A Descriptive Study Assessing the Effectiveness of Patient Blood Management Initiatives at a Tertiary Level Hospital in South Africa by Comparing the Utilisation of Iron Therapy (Oral and Intravenous) to Packed Red Blood Cell Transfusions Over a 10-Year Period

Groote Schuur Hospital, Cape Town, South Africa

Master of Medicine (MMed)

For candidate Dr Chadwin Frederick Corin (MBChB)

CHDCOR001

University of Cape Town

Faculty of Health Science

Department of Medicine

Groote Schuur Hospital

University of Cape Town

Supervisor: Professor Vernon Louw

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Acknowledgements

To my supervisor, Prof. Vernon Louw, I am grateful for guidance and availability throughout this process.

To Karryn Brown and Kelechi Nnene, many thanks for helping with reviewing the statistical analysis and write-up. The impact of this project would not have been possible without their contributions.

AI tools, such as Grok (built by xAI), were used for minor language editing and proofreading assistance in drafting sections of the manuscript.

Format

This is a publication-ready manuscript formatted according to the guidelines of Annals of Blood journal.

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List of Abbreviations

CI	Confidence Interval
CPI	Consumer Price Index
GDP	Gross Domestic Product
GSH	Groote Schuur Hospital
HIV	Human Immunodeficiency Virus
IDA	Iron Deficiency Anaemia
IQR	Interquartile Range
IV	Intravenous
LMICs	Low- and Middle-Income Countries
HICs	High-Income Countries
PBM	Patient Blood Management
PPP	Purchasing Power Parity
pRBC	Packed Red Blood Cells
TB	Tuberculosis
USD	United States Dollar
WCBS	Western Cape Blood Service
WHO	World Health Organization
WRA	Women of Reproductive Age
ZAR	South African Rand (Zuid-Afrikaanse Rand)

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TITLE PAGE

Title

A Descriptive Study Assessing the Effectiveness of Patient Blood Management Initiatives at a Tertiary Level Hospital in South Africa by Comparing the Utilisation of Iron Therapy (Oral and Intravenous) to Packed Red Blood Cell Transfusions Over a 10-Year Period.

Authors

Chadwin Corin^[a]; Kelechi Nnene^[a]; Karryn Brown^[a]; Vernon Louw^[a]

Affiliations

a Division of Clinical Haematology, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa

Correspondence

Dr. Chadwin Corin, MBChB, FCP(SA), Department of Medicine, Groote Schuur Hospital, Observatory, Cape Town 7925, South Africa; CHDCOR001@myuct.ac.za, +27 (0)21 909 3313.

ORCID: Chadwin Corin; 0009-0000-5729-268X

Author Contributions

(I) Conception and design: V. Louw and C. Corin
(II) Administrative support: K. Brown
(III) Provision of study materials or patients: V. Louw and C. Corin
(IV) Collection and assembly of data: C. Corin
(V) Data analysis and interpretation: V. Louw, C. Corin, K. Nnene and K. Brown
(VI) Manuscript writing: All authors
(VII) Final approval of manuscript: All authors

All authors meet the ICMJE criteria for authorship.

Running Title

Effectiveness of PBM at Groote Schuur

Manuscript Details

- Word Count: 4 922
- Number of Figures, Videos, and Tables: 4 Tables, 3 Figures, 1 Supplementary Table

Abstract

Background

Iron deficiency anaemia (IDA) remains a significant public health challenge in low- and middle-income countries (LMICs) like South Africa, where progress towards the World Health Assembly's 2030 target of reducing anaemia by 50% among women of reproductive age is insufficient. Patient Blood Management (PBM) initiatives, implemented at Groote Schuur Hospital (GSH) in 2018, aimed especially to optimise red cell mass and reduce reliance on packed red blood cell (pRBC) transfusions through enhanced utilisation of iron therapies. This study evaluates PBM's effectiveness by analysing expenditure trends on oral and intravenous (IV) iron therapies compared to pRBC transfusions over the 2013–2022 period.

Methods

This retrospective cohort study used GSH pharmacy and Western Cape Blood Service (WCBS) data, covering April 2013 to March 2023, segmented into pre-PBM (2013–2017) and post-PBM (2018–2022) periods. Expenditure on the available oral iron (Ferrous Sulphate tablets, Ferrous Gluconate syrup), IV iron (Iron Hydroxide Dextran), and pRBC transfusions was adjusted to 2022 constant USD values using South Africa's Consumer Price Index (CPI) and 2022 Purchasing Power Parity (PPP) factor of 7.23. Expenditure per 1 000 patient encounters and cost differentials per annum were calculated. Statistical analyses included Wilcoxon Rank-Sum, Mann-Kendall, Wilcoxon signed-rank tests, bootstrap methods (10 000 resamples) for 95% confidence intervals, sensitivity analyses excluding 2020 data and segmented interrupted time-series models.

Results

Since the initiation of PBM initiatives, iron therapy utilisation increased, with median annual expenditure per 1 000 patient encounters rising by 74.4% for oral iron therapy (from $16 to $28; Wilcoxon p=0.056; 95% CI: $0 to $21), 302.2% for IV iron therapy (from $25 to $99; p=0.008; 95% CI: $29 to $145), and 222% for combined iron therapy (from $41 to $131; p=0.008; 95% CI: $40 to $162). In contrast, median annual expenditure per 1 000 patient encounters on pRBC rose by only 3.2% (from $7 270 to $7 499; Wilcoxon p=0.548; 95% CI: $-665 to $1 474), below the 11.4% acquisition cost increase (Wilcoxon signed-rank p=0.652), potentially indicating reduced transfusion reliance. Cost differentials per annum showed an additional $90 for combined iron therapy, offset by $600 in pRBC savings, yielding a net savings of $510 (R3 680) per 1 000 patient encounters, with potential annual savings exceeding $305 400 (R2 208 042) at GSH. Sensitivity analyses excluding 2020 data (due to potential confounding effects of the COVID19 pandemic) showed trends remained directionally consistent (p≤0.176).

Conclusions

PBM increased iron therapy utilisation, reduced pRBC reliance, and achieved cost savings, positioning it as a more affordable strategy for IDA management in South Africa and LMICs. Clinical outcome studies are needed to further validate these findings.

Keywords

Patient Blood Management, Iron Deficiency Anaemia, Transfusion, Healthcare Expenditure, South Africa.

Highlight Box

- Key Findings: Post-PBM, iron therapy utilisation increased (74.4% oral, 302.2% IV per 1 000 encounters), pRBC reliance decreased (3.2% vs. 11.4% cost increase), with net cost savings of $510 (R3 680) per 1 000 encounters, potentially over $305 400 (R2 208 042) annually.
- What is Known and New: PBM's benefits are established in high-income countries (HICs); this study provides novel evidence of its impact and cost savings in an LMIC tertiary hospital.
- Implications and Actions Needed: PBM could reshape IDA management in resource limited settings. Investments in training, IV iron access, and prospective clinical studies are critical.

Introduction

1.1 Background

Iron deficiency anaemia (IDA) affects an estimated 1.62 billion people globally (24.8%), with a disproportionate burden in low- and middle-income countries (LMICs), particularly in Africa and South Asia (1). In South Africa, prevalence rates of IDA are high, with recent studies indicating a significant underestimate in earlier reports due to stringent diagnostic criteria (e.g., haemoglobin <12.0 g/dL plus serum ferritin <15 µg/L in healthy individuals without apparent disease) (2). More comprehensive data reveal anaemia prevalence ranging from 29.0% to 42.7% in pregnancy and 60.6% to 71.3% in HIV-infected pregnant women (3). Among non-pregnant women of reproductive age (WRA), anaemia, iron deficiency (ID), and IDA rates are 39.4%, 38.1%, and 21.6%, respectively, influenced by socioeconomic, biodemographic, nutritional, and inflammatory factors (3, 4). Iron deficiency is more common in females due to physiological demands such as menstrual blood loss and pregnancy-related iron requirements (5). Mechanisms include chronic blood loss from menstruation, increased iron needs during pregnancy and lactation, dietary inadequacies, and absorption issues exacerbated by inflammation from infections like HIV and TB. Beyond WRA, IDA extends to other vulnerable groups, including surgical populations, where preoperative anaemia affects 30-40% of patients and is associated with increased postoperative mortality, prolonged ICU stays, and higher healthcare costs (6).Peri- and post-operative causes of anaemia, such as surgical blood loss and inflammation, are non-gender dependent. Postpartum haemorrhage is particularly relevant, where anaemia can both precede and result from this devastating complication, contributing to maternal morbidity in LMICs (7). In South Africa, infectious diseases such as HIV and tuberculosis (TB) exacerbate IDA across diverse demographics, amplifying its impact in surgical and general adult populations (4-6).

IDA carries severe health consequences, including increased risks of preterm birth, low birth weight, perinatal mortality, and long-term cognitive and motor development impairments in children (8, 9). Economically, IDA imposes a substantial toll, with costs in LMICs estimated at

up to 4% of Gross Domestic Product (GDP) due to reduced productivity and healthcare expenditures (10). In South Africa, where HIV and TB prevalence is high, the economic burden may exceed $1 billion annually when adjusted for purchasing power parity (PPP) (10). Despite global commitments, such as the World Health Assembly's 2030 goal to halve anaemia prevalence in WRA, South Africa's progress remains stymied by poverty, infectious disease burdens, inadequate dietary iron intake, and limited access to effective interventions (5, 11).

Conventional treatments for IDA, such as oral iron supplements, intravenous (IV) iron therapies, and blood transfusions, face significant barriers. Oral iron is often limited by gastrointestinal side effects and poor adherence (12), while IV iron is constrained by availability and cost in resource-limited settings (13). Transfusions carry risks including transfusion-associated circulatory overload, infection, and alloimmunisation, further compounded by strained blood supply systems in LMICs (14). Recent studies in sub-Saharan Africa underscore the urgent need for tailored strategies to combat IDA and enhance transfusion practices amidst limited resources (4, 15).

Patient Blood Management (PBM), defined globally as "a patient-centred, systematic, evidence-based approach to improve patient outcomes by the management and preservation of a patient's own blood, while promoting patient safety and empowerment"(16), addresses these challenges through three pillars: optimising red cell mass (e.g., via iron therapy to treat anaemia), minimising blood loss, and improving tolerance of anaemia (16). At Groote Schuur Hospital (GSH), a tertiary academic referral centre affiliated with the University of Cape Town, PBM initiatives were introduced in 2018 with a major focus on the first pillar—enhancing iron therapy utilisation to optimise erythropoiesis and reduce reliance on packed red blood cell (pRBC) transfusions (17, 18). Globally, PBM has demonstrated reduced transfusion rates and healthcare costs in HICs (17, 18), yet its application in resource-constrained LMICs like South Africa remains under-explored (15, 19-21). Local evidence supports PBM as a viable solution, with studies showing improved blood utilisation and cost savings in South African hospitals (19-21). By prioritising iron therapy in PBM's first pillar, GSH aimed to address IDA's multifaceted burden, including in surgical populations where preoperative anaemia is prevalent (6, 19).

1.2 Rationale and Knowledge Gap

South Africa's high IDA prevalence and its socioeconomic ramifications demand evidence based, context-specific interventions. While international research highlights PBM's efficacy in HICs, its feasibility, sustainability and economic implications in LMICs with elevated infectious disease burdens and constrained healthcare infrastructure are less widely studied (15). Current estimates of IDA's economic impact in South Africa lack precision, and documentation of progress towards 2030 anaemia reduction targets is sparse (5, 10). This study addresses some of these gaps by evaluating the impact of PBM's implementation at GSH, a major tertiary hospital affiliated with the University of Cape Town, offering insights into its potential as a scalable, cost-effective model for LMICs.

1.3 Objective

This study aimed to assess the success of early PBM initiatives introduced at GSH in 2018 by analysing trends in expenditure on oral and IV iron therapies and pRBC transfusions from April

2013 to March 2023. It sought to determine PBM's effectiveness in enhancing IDA management, reducing transfusion dependence, and achieving significant cost savings within a South African tertiary care setting, with broader implications for LMICs. Primary outcome: median difference in annual expenditure per 1 000 patient encounters between pre- and post-PBM periods.

We present this article in accordance with the STROBE reporting checklist.

Methods

2.1 Study Design and Setting

This retrospective cohort study was conducted at GSH, a tertiary, adult academic referral centre, serving a catchment population of approximately 4 to 4.5 million in the Western Cape (22). The study period spanned April 2013 to March 2023, capturing financial years aligned with South Africa's fiscal calendar. PBM initiatives, launched in 2018, included staff education through lectures, blood utilisation committee discussions, and budget adjustments to allow for increased utilisation of iron therapies over transfusions without mandating changes in clinical practice. Data were segmented into pre-PBM (2013– 2017) and post-PBM (2018–2022) periods for comparative analysis.

2.2 Data Sources

All data were sourced via the GSH Information Unit. Expenditure data on iron therapies were sourced from pharmacy records via their computerised pharmaceutical management system, detailing direct costs for oral iron (Ferrous Sulphate tablets, Ferrous Gluconate syrup) and IV iron (Iron Hydroxide Dextran (Cosmofer®)). pRBC transfusion expenditure data were provided by the Western Cape Blood Service (WCBS), covering Red Cell Concentrate, Leucocyte-Poor Red Cell Concentrate. Total patient encounter data (inpatient and outpatient) were obtained to adjust for utilisation rates.

2.3 Data Processing

Data were received in password-protected Microsoft Excel spreadsheets, cleaned by reviewing for and removing duplicates, and verified for accuracy against original records. All financial data were adjusted to 2022 constant prices using South Africa's Consumer Price Index (CPI) from Statistics South Africa (23) to account for inflation, reflecting real domestic purchasing power over the 10-year period. These inflation-adjusted South African rands (ZAR) values were then converted to constant United States dollars (USD) using the 2022 PPP factor of 7.23, as reported by the World Bank (24) ensuring comparability across years and providing an internationally recognised benchmark, a standard approach in health economics for LMICs (25). Expenditure on oral iron therapy used the aggregated sum of costs of the various oral iron therapy options whereas expenditure on IV iron used aggregated costs of the only IV product available (Iron Hydroxide Dextran). pRBC transfusion expenditure encompassed expenditure on Red Cell Concentrate, LeucocytePoor Red Cell Concentrate, and Transfusion Crossmatched Red Cells. The four comparators are detailed in Table 1. Total annual expenditure was calculated for each financial year (April–March) and normalised to annual expenditure per 1 000 patient encounters to account for variations in healthcare utilisation. Acquisition costs were determined as follows: for pRBC transfusion, the average cost per unit

per financial year for each of the aforementioned red cell products (total expenditure divided by units issued); for iron therapies, the cost per unit at the start of each financial year (April)—one pack of 56 Ferrous Sulphate tablets, one 100 mL bottle of Ferrous Gluconate, and one 500 mg ampoule of Iron Dextran—all inflated to 2022 constant prices using the CPI.

2.4 Ethical Considerations

The study received ethical approval from the University of Cape Town Human Research Ethics Committee (reference number 765/2024). Due to its retrospective design, informed consent was waived, and there was no risk to patients. Patient confidentiality was maintained by using de-identified data, for analysis. Data were stored in password protected files accessible only to the research team, in compliance with the Declaration of Helsinki.

2.5 Data Analysis

Given the non-parametric distribution of the data, small number of annual observations (n=5 years per period on either side of the intervention), and potential outliers (e.g., 2020 due to COVID-19 disruptions), numerical variables were summarised using medians and interquartile ranges. The Wilcoxon Rank-Sum Test was used to compare the medians for total annual expenditure and annual expenditure per 1 000 patient encounters between pre- and post-PBM periods across these categories: oral iron therapy, IV iron therapy, combined iron therapy (oral + IV), pRBC transfusions, and combined therapies (iron + pRBC). The Mann-Kendall Test was used to evaluate monotonic trends in both total annual expenditure and annual expenditure per 1 000 patient encounters from 2013 to 2022 for each of the aforementioned categories. Bootstrap methods (10 000 resamples) were used to estimate 95% confidence intervals for median differences. To distinguish utilisation-driven changes from cost increases, a Wilcoxon signed-rank test compared year-on-year percentage increases in annual expenditure per 1 000 patient encounters to year-on-year inflation-adjusted acquisition cost increases. While normalisation to patient encounters account for overall utilisation variations, potential confounding from changes in case-mix (e.g, theatre volumes) was not directly adjusted for, as clinical outcome data were unavailable. Sensitivity analyses excluded 2020 data to address COVID-19-related disruptions, and re-running all statistical tests for each category, confirming that results were not significantly altered. Cost differentials per annum were calculated as the median difference in annual expenditure per 1 000 patient encounters between pre- and post-PBM periods for oral iron, IV iron, combined iron therapy, and pRBC transfusions. For pRBC, savings were estimated by comparing actual post-PBM expenditure to hypothetical costs if utilisation had matched acquisition cost increases. The net cost differential was computed as pRBC savings minus combined iron therapy cost increases to assess overall financial impact. Additionally, to triangulate the Mann-Kendall trends, we fitted a segmented interrupted time-series model (26) with a breakpoint at 2018, including terms for baseline level, pre-PBM slope, post-PBM level change, and post-PBM slope change; Newey-West standard errors (27) were used to account for autocorrelation, with estimates reported as coefficients with 95% Cis in the supplementary appendix. The interrupted time-series analysis was used exploratively to corroborate direction and magnitude, not for definitive causal inference.

For all statistical tests, significance was set at $p < 0.05$, though wide confidence intervals due to small sample sizes were noted as a limitation affecting precision. Statistical analyses were performed using Python (version 3.12.3) with the scipy.stats library for Wilcoxon Rank-Sum

and signed-rank tests as well as bootstrap methods (10 000 resamples), and the pymannkendall library for the Mann-Kendall trend test.

Results

PBM implementation at GSH in 2018 altered healthcare expenditure patterns for IDA management from 2013 to 2022. During this period the average number of annual patient encounters was approximately 600 000. Expenditure per 1 000 patient encounters served as the primary metric for utilisation trends, revealing increases in iron therapy use and reduced pRBC reliance. Cost differentials per annum underscored net savings, highlighting PBM's financial impact. These primary findings were triangulated using segmented interrupted time-series models to account for temporal trends and the 2018 intervention breakpoint. (Supplementary Table S1)

3.1 Oral Iron Therapy

The Wilcoxon Rank-Sum Test showed no significant difference in the median total annual expenditure on oral iron therapy when comparing pre-PBM (median: \$9 766; IQR: 9 236-\$16 347) to post-PBM periods (median: \$15 145; IQR: 14 151-16 901; $p = 0.310$; 95% CI: \$-799 to \$7 754), suggesting no substantial change in overall annual expenditure. However, when normalised for utilisation, expenditure per 1 000 patient encounters increased by 74.4%, from pre-PBM median of \$16 (IQR: \$15-\$27) to a post-PBM median of \$28 (IQR: \$25-\$34; Wilcoxon $p=0.056$; 95% CI: \$0 to \$21), indicating a trend towards greater use of oral iron therapies following PBM implementation. The Wilcoxon signed-rank test comparing year-on-year percentage increases in expenditure per 1 000 patient encounters to acquisition cost changes did not reach significance ($p = 0.734$). We could therefore not statistically distinguish utilisation-related changes from acquisition costs changes. Descriptively however, the increase in expenditure per 1 000 encounters exceeded price inflation, suggesting a possible utilisation effect, but this should be interpreted cautiously.. Additionally, the Mann-Kendall Test confirmed a significant monotonic upward trend in expenditure per 1 000 patient encounters over the full study period ($p = 0.004$, trend slope = \$1/year).

3.2 IV Iron Therapy

The Wilcoxon Rank-Sum Test indicated statistical significance for the median total annual expenditure on IV iron therapy when comparing pre-PBM (median: \$14 853; IQR: \$10 362–\$23 052) to post-PBM periods (median: \$52 388; IQR: \$36 914–\$83 237; $p=0.008$; 95% CI: \$17 331 to \$74 624), suggesting a substantial increase in overall annual expenditure. However, when normalised for utilisation, expenditure per 1 000 patient encounters increased by 302.2%, from a pre-PBM median of \$25 (IQR: \$17–\$38) to a post-PBM median of \$99 (IQR: \$69–\$164; Wilcoxon $p=0.008$; 95% CI \$29-\$145), indicating a trend towards greater use of IV iron therapies following PBM implementation. The Wilcoxon signed-rank test comparing year-on-year percentage increases in expenditure per 1 000 patient encounters to acquisition cost changes bordered on significance ($p=0.055$). Though not statistically significant this could suggest increased utilisation but should be interpreted with caution. Additionally, the Mann-Kendall Test confirmed a significant monotonic upward trend in expenditure per 1 000 patient encounters over the full study period ($p < 0.001$, trend slope = \$8/year).

3.3 Combined Iron Therapy (Oral + IV)

The combined iron therapy category used the aggregated sum of costs of the components for both oral and IV iron therapy options as described previously. The Wilcoxon Rank-Sum Test indicated statistical significance for the median total annual expenditure on combined iron therapy (oral + IV) when comparing pre-PBM (median: $24 619; IQR: $20 128–$39 897) to post-PBM periods (median: $67 533; IQR: $51 065–$100 698; p = 0.008; 95% CI: $13 910-$80 003), suggesting a substantial increase in overall annual spending. However, when normalised for utilisation, expenditure per 1 000 patient encounters increased by 222.0%, from a pre-PBM median of $41 (IQR: $32–$66) to a post-PBM median of $131 (IQR: $94–$198; Wilcoxon p=0.008; 95% CI: $40-$162), indicating a trend towards greater use of combined iron therapies following PBM implementation. Additionally, the Mann-Kendall Test confirmed a significant monotonic upward trend in expenditure per 1 000 patient encounters over the full study period (p < 0.001, trend slope = $9/year).

3.4 pRBC Transfusions

The Wilcoxon Rank-Sum Test did not indicate statistical significance for the median total annual expenditure on pRBC transfusions when comparing pre-PBM (median: $4 397 133; IQR: $4 113 692–$4 575 176) to post-PBM periods (median: $4 023 021; IQR: $3 625 755–$4 194 104; p = 0.095; 95% CI: $-862 430-$135 646), suggesting no substantial change in overall annual spending. However, when normalised for utilisation, expenditure per 1 000 patient encounters increased by only 3.2%, from a pre-PBM median of $7 270 (IQR: $6 668–$7 618) to a post-PBM median of $7 499 (IQR: $6 871–$8 226; Wilcoxon p=0.548; 95% CI: $-665-$1 474), which, when considered against an 11.4% increase in acquisition costs, suggests a reduction in transfusion use per patient encounter following PBM implementation. The Wilcoxon signed-rank test comparing year-on-year percentage increases in expenditure per 1 000 patient encounters to acquisition cost changes did not reach significance (p = 0.652), reinforcing that the observed modest rise was below price inflation. Additionally, the Mann-Kendall Test did not confirm a significant monotonic upward trend in expenditure per 1 000 patient encounters over the full study period (p=0.107).

3.5 Sensitivity Analysis

Sensitivity analyses excluding 2020 data for each of the above sections were conducted. Although there were marginal changes in the strengths of the various statistical tests, the overall conclusions drawn from them remained the same.

Oral Iron Therapy: 2020 data showed an outlier peak of $32 per 1 000 patient encounters. Repeating the statistical tests yielded similar results, with Wilcoxon p = 0.111 for the period comparison and Mann-Kendall p = 0.009 for the trend, affirming the robustness of utilisation increase.

IV Iron Therapy: 2020 data showed an outlier peak of $99 per 1 000 patient encounters. Repeating the statistical tests yielded similar results, with Wilcoxon p = 0.016 for the period comparison and Mann-Kendall p = 0.001 for the trend, affirming the robustness of the utilisation increase.

Combined Iron Therapy: 2020 data showed an outlier peak of $131 per 1 000 patient encounters. Repeating the statistical tests yielded similar results, with Wilcoxon p = 0.016 for

the period comparison and Mann-Kendall p = 0.001 for the trend, affirming the robustness of the utilisation increase.

pRBC Transfusions: 2020 data showed an outlier peak of $8 424 per 1 000 patient encounters. Repeating the statistical tests yielded similar results, with Wilcoxon p = 0.905 for the period comparison and Mann-Kendall p = 0.176 for the trend, affirming the robustness of the reduced reliance.

3.6 Cost Differential per Annum

To quantify PBM's financial impact, cost differentials per annum were calculated as the median difference in expenditure per 1 000 patient encounters between pre- and post-PBM periods (2018–2022). For oral iron, the differential was $12 per 1 000 encounters ($28 post-PBM - $16 pre-PBM), reflecting increased utilisation. For IV iron, the differential was $74 per 1 000 patient encounters ($99 - $25), indicating significant increases in IV therapy. Combined iron therapy showed a differential of $90 per 1 000 patient encounters ($131 - $41). For pRBC, savings were estimated by comparing actual post-PBM expenditure ($7 499) to hypothetical costs if utilisation had matched the 11.4% acquisition cost increase, raising pre-PBM costs ($7 270) to $8 099 per 1 000 patient encounters, yielding a savings of $600 per 1 000 patient encounters ($8 099 - $7 499). The net cost differential was calculated as: [Net Differential = pRBC Savings - Combined Iron Cost Increase = $600 - $90 = $510 (R3 680) per 1 000 patient encounters per annum] This net savings of $510 (R3 680) per 1 000 patient encounters is meaningful for an LMIC setting like South Africa, where healthcare budgets are constrained. With GSH's annual patient volume of approximately 600 000 encounters, this translates to potential savings of over $305 400 (R2 208 042) per year, sufficient to fund interventions such as additional IV iron supplies or PBM training programmes. This underscores PBM's cost-savings, enabling resource reallocation to address other pressing health needs (Figure 3).

3.7 Additional Observations

The proportion of total annual expenditure on iron therapy (oral + IV) relative to combined annual expenditure (iron + pRBC) increased from 0.57% in 2013 to 2.53% in 2022 ($p < 0.001$). No significant changes in the rate of acquisition cost changes were observed between pre- and post-PBM periods for oral iron (p = 0.905), IV iron (p = 0.111), or pRBC (p = 0.016), with the pRBC change suggesting a possible shift, though overall reinforcing utilisation as the primary driver of expenditure changes.

3.8 Interrupted Time-Series Analysis

To further evaluate the temporal impact of PBM implementation in 2018, segmented interrupted time-series models were fitted to expenditure per 1 000 patient encounters for each category, with a breakpoint at 2018. Models included terms for baseline level, pre-PBM slope, post-PBM level change, and post-PBM slope change, using Newey–West standard errors to account for autocorrelation (Supplementary Table S1). For oral iron, the model confirmed a pre-PBM upward trend (slope: $3.70/year, 95% CI: 2.75 to 4.65, p<0.001) that moderated post-PBM (slope change: -$2.20, 95% CI: -4.19 to -0.21, p=0.030), with a significant immediate level drop (-$4.90, 95% CI: -9.28 to -0.52, p=0.028). IV iron showed a stronger acceleration post-PBM (slope change: $24.50/year, 95% CI: 20.43 to 28.57, p<0.001) after a pre-PBM slope of $5.80/year (95% CI: 3.42 to 8.18, p<0.001). Combined iron mirrored this, with a post-PBM slope increase of $22.30/year (95% CI: 16.64 to 27.96, p<0.001). For pRBC, a pre-PBM upward

slope ($315.60/year, 95% CI: 240.42 to 390.78, p<0.001) was interrupted by a significant level drop (-$1006.40, 95% CI: -1580.80 to -432.00, p<0.001), with no significant slope change post-PBM (-$100.80/year, 95% CI: -324.99 to 123.39, p=0.378), supporting reduced reliance. These results are consistent with PBM-associated shifts while accounting for secular trends, although causal inference remains limited by the small sample size and observational design.

Discussion

4.1 Key Findings

PBM implementation at GSH in 2018 was associated with a 74.4% increase in oral iron expenditure per 1 000 encounters (Wilcoxon p = 0.056), 302.2% for IV iron (p = 0.008), and 222.0% for combined iron therapy (p = 0.008). The pattern of acquisition cost versus utilisation suggests that much of the IV iron increase, and possibly part of the oral iron increase, reflects greater use rather than price inflation. pRBC expenditure per 1 000 encounters grew by only 3.2% (Wilcoxon p = 0.548), below its 11.4% acquisition cost increase (Wilcoxon signed-rank p = 0.652), indicating reduced reliance on transfusions. The cost differential per annum revealed an additional $90 per 1 000 encounters for iron therapy, offset by $600 in pRBC savings, yielding a net savings of $510 (R3 680) per 1 000 encounters, potentially over $305 400 (R2 208 042) annually at GSH. The proportion of total annual expenditure on iron therapy (oral + IV) relative to combined annual expenditure (iron + pRBC) rose from 0.57% in 2013 to 2.53% in 2022 (p < 0.001), with trends robust against 2020 outliers (p ≤ 0.176). Interrupted time-series analysis triangulated these findings, confirming significant level and slope changes post-2018.

4.2 Strengths and Limitations

Strengths: The 10-year dataset, spanning April 2013 to March 2023 and adjusted to 2022 constant USD using South Africa's CPI and a PPP factor of 7.23, ensures robust temporal comparability and facilitates international benchmarking, particularly valuable for LMICs where such long-term economic analyses are scarce. The cost differential analysis, incorporating median differences normalised per 1 000 patient encounters, effectively quantifies PBM's financial impact by isolating utilisation-driven changes from acquisition cost inflation, thereby enhancing the study's policy relevance for resource-constrained healthcare systems aiming to reduce transfusion dependence. Sensitivity analyses excluding 2020 data addressed potential COVID-19 disruptions, maintaining trend consistency (p ≤ 0.176), while time-series trend test (Mann-Kendall) provided evidence of monotonic trends (e.g., p < 0.001 for IV iron). The inclusion of segmented interrupted time-series models triangulates the primary non-parametric analyses, providing quasi-experimental evidence of PBM's temporal impact while controlling for secular trends. Separate evaluations of oral and IV iron therapies offered nuanced insights into treatment modality shifts, and the use of multiple statistical approaches—including Wilcoxon Rank-Sum for period comparisons, Wilcoxon signed-rank test to distinguish use from cost drivers, and bootstrap methods (10 000 resamples) for 95% confidence intervals—bolstered analytical rigour. Acquisition cost calculations, employing compounded CPI adjustments and derived from unit prices (e.g., per pack for oral iron, per ampoule for IV iron), improved accuracy in attributing expenditure changes to PBM initiatives.

Limitations: The retrospective cohort design, reliant on existing pharmacy and blood service records, limits causal inference due to unmeasured confounders such as concurrent policy shifts (e.g., guideline updates outside PBM), market price fluctuations, or changes in patient demographics and disease prevalence (e.g., HIV/TB burdens amplifying IDA). Wide confidence intervals (e.g., $60–$154 for IV iron expenditure per 1 000 encounters) arise from small sample sizes (n=5 per period), reducing precision and statistical power that necessitate larger cohorts to differentiate statistical from clinical significance. The exclusive focus on acquisition costs overlooks activity-based expenses, such as transfusion administration or storage (estimated 3–4 times higher than acquisition (16)), potentially underestimating pRBC savings and overall cost-savings; moreover, per-unit acquisition costs may not account for bulk purchasing discounts or negotiated pricing variations. The absence of linked clinical outcomes, including transfusion rates, haemoglobin levels, or patient morbidity/mortality, restricts assessment of PBM's health impact beyond economic metrics, hindering direct validation of improved IDA management. The small number of annual observations (n=10, total number of annual observations over the 10-year study period) may limit the power of the interrupted time-series models, potentially leading to wide confidence intervals. Data segmentation into pre- and post-PBM periods assumes 2018 as a clean intervention point, yet gradual implementation (e.g., staff education without enforced practice changes) could dilute effects. Whilst sensitivity analyses mitigated 2020 outliers, residual pandemic effects (e.g., altered patient volumes) persist as a potential bias. Finally, generalisability is limited to tertiary settings in South Africa. However, the findings may be transferable to other tertiary facilities in South Africa by adapting base costs to local contexts. Further studies would be needed to validate these findings in primary or secondary-level facilities across LMICs.

4.3 Comparison with Similar Research

Global studies show PBM reduces transfusion needs and costs in HICs (17, 18). The minimal pRBC expenditure increase (3.2%) at GSH, against 11.4% acquisition costs, aligns with these findings, despite South Africa's high HIV and TB prevalence (5). The 302.2% IV iron utilisation increase mirrors LMIC trends with improved access (8), constrained by advanced formulation availability (14). The net savings of $510 (R3 680) per 1 000 encounters, or $305 400 (R2 208 042) annually, is a contribution demonstrating PBM's cost-savings in a LMIC tertiary hospital. This financial impact offers a scalable model for sub-Saharan Africa.

4.4 Explanations of Findings

The increase in IV iron utilisation (302.2%) likely reflects PBM-driven training, updated guidelines, and enhanced IV iron availability at GSH. The more modest oral iron increase (74.4%) may indicate adherence issues due to side effects (12). Reduced pRBC reliance (3.2% vs. 11.4%) suggests stricter transfusion thresholds post-PBM, aligning with global practices. The net savings of $510 (R3 680) per 1 000 encounters, driven by $600 pRBC savings offsetting $90 iron therapy costs, highlights PBM's financial efficacy, with utilisation shifts as the primary driver. These savings could fund expanded IDA interventions or other health priorities in South Africa. The 2020 expenditure peak correlates with a 30% drop in patient encounters due to COVID-19, yet sensitivity analyses ($p \leq 0.176$) affirm trend consistency.

4.5 Implications and Actions Needed

PBM's success in increasing iron therapy utilisation, reducing pRBC dependence, and potentially achieving an approximate net savings of over $305 400 (R2 208 042) annually at GSH positions it as a strategy for South Africa's IDA burden, estimated at over $1 billion annually (10). These savings could fund interventions such as IV iron procurement or PBM training, enhancing healthcare delivery in resource-constrained LMICs. Policymakers should scale PBM through pilot programs in Western Cape district hospitals, supported by provincial funding and integration into national health frameworks to meet 2030 anaemia goals. Clinicians should prioritise ongoing PBM education. Future research should include clinical outcomes (e.g., transfusion rates, haemoglobin levels) and activity-based costs (linking unit costs, staff time, transfusion administration and storage, and length of stay) via prospective studies to move from acquisition-only to full economic analysis which comprehensively assess cost-effectiveness and health impact. We propose that a follow-up study is performed that links expenditure changes to health impacts, incorporating retrospective data on transfusion rates and haemoglobin levels if available. Year-specific PPP factors could enhance analytical precision.

Conclusions

PBM implementation at GSH increased iron therapy utilisation (74.4% oral, 302.2% IV, 222.0% combined per 1 000 encounters), reduced pRBC reliance (3.2% vs. 11.4% acquisition cost increase), and achieved a net cost savings of $510 (R3 680) per 1 000 encounters, potentially over $305 400 (R2 208 042) annually. The proportion of expenditure on iron therapy rose from 0.57% to 2.53%. Sensitivity analyses excluding 2020 data confirmed these trends ($p \leq 0.176$), as supported by interrupted time-series analysis confirming post-PBM trend shifts. These findings support PBM as a potential cost-saving strategy for IDA management in South Africa and LMICs, with financial benefits enabling improvements in resource reallocation. Further studies including a detailed cost analysis including activity-based costs and clinical data would enhance understanding. Expanded infrastructure, clinician training, and prospective studies with clinical endpoints are needed to solidify PBM's role in national IDA strategies. While these results demonstrate PBM's potential in a tertiary-level urban LMIC hospital, replication in district hospitals is needed to confirm external validity across diverse healthcare settings.

Acknowledgments

The authors would like to thank Athenkosi Ndzondo and Salwa Kriel from the Groote Schuur Hospital Information Management Unit who assisted with providing the data required for this study. None other.

Footnote

Reporting Checklist

The authors have completed the STROBE reporting checklist.

Data Sharing Statement

Available from authors upon reasonable request.

Peer Review File

To be added by journal.

Funding

This work was supported by: None.

Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form. Vernon Louw has received speaker fees and/or grants and/or honoraria and/or travel support from Acino, Pharmacosmos, Vifor Pharma, Aspen, Austell, Inova Pharma and is a Non-Executive Director of the Western Cape Blood Service. The other authors declare no conflicts of interest.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the University of Cape Town Human Research Ethics Committee (reference number 765/2024). Individual consent was waived due to the retrospective nature of the study.

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Tables

Table 1: List and Description of Comparators

Comparator	Description
Oral Iron Therapy	Ferrous sulphate tablets and Ferrous gluconate syrup
IV Iron Therapy	Iron Hydroxide Dextran (Cosmofer®)
Combined Iron Therapy	Oral + IV Iron Therapy
pRBC Transfusions	Red Cell Concentrate, Leucocyte-Poor Red Cell Concentrate and Transfusion Crossmatched Red Cells. (Categories as listed by WCBS)

Table 2: Total Annual Expenditure on Oral Iron Therapy, IV Iron Therapy, and pRBC Products   (2022 Constant USD with ZAR in Brackets)

Issue Date	Oral Iron Therapy	Intravenous Iron Therapy	Blood Products	TOTAL
2013	$8 907 (R64 412)	$13 686 (R98 937)	$3 932 542 (R28 433 302)	$3 955 135 (R28 596 651)
2014	$9 706 (R70 171)	$7 870 (R56 893)	$4 304 841 (R31 122 954)	$4 322 417 (R31 250 018)
2015	$9 766 (R70 603)	$14 853 (R107 402)	$4 397 133 (R31 785 213)	$4 421 752 (R31 963 218)
2016	$15 849 (R114 594)	$23 138 (R167 320)	$4 522 270 (R32 702 009)	$4 561 257 (R32 983 923)
2017	$16 845 (R121 791)	$22 966 (R166 060)	$4 628 081 (R33 466 027)	$4 667 892 (R33 753 878)
2018	$16 341 (R118 164)	$33 359 (R241 161)	$4 379 186 (R31 660 506)	$4 428 886 (R32 019 831)
2019	$15 050 (R108 816)	$52 388 (R378 755)	$4 068 188 (R29 410 998)	$4 135 626 (R29 898 569)
2020	$13 252 (R95 828)	$40 469 (R292 591)	$3 442 411 (R24 894 680)	$3 496 132 (R25 283 099)
2021	$17 460 (R126 245)	$76 996 (R556 847)	$3 809 099 (R27 534 799)	$3 903 555 (R28 217 891)
2022	$15 145 (R109 492)	$89 477 (R646 931)	$4 023 021 (R29 086 323)	$4 127 643 (R29 842 746)

Table 3: Annual Expenditure per 1 000 Patient Encounters
(2022 Constant USD with ZAR in Brackets)

Issue Date	Oral Iron Therapy	Intravenous Iron Therapy	Blood Products
2013	$15 (R105)	$22 (R161)	$6 387 (R46 171)
2014	$16 (R113)	$13 (R92)	$6 950 (R50 249)
2015	$16 (R117)	$25 (R178)	$7 270 (R52 556)
2016	$27 (R192)	$39 (R281)	$7 594 (R54 901)
2017	$28 (R201)	$38 (R274)	$7 643 (R55 259)
2018	$27 (R193)	$54 (R393)	$7 137 (R51 597)
2019	$24 (R177)	$85 (R615)	$6 605 (R47 741)
2020	$32 (R234)	$99 (R716)	$8 424 (R60 907)
2021	$37 (R266)	$162 (R1 174)	$8 029 (R58 045)
2022	$28 (R204)	$167 (R1 206)	$7 499 (R54 214)

Table 4: Average Year-on-Year Percentage Acquisition Price Changes (%)

Year	Oral Iron	IV Iron	pRBC
2013	0.00	0.00	0.00
2014	-16.59	4.04	4.94
2015	53.05	-10.73	2.92
2016	-4.36	7.57	4.33
2017	9.33	1.51	2.55
2018	-3.38	-13.62	-0.76
2019	-4.19	-15.12	0.38
2020	9.03	-3.19	0.50
2021	2.19	-4.31	-0.95
2022	-9.67	1.03	-2.82

Figures

Figure 1: Total annual patient encounters (inpatient: purple; outpatient: green) from 2013 to 2022, with a marked drop in 2020 due to COVID-19 restrictions. *Note: Total annual patient encounters include repeated visits by the same individuals seeking care.*

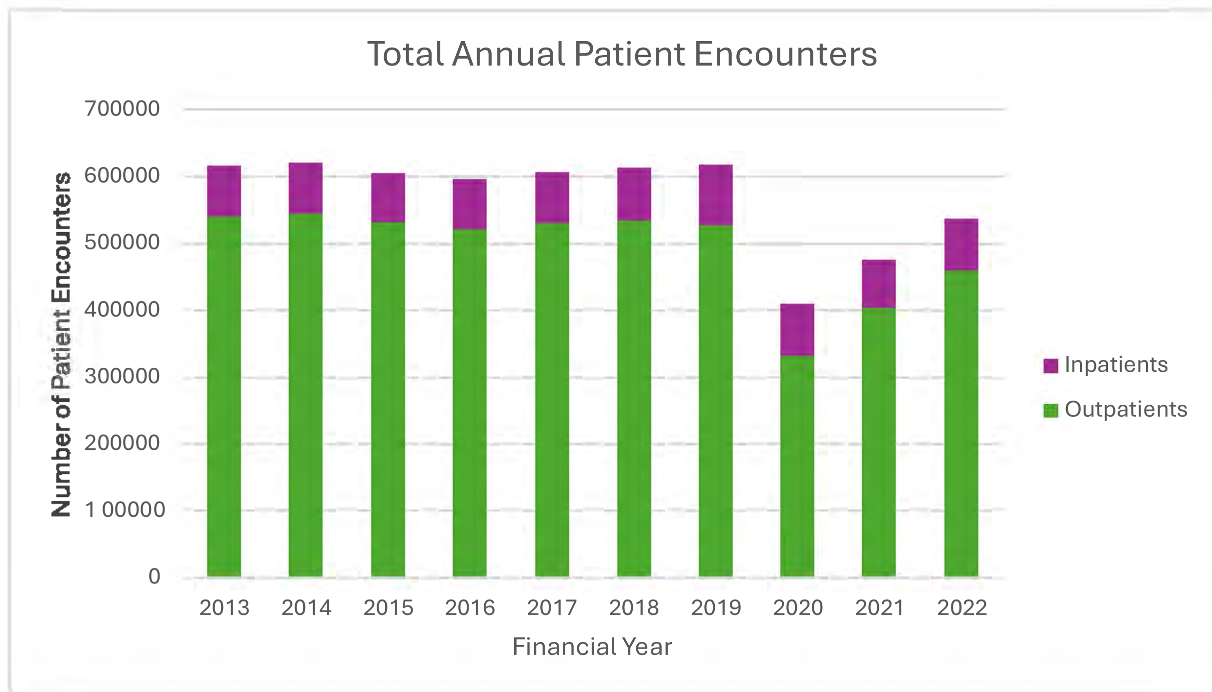


Figure 2: Line chart depicting average year-on-year percentage acquisition price changes for oral iron therapy (blue), IV iron therapy (orange), and pRBC transfusions (green) from 2013 to 2022, highlighting variability.

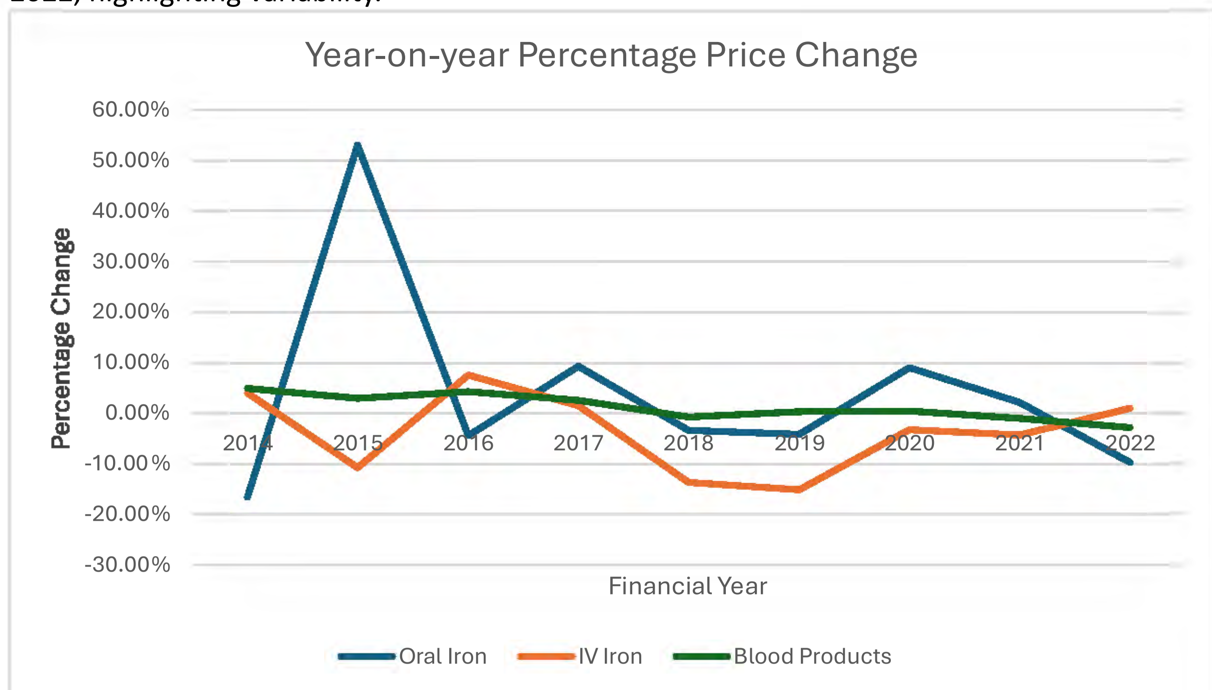
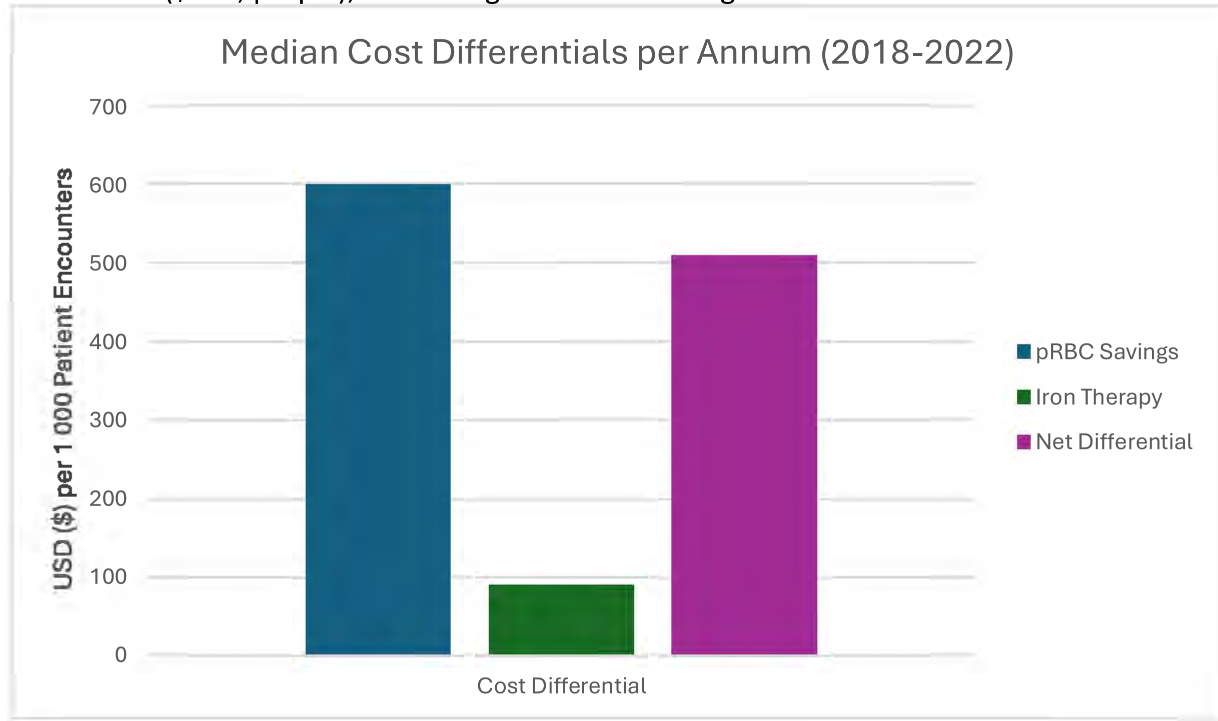


Figure 3: Median cost differentials per annum per 1 000 patient encounters (2018–2022) for pRBC savings ($600, blue), iron therapy (oral and intravenous) ($90, green), and net differential ($510, purple), illustrating PBM's cost savings.



Appendices

Appendix A: HUMAN RESEARCH ETHICS COMMITTEE APPROVAL

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

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04 October 2024

HREC REF: 765/2024

Prof V Louw
Division of Clinical Haematology
E-5 NGSH
Email: Vernon.louw@uct.ac.za
Student: chdcor001@myuct.ac.za

Dear Prof Louw

PROJECT TITLE: A DESCRIPTIVE STUDY COMPARING THE UTILISATION OF ORAL AND INTRAVENOUS IRON THERAPY COMPARED TO PACKED RED BLOOD CELL TRANSFUSIONS AT A TERTIARY LEVEL HOSPITAL IN SOUTH AFRICA OVER THE PAST 10 YEARS- (MMED CANDIDATE-DR CHADWIN CORIN)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study,

Approval is granted for one year until the 30 October 2025.

Please submit a progress form, using the standardised Annual Report Form (FHS016) or FHS017 if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Chadwin Corin will also be involved in this study.

Please quote HREC REF 765/2024 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research

HREC/ref 765/2024

Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix B: GROOTE SCHUUR HOSPITAL APPROVAL

GROOTE SCHUUR HOSPITAL
Enquiries: Mr Lionel Naidoo
e-mail: GSHResearch.Request@westerncape.gov.za

Professor V. Louw
Division of Clinical Haematology

E-mail: vernon.louw@uct.ac.za

Dear Prof Louw

RESEARCH PROJECT: A descriptive study comparing the utilisation of oral and intravenous iron therapy compared to packed red blood cell transfusions at a tertiary level hospital in South Africa over the past 10 years

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 October 2025**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) **Confidentiality must always be maintained.**
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) If the researcher is not GSH staff member, a supernumerary contract is required before commencement of the research.
m) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
n) **Kindly submit a copy of the publication or report to this office on completion of the research.**
o) **At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**
p) **Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**
q) **All Clinical Trials to be registered on Clinicom with Michelle Riley. michelle.riley@westerncape.gov.za**
r) **All clinical personnel viewing/using patient folders for research purposes, must be carried out according to the following: Patient folders must be researched in the Medical Records Department (Medical Research Suite, A14, New Main Building). No research patient folders may be removed from the Medical Records Department. Patient folders required for research purposes may not be requested via clerical staff and the Clinicom system. Non-compliant researchers could have their GSH institutional research approval revoked.**

I would like to wish you every success with the project.

Yours sincerely

LIONEL NAIDOO
HEAD: ALLIED HEALTH
Date: 22 January 2025
C.C. Mr. L. Naidoo, Mr. A. Mohamed, Dr H. Aziz, Professor M. Setshedi

G46 Management Suite, Old Main Building,
Observatory 7925
Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935
www.westerncape.gov.za/health

Appendix C: Annals of Blood – Author Guidelines

3. MANUSCRIPT SUBMISSION REQUIREMENTS

The length of manuscripts must adhere to the specifications under the section "MANUSCRIPT CATEGORIES".

Manuscripts should be presented in the following order: (i) Title page; (ii) abstract and keywords; (iii) the main text; (iv) Acknowledgments; (v) Footnote; (vi) References; (vii) Tables; (viii) Figures; (ix) Videos; (x) Figure Legends; (xi)Supplementary material.

3.1 Title Page

The title page should include: a) the title of the article; b) the authors' full names and institutional affiliations; c) the degree information, address [full address for the corresponding author(s)], telephone number and effective e-mail address of the corresponding author(s) (extremely important for subsequent timely communication); d) if available, the 16-digit ORCID of the author(s); e) a running title of no more than 60 characters (including spaces); f) disclaimers (if applicable); g) word count; h) number of figures and tables; i) contributions (required for certain article types; see below detailed description).

3.2 Authorship and Author contributions

3.2.1 Authorship

Authors should meet all four of the ICMJE's authorship criteria listed below for authorship (1):

1) Substantial contributions to the conception and design of the study; or the acquisition, analysis, or interpretation of the data for the work; AND
2) Drafting the article or reviewing it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributors who meet fewer than all 4 of the above criteria for authorship should not be listed as authors, but they should be acknowledged. Examples of activities that alone (without other contributions) do not qualify a contributor for authorship are acquisition of funding; general supervision of a research group or general administrative support; writing assistance, technical editing, language editing, and proofreading. Additionally, AI tools cannot be listed as an author of a paper as AI tools cannot meet the requirements for authorship and cannot take responsibility for the submitted work (1-3).

Authors must disclose in the Cover letter, Materials and Methods, and the Acknowledgement for applying any AI tools (e.g., ChatGPT, Bing) in the writing of a manuscript, production of images or graphical elements of the paper, or in the collection and analysis of data. Disclosure should include - but is not limited to - all prompts used to generate new text, or to convert text or text prompts into tables or illustrations; the full prompt used to generate the research results; the time and date of a query; and the AI tool used and its version. Authors are fully responsible for the content of their manuscript, even those parts produced by an AI tool, and are thus liable for any breach of publication ethics. For more recommendations, please refer to the WAME Recommendations on Chatbots and Generative Artificial Intelligence in Relation to Scholarly Publications: https://wame.org/page3.php?id=106 (21).

Please carefully check the authorship of your manuscript before submission. Except for grammatical corrections, any other changes of authorship after submission require a sound scientific justification.

3.2.2 Author contributions

Of note, the "Contributions" section is required for original articles, review articles, clinical practice guidelines, expert consensus, case reports, case series, surgical techniques, and study protocols.

Author contribution describes the contribution each author made to the manuscript. The 'Contributions' section should be presented as follows:

(I) Conception and design:
(II) Administrative support:
(III) Provision of study materials or patients:
(IV) Collection and assembly of data: (V) Data analysis and interpretation:
(VI) Manuscript writing: All authors
(VII) Final approval of manuscript: All authors

Note: With VI and VII, "All authors/Both authors (when there are only two authors)" is obligatory, while the other credits are case-based; The 'Contributions' section is not required when there is only one author.

See more details of authorship and contributorship: https://aob.amegroups.org/page/about/authorship-and-contributorship.

3.3 Abstract and Keywords

The abstract must adhere to the specifications under section 'MANUSCRIPT CATEGORIES'. The abstract should not contain any citations, figures, tables, or undefined abbreviations or acronyms. General statements (e.g., "the significance of the results is discussed'') should be avoided. After the Abstract, 3-5 keywords should be provided.

Where relevant, the study project registration number (e.g., registration number for a clinical trial, a clinical guideline, a systematic review, and meta-analysis, or an animal study) should be included at the end of the abstract. For studies that have a registration number, this number should be included initially when a trial acronym is used to refer to the trial in the report or to other trials discussed in the paper. For data that have been deposited in a public repository and/or are the subject of analysis elsewhere, the distinctive, persistent data set identifier, the repository name, and the number should be included at the end of the abstract.

3.4 Main Text

The structure of the main text must adhere to the specifications under the section "MANUSCRIPT CATEGORIES". In general, the main text of many articles in different types contains a) Introduction; b) Methods; c) Results; d) Discussion; and e) Conclusions. However, there are differences and modifications for different types of articles regarding the above sections. Of note, a highlight box is required for some article types.

3.4.1 Highlight Box

A highlight box is used to highly summarize the key findings/recommendations, innovation, and potential implications of the study.

Manuscript categories that require a highlight box: Original Article, Systematic Review, Scoping Review, Clinical Practice Guideline, Expert Consensus, Case Report, Case Series, and Surgical Technique.

Word limit: The box should be concise with no more than 250 words for Original Article, Systematic Review, Scoping Review, Case Report, Case Series, and Surgical Technique or 300 words for Clinical Practice Guideline and Expert Consensus.

Template 1: Highlight Box for Original Article, Systematic Review, Scoping Review, Case Report, and Case Series.

Key findings
• Report here about the key findings of the study.
What is known and what is new?
• Report here about what is known. • Report here about what this manuscript adds.

What is the implication, and what should change now?

- Report here about the implications and actions needed.

Template 2: Highlight Box for Clinical Practice Guideline and Expert Consensus.

Key recommendations

- Report here about key recommendations.

What was recommended and what is new?

- Report here about what was recommended in existing evidence.
- Report here about what are the changes of recommendation.

What is the implication, and what should change now?

- Report here about the implications and actions needed.

Template 3: Highlight Box for Surgical Technique

Surgical highlights

- Report here about highlights of the surgical technique.

What is conventional and what is novel/modified?

- Report here about how conventional surgical techniques are applied.
- Report here about what modifications or innovations of surgical technique are done.

What is the implication, and what should change now?

- Report here about the implications and actions recommended.

3.4.2 Introduction

The introduction should give a brief description of what we already know and what we don't know, with a clear rationale defense based on the above. The introduction needs to very clearly specify the question the study proposes to answer, and what the purpose of the study is.

For Original Article, Review Article, Systematic Review, Scoping Review, Narrative/Literature Review, Clinical Practice Review, Clinical Practice Guideline, Expert Consensus, Case Report, Case Series, and Study Protocol, we recommend that authors use a structured introduction to increase the readability:

- a) Background

- b) Rationale and knowledge gap
- c) Objective

3.4.3 Methods

Authors should report methods as exhaustively as possible to make the study more transparent and reproducible. Specific reporting guidelines for each article type can be found at: https://www.equatorhttps://www.equator-network.org/network.org/ (4)

3.4.4 Results

The report of the study results needs to be properly detailed and paired well with the figures and tables rather than repeating them. It is important to note that the results should be presented objectively and not overly interpreted (interpretation should be done in the Discussion). In particular, the author needs to ensure that the results and data are consistent and accurate throughout the manuscript. Any inconsistencies and inaccuracies in the data and results may cause the editorial office and reviewers to be extra concerned about the scientific validity and authenticity of the study.

Authors can find further requirements and recommendations on statistical considerations of the results in "STATISTICAL REQUIREMENTS".

3.4.5 Discussion

The discussion should be evidence-based, comprehensive, in-depth, and cutting-edge.

For Original Article, Systematic Review, Scoping Review, Case Report, and Case Series a separate Discussion section is required. And, we recommend that authors use a structured discussion to increase the readability:

- a) Key findings
- b) Strengths and limitations
- c) Comparison with similar research
- d) Explanations of findings
- e) Implications and actions needed

For Review Article, Narrative Review/Literature Review, Clinical Practice Review, Mini-Review, Clinical Practice Guideline, and Expert Consensus, although a separate Discussion section is not required, authors are encouraged to include evidence-based, comprehensive, in-depth, and cutting-edge discussion throughout the main body content. In particular, we recommend including a separate section on strengths and limitations in the main body to promote a more intellectual interpretation.

3.4.6 Conclusions

Conclusions are summaries of the entire article. Conclusions need to be concise, usually using only one paragraph. Conclusions need to be scientifically deducible from the results available and the information presented, not exaggerated, out of scope, or even wrong.

Manuscript categories that require a separate conclusions section: Original Article, Review Article, Systematic Review, Scoping Review, Narrative/Literature Review, Clinical Practice Review, Clinical Practice Guideline, Expert Consensus, Case Report, and Case Series.

3.5 Acknowledgments

All contributors who do not meet the criteria for authorship should be listed in the 'Acknowledgments' section. Examples of those who might be acknowledged include an individual who provided purely technical help, writing or language editing assistance, or a department chairperson who provided only general support. If a part of the manuscript has been presented elsewhere (e.g., meeting presentation/poster history), a corresponding statement should be provided in the acknowledgment section.

Do not include funding sources in the Acknowledgments. Funding information should be stated in the "Funding" section of the "Footnote".

3.6 Footnote

3.6.1 Reporting Checklist

For articles written in accordance with specific reporting guidelines, the author must include the "Reporting Checklist" section in the footnote and indicate, "The authors have completed the XXXX reporting checklist."

If the manuscript is accepted for publication, the author's completed checklist will be published online alongside the manuscript.

3.6.2 Data Sharing Statement

If an original article includes any data that are not publicly available, the authors are required to fill in a datasharing statement form, which should be submitted along with their manuscript. If the article is accepted for publication, the Data Availability Statement (form) will be published online alongside the article. The data sharing statement form can be downloaded here.

3.6.3 Peer Review File

With a commitment to openness and accountability, and to increase the level of transparency throughout our peer review process, our editorial office has decided to fully implement the transparent peer review (TPR) process for all new submissions from March 15, 2023.

For more details, please refer to: https://aob.amegroups.org/announcement/view/171.

3.6.4 Funding

Report all funding sources for the work in question here. If the research was carried out without funding, "None" should be stated in this section.

In providing details of funding, authors should adhere to the following guidance:

- The sentence should begin: 'This work was supported by …'
- The full official funding agency name should be given, (i.e., 'National Institute of Health', not 'NIH'). Grant numbers should be given in brackets [e.g., (grant number xxxx)].
- Multiple grant numbers should be separated by a comma [e.g. (grant numbers xxxx, yyyy]].
- Agencies should be separated by a semi-colon (with 'and' before the last funding agency)
- Where certain sources of funding were received by a specific author, the following text should be added after the relevant agency or grant number: 'to [author initials]'.

Example: 'This work was supported by the National Institutes of Health (AA123456 to C.S., BB765432 to M.H.); and the Alcohol & Education Research Council (hfygr667789).'

3.6.5 Conflicts of Interest

All authors will be asked to fill in the ICMJE's unified disclosure form (the latest version). The form could be downloaded at: https://cdn.amegroups.cn/static/public/coi_disclosure.docx. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The corresponding author should use the information in the form completed by each author to create the COI statement for the manuscript. The statement (but not the forms) must be included along with the submission. The statement should include the initials of the author along with the conflicts of interest. The following examples show the format in which the Conflicts of Interest statement should appear in the manuscript:

"Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare."

"Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form. KSS and VS are former employees of Scanco Medical AG. NV is a current employee of Scanco Medical AG. The other authors have no conflicts of interest to declare."

If the paper is accepted, the completed ICMJE's unified disclosure forms will be required and will be published alongside the article.

See the journal's policy on conflicts of interest: https://aob.amegroups.org/page/about/conflicts-ofhttps://aob.amegroups.org/page/about/conflicts-of-interestinterest.

3.6.6 Ethical Statement

Statement #A is a must for every article, followed by statement #B.

Statement #B should be described ①based on whether the specific content of the article requires an additional ethical statement; ②both in the Methods section and the "Ethical Statement" section of Footnote.

Statement #C should be noted as it is related to Informed Consent.

#A. (a Must) Statement for every article

Please note that all articles submitted to our journal must include an Ethical Statement in the Footnote, containing the following wording: "The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved."

#B. The specific content of the article requires an additional ethical statement

(a) Human Experiments

For research involving human experiments, the article must include a statement that ethical approval was obtained (or a statement that it was not required and why), including the name of the ethics committee(s) or institutional review board(s), the number/ID of the approval(s), and a statement that the participants gave informed consent before taking part (or a statement that it was not required and why). Authors should also state that the study conformed to the provisions of the Declaration of Helsinki and its subsequent amendments, available at: https://www.wma.net/policies-post/wma-declaration-of-helsinkihttps://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjectsethical-principles-for-medical-research-involving-human-subjects (22). For example:

(For prospective experiments) Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the institutional/regional/national ethics/committee/ethics board of ******* (No.: the registration number of the ethics board) and informed consent was obtained from all individual participants.

(For retrospective experiments) Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved

by the institutional/regional/national ethics/committee/ethics board of ******* (No.: the registration number of the ethics board) and individual consent for this retrospective analysis was waived.

(b) Animal Experiments

For any experiments involving animals, the authors must indicate the nature of the ethical review permissions, relevant licenses (e.g., Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals by which the research was conducted. Describe this information in both the "Method" section and the "Ethical Statement" section in Footnote. For example:

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Experiments were performed under a project license (No.: the license number) granted by the institutional/regional/national ethics/committee/ethics board of *******, in compliance with ******* national or institutional guidelines for the care and use of animals.

In addition, we strongly recommend that authors register experiments that include animals and state the registration number in the methods and footnote. For authors' reference, registration platforms such as Open Science Framework (23) and Animal Study Registry(24) are commonly used.

(c) Case Report and Case Series

Whenever possible, signed consent should be obtained from the patient (or their parent/guardian) to write and publish a Case Report or Case Series. This is particularly important where the unique nature of the incident being reported makes it possible for the subject to be identified (such as when the patient is over 100 years old; the manuscript has photographs or images or has a rare disease). Beyond that, please keep patient details anonymous whenever possible, for example, occupations unrelated to the disease/condition. If informed consent cannot be obtained, for example, if the patient has passed away and the author is unable to obtain signed consent from the guardian or family of the deceased patient, the authors need to state that they have made the best efforts to contact the relative and that the article has been sufficiently anonymized to cause no harm to the patient or his or her family.

Authors should also state that the study conformed to the provisions of the Declaration of Helsinki and its subsequent amendments, available at: https://www.wma.net/policies-post/wma-declaration-ofhttps://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjectshelsinki-ethical-principles-for-medical-research-involving-human-subjects (22). Please describe this information in both the "Case Presentation" section and the "Ethical Statement" section on Footnote. For example:

(For manuscripts that have patient consent) Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

(For manuscripts that do not have patient consent) Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent

amendments. Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made.

(For manuscripts that are waived from patient consent) Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Publication of this case report and accompanying images was waived from patient consent according to the xxx ethics committee/institutional review board.

#C. Informed Consent

Written informed consent for the publication of details relating to a person must be obtained from that person (or their parent or legal guardian in the case of children under 18) for all manuscripts that include images, details, or videos. The consent must be for publication of their details under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0) (such that they will be freely available on the internet). If the person has deceased, consent for publication must be acquired from their next of kin. A statement that written informed consent for publication was obtained must be included in the manuscript.

To get consent for publication, authors can use the consent form (download the form for the patient or the form for the participant) or a consent form from their institution or region, if suitable. The consent form must specify that the details/images/videos will be freely available on the internet and that the general public will be able to view them. Authors do not need to provide a copy of the consent form to the editorial office; however, if the Editor requests it, the consent form must be provided and will be kept confidential.

Consent for image publication may not be necessary for circumstances where photographs are completely unidentified and there are no details on persons mentioned within the text. The Editor has the final say on whether or not consent to publish is required.

The Editorial Office may request copies of the informed consent documentation at any time. While the Editorial Board recognizes that it might not always be possible or appropriate to seek such consent, the onus will be on the authors to demonstrate that this exception applies in their case.

The Journal retains the right to reject any manuscript based on unethical conduct in either human or animal studies.

3.7 References

Sources should be referenced according to the Vancouver reference style. Referencing AI-generated material as the primary source is not acceptable. For guidance on references, please refer to: https://www.icmje.org/recommendations/.

In the text, references should be identified using numbers in round brackets. Where more than one number is required, they should appear consecutively [e.g., "cancer-related mortality (19)"; “adenocarcinoma (29,30)”; “raised significantly (15, 20, 31-33)”]. References (including in the text, tables, and figure legends) should be numbered consecutively and consistently according to the order in which they first appear in the text.

In the reference list, the titles of journals should be abbreviated according to the style used in Index Medicus. For reports with up to three authors, all the author names should be listed. However, if a report has more than three authors, the first three authors should be listed followed by “et al.”

- McLeer-Florin A, Lantuéjoul S. Why technical aspects rather than biology explain cellular heterogeneity in ALK-positive nonsmall cell lung cancer. J Thorac Dis 2012;4:240-1.

- Lin X, Li W, Lai J, et al. Five-year update on the mouse model of orthotopic lung transplantation: Scientific uses, tricks of the trade, and tips for success. J Thorac Dis 2012;4:247-58.

Below are two examples for the management of the reference:

a. If you manage references manually or in another way, you could refer to the reference example below: Lin X, Li W, Lai J, et al. Five-year update on the mouse model of orthotopic lung transplantation: Scientific uses, tricks of the trade, and tips for success. J Thorac Dis 2012;4:247-58.
b. If you use "Endnote" (a commercial reference management software package produced by Clarivate Analytics, used to manage bibliographies and references when writing essays and articles), the reference style file for AME journals can be directly downloaded here:
https://cdn.amegroups.cn/static/public/reference-style.ens.

3.8 Tables

Tables are recommended to be provided in separate files. Tables should be self-contained and complement, but not duplicate, the information contained in the text. All tables should be numbered consecutively in the order in which they are mentioned in the text. Each table should be on a separate page; tables must be typed and editable in a tabular format that is convenient for copyediting and typesetting; they should not be inserted as images. Please refer to the examples for different cases.

Each column must have an appropriate heading, and if measurements are given, the units should be provided in the column heading. Column headings should be brief, with units of measurement in parentheses; all abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in this order), and *, **, *** should be reserved for P values. Statistical measures such as SD or SEM should be identified in the headings.

If the tables have been reproduced from another source, a letter or permission from the copyright holder (usually the publisher) authorizing the reproduction of the material must be submitted as supplemental material along with the manuscript.

3.9 Figures

Figures should be provided in separate files. All illustrations (line drawings and photographs) are classified as figures. Figures should be cited in the order in which they appear in the text. Magnifications should be indicated using a scale bar on the illustration.

- File types, resolution, size: Please refer to the specification (file types, resolution, image size, file size, etc.) for more detailed requirements. For the flow diagram of a study/trial (e.g. CONSORT diagram), please provide the diagram in an editable form, e.g. Word (.doc) or PowerPoint (.ppt) file, etc.
  For photographs, clinical images, photomicrographs, gel electrophoresis, and other types that include labels, arrows, or other markers, please submit 2 versions: one version with the markers and one without. An explanation for all labels, arrows, or other markers should be included in the figure legend.
- Figure legends: Legends should be provided for figures, including the figure title, the full name of any abbreviation in the figure, a detailed description of any symbol in the figure (e.g., some color notation or arrows), and a separate description of each figure if it is a combination of several figures, etc.
- Copyright: If the figures have been reproduced from another source, a letter from the copyright holder (usually the publisher) authorizing the reproduction of the material must be attached to the cover letter (see the "COPYRIGHT AND PERMISSION" section).
- Patient Privacy: Where illustrations include recognizable individuals, living or deceased, great care must be taken to ensure that consent for publication has been given (see the "Ethical Statement" section). A statement like "This image is published with the patient/participant's

consent." should be included at the end of the figure legend. Patient anonymity should be preserved. Nonessential identifying details should be omitted. For example, photographs need to be cropped sufficiently to prevent human subjects from being recognized and the eyes and eyebrows (at a minimum) must be masked using Coarse Pixilation to make the individual unrecognizable. However, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are de-identified, authors should ensure that such changes do not distort scientific meaning.

In-text citations

- Cite figures with the format: Figure 1A, Figure 1B, Figure 2, Figure 3, etc. When consecutive subparts of a figure are cited, they should be cited as Figure 1A-1D, Figure 2B-2L, etc.
- Cite figures in ascending numeric order upon the first appearance in the manuscript file. This includes citations to text boxes and tables. In the published article, figures are inserted according to the placement of their first citation and caption in the article.
- Lettered subparts of whole figures may be cited in any order in the text if the first mention of each whole figure is in numerical order. For example, Figure 1 contains 4 subparts (i.e., Figure 1A, 1B, 1C, 1D). These subparts should be cited consecutively unless Figure 1 as a whole is already cited before Figure 1A, 1B, 1C, and 1D.

3.9.1 Western Blot Figures

A separate note is worthwhile, as the problem of Western Blot figures is particularly serious in published studies in the academic community. To further improve the reporting transparency of Western Blot figures when Western Blot experiments are used in a study, we strongly recommend that its report adopt several recommendations as follows.

- Ensure that the raw data is accessible to readers. The authors could provide the original images without cropping or any other processing in the Supplement.
- Make sure that the Western Blot figure contains at least one molecular weight marker above and below the protein of interest.
- Crop as few as possible. The presence of non-specific bands is very common and the reader needs to be aware of these.
- Better to present with dot plots, which can inform readers about sample size and spread of data.
- Report Methods in detail, including the amount of total protein loaded onto the gel, details of the membrane blocking protocol, antibody identifiers and details of antibody labeling protocol, type and number of replicates performed, etc.

For more details, examples, and templates on how to better report Western Blot figures authors can view: https://osf.io/yr7am (25); https://pubmed.ncbi.nlm.nih.gov/36095010/ (26)

3.10 Videos

Videos should be provided in separate files. The journal will accept digital files in mp4, flash video (flv.), MPEG (MPEG video file), DVD video, mov., avi., and mwv. formats or videos on CD / DVD. Contributors are asked to be succinct, and the editorial office reserves the right to request a shorter video if necessary. Video files can be submitted online at: https://aob.amegroups.org/pages/view/submit-multimedia-files.

- Duration: Video files should be limited to 20 minutes.
- Quality: Please set the video aspect ratio as 4:3 or 16:9 (widescreen). The original video should be of high quality with the resolution ≥1280×720, the frame rate ≥24 frames per second, and the bit rate ≥5 Mbps.

- In-video text and audio: Videos should have text or symbols or audio descriptions. All text notes, explanations, descriptions, etc. in the video must be provided in English. Any patient information should be erased from the video.
- Video legends: Legends should be provided for the video files. The video files should be numbered consecutively in their order of reference in the text.
- Copyright: If the videos have been reproduced from another source, a letter from the copyright holder (usually the publisher) authorizing the reproduction of the material must be attached to the cover letter. It is especially worth noting that if background music appears in a video, the author should also obtain authorization from the copyright owner of that music if that music is involved in copyright licensing (see the "COPYRIGHT AND PERMISSION" section).
- File name: please name the videos as Video 1, Video 2, Video S1, Video S2, etc. upon submission.

In-text citations

- Cite videos with the format: Video 1, Video 2, Video S1, Video S2, etc.
- Cite videos in ascending numeric order upon the first appearance in the manuscript file.

For promotion, all accepted videos will be subsequently included in AME Surgical Video Database (ASVIDE: https://www.asvide.com) and its youtube channel (https://www.youtube.com/channel/UCA4NnVYmMW2NS5QrnLEVQNg).

3.11 Supplementary Appendix

The Supplementary Appendix should be paginated, with a table of contents, followed by the list of investigators (if there are any), text (such as methods), figures, tables, and then references. The supplementary appendix should not be included in the article's reference list.

The Appendix must be submitted in a Word file. The Appendix will not be edited for style. It will be presented online as additional information provided by the authors.

The published article will contain a statement that supplementary material exists online and will provide the reader with a URL and/or link. Refer to the following example for how to reference the supplementary appendix in the text of the article: "Many more regressions were run than can be included in the article. The interested reader can find them in a supplementary appendix online."

Appendix D: Supplementary Table S1 – Interrupted Time-Series Model Estimates

Supplementary Table S1: Interrupted Time-Series Model Estimates for Expenditure per 1 000 Patient Encounters (2022 Constant USD)

Parameter	Oral Iron Estimate (95% CI, p-value)	IV Iron Estimate (95% CI, p-value)	Combined Iron Estimate (95% CI, p-value)	pRBC Estimate (95% CI, p-value)
Baseline (Intercept)	13.00 (10.09 to 15.91, p<0.001)	15.80 (8.26 to 23.34, p<0.001)	28.80 (18.68 to 38.92, p<0.001)	6537.60 (6358.56 to 6716.64, p<0.001)
Pre-PBM Slope	3.70 (2.75 to 4.65, p<0.001)	5.80 (3.42 to 8.18, p<0.001)	9.50 (6.30 to 12.70, p<0.001)	315.60 (240.42 to 390.78, p<0.001)
Level Change at 2018	-4.90 (-9.28 to -0.52, p=0.028)	8.00 (-0.81 to 16.81, p=0.075)	3.10 (-8.41 to 14.61, p=0.598)	-1006.40 (-1580.80 to -432.00, p<0.001)
Post-PBM Slope Change	-2.20 (-4.19 to -0.21, p=0.030)	24.50 (20.43 to 28.57, p<0.001)	22.30 (16.64 to 27.96, p<0.001)	-100.80 (-324.99 to 123.39, p=0.378)

Note: Models used OLS with Newey-West standard errors (lag=1) to account for autocorrelation. Time is years since 2013 (0-9).