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**Preoperative anemia management with intravenous iron: a systematic review**

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## Preoperative anemia management with intravenous iron: a systematic review

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## Executive summary

### Background

Iron deficiency anemia is a common condition in patients presenting for surgery, but despite its negative health impacts, the condition remains frequently unmanaged. Optimizing the patient's own red cell mass should be addressed in the preoperative period. Intravenous iron has been advocated as an effective treatment modality.

### Objectives

The objective of this systematic review was to critically appraise and synthesize the best available evidence related to the effectiveness and economic aspects of intravenous iron administration on the correction of iron deficiency anemia in the preoperative period.

### Inclusion criteria

#### *Types of participants*

Adult patients 18 years of age and older receiving intravenous iron compared with those taking iron orally, and those who were not on iron or were transfused with red blood cells for the

correction of anemia. Studies assessing the economic aspects of anemia management were also considered.

### ***Types of intervention(s)/phenomena of interest***

The quantitative component of the review considered studies that evaluated the management of anemia with iron infusions compared to oral iron treatment alone, oral iron in combination with erythropoietin, erythropoietin alone or hemoglobin correction with blood transfusion.

The economic component of this review considered studies that evaluated the costs and benefits of iron infusions compared to oral iron treatment or hemoglobin correction with blood transfusion for the treatment of preoperative anemia.

### ***Types of studies***

The quantitative component of the review considered any experimental study design including randomized controlled trials (RCTs), non-RCTs and quasi-experimental studies for inclusion.

The economic component of the review considered cost effectiveness, cost utility and cost benefit studies for inclusion.

### ***Types of outcomes***

The quantitative component of this review considered studies that reported on the impact of intravenous iron administration on: hemoglobin levels, red blood cell transfusion, length of stay in hospital, rate of readmission within 30 days of discharge, incidence of transfusion-related complications and changes in functional outcomes.

The economic component of the review focused on cost benefits resulting from intravenous iron administration.

### **Search strategy**

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilized in this review. Studies published in English, German, Italian and Dutch from 2001 until December 2012 were considered for inclusion in this review.

### **Methodological quality**

The studies were independently assessed by two reviewers using standardized critical appraisal instruments from the Joanna Briggs Institute.

### **Data collection**

Quantitative data was extracted from papers included in the review using the standardized data extraction tool from the Joanna Briggs Institute, specifically the Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI). Economic data was extracted from papers included in the review using the standardized data extraction tool from the Joanna Briggs Institute Analysis of Cost, Technology and Utilisation Assessment and Review Instrument (JBI-ACTUARI).

### **Data synthesis**

This review set out to conduct both meta-analyses of the findings of effectiveness studies using JBI-MAStARI and pooling of economic findings using JBI-ACTUARI. Because of the number of studies found, this was not possible and the findings are therefore presented in tabular or narrative form.

### **Results**

The quantitative component of the review identified two RCTs for inclusion with one of the trials favoring intravenous iron over oral iron for anemia correction. Only a subgroup could be included from the second trial and the results were inconclusive. Data was heterogeneous and did not allow a meta-analysis.

The search for the economic component of the review revealed no examination of the cost effectiveness of preoperative correction of iron deficiency anemia with intravenous iron.

### **Conclusions**

The review found insufficient data to make firm conclusions about the effectiveness of preoperative intravenous iron administration for the correction of anemia. Neither could we establish firm conclusions on the potential cost savings due to intravenous iron supplementation.

### **Keywords**

Preoperative anemia, iron deficiency, intravenous iron, oral iron, blood transfusion, adverse effects, cost-benefit, cost-effectiveness

## **Background**

Most countries from around the world will be facing significant demographic changes over the next two decades. These changes will result in a dramatic increase in the older population and a decrease of the young.<sup>1</sup> The demographic changes will result in more complex surgical procedures in the elderly and consequently lead to an increase in demand for blood products and a sharp drop in donations from a lack of young donors. This looming shortfall has to be addressed urgently.

The transfusion of red blood cells (RBC) for the correction of anemia is a widely accepted treatment modality and a common occurrence in the perioperative period. In the US, 16 million units of blood are collected each year but only 20% of all transfusions are given for hemorrhagic shock to the hemodynamically unstable patient and may therefore be potentially lifesaving.<sup>2</sup> Most RBCs are prescribed to stable patients according to empirical guidelines. However, guidelines appear to be frequently ignored or underutilized and many clinicians revert to transfusion practices based on individual beliefs.<sup>3</sup> Despite an increasing body of evidence that perioperative allogeneic transfusion contributes to negative outcomes, such as increased length of stay (LOS), increased infection rates, increased occurrence of transfusion-related lung injury (TRALI), transfusion-related circulatory overload (TACO) and the high number of deaths, this form of anemia management continues.<sup>2</sup> Many of these transfusion events can be avoided if more attention is spent on optimizing preoperative hemoglobin values and the patients iron status.

Iron deficiency anemia (IDA) is a common condition. Age, socioeconomic circumstances, poor nutrition, and physiological processes (i.e. pregnancy) can result in anemia.<sup>4</sup> Many pathological states also commonly lead to severe iron depletion. These include inflammatory bowel disease, colorectal cancer and menorrhagia. In patients presenting for surgery iron deficiency, with or without anemia, is found in up to 75% of non-cardiac surgical patients.<sup>5</sup> This frequently results in an increased number of cardiac complications, days in hospital, allogeneic transfusion events and deaths. A more recent publication confirmed the incidence of anemia and stated that even mild forms of anemia increase 30-day mortality.<sup>6</sup> These findings imply that preoperative anemia screening and correction should become an integral part of the preoperative assessment and management process.

In many countries transfusion-related costs are of no consequence to the physician or the patient. In some countries like Australia, these costs are not even of any consequence for the hospital. This situation does not provide a platform for initiatives to facilitate change.

Patients from these high risk groups should be assessed, ideally at least four weeks prior to major surgery particularly. This would allow clinicians to interpret blood results with a window of opportunity to act. If the surgery is not urgent a delay should also be considered to investigate the cause of the anemia. In the common occurrence of iron deficiency anemia, there is increasing evidence that in urgent cases a more contemporary approach with intravenous iron might benefit the patient.<sup>7</sup>

The economic benefits of preoperative anemia correction are difficult to assess. Cost of transfusion and transfusion-related morbidity has to be balanced against the cost of robust preoperative anemia management. The Canadian Ontario Transfusion Coordinators (ONTraC) program placed a network of nurse transfusion coordinators in 23 hospitals. These hospitals accounted for 65% of allogeneic red blood cell transfusions. Most hospitals reduced their red cell consumption significantly allowing for estimated potential annual cost savings of 14.6 million Canadian dollars.<sup>8</sup>

A preliminary search of MEDLINE, The Cochrane Library, Embase, and Health Business Elite found no existing systematic reviews of effectiveness evidence and economic evidence on intravenous iron administration on the correction of iron deficiency anemia in the preoperative period.

Therefore this systematic review will aim to critically appraise, synthesize and present the best available evidence related to the effectiveness and economic cost-benefit ratio of intravenous iron administration on the correction of preoperative iron deficiency anemia.

## Objectives

The quantitative objective is to identify the effectiveness of intravenous iron administration on the correction of iron deficiency anemia in the preoperative period.

More specifically, the objectives are to identify the effectiveness of iron infusion on the rate of RBC transfusion, the incidence of transfusion-related comorbidities such as postoperative infection, immunological morbidity and mortality, as well as changes in functional capacity that could impact on quality of life.

The economic objective of this review is to identify the cost aspects of anemia management.

More specifically, the objectives are to identify the evidence of cost benefits on preoperative anemia correction and the potential for cost savings on blood products and indirect cost savings on transfusion related adverse effects.

## **Inclusion criteria**

### ***Types of participants***

The quantitative component and also the economic component of the review considered studies that included adult patients older than 18 years presenting for major surgery, regardless of gender, ethnicity, diagnosis and co-morbidities with preoperative anemia.

### ***Types of intervention(s)/phenomena of interest***

The quantitative component of the review considered studies that evaluated the management of anemia with iron infusions compared to oral iron treatment alone, oral iron in combination with erythropoietin, erythropoietin alone, or hemoglobin correction with blood transfusion. This included the dosage of iron, the frequency of its administration and the timeframe of treatment prior to surgery. In addition, it also assessed how intervention was employed, the personnel involved and the time spent to complete management.

The economic component of this review considered studies that evaluated the costs and benefits (cost-effectiveness, cost-utility, or cost-benefit) of iron infusions compared to oral iron treatment or hemoglobin correction with blood transfusion for the treatment of preoperative anemia.

### ***Types of studies***

The quantitative component of the review considered any experimental study design, including RCTs, non-RCTs, quasi-experimental, and before and after studies, for inclusion.

The economic component of the review considered cost effectiveness, cost-utility, and cost-benefit studies for inclusion.

### ***Types of outcomes***

The quantitative component of this review considered studies that included (but was not limited to) the following outcome measures:

- Effect of iron administration on hemoglobin levels
- Rate of RBC transfusion measured as proportion of patients transfused with allogeneic RBC and the average number of units transfused
- Length of stay in hospital
- Rate of readmission within 30 days of discharge
- Incidence of transfusion related co-morbidities measured as infection rates, occurrence of transfusion related lung injury (TRALI), transfusion related circulatory overload (TACO), and number of deaths.
- Impact of intravenous iron administration on functional outcomes.

The economic component of the review considered (but was not limited to) the following outcome measures:

- Reduction in costs for units of allogeneic blood avoided

- Reduction in costs associated with a reduction in length of stay in hospital
- Reduction in transfusion laboratory costs and nursing time
- Increase in costs for iron administered and nursing time.

## Search strategy

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilized in this review. An initial limited search of MEDLINE was undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the articles. A second search using all identified keywords and index terms was then undertaken across all included databases. Next, the reference list of all identified reports and articles was searched for additional studies. Studies published in English, German, Italian and Dutch were considered for inclusion in this review. Awareness of transfusion and anemia related outcomes have been addressed over the last 10 years. Therefore studies published from 2001 to December 2012 were considered for inclusion in this review.

The databases searched included:

- PubMed
- EMBASE
- The Cochrane Library
- Health Business Elite database
- NHS Economic Evaluation Database (NHS EED)
- Health Economic Evaluation Database (HEED).

The search for unpublished studies included: MedNar and ProQuest Dissertation and Thesis.

## Method of the review

Quantitative papers selected for retrieval was assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MASARI) (Appendix V). Any disagreements that arose between the reviewers was resolved through discussion, or with a third reviewer.

Economic papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Analysis of Cost, Technology and Utilization Assessment and Review Instrument (JBI-ACTUARI) (Appendix V). Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer.

## Data collection

Quantitative data was extracted from papers included in the review using the standardized data extraction tool from JBI-MASARI (Appendix VI). The data extracted included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Economic data was extracted from papers included in the review using the standardized data extraction tool from JBI-ACTUARI (Appendix VI). The data extracted included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

## **Data synthesis**

Quantitative papers was, where possible, pooled in statistical meta-analysis using JBI-MAStARI. All results were subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals were calculated for analysis. Heterogeneity was assessed statistically using the standard Chi-square. Where statistical pooling was not possible the findings were presented in narrative form including tables and figures to aid in data presentation where appropriate.

Quantitative papers were, where possible, pooled in statistical meta-analysis using JBI-MAStARI. All results were subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals were calculated for analysis. Heterogeneity was assessed statistically using the standard Chi-square. Where statistical pooling was not possible the findings were presented in narrative form including tables and figures to aid in data presentation where appropriate.

Economic findings were, where possible, pooled using JBI-ACTUARI and presented in a tabular summary. Where this was not possible, findings were presented in narrative form.

## **Results**

### *Description of studies*

Seventy-nine potentially relevant papers were identified in database searches. Titles and abstracts were examined for 63 papers. Three full text papers were retrieved for comprehensive examination. One paper was excluded after full text examination and two studies were selected for critical appraisal (Figure 1). On final assessment, two studies were identified as fulfilling all of the criteria for inclusion.



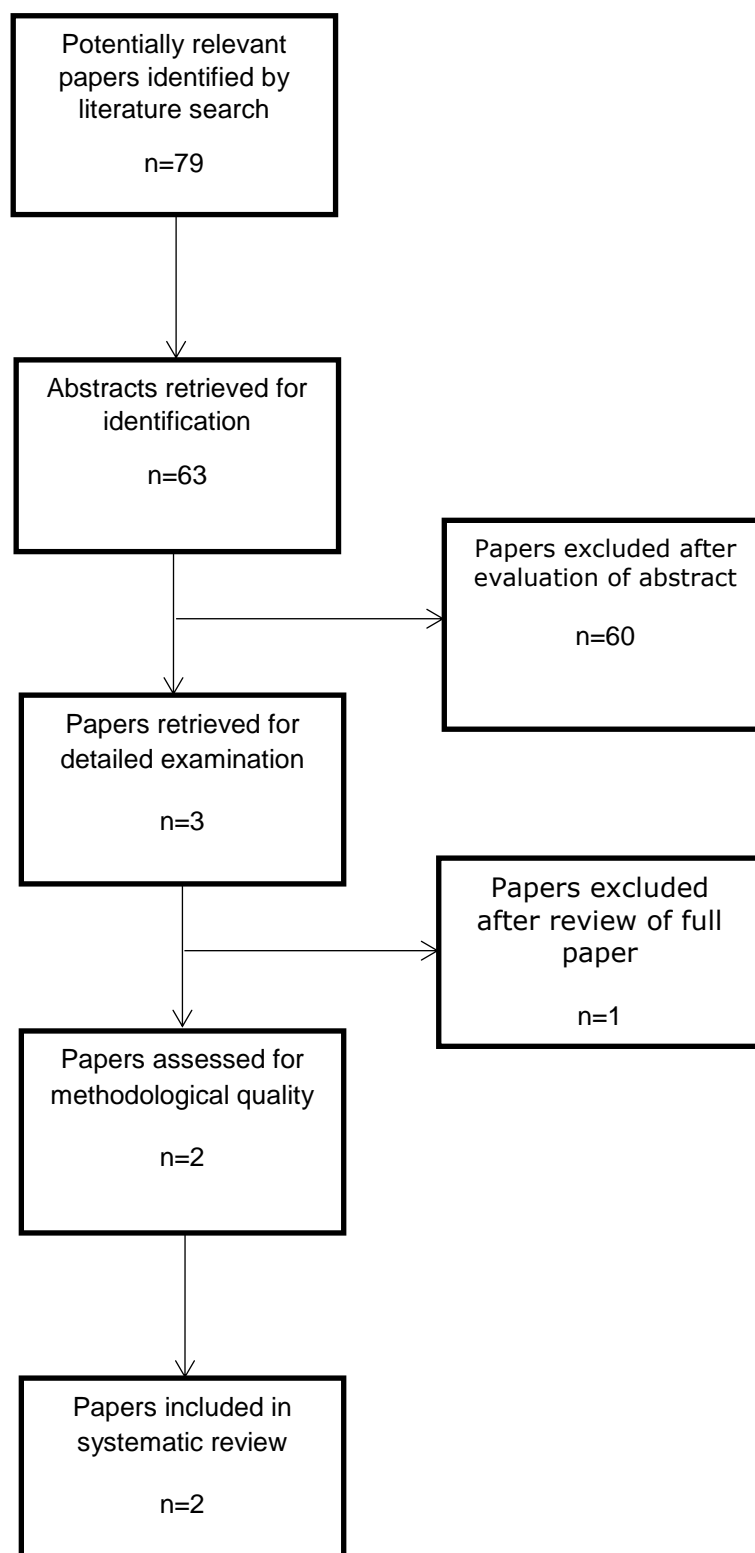


Figure 1: Identification and selection of studies

The first included study by Kim et al. was an open-label, prospective, randomized, multicenter trial conducted at three hospitals (including a tertiary referral center) in Seoul, Korea.<sup>9</sup> Patients enrolled were women with menorrhagia, where the condition resulted in IDA and hemoglobin levels of <9 g/dl. Patients were randomized to receive either intravenous iron sucrose or oral iron protein succinylate, starting three weeks prior to scheduled surgery. Based on a two-tailed  $\alpha$  of 0.05, it was determined that 36 patients per group were required to detect a 1-g/dl Hb difference in the primary outcome variable with a power of 80%.

No severe adverse effects were observed in the study period. Seventy-six patients were randomized and 30 completed the study in the intravenous iron arm and 26 in the oral arm. Thirty (76.7%) patients reached the target Hb in the intravenous iron group compared with 20 (11.5%) in the oral iron group RR, 95% CI ( $p < 0.0001$ ). Hb and ferritin were also significantly higher in the intravenous group at the end of the study. The intravenous iron group had a greater increase in the Hb level than the oral iron group (3.0 vs. 0.8 g/dl, respectively;  $p < 0.0001$ ) associated with an increase in the ferritin level (170.1 vs. 4.1  $\mu\text{g/l}$ ;  $p < 0.0001$ ). This was a well-conducted study in a patient cohort with significant iron deficiency anemia. The other phenomena of interest for this review, the rate of RBC transfusion, the average number of units transfused, the length of stay in hospital, the rate of readmission within 30 days of discharge, the incidence of transfusion related co-morbidities, the number of deaths and the impact of intravenous iron administration on functional outcomes, were not reported in this study.

The second (partially) included study by Edwards et al. was a single-center study in patients with suspected bowel cancer scheduled to undergo a bowel resection.<sup>10</sup> The study was powered at 80% to detect a 0.5 g/dl hemoglobin change between recruitment and the day of admission. In addition the hemoglobin value on the day of hospital discharge was recorded. All patients of a particular period, fulfilling the inclusion criteria, were enrolled and allocated to a treatment (intravenous iron) group or a placebo group. No significant difference was found for the primary outcome parameter between the groups and mean changes in hemoglobin value between recruitment and at presentation for surgery were -0.19 g/dl for the intravenous iron group and -0.50 g/dl for the placebo group. IQR, 95%CI ( $p=0.355$ ).

Only 18 subjects (nine in each arm) out of a total of 62 participants were anemic. The subgroup results could be included in this review, as the patients demonstrated the inclusion criteria for this review. The analysis of the anemic subgroup did not show any outcome differences. Mean change from recruitment to preoperative values were -0.46 g/dl (-0.79, -0.12) in the intravenous iron group compared with -0.11 g/dl (-0.63, 0.41) in the placebo group ( $p=0.223$ ). There was no separate analysis or reporting of the discharge hemoglobin in the anemic subgroup. In addition, no differences were demonstrated in any of the secondary outcome measures hematocrit, mean cell Hb (MCH), reticulocytes, serum iron, ferritin and transferrin saturation.

The other phenomena of interest for this review – the rate of RBC transfusion, the average number of units transfused, the length of stay in hospital, the rate of readmission within 30 days of discharge, the incidence of transfusion related co-morbidities, the number of deaths and the impact of intravenous iron administration on functional outcomes – were not reported in this study.

## Discussion

### The burden of anemia

As the most common global nutritional deficiency, the burden on society resulting from anemia is immense. Anemia-related symptoms such as fatigue, impaired cognitive function and poor exercise tolerance lessen quality of life that leads to huge productivity losses.<sup>11</sup>

The prevalence of IDA varies, depending on sources, definitions and patient cohorts.<sup>12,13</sup> Iron deficiency, with or without anemia, is found in up to 75% of patients presenting for surgery.<sup>14</sup> A growing body of evidence suggests that this has serious consequences for the perioperative period. IDA frequently leads to an increased number of cardiac complications, an increased number of days in hospital and a greater number of allogeneic transfusion events.<sup>3</sup> Preoperative anemia was also shown to independently increase perioperative mortality.<sup>5</sup> A more recent publication involving 227,425 patients, of whom 69,229 (30.44%) had preoperative anemia, confirmed the high incidence and concluded that even mild forms of anemia increase 30-day mortality.<sup>6</sup>

Anemia is commonly aggravated in the postoperative period. Intraoperative blood loss, wound drainage, hemodilution and frequent venipuncture for testing are all contributing factors. In addition, pre-existing iron depletion prevents effective perioperative erythropoiesis impairing post-operative functional recovery.<sup>15</sup>

### Impact on blood usage and utilization

When it comes to the surgical setting, which is the particular focus of this review, the presence of anemia often results in RBC transfusion. This continues to be a widely accepted treatment modality despite the clear and well described potential adverse effects and outcomes.<sup>16</sup> Donated blood is often claimed and perceived to be “safe”, prompting many clinicians to transfuse as a default position. Old dogmas prevail and the decision to transfuse is not only taken lightly but also often triggers a minimum transfusion of two units.<sup>17</sup> This is especially important as there appears to be a significant dose dependent effect of transfusion related adverse effects. It needs to be emphasized that not only total avoidance but also minimization of exposure to blood would potentially prevent harm and benefit the patient.<sup>18</sup>

By donating blood, donors place a valuable resource into the clinicians' hands with the assumption that it will be dealt with responsibly. This responsibility should be taken into account each time blood products are prescribed. It can however be noted that prescribing a blood transfusion is a process which remains too easy, is rarely discussed and often left to the inexperienced medical officer.<sup>19</sup> A common lack of documentation and/or consent accentuates the lack of scrutiny applied to the process of transfusion. The transfusion event is poorly monitored, is often inappropriate, unjustified and, due to various different funding models, sometimes comes at no cost for the health care provider (i.e. Australia).<sup>20</sup> These factors combined make it unlikely that clinical practice will change.

### Risk groups and identification

This review highlights that many patients who present for surgery are at risk of iron deficiency. This subsequently exposes them to a number of potential complications and a higher transfusion risks. This risk increases with the type and extent of the surgery, but also with the underlying disease process.<sup>21</sup>

Certain types of patients stand out and should make the clinician cautious. Patients with gastro-intestinal malignancies show the highest prevalence of IDA.<sup>5</sup> Chronic and longstanding blood loss results in iron loss and iron store depletion. Inflammatory bowel disease exposes patients to similar risks.<sup>22</sup> Women with menorrhagia often suffer from heavy menstrual bleeding for many years leading to gradual iron depletion. In these, generally otherwise healthy women, the condition is often well tolerated for a very long time and women frequently present with severe IDA to emergency departments when the tipping point is reached (personal observation). Patients scheduled for cardiac or orthopedic surgeries commonly combine many disadvantages. Advanced age, significant comorbidities such as congestive heart failure, ischemic heart disease, osteoarthritis and renal disease often compound the problem and ID and IDA becomes multifactorial.<sup>23</sup> An inflammatory state as a result of the chronic disease process leads to hepcidin increases and down regulation of iron absorption and utilization.<sup>24</sup> Certain medication may also further impair absorption (i.e. proton pump inhibitors, antacids) and other drugs can contribute to blood loss (aspirin, clopidogrel, warfarin, NSAIDs) threatening iron metabolism and iron balance.<sup>25, 26</sup> As many of the described findings are treatable and/or preventable it is obvious that preoperative anemia screening, detection and correction, particularly in patient groups at risk of IDA, should become an integral part of the preoperative assessment and management process. Iron deficiency with or without anemia is not a physiological state. It must therefore be considered a “disease process”. In medical practice we are required to treat disease and as such, anemia correction deserves much more attention. This makes it all the more surprising that our study found such a limited numbers of related studies.

#### Approach to change

It is clear, however, that high level evidence alone will not guarantee knowledge translation. Conducting audits and providing feedback can be a powerful intervention and provide the adequate tool in achieving the desired change in clinical practice.<sup>27, 27</sup> This was reiterated very recently by a panel of experts at the International Consensus Conference on Transfusion and Outcomes held in April 2009 in Phoenix.<sup>28</sup> The panel concluded that there is little evidence to support a beneficial effect from the greatest number of transfusions currently being given to patients.

Experts and authorities from around the world, including the World Health Organization, have recognized the need for change and the importance of more appropriate treatment approaches.<sup>29,30</sup> This can be facilitated through the implementation of Patient Blood Management (PBM) programs. It is crucial, however, that awareness is created and that PBM programs are driven by a local team underpinned by government support. Recognizing the importance of such change, accreditation, education and audit should consequently be linked in with PBM, and be compulsory. Even short educational sessions improved transfusion practice in the perioperative setting.<sup>31</sup> Physicians who understand transfusion indications and are receptive to input from colleagues apply a significantly higher quality transfusion practice.<sup>32</sup> Education, therefore, in addition to a willingness to accept “expert advice” is fundamental.

#### Models of practice

Pregnancy is one of the key areas where this has been explored. Pregnant women are a well-recognized risk group for developing ID and IDA. In the context of this review, the existing evidence from this patient cohort could not be included because the condition is not considered “preoperative” per se. However, 30% of women deliver by caesarean section, a surgical procedure with an average blood

loss of 400 ml. In addition to this, even normal vaginal delivery is often associated with significant blood loss.

Several studies have shown significant benefits from the administration of intravenous iron compared to oral iron supplementation.<sup>13,33</sup> Changes in Hb allowed women to be better prepared for delivery. This also enabled women to tolerate and recover better from blood loss associated with labor, which in 13% of women is moderate to severe.<sup>12</sup> Restoration of iron stores often alleviates ID-associated symptoms. These benefits are also felt in the post-partum period by reducing the incidence of post-partum depression and prolonging breast feeding episodes.<sup>13,34</sup> Therefore, despite the lack of evidence in the “surgical” population, some of the results from obstetric patients can offer insight and may be translated.

#### Interim solutions

In the absence of multiple RCTs in the literature providing guidance, one has to appreciate that prospective and retrospective cohort studies have described intravenous iron as an effective intervention.<sup>35-37</sup> Due to a high risk of serious adverse events associated with infusions of iron dextran, physicians have been cautious about intravenous intervention and have frequently substituted it with the transfusion of RBCs to correct any preoperative anemia.<sup>38</sup> In some clinical settings, however, it has been demonstrated that intravenous iron appears to be beneficial, particularly in iron deficient patients, with or without anemia.<sup>37,39</sup> Newer types of low molecular weight intravenous irons offer a much improved safety profile resulting in significantly lower incidences of adverse effects.<sup>40</sup> In recent years, this has led to the expansion of licensed indications for iron sucrose and ferric carboxymaltose, for example. It is surprising therefore that this treatment has not been studied extensively and there is not enough data from RCTs to support this approach. Accumulating observational data appears promising but randomized trials are needed to evaluate efficacy and cost effectiveness. In addition to dose requirements, trials are needed to determine the ideal time of administration and to identify the patient groups most in need of this intervention.

The majority of surgery is undertaken in an elective setting. Clinicians should strive for optimal patient outcomes in an attempt to minimize morbidity and mortality.<sup>4</sup> The development of patient blood management guidelines should assist in addressing anemia in order to minimize patient exposure to allogeneic blood, to enhance patient recovery and contribute to overall cost savings within health sectors, already under enormous financial strain.<sup>41</sup> Divided into three pillars, reflecting the pre-, intra- and post-operative phase, the preoperative period should focus on the detection and correction of anemia and iron deficiency. One could argue that no patient with anemia booked for elective surgery should enter the operating room. It is however crucial to identify patients with the appropriate test, communicate this well amongst involved specialties, and decide on the right strategy and treatment modality in order to achieve the best possible improvement in iron status and hemoglobin values.<sup>14</sup>

#### Economic implications

The search for the economic component of the review revealed no RCTs examining the cost effectiveness of the preoperative correction of iron deficiency anemia with iv iron. Considering the enormous health care expenditure for the provision of blood and blood products this is another interesting finding. In Australia for example the total cost to government to cover the demands for these products reached almost a total of \$1 billion in 2010/11.<sup>20</sup> In many instances, transfusion of RBCs remains the default position for the correction of preoperative anemia. As mentioned above, the risks of

transfusions are well demonstrated and acknowledged. Murphy established a direct link between transfusion of patients undergoing cardiac surgery and infection rates. Transfusion avoidance by anemia correction could have resulted in a 40% overall reduction in hospital cost.<sup>42</sup> The rising costs and looming shortage and availability of RBCs add to the multiple disadvantages of allogeneic transfusions.

Analyzing the cost of transfusion in the surgical setting should involve all steps required at a hospital level, called activity based cost. This is crucial in order to reflect the true cost of blood but is very complex. Due to fundamental differences in health jurisdictions, these cost factors are not universally applicable, but it is possible to establish identifying principles. Irrespective of the health system examined, it is highly likely that the real cost of blood has been underestimated in the past.<sup>43</sup> Many jurisdictions are already employing implementation of tools that identify activity for blood usage and this will certainly assist in rigorous cost analysis.

Blood management has been on the agenda for some time. It is therefore surprising that, despite a vast amount of publications and multiple guidelines available, knowledge translation is lacking and many transfusion events remain inappropriate.

Unmanaged anemia leads to a significant increase in transfusion. A Canadian program demonstrated successfully improved clinical outcomes and cost savings by managing patients appropriately in the preoperative period.<sup>3</sup> A recent publication on the implementation of a local blood management algorithm in major orthopedic surgery illustrated that cost-savings can be achieved.<sup>44</sup> In a RCT setting oral iron supplementation has been shown to reduce transfusion incidence resulting in significant cost savings.<sup>46,45</sup> Depending on the time frame prior to surgery and the severity of the anemia and/or iron depletion, intravenous iron administration appears to be an even more effective approach.<sup>35,37,46</sup>

It is important to remember that the main target of patient care is patient outcome. Patient blood management should be standard care for all patients in the surgical setting. Even if total transfusion avoidance is not feasible for all patients, overall reductions are achievable. Endorsing appropriate transfusion approaches in combination with preoperative optimization should result in improved patient well-being, and cost savings are likely to be a logical flow on effect.

## **Conclusion**

There is a significant gap in the literature. Our study found insufficient data to make firm conclusions about the efficacy of preoperative intravenous iron administration for the correction of anemia based on clinical trial settings. Neither could we establish firm conclusions on the potential cost savings due to intravenous iron supplementation

### ***Implications for practice***

There is inadequate RCT evidence at present to guide clinical practice.

### ***Implications for research***

An adequately powered RCT is needed to determine whether anemia can be adequately corrected and is cost effective when preoperative intravenous iron is administered.

### ***Conflict of Interest***

None

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3. Tinmouth A, Macdougall L, Fergusson D, Amin M, Graham ID, Hebert PC, et al. Reducing the amount of blood transfused: a systematic review of behavioral interventions to change physicians' transfusion practices. *Archives of internal medicine*. 2005 Apr 25;165(8):845-52.
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46.Van Wyck DB, Mangione A, Morrison J, Hadley PE, Jehle JA, Goodnough LT. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. *Transfusion.* 2009 Dec;49(12):2719-28.

## Appendix I: Search strategy

### PubMed

("surgical procedures, operative"[MeSH Terms] AND "preoperative care"[MeSH Terms]) AND ("iron/deficiency"[MeSH Terms] OR "anemia"[MeSH Terms] OR "anemia, iron-deficiency"[MeSH Terms]) AND ("blood transfusion"[MeSH Terms] OR ("hematinics/administration and dosage"[MeSH Terms] OR "hematinics/therapeutic use"[MeSH Terms]) OR ("erythropoietin/administration and dosage"[MeSH Terms] OR "erythropoietin/therapeutic use"[MeSH Terms]) OR ("iron/administration and dosage"[MeSH Terms] OR "iron/therapeutic use"[MeSH Terms]) OR ("iron compounds/administration and dosage"[MeSH Terms] OR "iron compounds/therapeutic use"[MeSH Terms]) OR ("infusions, intravenous"[MeSH Terms] AND "iron"[MeSH Terms])) AND ("2003/02/14"[PDat] : "2013/02/10"[PDat] AND English[lang])("surgical procedures, operative"[MeSH Terms] AND "preoperative care"[MeSH Terms]) AND ("iron/deficiency"[MeSH Terms] OR "anemia"[MeSH Terms] OR "anemia, iron-deficiency"[MeSH Terms]) AND ("blood transfusion"[MeSH Terms] OR ("hematinics/administration and dosage"[MeSH Terms] OR "hematinics/therapeutic use"[MeSH Terms]) OR ("erythropoietin/administration and dosage"[MeSH Terms] OR "erythropoietin/therapeutic use"[MeSH Terms]) OR ("iron/administration and dosage"[MeSH Terms] OR "iron/therapeutic use"[MeSH Terms]) OR ("iron compounds/administration and dosage"[MeSH Terms] OR "iron compounds/therapeutic use"[MeSH Terms]) OR ("infusions, intravenous"[MeSH Terms] AND "iron"[MeSH Terms])) AND ("2003/02/14"[PDat] : "2013/02/10"[PDat] AND English[lang])

Database: Embase<1980 to 2012 Week 35>

### Search Strategy:

- 
- 1 exp Surgical Procedures, Operative/ (2924635)
  - 2 exp Preoperative Care/ (32993)
  - 3 Iron deficiency/ (7861)
  - 4 anemia/ (94470)
  - 5 Anemia, Iron-Deficiency/ (11933)
  - 6 exp Blood Transfusion/ or Hematinics/ad, tu [Administration & Dosage, Therapeutic Use] (110562)
  - 7 Erythropoietin/ad, tu [Administration & Dosage, Therapeutic Use] (655)
  - 8 Iron/ad, tu [Administration & Dosage, Therapeutic Use] (1851)
  - 9 exp Iron Compounds/ad, tu [Administration & Dosage, Therapeutic Use] (77)
  - 10 Infusions, Intravenous/ (310622)
  - 11 Iron/ (98811)
  - 12 anemia/dm, dt, pc, rh, th [Disease Management, Drug Therapy, Prevention, Rehabilitation, Therapy] (18509)
  - 13 iron deficiency anemia/dm, dt, pc, rh, th [Disease Management, Drug Therapy, Prevention, Rehabilitation, Therapy] (5041)
  - 14 1 and 2 (32993)
  - 15 3 or 4 or 5 (109211)
  - 16 10 and 11 (1175)
  - 17 6 or 7 or 8 or 9 or 16 (113583)
  - 18 14 and 15 and 17 (120)
  - 19 12 or 13 (23150)
  - 20 14 and 19 (134)

21 18 or 20 (166)

22 exp "Costs and Cost Analysis"/ (225568)

23 economics.mp. or economics/ (242587)

24 22 or 23 (420714)

25 21 and 24 (15)

26 limit 21 to (evidence based medicine or consensus development or meta analysis or outcomes research or "systematic review") (5)

27 limit 21 to (clinical trial or RCT or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) (44)

28 26 or 27 (46)

ACTUARI

PubMed

("economics"[MeSH Subheading] OR "costs and cost analysis"[MeSH Terms] AND ("2003/02/14"[PDat] : "2013/02/10"[PDat] AND English[lang])) AND (("surgical procedures, operative"[MeSH Terms] AND "preoperative care"[MeSH Terms]) AND ("iron/deficiency"[MeSH Terms] OR "anemia"[MeSH Terms] OR "anemia, iron-deficiency"[MeSH Terms]) AND ("blood transfusion"[MeSH Terms] OR ("hematinics/administration and dosage"[MeSH Terms] OR "hematinics/therapeutic use"[MeSH Terms]) OR ("erythropoietin/administration and dosage"[MeSH Terms] OR "erythropoietin/therapeutic use"[MeSH Terms]) OR ("iron/administration and dosage"[MeSH Terms] OR "iron/therapeutic use"[MeSH Terms]) OR ("iron compounds/administration and dosage"[MeSH Terms] OR "iron compounds/therapeutic use"[MeSH Terms]) OR ("infusions, intravenous"[MeSH Terms] AND "iron"[MeSH Terms])) AND ("2003/02/14"[PDat] : "2013/02/10"[PDat] AND English[lang])) AND ("2003/02/14"[PDat] : "2013/02/10"[PDat] AND English[lang])

## Appendix II: Search results

Beattie WS, Karkouti K, Wijeyesundera DN, Tait G. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. *Anesthesiology*. 2009 Mar;110(3):574-81.

Browning RM, Trentino K, Nathan EA, Hashemi N. Preoperative anaemia is common in patients undergoing major gynaecological surgery and is associated with a fivefold increased risk of transfusion. *Aust N Z J Obstet Gynaecol*. 2012 Oct;52(5):455-9.

Christodoulakis M, Tsiftsis DD. Preoperative epoetin alfa in colorectal surgery: a randomized, controlled study. *Ann Surg Oncol*. 2005 Sep;12(9):718-25.

Cuenca J, Garcia-Erce JA, Martinez F, Cardona R, Perez-Serrano L, Munoz M. Preoperative haematinics and transfusion protocol reduce the need for transfusion after total knee replacement. *International journal of surgery (London, England)*. 2007 Apr;5(2):89-94.

Cuenca J, Garcia-Erce JA, Martinez F, Perez-Serrano L, Herrera A, Munoz M. Perioperative intravenous iron, with or without erythropoietin, plus restrictive transfusion protocol reduce the need for allogeneic blood after knee replacement surgery. *Transfusion*. 2006 Jul;46(7):1112-9.

Edwards TJ, Noble EJ, Durran A, Mellor N, Hosie KB. Randomized clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery. *Br J Surg*. 2009 Oct;96(10):1122-8.

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Garrido-Martin P, Nassar-Mansur MI, de la Llana-Ducros R, Virgos-Aller TM, Fortunez PM, Avalos-Pinto R, et al. The effect of intravenous and oral iron administration on perioperative anaemia and transfusion requirements in patients undergoing elective cardiac surgery: a randomized clinical trial. *Interact Cardiovasc Thorac Surg*. 2012 Dec;15(6):1013-8.

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### Appendix III: Studies selected for retrieval

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## Appendix IV: Studies not selected for retrieval

Christodoulakis M, Tsiftsis DD. Preoperative epoetin alfa in colorectal surgery: a randomized, controlled study. *Ann Surg Oncol*. 2005 Sep;12(9):718-25.

Cuenca J, Garcia-Erce JA, Martinez F, Cardona R, Perez-Serrano L, Munoz M. Preoperative haematinics and transfusion protocol reduce the need for transfusion after total knee replacement. *International journal of surgery (London, England)*. 2007 Apr;5(2):89-94.

Cuenca J, Garcia-Erce JA, Martinez F, Perez-Serrano L, Herrera A, Munoz M. Perioperative intravenous iron, with or without erythropoietin, plus restrictive transfusion protocol reduce the need for allogeneic blood after knee replacement surgery. *Transfusion*. 2006 Jul;46(7):1112-9.

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Nasir A, Yasmin H, Korejo R. Management of iron deficiency anaemia in gynaecological patients at Jinnah Postgraduate Medical Centre, Karachi. *J Pak Med Assoc*. 2011 Oct;61(10):998-1001.

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Santos-Ampuero MA, Martin-Celemin R, Orts-Rodriguez M, Carmona A, Villabona E, Planas A. Perioperative anemia management in colorectal surgery: Single-center retrospective cohort evaluation. *Transfusion Alternatives in Transfusion Medicine*. 2010;11:31.

## Appendix V: Appraisal instruments

### MAStARI appraisal instrument

#### JBIC Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer ..... Date .....

Author ..... Year ..... Record Number .....

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Were participants blinded to treatment allocation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Was allocation to treatment groups concealed from the allocator?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Were the outcomes of people who withdrew described and included in the analysis?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Were those assessing outcomes blind to the treatment allocation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Were the control and treatment groups comparable at entry?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Were groups treated identically other than for the named interventions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Were outcomes measured in the same way for all groups?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Were outcomes measured in a reliable way?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Was appropriate statistical analysis used?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall appraisal:    Include                     Exclude                     Seek further info.

Comments (Including reason for exclusion)

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**ACTUARI appraisal instrument**

**JBI Critical Appraisal Checklist for Economic Evaluations**

Reviewer ..... Date .....

Author ..... Year ..... Record Number .....

	Yes	No	Unclear	Not Applicable
1. Is there a well defined question?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Is there comprehensive description of alternatives?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Are all important and relevant costs and outcomes for each alternative identified?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Has clinical effectiveness been established?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Are costs and outcomes measured accurately?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Are costs and outcomes valued credibly?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Are costs and outcomes adjusted for differential timing?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Is there an incremental analysis of costs and consequences?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Do study results include all issues of concern to users?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Are the results generalisable to the setting of interest in the review?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall appraisal: Include  Exclude  Seek further info.

Comments (Including reasons for exclusion)

\_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

## Appendix VI: Data extraction instruments

### MAStARI data extraction instrument

#### JBI Data Extraction Form for Experimental / Observational Studies

Reviewer ..... Date .....

Author ..... Year .....

Journal ..... Record Number .....

#### Study Method

RCT                       Quasi-RCT                       Longitudinal   
 Retrospective                       Observational                       Other

#### Participants

Setting \_\_\_\_\_

Population \_\_\_\_\_

#### Sample size

Group A \_\_\_\_\_ Group B \_\_\_\_\_

#### Interventions

Intervention A \_\_\_\_\_

Intervention B \_\_\_\_\_

Authors Conclusions:  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

Reviewers Conclusions:  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_



### Clinical Effectiveness Results

Study design

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Year range of primary studies

---

Analysis used

---

Clinical outcome results

---

### Economic Effectiveness results

Date/s of economic data

---

Modeling used

---

Measure of benefits used in economic evaluation

---

Direct costs

---

Indirect costs

---

Currency

---

Statistical analysis

---

Estimated benefits used in EE

---

Cost results

---

Synthesis of costs and results

---

### Outcome category

		Clinical effectiveness		
		+	0	-
Cost	+	● A	○ B	○ C
	0	○ D	○ E	○ F
	-	○ G	○ H	○ I

Key	
Effectiveness	Cost
+	Better Lower
0	Equal Equal
-	Poorer Higher

**Appendix VII: Included studies**

MAStARI

Author/year/country	Kim Y H, Chung H H, Kang S B, Kim S C, Kim Y T\2009\Korea
Study	Safety and usefulness of intravenous iron sucrose in the management of preoperative anaemia in patients with menorrhagia
Method	RCT
Participants	76 patients with haemoglobin levels < 9.0 g/dl who were scheduled to undergo surgical treatment
Intervention	Randomized to receive either intravenous iron sucrose or oral iron
Outcomes	To detect a 1-g/dl Hb difference adverse effects compliance
Risk of bias/allocation concealment	Premature cessation of the oral iron arm, relatively small number, some protocol violations that limited the clinical and laboratory data were possible
Level of evidence	II
Notes	Intravenous iron was superior to oral iron in this study. The target haemoglobin was achieved in a significantly higher percentage of patients after intravenous iron administration. There was also a significant difference in the magnitude of haemoglobin increase and the ferritin levels in the iv group. No serious adverse events were recorded in either group.

Author/year/country	Edwards T J, Noble, E J, Durran A, Mellor, N, Hosie K B /2009/ UK
Study	RCT of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery
Method	RCT, prospective, blinded, placebo-controlled
Participants	62 adult patients to undergo bowel resection for suspected colorectal cancer
Intervention	Intravenous placebo vs intravenous iron sucrose
Outcomes	The primary outcome measure was change in Hb concentration between recruitment and day of admission. Secondary outcomes were transfusion rate, changes in serum iron markers over the same time period, length of hospital stay and adverse perioperative events.
Risk of bias/allocation	Excluding patients with previous transfusion and on oral iron, patients

concealment	with potential profound anaemia, majority of patients randomised were not iron deficient or anaemic
Level of evidence	II
Notes	Only 9/34 patients with anaemia in the intravenous group and 9/26 patients with anaemia in the oral group. This allows the assumption that in most cases treatment with iron was not going to be successful, irrelevant of the route of administration



**Appendix VIII: Excluded studies**

Author/year/country	Garrido-Martin, P, Nassar-Mansur, M I, de la Llana-Ducros, R, Virgos-Aller, T M, Fortunez, P M, Avalos-Pinto, R, Jimenez-Sosa, A, Martinez-Sanz, R /2012/ Spain
Study	The effect of intravenous and oral iron administration on perioperative anaemia and transfusion requirements in patients undergoing elective cardiac surgery: a randomized clinical trial
Method	RCT, prospective, double-blind, placebo-controlled, observational clinical trial
Participants	159 adult patients presenting for cardiac surgery
Intervention	Three groups, all treated pre-and postoperatively Group I intravenous iron sucrose. GII oral iron. GIII placebo
Outcomes	Increase in haemoglobin: transfusion requirements
Risk of bias/allocation concealment	Study underpowered to show a difference, patient selection included all patients in the study period irrespective of the iron status
Level of evidence	II
Notes	There is no information on the number of patients with iron deficiency or anaemia

## **Appendix IX: List of study findings/conclusions**

There is a significant gap in the literature. Our study found insufficient data to make firm conclusions about the efficacy of preoperative intravenous iron administration for the correction of anemia based on clinical trial settings. We were also unable to establish firm conclusions in respect to the potential cost savings due to intravenous iron supplementation.

Aside from the risk posed to the individual patient, continuation of commonly observed transfusion practices will result in significant consequences to our health system as a whole. To accommodate the future challenges, prevention – by improving and preserving the patient's red cell mass and thereby reducing the number of allogeneic red cell transfusions – must be an important goal. Anemia management is at the core of this approach.