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PATIENT BLOOD MANAGEMENT

TRANSFUSION

The fatigue after infusion or transfusion pilot trial and feasibility study: A three-armed randomized pilot trial of intravenous iron and blood transfusion for the treatment of postpartum anemia

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Abstract

Background: Evidence for the management of moderate-to-severe postpartum anemia is limited. A randomized trial is needed; recruitment may be challenging.

Study Design and Methods: Randomized pilot trial with feasibility surveys. *Inclusion*: hemoglobin 65–79 g/L, ≤7 days of birth, hemodynamically stable. *Exclusion*: ongoing heavy bleeding; already received, or contraindication to intravenous (IV)-iron or red blood cell transfusion (RBC-T). *Intervention/control*: IV-iron; RBC-T; or IV-iron and RBC-T. Primary outcome: number of recruits; proportion of those approached; proportion considered potentially eligible. *Secondary outcomes*: fatigue, depression, baby-feeding, and hemoglobin at 1, 6 and 12 weeks; ferritin at 6 and 12 weeks. Surveys explored attitudes to trial participation.

Results: Over 16 weeks and three sites, 26/34 (76%) women approached consented to trial participation, including eight (31%) Māori women. Of those potentially eligible, 26/167 (15.6%) consented to participate. Key participation enablers were altruism and study relevance. For clinicians and stakeholders the availability of research assistance was the key barrier/enabler. Between-group rates of fatigue and depression were similar. Although underpowered to

Abbreviations: ACTRN, Australian New Zealand Clinical Trials Registry; BMI, body mass index; CI, confidence interval; CONSORT, Consolidated Standards of Reporting Trials; FCM, ferric carboxymaltose; FIT, fatigue after infusion or transfusion; g/L, grams per liter; Hb, hemoglobin; IBM, International Business Machines; IV-iron, intravenous iron; IQR, interquartile range; MD, mean difference; MELAA, Middle Eastern, Latin American, African and other ethnicities; MFI, multidimensional fatigue inventory; μg/L, micrograms per liter; mL, milliliter; PPA, postpartum anemia; RBC-T, red blood cell transfusion; SD, standard deviation; SPSS, Statistical Package for the Social Sciences.

address secondary outcomes, IV-iron and RBC-T compared with RBC-T were associated with higher hemoglobin concentrations at 6 (mean difference [MD] 11.7 g/L, 95% confidence interval [CI] 2.7–20.7) and 12 (MD 12.8 g/L, 95% CI 1.5–24.2) weeks, and higher ferritin concentrations at 6 weeks (MD 136.8 mcg/L, 95% CI 76.6–196.9).

Discussion: Willingness to participate supports feasibility for a future trial assessing the effectiveness of IV-iron and RBC-T for postpartum anemia. Dedicated research assistance will be critical to the success of an appropriately powered trial including women-centered outcomes.

KEYWORDS

anemia, blood transfusion, breastfeeding, erythrocyte transfusion, fatigue, ferric compounds, hematinics, intravenous infusion, iron, iron deficiency, iron-deficiency anemia, postpartum period

1 | INTRODUCTION

Postpartum anemia (PPA) is a low hemoglobin concentration (Hb) in the weeks after birth. Low hemoglobin results in reduced oxygen-delivering capacity whereby the physiological demands of the tissues and vital organs may be unmet.[1,2] PPA is estimated to affect one-third of postpartum women globally[3]; however, prevalence is poorly reported.[4] In New Zealand, there is limited national and local guidance on postpartum hemoglobin testing, reflected in significant variation in the proportion of women tested (15%–59%).[5] We previously reported that of the 46% of women tested, 38% had PPA (Hb <100 g/L).[5] Pre-birth anemia and postpartum hemorrhage are the most significant contributors to PPA.[6–11]

PPA is strongly associated with maternal mortality and severe morbidity, including admission to intensive care, particularly after major postpartum hemorrhage.[11–13] Less severe, but more common morbidities that impact the health and well-being of mothers and babies include fatigue, depression, impaired bonding, difficulty breastfeeding, increased infections, and prolonged hospital stays.[7,14–22] Anemia-related fatigue was recently identified by women and clinicians as a major concern after birth, impacting well-being and the ability to parent (Caljé et al. 2023, unpublished data). Because of the bi-directional relationship between fatigue and depression, the treatment of anemia-related fatigue after birth has the potential to mitigate postpartum distress.[20,23] Despite the significance of PPA, the impact of different treatments is understudied with more focus on hematological parameters than maternal and infant well-being.[24–26]

In well-resourced countries, treatment options for more severe PPA include red blood cell transfusion (RBC-T) and intravenous (IV)-iron, alone or in combination, but it is unclear which treatment is the best. RBC-T is a limited resource and is associated with transfusion reactions including alloimmunization, with serious implications for subsequent pregnancies.[27] In the last decade, third-generation high-single-dose IV-iron formulations have been increasingly used[28,29] as an alternative to, or alongside, RBC-T for the treatment of more severe PPA,[5] and associated with escalating healthcare costs.[30]

Despite the increasing popularity of IV-iron, and Patient Blood Management recommendations supporting its use as an alternative to RBC-T for hemodynamically stable women with PPA,[27,31,32] there is a lack of evidence on the comparative safety and effectiveness of IV-iron and/or RBC-T for both woman-centered and laboratory-based outcomes (Caljé et al. 2023).[33] This lack of evidence likely contributes to treatment variation.

Adverse outcomes from PPA disproportionately affect women from isolated populations, migrant and minority groups, due to material disadvantages including food insecurity, and limited access to transport, communication, education, and healthcare.[2,34] These social determinants of health are also likely to be drivers of differences for Māori (Indigenous people) and Pacific women in New Zealand,[35] who have a higher incidence of anemia before and after birth than women of other ethnicities.[5]

PPA and fatigue are largely preventable, treatable physiological factors that require evidence-informed care. Gold-standard randomized clinical trial evidence directly comparing IV-iron, RBC-T, or a combination is urgently needed to guide practice, and should include populations most likely to benefit. Such a trial may be challenging, particularly after postpartum hemorrhage,[36] vulnerability after birth,[37] and anemia-related fatigue. Engagement with, and participation of, groups most likely to benefit may also be challenging, due to diminished trust in the health system including racism[38] and distrust of research/ers.[37,39]

We conducted the Fatigue after Infusion or Transfusion (FIT) Pilot Trial and Feasibility Study to answer the question: Are women and healthcare professionals willing to participate in and support a trial of IV-iron, RBC-T, or IV-iron and RBC-T for clinically stable women with moderate-to-severe PPA? The aim of this pilot trial was to assess the feasibility of a future adequately powered, large-scale trial to assess the effectiveness of treatments on well-being and hematological outcomes for women with moderate-to-severe PPA.

2 | MATERIALS AND METHODS

This study was a multicenter three-arm open-label randomized controlled pilot trial, and survey of eligible participants, and clinicians/researchers. Eligible women were invited to participate in the randomized trial and complete surveys; those who declined trial participation were invited to complete a survey only. Clinicians (doctors, midwives, and nurses) and research personnel at participating sites were invited to complete a survey.

This study was undertaken and reported following CONSORT guidelines for randomized pilot and feasibility studies,[40] and multi-arm parallel-group randomized trials.[41] The study was approved by the Southern Health and Disability Ethics Committee (2022FULL12924) and local governance committees at participating hospitals. It was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622001105730p). We formed a multidisciplinary and ethnically diverse FIT Pilot Trial Equity Advisory Group to advise on study design to support inclusion of Māori and Pacific women.

2.1 | Participants and setting

The study was conducted across three public, ethnically diverse, maternity units in New Zealand: Auckland City, Waikato, and Christchurch Women's hospitals, with 4629, 4113, and 5365 births in 2021, respectively.[42] Postpartum women with liveborn babies ≥20 weeks gestation, and any mode of birth, were eligible with an Hb 65–79 g/L ≤ 7 days of birth, clinically stable and suitable to receive IV-iron and/or RBC-T (determined by the treating clinician), and able to provide informed consent. Exclusion criteria were ongoing heavy bleeding, already received IV-iron and/or RBC-T as PPA treatment, aged <16 years, religious, cultural, or other objections to RBC-T or IV-iron, IV-iron in the preceding 4 weeks, history of non-iron-deficiency anemia (i.e., hemoglobinopathies), hemochromatosis, bacteraemia, hypophosphataemia, hepatic or renal impairment, hypersensitivity to IV-iron or previous serious reaction to RBC-T, cardiac or respiratory failure, heart surgery or organ transplant.

Eligible women were identified by clinicians. Study information was provided by local clinicians or research personnel. We aspired to recruit a study population that at least reflected the proportion of Māori and Pacific women birthing within each region. To encourage engagement and participation of Māori women, we incorporated Te Reo Māori (Indigenous language) and Samoan phrases into study information, encouraged a whānau (family)-friendly environment, and ensured women had sufficient time to consider participation. Research personnel invited local site researchers and clinicians, including midwives, nurses, obstetricians, and anesthetists, to complete a feasibility survey.

2.2 | Randomization

Following informed consent, women were randomly allocated by block method in a 1:1:1 ratio using a custom computer-generated web-based system. Neither the research personnel, healthcare professionals, nor participants were blinded. The allocation sequence was not accessible to the research personnel or healthcare professionals. Block sizes were randomly varied to enhance allocation concealment.

2.3 | Interventions

Women were randomized to receive: IV-iron; RBC-T; or IV-iron and RBC-T. IV-iron was given as a single dose of 1000 mg ferric carboxymaltose (FCM) following manufacturer recommendations.[43,44] For RBC-T, the number of red blood cell units was determined by the responsible clinician. All interventions were administered within 24 h of randomization by clinicians within the normal standard of care and according to local hospital policies, including close monitoring of vital signs before, during, and after administration. Although not prohibited, oral iron was not recommended in addition to study interventions. Data were collected on oral iron use.

2.4 | Outcomes and measurements

The primary outcome of trial recruitment was assessed in three ways: number of women recruited, trial-approached recruitment rate, and overall recruitment rate. The trial-approached recruitment rate was calculated as the number of randomized participants/the number of women approached. The overall recruitment rate was estimated from the number of randomized participants/the number of potentially eligible women.

Potential eligibility was assessed from routinely collected hospital and laboratory data including all women with Hb 65–79 g/L ≤ 7 days of birth, at each site during the study period; hemodynamic instability, prior treatment or other exclusion criteria could not be determined from routinely collected data.

Secondary outcomes included: demographic profiles of eligible and recruited women; the proportion of Māori and Pacific women recruited; adverse events including infusion/transfusion reactions; enablers and barriers to recruitment for women, clinicians, and research personnel; the proportion of outcome measures completed; differences in physical fatigue scores; hemoglobin and ferritin concentrations; depression scores and baby-feeding codes. Demographic and simple obstetric data, of the potentially eligible women, were obtained from routinely collected hospital data.

Fatigue and depression scores, hemoglobin concentrations, and baby-feeding codes were measured at 1, 6, and 12 weeks from trial entry. Ferritin was not measured at 1 week, as it may be erroneously high due to inflammation associated with birth,[24,32] and transient oxidative stress in response to IV-iron.[45]

2.5 | Questionnaires and surveys

Data on fatigue and depression scores were collected via self-reported questionnaires for women included in the randomized trial; baby-feeding codes were completed by research personnel with the women. The Multidimensional Fatigue Inventory (MFI) is a validated questionnaire used in postpartum research.[46–49] This 20-item tool measures five fatigue domains including reduced activity, reduced motivation, general, physical, and mental fatigue. Scores range from 20 to 100 with higher scores indicating greater levels of fatigue.[50] Although the MFI was not designed to evaluate fatigue in the postnatal period, it has high feasibility, reliability, and validity in postpartum women.[51] Physical fatigue is considered the earliest arising complaint in acute anemia[48] and significantly correlates with hemoglobin concentrations.[51] The Edinburgh Postnatal Depression Scale is a widely used validated questionnaire and screening tool for symptoms of depression.[52,53] Baby-feeding was coded as exclusive, fully, or partially breastfed, or artificially fed as per standard hospital baby-feeding data definitions.[54]

Four different surveys were administered across three groups, collecting information on recruitment and feasibility, using multiple-choice questions, Likert-scale responses, and open free-text questions (see Supplementary material). At the time of consent, women participating in the randomized trial completed a survey on enablers and barriers to participation, and an end-of-study survey on acceptability and feasibility of trial interventions and outcome measures. Women who declined trial participation but consented to a survey provided information on enablers and barriers to participation. The researcher/clinician survey gathered data on study procedures, and enablers and barriers to site trial participation. Descriptive analyses summarized the multiple-choice and Likert-scale responses. Free-text responses were analyzed thematically and illustrated the enablers and barriers from the descriptive analysis if they aligned. New themes that emerged from free-text responses were presented in narrative form, with the proportion of similarly themed survey responses.

2.6 | Sample size

The sample size was determined by study duration. A formal sample size calculation was not estimated as per the CONSORT guideline for pilot trials and feasibility studies.[40]

2.7 | Statistical methods

Baseline differences between randomized and non-randomized participant women were assessed using Fisher's exact and Kruskal–Wallis tests for normally and non-normally distributed continuous data. Prespecified analyses of physical fatigue, hemoglobin, and ferritin concentrations used repeated measures in analysis of variance, over each time point, with baseline measurements as covariates. Where significant differences were found, post-hoc multiple comparisons were undertaken, including adjustment for baseline to determine where the difference lies. Significance was set at an α level of .05. Data were analyzed using IBM SPSS (Version 28).

3 | RESULTS

From October 10, 2022 to January 29, 2023, 34 women were approached to participate in the randomized trial and 26 provided consent (trial-approached recruitment rate 74%); the remaining eight women consented to a survey only (Figure 1). The overall recruitment was 16% (26/167). Baseline data were similar between groups. The profiles of study participants and potentially eligible women are described in Table 1. Women who consented to a survey only had a higher mean (standard deviation, SD) blood loss compared to randomized women: 1862 (663) versus 1080 (518) mL ($p = .001$). Compared to the

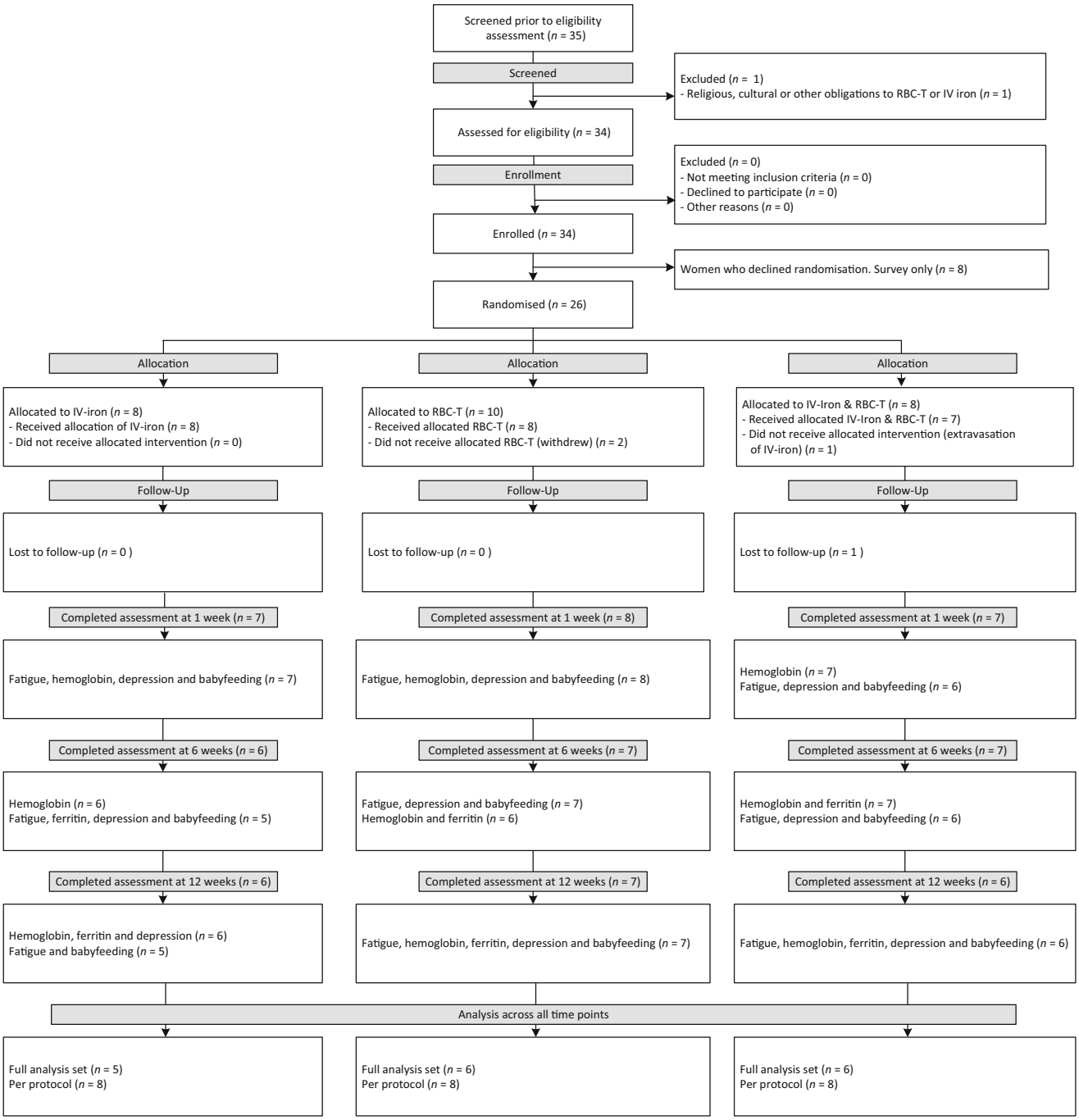

FIGURE 1 Study flow diagram. IV-iron, intravenous iron; RBC-T, red blood cell transfusion.

population of women who gave birth in New Zealand,[42] the proportion of Māori women consenting to trial participation was higher (31%, 8/26, vs. 26%, 16,235/62,433) but lower for Pacific women (4%, 1/26 vs. 10%, 5998/62,433).

Two women withdrew after randomization to the RBC-T group, prior to receiving the allocated intervention (Figure 1), and had no further involvement in the study. The reasons for withdrawal were a delay in receiving the intervention, and not wanting to receive RBC-T. Eight women in each group received the intended intervention. For one woman in the IV-iron and RBC-T group, the FCM infusion was discontinued after receiving 50% of the infusion, due to extravasation at the IV-insertion site. No other adverse events or transfusion reactions were reported. Of the women allocated to receive RBC-T, 75% (12/16) received one unit, and 25% (4/16) received two units; none received off-protocol IV-iron. None of the women randomized to receive IV-iron received off-protocol RBC-T. None of the women reported oral iron

TABLE 1 Characteristics of the recruited and potentially eligible study population.

Characteristic	Survey only	Randomized trial	Potentially eligible[a]
n **(%)**	***n*** **= 8**	***n*** **= 26**	***n*** **= 167**
Study site			
Auckland	1 (13)	5 (19)	78 (47)
Waikato	2 (25)	3 (12)	39 (23)
Canterbury	5 (62)	18 (69)	50 (30)
Age in years, mean (SD)	26.2 (7.4)	29.7 (6.0)	29.9 (6.2)
Missing			1 (0)
Ethnicity, prioritized[b]			
Māori	3 (36)	8 (31)	42 (25)
Pacific	1 (13)	1 (4)	19 (12)
Asian (excluding Indian)	1 (13)	3 (11)	35 (21)
Indian	1 (13)	1 (4)	14 (9)
MELAA		2 (8)	10 (6)
European	2 (25)	11 (42)	42 (25)
Other Ethnicity	-	-	4 (2)
Missing			1 (0)
Booking BMI kg/m^2, mean (SD)	26.4 (24.2, 28.6)[c]	26.6 (23.8, 31.6)[c]	28.2 (7.0)
Underweight BMI < 18.50	-	1 (4)	1 (1)
Healthy BMI 18.5–24.99	2 (25)	8 (31)	52 (31)
Overweight BMI 25.0–29.99	4 (50)	10 (38)	55 (33)
Obese BMI ≥ 30.0	2 (25)	6 (23)	44 (26)
Missing	-	1 (4)	15 (9)
Deprivation quintile			
1 (least deprived)	1 (12)	7 (27)	33 (20)
2	3 (38)	3 (12)	31 (19)
3	2 (25)	5 (19)	27 (16)
4		7 (27)	46 (27)
5 (most deprived)	2 (25)	4 (15)	26 (16)
Missing	-		4 (2)
Primiparous at booking	7 (88)	14 (54)	111 (66)
Missing	-	-	3 (2)
Smoking	2 (25)	3 (12)	19 (11)
Missing	-	2 (8)	2 (1)
Mode of birth			
Normal vaginal	4 (50)	7 (27)	63 (38)
Operative vaginal	2 (25)	11 (42)	48 (29)
Caesarean	2 (25)	8 (31)	55 (33)
Missing	-	-	1 (0)
Total estimated blood loss (mL), mean (SD)	1863 (663)	1081 (518)	1444 (920)
Anemic before birth (Hb <105 g/L)	3 (38)	10 (39)	-
Baseline Hb after birth, mean (SD)	76.0 (74.3, 78.3)[c]	76.0 (73.0, 78.0)[c]	74.1 (4.12)
Iron-deficiency before birth (ferritin <30 mg/L)	5 (62.5)	17 (73.9)	-
Missing	1 (13)	3 (12)	

TABLE 1 (Continued)

Characteristic	Survey only	Randomized trial	Potentially eligible[a]
n (%)	*n* = 8	*n* = 26	*n* = 167
Baseline ferritin, mean (SD)	-	29.0 (26.8)	-
Missing		2 (8)	

Abbreviations: BMI, body mass index; Hb, hemoglobin; MELAA, Middle Eastern, Latin American, African and other ethnicities; SD, standard deviation.
[a]Potentially eligible women were those who birthed at the recruiting site and who had an Hb 65–79 g/L, ≤7 days of birth.
[b]Individual ethnicity data are allocated to a single group using a prioritized system: Māori > Pacific > Indian > Asian (excl. Indian) > Other > European.[42]
[c]Median (IQR).

use during the study period. The completion rates of all assessments were 83% (21/24) at 1, and 75% (18/24) at 6 and 12 weeks (Figure 1).

3.1 | Secondary outcomes

There were no differences in physical fatigue scores among groups at any time point (Table 2). IV-iron with or without RBC-T had higher observed exclusive breastfeeding at 1 week, compared to RBC-T only who mostly partially breastfed ($p = .02$) (Table 2). Prespecified multiple comparisons found hemoglobin concentration was higher after IV-iron and RBC-T, compared to RBC-T only at 6 (mean difference [MD] 11.7 g/L, 95% confidence interval [CI] 2.7–20.7, $p = .012$), and 12 weeks (MD 12.8 g/L, 95% CI 1.5–24.2, $p = .023$). Ferritin concentration was higher after IV-iron compared to RBC-T at 6 (MD 95.6 mcg/L, 95% CI 28.0–163.3, $p = .011$), and 12 (MD 92.3 mcg/L, 95% CI 13.7–170.9, $p = .018$) weeks. Ferritin concentration was higher after IV-iron and RBC-T compared to RBC-T only at 6 (MD 136.8 mcg/L, 95% CI 76.6–196.9, $p < .0001$), but not 12 (MD 66.0 mcg/L, 95% CI −18.6 to 150.5, $p = .048$) weeks. There were no differences in hemoglobin and ferritin concentrations between IV-iron only, and IV-iron and RBC-T.

3.2 | Survey results

Of the 26 women who consented to participate in the randomized trial, 88% (23/26) completed a recruitment survey. They reported feeling exhausted (39%, 9/23), having low well-being (44%, 10/23), discomfort or pain (30%, 7/23), needing to focus on baby cares (35%, 8/23), or having a baby in the neonatal unit (9%, 2/23). Over a third of the women had preferences for receiving IV-iron (35%, 8/23) or RBC-T (35% 8/23) yet consented to randomization.

Most (79%, 19/24) randomized women who received interventions and follow-up completed an end-of-study survey. Of these, 90% (17/19) received home follow-up visits. The majority were very satisfied or somewhat satisfied with their pregnancy care (95%, 18/19), birth care (68%, 13/19), postnatal care (74%, 14/19), and care in the FIT Pilot Trial (90%, 17/19). Of those completing the survey, 100% (19/19) strongly agreed that the follow-up visits were flexible around their needs; 84% (16/19) strongly agreed FIT Pilot Trial participation was a positive experience, 90% (17/19) would participate again, and 95% (18/19) would recommend participation to a friend. Key enablers and barriers to trial participation for all survey participants are outlined in Table 3.

Twenty-nine clinicians, researchers, and stakeholders completed surveys: hospital midwives (31%, 9/29); nurses (3%, 1/29); senior obstetricians (14%, 4/29); registrar obstetricians (24%, 7/29); senior anesthetists (7%, 2/29); research personnel (14%, 4/29); maternity managers (3%, 1/29); and Patient Blood Management clinical specialists (3%, 1/29). Of those surveyed, 24% (7/29) had invited women to participate, and of these 71% (5/7) had consented women to participate in the FIT Pilot Trial. Over half (58%, 15/29) prescribed RBC-T and IV-iron within their professional role.

Respondents answered positively (strongly agree/somewhat agree) to most (86%, 12/14) of the questions about enablers to site participation, indicating more enablers than barriers. Having dedicated research staff was described as a key enabler (31%, 9/29) and barrier (14%, 4/29) to recruitment. In free-text responses, 31% (9/29) of the respondents described that receiving early treatment prior to trial consideration was a common barrier to recruitment at some sites (Table 3). Almost 80% (23/29) of the clinicians, researchers, and stakeholders were keen for their site to participate in a future trial.

4 | DISCUSSION

The current treatment options for hemodynamically stable women with moderate-to-severe PPA are IV-iron, RBC-T, or a combination of both.[5] However, it is unclear

TABLE 2 Secondary outcomes for per protocol randomized women by intervention arm.

Clinical factors	IV-iron	RBC-T	IV-iron and RBC-T	
***N* = 24**	***n* = 8**	***n* = 8**	***n* = 8**	***p* value**
Physical fatigue[a]				
Baseline	12.9 (4.1)	13.8 (1.9)	14.4 (3.9)	.686
Week 1	10.7 (3.6)	10.3 (3.3)	13.04 (2.6)	.277
Week 6	8.4 (3.0)	8.4 (3.2)	10.8 (2.9)	.314
Week 12 median (IQR)	9.0 (5.3)	8.7 (2.8)	8.7 (2.9)	.986
Hb (g/L)				
Baseline	74.1 (3.6)	75.0 (2.9)	75.0 (3.5)	.834
Week 1	103.0 (12.4)	102.8 (10.4)	106.0 (11.6)	.836
Week 6	124.2 (5.1)	119.2 (8.0)	130.9 (5.4)	.013
Week 12	131.0 (8.5)	121.8 (8.6)	134.7 (5.2)	.021
Ferritin (μg/L)				
Baseline	28.6 (30.1)	26.8 (28.1)	31.5 (25.5)	.943
Week 6	104.4 (40.7)	17.0 (13.9)	154.1 (56.4)	<.001
Week 12	106.2 (93.5)	12.3 (9.0)	87.8 (20.8)	.011
Depression[b]				
Baseline	7.4 (3.4)	9.1 (8.6)	10.5 (4.5)	.624
Week 1	8.9 (5.5)	9.6 (8.5)	8.2 (2.6)	.912
Week 6	4.8 (2.6)	3.6 (4.8)	6.2 (3.1)	.476
Week 12	5.7 (5.8)	6.4 (4.4)	4.8 (2.8)	.818
Baby-feeding[c] baseline *n* (%)				.534
Exclusive breastfeeding	5 (63)	4 (50)	6 (76)	
Fully breastfeeding	2 (25)	0 (0)	0 (0)	
Partial breastfeeding	1 (12)	3 (38)	1 (12)	
Artificial breastfeeding	0 (0)	1 (12)	1 (12)	
Baby-feeding Week 1				.021
Exclusive breastfeeding	5 (71)	2 (25)	5 (83)	
Fully breastfeeding	0 (0)	0 (0)	0 (0)	
Partial breastfeeding	2 (29)	6 (75)	0 (0)	
Artificial breastfeeding	0 (0)	0 (0)	1 (17)	
Baby-feeding Week 6				.111
Exclusive breastfeeding	3 (60)	1 (14)	5 (83)	
Fully breastfeeding	0 (0)	0 (0)	0 (0.0)	
Partial breastfeeding	1 (20)	4 (57)	0 (0.0)	
Artificial breastfeeding	1 (20)	2 (29)	1 (17)	
Baby-feeding Week 12				.149
Exclusive breastfeeding	3 (50)	2 (29)	5 (83)	
Fully breastfeeding	0 (0)	0 (0)	0 (0)	
Partial breastfeeding	1 (17)	0 (0)	0 (0)	
Artificial breastfeeding	2 (33)	5 (71)	1 (17)	

Note: Data as mean (SD) or *n* (%).

Abbreviations: Hb, hemoglobin; IV, intravenous; RBC-T, red blood cell transfusion.

[a]Measured as a domain of the Multidimensional Fatigue Inventory.[51,52]

[b]Measured on the Edinburgh Postnatal Depression Scale.[53,54]

[c]Baby-feeding is coded as per standard Ministry of Health definitions.[55]

which regimen is the best, and whether an appropriately designed and powered randomized trial to answer this question is feasible. We are not aware of any randomized clinical trial that has compared these three treatments. The only published comparable study is a two-armed randomized pilot trial of IV-iron versus RBC-T for PPA, with 13 participants and a substantially lower trial-approached recruitment rate of 21% (13/62).[46]

Our key finding is that a large proportion of eligible women who were approached consented to participate in the randomized trial, and the majority completed the study as per protocol. There are several likely factors contributing to the much lower overall recruitment rate of potentially eligible women we observed. This includes a lack of research assistance to enable higher rates of approaching potential participants but may also be explained by an unknown proportion being considered hemodynamically unstable and therefore ineligible; and/or clinician preference for early treatment, especially with IV-iron, which was identified by survey respondents as a barrier to recruitment. Early treatment prior to trial consideration also appears to be driven by workplace pressures for patient flow to transfer or discharge. The main reasons identified for women declining participation in Holm et al.'s pilot trial were the number of follow-up visits (11 vs. 3 in the FIT Pilot), risks associated with RBC-T, and maternal exhaustion.[46] In our study, women valued home follow-up visits, finding them easy to arrange and convenient in the newborn period. This women-centered approach is likely to have enhanced participation, although it is resource-intensive.

Peripartum women have long been underrepresented in clinical trials, resulting in a limited evidence-base for many interventions offered around the time of birth.[37,39,55] Perceptions of women's vulnerability limiting their ability to make fully informed decisions are likely to be a contributing factor. Despite many participants facing individual challenges to recruitment (pain, anxiety, physical and emotional exhaustion[36]) and anemia symptoms such as dizziness, three-quarters of approached women consented to trial participation, demonstrating that barriers to recruitment after birth are not insurmountable. Many of the known factors that enhance participation in peripartum studies were identified by trial participants: face-to-face engagement with clinical/research personnel; relevance of the research; understanding potential benefits/harms; altruism; wanting to contribute to science; support/advice from family and/or healthcare professionals; and the collateral benefits of enhanced care and learning.[39,55,56] The withdrawal of two participants randomized to RBC-T highlighted the importance of clear trial information on research processes including randomization, important factors that influence recruitment[37,56] and retention.

Despite a perception that groups that experience disadvantage are less likely to participate in peripartum trials,[37,55] we successfully included Māori participants with a proportion higher than the national birthing population. This approach to engagement is understood to generate findings to improve health outcomes for Māori to at least the same standard as for non-Māori, thereby preventing research from contributing to increasing inequities.[57] We engaged extensively with women, clinicians, and stakeholders in planning the FIT Pilot Trial. This early engagement is a key factor that can mitigate potential barriers to recruitment and retention in clinical trials.[39] Furthermore, we aimed to be culturally responsive,[58] respectful, whānau-centered, and included Te Reo Māori language in the trial information, approaches known to support equity-based research for Māori as Indigenous people.[59] The lower recruitment rate of Pacific women highlights the importance of including recruiting centers with high proportions of births to Pacific women.

Aligning with the literature on enhancing recruitment in perinatal clinical trials,[37,60] the healthcare and research personnel clearly identified that having dedicated research staff was the key enabler (or barrier) to successfully recruit and retain participants, enabling site participation and mitigating demands on time-constrained clinical staff.[36] Knowledge of local research personnel on the recruitment and randomization processes was variable, identifying the need for improved in-service training on the study to enhance recruitment rates at some sites.[60]

Like our study, the pilot trial by Holm et al. found no difference in physical fatigue scores or depression at any time points[46]; both studies are limited by size and are likely underpowered to detect such differences. Although our study found differences in baby-feeding at 1 week favoring IV-iron use, this finding is limited as our sample size was too small to justify prespecified analyses at each time point. Interestingly in our interviews, clinicians identified a perception that RBC-T promotes breastfeeding (Caljé et al. 2023, unpublished data). This conflicts with findings from an Australian study of women with postpartum hemorrhage, with lower breastfeeding rates for transfused women compared to non-transfused women (adjusted relative risk 0.94, 99% CI: 0.92–0.95).[61]

Although the sample size was small, and findings must be interpreted cautiously, our finding that IV-iron compared with RBC-T resulted in greater differences in ferritin concentrations is supported by findings from

TABLE 3 Key enablers and barriers to trial participation for women, health professionals, and researchers.

Enablers	Barriers
Women consenting to trial participation ($n = 23$) **Recruitment survey**[a]	**Women who declined trial participation** ($n = 8$) **Non-consent to recruitment survey**[a]
Wanting to help other women (87%, 20/23) "... to help find the best way to help people that experience blood loss during birth." "Feeling useful in researching postnatal care options."	**A preference for not wanting to receive blood transfusion** (38%, 3/8)
Understanding the trial information (83%, 19/23)	**Low well-being, discomfort, or pain** (25%, 2/8)
Understanding the risks/benefits of RBC-T (74%,17/23)	**Not wanting follow-up visits** (25%, 2/8)
Understanding the risks/benefits of IV-iron (61%, 14/23)	**Wanting to focus on parenting** (25%, 2/8)
Wanting follow-up visits (57%, 13/23)	**A preference for wanting to receive blood transfusion** (13%, 1/8)
Relevance of the research (52%, 12/23)	**A preference to choose treatment** (13%, 1/8)
Wanting to answer fatigue and depression questionnaires (52%, 12/23)	**Lack of support from family to participate in the trial** (13%, 1/8)
Health and safety concerns (48%, 11/23)	**Needle phobia (negating blood tests)** (13%, 1/8)
Enough time to decide (48%, 11/23)	**Concerns about COVID vaccine traces in RBC-T** (13%, 1/8)
Family support (30%, 7/23)	**Health and safety concerns** (13%, 1/8)
Women consenting to trial participation ($n = 19$) **End-of-study survey enablers**[b]	**Women consenting to trial participation** ($n = 19$) **End-of-study survey barriers**[b]
I did not mind extra blood tests (100%, 19/19)	**Not wanting online follow-up** (53%, 10/19)
It was useful to know blood test results (89%, 17/19)	**Preferring not to have follow-up in the home** (10%, 2/19)
Arranging follow-up visits was easy (89%, 17/19)	**Family was not involved in follow-up** (10%, 2/19)
Positive experience (89%, 17/19) "Being someone who generally has quite low iron levels, it benefited me in ways I didn't think was possible. I believe that if I wasn't involved, I wouldn't have had such an easy postpartum journey." "I liked being part of some useful research!"	**Challenging time frames for follow-up blood tests** (free text response, 5%, 1/19) "The rigid timeframe for blood tests to be taken, not so flexible." "More reminders to do the surveys and blood test. Busy being a parent and it easily slips your mind."
Researchers respected my culture (84%, 16/19)	**Arranging follow-up visits was not easy** (5%, 1/19)
Preference for face-to-face follow-up (89%, 17/19)	**Not wanting face-to-face follow-up** (5%, 1/19)
Improving iron-deficiency anemia knowledge (79%, 15/19) "The trial enhanced my understanding of iron and the role it plays in holistic wellbeing." "I understand more about my health."	**Breastfeeding struggles** (free-text response, 5%, 1/19) "I am struggling with breastfeeding and trying to increase my milk supply after giving birth. A lot of times I wonder if my anemia has affected my milk supply. Maybe I should have received both blood and iron transfusion."
Family was involved (79%, 15/19)	
Preference for home follow-up visits (79%, 15/19)	
Clinicians, researchers, and stakeholders ($n = 29$) **Survey of trial processes**[b]	**Clinicians, researchers, and stakeholders** ($n = 29$) **Survey of trial processes**[b]
Research staff assistance is needed for the trial processes, that is, consent, recruitment, treatment allocation, follow-up, and data collection (91%, 26/29) "It was very helpful to have the research midwife onsite ... a future study would need to be a well-funded study including dedicated research assistance at each site."	**Insufficient staff with dedicated research time and capacity** (free-text response, 14%, 4/29) "The lack of research assistance at one site meant it was difficult to recruit and to follow-up."
The pilot trial supports the need for further research (91%, 26/29) "This is an important clinical area to ascertain best practice."	**Information was not easy to understand for clinicians** (7%, 2/29)

TABLE 3 (Continued)

Enablers	Barriers
Information for clinicians (59%, 17/29) **and women was easy to understand** (59%, 17/29) "Women seemed keen to help out, and they understood the trial overall."	**The recruitment, consent** (21%, 6/29), **and randomization for clinicians** (14%, 4/29) **were not clear or easy to understand** "The process is long and time consuming." "I found the paperwork and information for both staff and patients quite daunting."
Inclusion criteria was easy to understand (72%, 21/29)	**Receiving treatment prior to consideration of trial eligibility** (free-text response, 31%, 9/29) "a lot of women received IV-iron (mostly in theater) without being considered for the trial."
Women are more likely to participate if they have support from their family (97%, 28/29) **or health professional** (97%, 28/29)	**Workforce pressures and pressure to treat early to facilitate transfer or discharge** (free-text response, 14%, 4/29) "Shortages of beds and staff result in increased pressure to discharge women and the perception that giving RBCs rather than iron will help that." "Sometimes the acuity on the ward causes early intervention—some patients were missed for the trial."
The recruitment and consent processes were clear and easy to understand (62%, 18/29) "The trial was very easy to understand and participate in."	**Busy staff and competing demands** (free-text response, 17%, 5/29) "Staffing levels on a busy ward for doctors, midwives, and nurses meant a lack of time to fully understand the trial procesess and organize/identify eligible women."
Education for medical staff, especially junior doctors who most often prescribe for PPA (free-text response, 17%, 5/29) "I feel like a lot of work can be done to prep the doctors, especially junior doctors more for these trials."	**Women are too tired after birth to consider trial participation** (free-text response, 7%, 2/29) "Women were VERY tired—this was a barrier to participating."
Use of visual tools or videos to explain the study information (free-text response, 3%, 1/29) "... visual tools and aids to make patient's understand, or a short video?"	**Need to improve buy in from senior medical staff** (free-text response, 3%, 1/29) "We could really have done with better buy-in and support from the senior doctors."

Abbreviations: IV, intravenous; RBC-T, red blood cell transfusion.
[a]Multiple choice and free-text responses/exemplars.
[b]Likert responses (strongly and somewhat agree combined) with free-text responses/exemplars.

Holm et al.,[46] although we found no difference in hemoglobin for this comparison. There are no comparable studies for our findings that IV-iron and RBC-T, compared to RBC-T only resulted in greater differences in hemoglobin and ferritin. Our finding of no difference between IV-iron compared to IV-iron and RBC-T for hemoglobin and ferritin concentrations at all time points has clinically significant implications for potentially reducing RBC-T as a limited resource and should guide future research.

The reporting of one case of IV-iron site discoloration (skin staining) highlights an adverse reaction with potential long-term consequences for women that have resulted in adverse event notifications.[62] The New Zealand medicines safety authority[44] and pharmaceutical consumer information[43] state extravasation and long-lasting brown discoloration of the skin are uncommon following FCM IV-iron administration.[44] Two clinical trials[46,49] reported significant risks of skin staining with IV-iron.

Our pilot trial assessed the feasibility of undertaking an appropriately designed and powered randomized trial of IV-iron and/or RBC-T, for women with moderate-to-severe PPA. We found it feasible to conduct a multicenter trial with an equity-based approach to recruitment that resulted in a high recruitment rate, supported by women's altruism and understanding of the study's relevance. However, the provision of dedicated research assistance at each site will be critical to the success of any such future trial.

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All authors have contributed to the intellectual planning of the project, supervision, writing of the manuscript, and have approved the submission of the manuscript. The Lead Investigator recruited participants at one site,

oversaw recruitment and trial management at all sites, and analyzed the trial and survey data including thematic analysis of the free-text survey responses. The statistical analysis of the trial data was undertaken with the support of biostatistician Zeke Wang. Data management and web randomization were provided by Data Management Services, Liggins Institute, University of Auckland.

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CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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