzerland. Furthermore, about 80% to 90% of the patients are successfully treated (meaning rise of laboratory parameter(s) and symptom relief) within the first treatment cycle. However, some patients require up to three treatment cycles (9 months) to fully recover. For RLS patients it was not possible to make assumptions based on expert experience but it was considered, that a similar time horizon can be applied given that the RCTs in this indication used similar treatment durations as the RCTs investigating fatigue (oral iron treatment for 24 weeks was the maximum in the RCTs investigating RLS). Consequently, for both populations a time horizon of one year is considered long enough to model all relevant consequences related to the initial decision regarding first-line treatment strategy. Different dosages and frequencies of administration across the different therapies will be taken into account. Considered health states are compliance, compatibility, and severe side effects (e.g. phlebitis, severe hypersensitivity reactions as derived from the known effectiveness studies).

Empirical evidence on probabilities will stem from the above-mentioned clinical trials, as well as from secondary data sources, as an extensive search of clinical literature will be conducted (both RCTs and other study designs including empirical evidence of transition probabilities). It is to consider that the probabilities of compliance, compatibility, and severe side effects, may possibly not be available specifically for the populations with fatigue and restless legs syndrome, or may not necessarily differ between these two populations. If applicable according to clinical knowledge, a potential lack of RCT-based, population-specific probabilities will be resolved by adopting probabilities from another population or setting. For example, probabilities stemming from RCTs of non-anemic patients with fatigue have the highest priority for the decision tree of the respective population. Whenever an according probability is missing, RCTs will be checked whether data from other populations or non RCT data might be a suitable approximation. The clinical experts will be consulted in such a case.

Drug costs will be based on prices from the “Spezialitätenliste (SL)”. Drug administration costs as well as costs due to management of adverse events will be based on TARMED positions, the “Analysenliste (AL)”, and the “Mittel- und Gegenständeliste (MiGeL)”. If inpatient treatment is a causal result of the iron therapy (e.g. due to a severe adverse event), its costs will be included based on SwissDRG.

Uncertainty will be addressed by a univariate sensitivity analysis. This analysis aims to identify the parameters whose uncertainty has the largest influence on the result. In addition, a

probabilistic sensitivity analysis, in which all parameters with uncertainty will be varied within their confidence intervals, shall yield a credible interval for the estimated result.

The budget impact will likewise be estimated from a health care payer perspective and will be based on the resulting direct medical costs and epidemiologic data available for Switzerland.

# 5 References


1. Favrat, B., et al., *Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women--PREFER a randomized, placebo-controlled study.* PLoS One, 2014. **9**(4): p. e94217.
2. Krayenbuehl, P.A., et al., *Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration.* Blood, 2011. **118**(12): p. 3222-7.
3. Vaucher, P., et al., *Effect of iron supplementation on fatigue in nonanemic menstruating women with low ferritin: a randomized controlled trial.* Cmaj, 2012. **184**(11): p. 1247-54.
4. Verdon, F., et al., *Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial.* BMJ, 2003. **326**(7399): p. 1124.
5. Allen, R.P., et al., *Clinical efficacy and safety of IV ferric carboxymaltose (FCM) treatment of RLS: a multi-centred, placebo-controlled preliminary clinical trial.* Sleep Med, 2011. **12**(9): p. 906-13.
6. Earley, C.J., et al., *A randomized, double-blind, placebo-controlled trial of intravenous iron sucrose in restless legs syndrome.* Sleep Med, 2009. **10**(2): p. 206-11.
7. Trenkwalder, C., et al., *Ferric carboxymaltose in patients with restless legs syndrome and nonanemic iron deficiency: A randomized trial.* Mov Disord, 2017.
8. Grote, L., et al., *A randomized, double-blind, placebo controlled, multi-center study of intravenous iron sucrose and placebo in the treatment of restless legs syndrome.* Mov Disord, 2009. **24**(10): p. 1445-52.
9. Cho, Y.W., R.P. Allen, and C.J. Earley, *Clinical efficacy of ferric carboxymaltose treatment in patients with restless legs syndrome.* Sleep Med, 2016. **25**: p. 16-23.
10. Wang, J., et al., *Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: A randomized, double-blind, placebo-controlled study.* Sleep Med, 2009. **10**(9): p. 973-5.
11. Lee, C.S., et al., *Comparison of the efficacies of oral iron and pramipexole for the treatment of restless legs syndrome patients with low serum ferritin.* European Journal of Neurology, 2014. **21**(2): p. 260-6.
12. Birgegard, G., K. Schneider, and J. Ulfberg, *High incidence of iron depletion and restless leg syndrome (RLS) in regular blood donors: intravenous iron sucrose substitution more effective than oral iron.* Vox Sanguinis, 2010. **99**(4): p. 354-61.
13. Macher, S., et al., *High-dose intravenously administered iron versus orally administered iron in blood donors with iron deficiency: study protocol for a randomised, controlled trial.* Trials [Electronic Resource], 2016. **17**(1): p. 527.
14. Giger, M. and R. Achermann, *[Iron substitution in outpatients in Switzerland: Increase of costs associated with intravenous administration].* Z Evid Fortbild Qual Gesundhwes, 2013. **107**(4-5): p. 320-6.
15. Gutzwiller, F.S., et al., *Health economic assessment of ferric carboxymaltose in patients with iron deficiency and chronic heart failure based on the FAIR-HF trial: an analysis for the UK.* Eur J Heart Fail, 2012. **14**(7): p. 782-90.
16. Hofmarcher, T. and S. Borg, *Cost-effectiveness analysis of ferric carboxymaltose in iron-deficient patients with chronic heart failure in Sweden.* J Med Econ, 2015. **18**(7): p. 492-501.
17. Lim, E.A., et al., *Cost-utility of ferric carboxymaltose (Ferinject(R)) for iron-deficiency anemia patients with chronic heart failure in South Korea.* Cost Eff Resour Alloc, 2014. **12**: p. 19.
18. Comin-Colet, J., et al., *A Cost-effectiveness Analysis of Ferric Carboxymaltose in Patients With Iron Deficiency and Chronic Heart Failure in Spain.* Rev Esp Cardiol (Engl Ed), 2015. **68**(10): p. 846-51.

19. Fragoulakis, V., et al., *Economic evaluation of intravenous iron treatments in the management of anemia patients in Greece.* Clinicoecon Outcomes Res, 2012. **4**: p. 127-34.
20. Wong, G., et al., *An economic evaluation of intravenous versus oral iron supplementation in people on haemodialysis.* Nephrol Dial Transplant, 2013. **28**(2): p. 413-20.
21. Brock, E., et al., *Budget impact of parenteral iron treatment of iron deficiency: methodological issues raised by using real-life data.* Eur J Health Econ, 2014. **15**(9): p. 907-16.
22. Pollock, R.F. and G. Muduma, *A budget impact analysis of parenteral iron treatments for iron deficiency anemia in the UK: reduced resource utilization with iron isomaltoside 1000.* Clinicoecon Outcomes Res, 2017. **9**: p. 475-483.
23. Theidel, U., et al., *Budget impact of intravenous iron therapy with ferric carboxymaltose in patients with chronic heart failure and iron deficiency in Germany.* ESC Heart Fail, 2017. **4**(3): p. 274-281.
24. Swiss Medical Board, *Orale oder parenterale Behandlung des Eisenmangels*. 2014.
25. Mueller, N., et al., *Health impact assessment of cycling network expansions in European cities.* Preventive Medicine, 2018. **109**: p. 62-70.
26. Ponikowski, P., et al., *Rationale and design of the CONFIRM-HF study: a double-blind, randomized, placebo-controlled study to assess the effects of intravenous ferric carboxymaltose on functional capacity in patients with chronic heart failure and iron deficiency.* ESC heart failure, 2014. **1**(1): p. 52-58.
27. Holm, C., et al., *Single-dose intravenous iron infusion or oral iron for treatment of fatigue after postpartum haemorrhage: a randomized controlled trial.* Vox Sanguinis, 2017. **112**(3): p. 219-228.
28. Andrews, J., et al., *GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations.* J Clin Epidemiol, 2013. **66**(7): p. 719-25.

# Appendix: Search strategy for studies directly comparing oral versus intravenous iron therapy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Search date: 30.10.2017, 8.25 am

Search strategy:

1 ferrous.ti,ab. (11808)
2 ferric.ti,ab. (17369)
3 iron.ti,ab. (167042)
4 1 or 2 or 3 (180094)
5 exp Iron/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy] (7964)
6 exp Iron Compounds/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy] (9348)
7 exp iron, dietary/ (2940)
8 4 or 5 or 6 or 7 (185517)
9 therapy.ti,ab. (1644005)
10 administration.ti,ab. (786244)
11 intake.ti,ab. (242338)
12 supplement*.ti,ab. (290856)
13 replac*.ti,ab. (390570)
14 therapeutic.ti,ab. (868120)
15 administered.ti,ab. (512949)
16 exp therapeutics/ (4157779)
17 treat*.ti,ab. (4976609)
18 exp Dietary Supplements/ (63529)
19 exp Pharmaceutical Preparations/th [Therapy] (253)
20 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (9404795)
21 gluconate.ti,ab. (6859)
22 sucrose.ti,ab. (63146)
23 dextran.ti,ab. (33373)
24 carboxymaltose.ti,ab. (289)
25 isomaltoside.ti,ab. (96)
26 ferumoxytol.ti,ab. (296)
27 21 or 22 or 23 or 24 or 25 or 26 (102449)
28 sulphate.ti,ab. (34897)
29 sulfate.ti,ab. (133982)
30 gluconate.ti,ab. (6859)
31 lactate.ti,ab. (97717)
32 bisglycinate.ti,ab. (33)
33 citrate.ti,ab. (40906)

34 edta.ti,ab. (35087)
35 fumarate.ti,ab. (8206)
36 succinate.ti,ab. (22386)
37 saccharate.ti,ab. (140)
38 orthophospate.ti,ab. (3)
39 pyrophosphate.ti,ab. (14907)
40 electrolytic.ti,ab. (6267)
41 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 (383265)
42 randomized controlled trial.pt. (497868)
43 controlled clinical trial.pt. (99285)
44 randomized.ab. (434647)
45 randomised.ab. (87593)
46 placebo.ab. (203156)
47 clinical trials as topic.sh. (195751)
48 randomly.ab. (299524)
49 Random*.tw. (1018137)
50 trial.ti. (196266)
51 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 (1457594)
52 exp animals/ not humans.sh. (4683036)
53 51 not 52 (1335929)
54 8 and (20 or 27 or 41) and 53 (6129)
55 exp fatigue/ (27482)
56 fatigue.ti,ab. (83048)
57 exp lethargy/ (367)
58 tired.ti,ab. (1818)
59 tiredness.ti,ab. (3515)
60 55 or 56 or 57 or 58 or 59 (96239)
61 exp restless legs syndrome/ (3341)
62 restless legs syndrome.ti,ab. (3460)
63 restless leg syndrome.ti,ab. (460)
64 restless.ti,ab. (5283)
65 leg.ti,ab. (83701)
66 legs.ti,ab. (31051)
67 64 and (65 or 66) (4182)
68 Willis.ti,ab. (3232)
69 Ekbom.ti,ab. (190)
70 disease.ti,ab. (2775008)
71 68 and 69 and 70 (114)
72 61 or 62 or 63 or 67 or 71 (4703)
73 60 or 72 (100672)
74 8 and (20 or 27 or 41) and 73 (769)

75 74 not 52 (739)

76 8 and (20 or 27 or 41) and 73 and 53 (130)

Database: CENTRAL

Search date: 30.10.2017, 9.08 am

Search strategy:

#1 iron:ti,ab,kw 6496

#2 ferrous:ti,ab,kw 1030

#3 ferric:ti,ab,kw 880

#4 [25-#3] 6882

#5 MeSH descriptor: [Iron] explode all trees 1901

#6 #1 or #2 or #3 or #5 6882

#7 therapy:ti,ab,kw 364298

#8 administration:ti,ab,kw 199836

#9 intake:ti,ab,kw 32439

#10 supplement*:ti,ab,kw 42067

#11 replac*:ti,ab,kw 25996

#12 therapeutic:ti,ab,kw 60186

#13 administered:ti,ab,kw 74199

#14 treat*:ti,ab,kw 546944

#15 MeSH descriptor: [Therapeutics] explode all trees 288047

#16 MeSH descriptor: [Dietary Supplements] explode all trees 10246

#17 MeSH descriptor: [Pharmaceutical Preparations] explode all trees 64721

#18 [26-#17] 803100

#19 (gluconate or sucrose or dextran or carboxymaltose or isomaltoside or ferumoxytol):ti,ab,kw 4448

#20 (sulphate or sulfate or gluconate or lactate or bisglycinate or citrate or edta or fumarate or succinate or saccharate or orthophospate or pyrophosphate or electrolytic):ti,ab,kw 25386

#21 #6 and (#18 or #19 or #20) 5906

#22 MeSH descriptor: [Fatigue] explode all trees 2431

#23 fatigue:ti,ab,kw 20411

#24 MeSH descriptor: [Lethargy] explode all trees 6

#25 tired:ti,ab,kw 207

#26 tiredness:ti,ab,kw 740

#27 [27-#26] 20935

#28 MeSH descriptor: [Restless Legs Syndrome] explode all trees 232

#29 restless legs syndrome:ti,ab,kw 535

#30 restless:ti,ab,kw 669

#31 leg*:ti,ab,kw 18049

#32 syndrome:ti,ab,kw 52820

#33 {and #30-#32} 544

#34 willis:ti,ab,kw 69

#35 ekbom:ti,ab,kw 18

#36 disease:ti,ab,kw 230810

#37 [28-#36] 16

#38 #28 or #29 or #33 or #37 548

#39 #27 or #38 21417

#40 #6 and (#18 or #19 or #20) and #39 193