Randomised controlled stratified trial of iron therapy by anaemia severity: effects on functional outcomes in adult women

Executive summary

Anaemia affects >500 million women (30%) globally and is the third leading cause of years lived with disability in the world. Iron deficiency is the main cause of anaemia and is associated with symptoms of fatigue, lethargy, and pica. Global nutrition policies recommend iron supplementation and fortification to prevent and treat anaemia, targeting a 50% reduction in anaemia by 2030. The burden of anaemia is calculated using thresholds for anaemia severity (mild/ moderate/ severe) that have been statistically assigned to corresponding disability weights. These thresholds are not 'functionally based' on validated, clinical symptoms and health impacts. As such, the true impact of mild, moderate and severe anaemia may be misconstrued, limiting global estimates of the burden of anaemia and the evaluation of cost-effective anaemia control interventions.

To address this unmet need and facilitate policy, we propose a double-blind, placebo-controlled, individually randomised, parallel-group, superiority trial that prospectively tests intravenous iron in adult women with iron deficiency anaemia within each anaemia severity level. The aim of the trial is to evaluate the impact of improved anaemia status on key functional outcomes such as fatigue, exercise performance and wellbeing after treatment by intravenous iron or placebo.

This trial will provide evidence for proposing functional thresholds for anaemia severity that are aligned to descriptors of disability weights, in turn allowing for a more evidence-based analysis of the burden of anaemia and the true impact of anaemia reduction interventions.

Research Team

The investigator team will comprise: Professor Sant-Rayn Pasricha (SP) – overall lead investigator; Dr Imrul Hasan (IH) – International Centre for Diarrhoeal Diseases Research, Bangladesh – icddr,b chief investigator; Dr Jena Hamadani (JH); A/Prof Sabine Braat (SB); Prof Peter Peeling (PP); and A/Prof Natalie Carvalho (NC). SP, IH, JH, SB and NC have collaborated for ~8 years. This diverse, multidisciplinary, experienced, international team comprises world experts with the skillsets required to deliver this trial and translate results to impact.

Implementation of impactful field trials in global health and anaemia: SP, IH and JH have led complex clinical trials in resource-limited field settings in Bangladesh on topics including anaemia control, women's health and child development, and effects of COVID on health, with biostatistics supported by SB[1,2] and economic evaluations supported by NC.[3]

Anaemia/ intravenous iron: SP (WEHI, Melbourne Australia) is a clinical haematologist who runs a comprehensive research program addressing anaemia through international field trials, the application of advanced techniques to samples from these trials, and support for the World Health Organization (WHO) policy and implementation. SP and IH have experience leading trials of intravenous iron in low-income setting trials.[4]

Functional health assessment in the field: IH and JH (icddr,b Bangladesh) are experts in adapting complex clinical, neurophysiological and behavioural tools for assessing neurodevelopment, mental health, and educational attainment tools for field studies, including in partnership with SP.[5-9]

Biostatistics: SB (University of Melbourne, Australia) is a clinical trial biostatistician with >25 years industry and academic experience, mentors IH, and has analysed >10 major RCTs in the last 10 years, and has partnered with SP for ~8 years on field trials in Bangladesh.

Exercise and iron deficiency: PP (University of Western Australia, Australia) is an applied sports physiologist and leading expert on the impact of exercise on iron metabolism, with a focus on practical strategies that can optimise iron stores in active populations.[10-12]

Disability weight methodology: NC (University of Melbourne, Australia) is a health economist with extensive experience developing and modelling Global Burden of Disease (GBD) disability weights; e.g., using a population-based survey of >4,000 members of the public in Australia to develop severity weights for a range of non-fatal states.[13] NC has partnered with SP and worked in Bangladesh for >5 years.

How the team will work together to achieve the project aims: This project leverages well-established, productive collaborations. The team maintains an equitable partnership with shared authorship of publications (e.g. sharing first/ last authorships) and leadership of grants. SP will hold overall responsibility for the trial. IH will lead icddr,b implementation of the project in the field.

Background

Anaemia is a reduction in haemoglobin concentration below tissue oxygenation requirements that may impair brain development and learning, maternal health, and quality of life. According to GBD estimates, anaemia affects about 1 in 4 (1.9 billion) people globally, and is the third leading cause of total years lived with disability worldwide.[14,15] WHO estimates that ~30% of women aged 15-49 years (>500 million) and ~40% of preschool children (~270 million) were anaemic globally in 2019. WHO and Sustainable Development Goals target a **50% reduction** in anaemia by 2025,[16] driving substantial government, multi-lateral organisation and philanthropic investment and global attention towards alleviating this burden. Current strategies to meet these targets typically rely on iron fortification and supplementation. However, **no country is on track** to meet its anaemia reduction targets; indeed, the prevalence of anaemia in women is increasing.[17,18]

Estimates of anaemia burden are driven by two key parameters: the *prevalence* of anaemia, and the *impact* of anaemia on health. Both prevalence and impact are linked to anaemia severity category (mild/ moderate/ severe). 'Disability weights' assigned to each severity category (mild/ moderate/ severe) of anaemia are based on the health loss associated with symptoms and clinical complications designated to each severity category (Table 1).

Table 1: Disability weights and descriptors from Global Burden of Disease (GBD Collaborators, Lancet Haematology 2023)[19]

Anaemia severity	Health state description	Disability weight
Mild anaemia	feels slightly tired and weak at times, but this does not interfere with normal daily activities.	0.004
Moderate anaemia	feels moderate fatigue, weakness and shortness of breath after exercise, making daily activities more difficult.	0.052
Severe anaemia	feels very weak, tired and short of breath, and has problems with activities that require physical effort or deep concentration.	0.149

Disability weights assigned based on perceived disease severity, ranging from 0 (full health) to 1 (equivalent to death).

The burden of anaemia is quantified as 'Years Lived with Disability' (YLDs), calculated as the product of prevalence of anaemia (by severity) and the corresponding disability weight. However, presently the burden of anaemia calculation is based on thresholds for anaemia severity that were assigned by WHO, based on arbitrary statistical rules (Table 2). The thresholds do not represent validated 'functional' thresholds where symptoms and clinical complications, as described in Table 1, occur. As such, the potential misalignment of disability weights and the thresholds at which they can be considered to occur have a consequential impact on the calculation of the global burden of anaemia. This disconnect may over- or under-estimate the true impact of anaemia and limits the value of cost-effectiveness analysis of various anaemia reduction interventions and programs.

Table 2: Haemoglobin thresholds used to define severity for global burden of disease estimates of anaemia burden in adolescents and adults (GBD Collaborators, Lancet Haematology 2023)[14]

Sex	Age	Mild anaemia	Moderate anaemia	Severe anaemia
Both	5-14 years	110 - 114 g/L	80 - 109 g/L	< 80 g/L
Male	15+ years	110 - 129 g/L	80 - 109 g/L	< 80 g/L
Female, non-pregnant	15+ years	110 - 119 g/L	80 - 109 g/L	< 80 g/L
Female, pregnant	15+ years	100 - 109 g/L	70 - 99 g/L	< 70 g/L

The threshold interval represents the minimum and maximum haemoglobin values.

Intervention programs target anaemia in women of reproductive age

Alleviating the burden of anaemia in women of reproductive age remains a global health priority. WHO recommends preventing and treating anaemia in women with daily or intermittent iron supplements and fortification of staple foods and condiments with iron.[20] In India, the Anaemia Mukt Bharat (AMB)/ Anaemia Free strategy targets the reduction of anaemia in children, adolescents and women through six interventions across six institutional mechanisms, costing the government

INR743 million (USD~88.4 million) annually (FY2021-2022).[21] More recently, WHO have identified broader opportunities to reduce anaemia burden through malaria and infection control and enhanced attention to women's health.[22] The World Bank Group have estimated that achieving these targets would require an investment of an additional US$12.9b over 10 years, almost all of which would be assigned to iron interventions in various forms.[23] The rationale for this investment is based on achieving a return of 12:1 for each dollar invested; however, this investment can only be justified if reductions in anaemia are directly linked to functional health gains.

Clinical and subclinical health consequences of iron deficiency

Progressive iron deficiency eventually causes iron deficiency anaemia, with well-characterized symptoms of fatigue and lethargy. Individuals with iron deficiency anaemia may also present with pica (compulsive consumption of non-nutritive foods such as soil or ice)[24] and restless leg syndrome during sleep.[25]

One way to estimate the health deficit in women's lives due to iron deficiency is to measure the benefit in relevant health outcomes observed after treatment with iron, ideally using an experimental design (i.e. randomised placebo-controlled trial). A meta-analysis of randomised controlled trials evaluating effects of daily iron supplementation in women found that iron supplementation significantly improved maximal (VO_{2max}) and submaximal exercise performance (Heart Rate and % VO_{2max} needed to complete a defined task).[26] By subgroup analysis, iron improved VO_{2max} was seen not only in anaemic women but also in non-anaemic iron deficient women and among women in whom baseline iron status had not been ascertained. The implication of these findings is that iron deficiency may impair physical exercise performance in women.[27] However, the threshold of anaemia at which these impacts occur, and the relationship between anaemia severity and severity of impact, has never been determined.

Using sensitive tests of cognitive functioning, iron supplementation has also been shown to benefit cognitive performance,[28] fatigue and wellbeing[29,30] in non-anaemic, iron deplete pre-menopausal women. In women with fatigue and ferritin concentrations below 50 µg/L, iron supplementation alleviates symptoms.[31] More recently, a randomised trial of intravenous (IV) iron (ferric carboxymaltose) in non-anaemic or borderline anaemic women with ferritin <50 µg/L and unexplained fatigue demonstrated an improvement in the Piper fatigue scale.[32] Iron supplementation has been shown to improve work productivity in Chinese textile workers, with no differences in physiologic response between women who had baseline anaemic and non-anaemic iron deficiency.[33] However, the association between anaemia severity and severity of impact has never been determined.

These studies provide an indication of the health domains which may be adversely affected by iron deficiency anaemia and can be reversed: fatigue and wellbeing, pica, exercise tolerance, work productivity, and perhaps cognitive performance. However, they do not provide a clear indication of the association between severity of these symptoms and anaemia severity.

Unmet Need

In order to justify substantive ongoing investments in anaemia control, the true impact of anaemia at each level of severity in women must be understood. However, the functional effects of mild, moderate and severe anaemia are uncertain. Symptoms assigned to each haemoglobin severity category in disability weight surveys (Table 1) were not based on direct empirical evidence of symptoms at each severity. This constrains true estimates of the functional health impact-related burden of disease attributable to anaemia, and limits economic evaluation of the benefits of interventions for treating and preventing anaemia. *The key unmet need is empiric evidence of the relationship in women between haemoglobin levels and severity of functional impairments such as symptoms (e.g. fatigue), wellbeing (e.g. quality-of-life, depression), productivity and physical activity, to enable improved assignment of haemoglobin thresholds to anaemia severity categories.*

Research Design

We aim to define the functional impact of iron deficiency anaemia at different anaemia severities, through an individually randomised placebo-controlled trial of iron therapy in adult women of reproductive age (18 – 45 years) with iron deficiency anaemia stratified by anaemia severity that will carefully measure responses on key functional outcomes including fatigue, quality of life, activity, sleep, and exercise performance. The trial will have sufficient statistical power to identify a small

effect size of iron therapy compared to placebo for outcomes in mild and moderate strata separately, the quasi-experimental cohort alongside the trial will enable estimation of the effect of iron therapy compared to placebo around the threshold of severe anaemia, as well as model the associations between haemoglobin concentration and clinical responses across all anaemia severity levels, thereby defining the lived, functional impact of anaemia. This will enable the development of validated 'functional' haemoglobin thresholds that align with GBD health state descriptions and corresponding disability weights.

Trial design: Double-blind placebo-controlled individually randomised parallel-group superiority trial of iron treatment in Bangladeshi adult women (18-45 years) with iron deficiency anaemia, stratified by anaemia severity (mild/ moderate), coupled with a cohort of iron treated women with iron deficiency severe anaemia in a quasi-experimental pre-post treatment design.

Study setting: The trial will be set in our established trial site in Rupganj Upazila, a rural region in Bangladesh (176sq km) with a population of ~640K. It will be implemented through a partnership between WEHI in Australia and icddr,b in Bangladesh; a collaboration with success in major field trials of novel health interventions. Our team have worked in this site for ~10 years, first through the BRISC trial, a large randomised controlled trial (N=3300) of iron interventions in infants that assessed functional outcomes including child development and growth,[1] and through the fully recruited ongoing EDIVA trial (N=900), which is testing the impact of antenatal IV iron (as ferric carboxymaltose) on maternal and newborn health. Our field studies indicate an overall prevalence of anaemia in non-pregnant women in this site of 31.2% (mild 21.1%, moderate 10.0%, severe 0.1%).

Intervention and control: In this study, we will utilise high dose IV iron as a model iron intervention that will achieve rapid increases in haemoglobin without concern for adherence.

- Intervention: a single dose of IV iron (ferric carboxymaltose) 20mg/kg up to 1000mg diluted in 250mL saline, over 15 minutes, at randomisation.
- Control: a single dose of placebo (IV fluid) 250mL over 15 minutes at randomisation.

The trial will comprise two treatment groups (Figure 1). Mild and moderate anaemic participants will be randomised to the intervention or control. Severe anaemic participants will not be randomised but will be treated with the intervention as treatment with placebo is not ethically acceptable. We will take advantage of our experience using ferric carboxymaltose (FCM, CSL-Vifor), a modern IV iron formulation that enables delivery of high doses of iron to be safely administered in a single rapid infusion to treat iron deficiency.[3,4] We will provide placebo treatments to ensure blinding and hence unbiased assessments of functional outcomes. Both interventions will be administered behind a drape to prevent unblinding (as the active intervention is black in colour). The ferric carboxymaltose and placebo will be administered by study nurses who have been fully trained in the safe delivery of IV iron and placebo, as well as Good Clinical Practice certified. All participants in the placebo group will be offered iron treatment at the end of the study if they remain iron deficient anaemic. The cost of FCM is US$56 per dose, and placebo (normal saline) is US$1 per person. FCM is available in Bangladesh. We have administered >1500 doses in low income settings.[4]

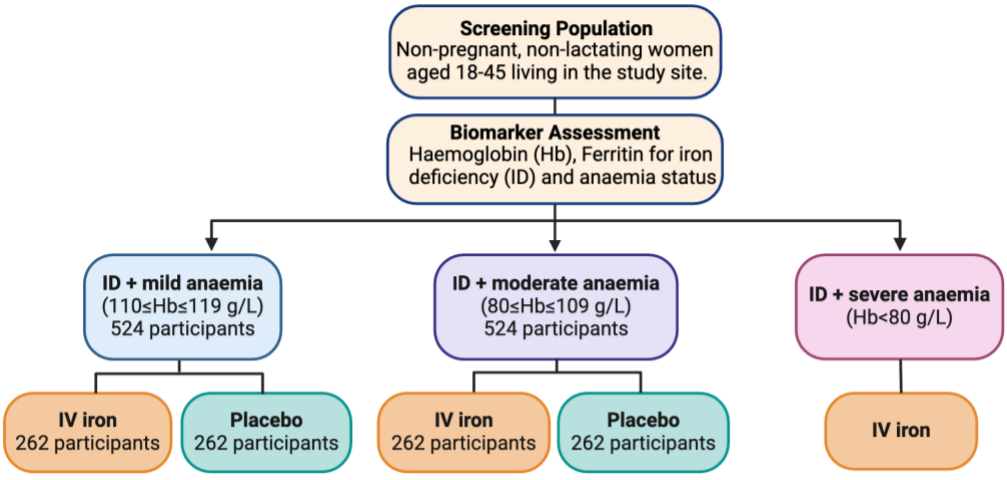

Figure 1: Study design. Screening for eligible participants will commence at the household level with non-pregnant, non-lactating women (18-45 years of age) who will be invited to be screened for anaemia by measuring capillary haemoglobin

levels. If anaemic (capillary haemoglobin ≤119g/L), venous blood will be collected for assessment of iron deficiency (ID) (ferritin <30ug/L) and anaemia (haemoglobin by automated analyser). Following consent procedures, participants with iron deficiency anaemia will be stratified to mild, moderate or severe anaemia groups, based on venous haemoglobin levels. Participants with mild or moderate anaemia will then be randomised to intravenous (IV) iron or placebo intervention. All participants with severe anaemia will be treated with IV iron.

Eligibility criteria:

- Non-pregnant, non-lactating women aged 18-45 years living in the study site and expected to remain in the site for the next 3 months.
- Anaemic (venous haemoglobin measured on a Sysmex automated analyser), with recruitment to the trial stratified by *mild* (haemoglobin 110-119g/L), *moderate* (haemoglobin 80-109g/L) anaemia and *severe* (haemoglobin <80g/L) anaemia.
- Iron deficient with a ferritin concentration <30ug/L, measured at icddr,b. This ferritin threshold reflects thresholds now recommended by international clinical authorities e.g. the RCPA.[35]

Sensitisation for the trial will occur in the community through visual information displayed in participating health centres, talks given during health clinics, local 'town hall' meetings, and consultation with key local health workers and village leaders.

Follow up: Participants will be followed up at the health centre every 4 weeks for 8 weeks (total of 2 visits following treatment) (Table 3). All follow-up visits and study protocols will be conducted by trained icddr,b study staff members.

Outcomes: will map to GBD health state descriptors for mild, moderate and severe anaemia (Table 1) and other key parameters that influence evaluation of anaemia control interventions.

Primary outcome: The primary outcome will be the FACIT-Fatigue scale total score (range 0-52 with 0 being the poorest possible score and 52 being the highest possible score indicating no fatigue), a 13-item measure that assesses fatigue over the previous 7 days, extensively used in previous trials of IV iron. The FACIT-fatigue scale is an established and well-characterised tool used to assess fatigue and its impact on functioning and daily activities in a range of chronic diseases[36]. It is validated in patients with iron deficiency anaemia receiving IV iron treatment[36].

Secondary outcomes:

- Health-related quality of life (SF-36, EQ-5D-5L)
- General Health Status (Global Health Physical and Mental Scores [PROMIS Scale v1.2][37])
- Physical Function Score (PROMIS Scale v2.0 4a, a 4-item questionnaire)[37]
- Depression (Center for Epidemiological Studies-Depression scale, CESD)
- Cognitive performance (Wechsler Adult Intelligence Scale, fifth Edition [WAIS–V])
- Productivity losses questionnaire (to capture impact on women's and caregiver's productivity, which we have previously developed for this context for the EDIVA trial)
- 24-hour physical activity (total movement, non-sedentary time, step count, moderate to vigorous physical activity) and sleep measurements (total sleep time, sleep efficiency, sleep onset latency) for 72 hours using wearable monitors
- Aerobic capacity (Queens College 3-minute step test to measure estimated VO_2 max)
- Muscular Strength (Hand grip dyno test)
- Muscular Endurance (1-minute sit-up test)
- Pica symptoms (PICA symptoms questionnaire)
- Body composition measurements (body mass index and waist-to-hip ratio)
- Haematologic and iron parameters (Hb and ferritin, CRP to adjust for inflammation)

Safety outcomes: We will collect safety outcomes (adverse events from randomisation to study exit) using a general health questionnaire and code these using the Common Terminology Criteria for Adverse Events (CTCAE) system for standardised and consistent safety reporting.

Table 3: Summary study visit schedule

	Screen	Visit (V)1 Baseline	V2 - within 1 week of V1	V3 - 4 weeks after V2	V4 - 8 weeks after V2
Capillary Hb[a]	×				
Venous Hb[a], ferritin, CRP[a]	×	×		×	×
Consent		×			
Randomisation			×		

Intervention (IV iron or placebo)			×		
Socio-economic questionnaire		x			
FACIT-Fatigue[b]		×		×	×
SF-36		×			×
EQ-5D-5L		×			×
CESD[c]		×			×
PROMIS Scale v1.2 (Global Health)		x			x
PROMIS Scale v2.0 4a (Physical)		x			x
WAIS-V		×			×
Pica symptoms questionnaire		×			×
Activity (24-hour monitor for 72 hours)		×			×
Queens College 3-minute step test		×			×
Hand grip dyno test		×			×
1-minute sit-up test		×			×
Body composition measurements		×			×
Productivity losses questionnaire		×			×

[a]Hb: haemoglobin, CRP: c-reactive protein to adjust for inflammation. [b]FACIT: Functional Assessment of Chronic Illness Therapy - fatigue scale, [c]CESD: Center for Epidemiological Studies-Depression scale.

Sample size: The sample size is based on the FACIT-Fatigue Scale, which has an established minimal clinically important difference in trials of iron therapy of 3 and a standard deviation of ~10.[36] The sample size for each of the mild and moderate stratum will be 524 women (262 per treatment group, 1048 across both strata) including 10% loss to follow up (90% power, 5% two-sided alpha) which will enable detection of a 3-point treatment difference in change from baseline to 8 weeks in the FACIT total score assuming a standard deviation of 10, thus the trial will be sensitive to a standardised effect size of 0.3 (small effect). The sample size for the severe stratum is determined by recruitment achievable while the trial is open for the mild and moderate strata.

Recruitment: We will first enumerate ~30 000 adult women aged 18-45 living in the study area through local health records and a house-to-house census. Secondly, we will visit adult women at home to screen for anaemia using the HemoCue 301 portable haemoglobin measurement instrument. Individuals with capillary blood haemoglobin ≤119g/L will then have venous blood collected for measurement of ferritin and haemoglobin to determine iron deficiency and confirm anaemia status. Ferritin testing will be performed at our accredited laboratory in icddr,b in Dhaka, requiring transport of samples for testing and meaning participants cannot be screened and recruited on the same day. Following confirmation of iron deficiency anaemia status (ferritin < 30ug/L, and haemoglobin ≤119g/L), individuals will be recalled and invited to attend trial centres for the informed consent procedure, recruitment into the study and baseline measurements.

We expect ~30% of women to be anaemic (20% mild, 10% moderate, <1% severe), and 19% of anaemic women to have iron deficiency.[38] Screening 30 000 women will yield 9000 women with anaemia (6000 mild, 3000 moderate); of these, we will identify ~1146 women with mild, and ~573 women with moderate, iron deficiency anaemia enabling us to recruit for each stratum. We expect to recruit ~57 women will have severe iron deficiency anaemia. We have extensive experience screening large numbers of individuals in this site: across our trials we have screened ~50,000 pregnant women and ~6000 infants for eligibility to trials.

Allocation: We have experience in field randomisation, allocation concealment, and packaging for double-dummy double-blind trials e.g. in our BRISC trial of 3300 children in rural Bangladesh.[1] Women with mild and moderate anaemia will be randomised in a 1:1 ratio to either intervention or control, stratified by anaemia severity, using randomly-permuted blocks of varying size, computer generated by an independent statistician. Allocation codes will be provided centrally (field worker call to the study office) using a list to preserve concealment, once eligibility and consent is confirmed. The intervention and placebo will be prepared by a study pharmacist who will conceal allocation when providing the drug to the study nurse for administration. Participants, investigators, and statisticians will be blinded until database lock. The cohort of women with severe anaemia will all be treated with the active intervention.

Data collection and management: We have extensive experience collecting data from trials in remote, resource-limited settings. SQL will be the main data capture platform for participant data, which allows for audit logs and exporting data to statistical packages. Data will be digitally collected on electronic tablets through SQL and transmitted to a central database server at icddr,b, where it

will be backed up daily, with weekly backup to WEHI, Melbourne. The SQL database and data will be stored on secure, password protected servers and access controlled via user rights.

Statistical methods: A detailed statistical analysis plan will be made public prior to database lock. Analysis will follow the intention-to-treat principle. The primary outcome of the FACIT total score collected at baseline, 4 weeks and 8 weeks post-intervention will be analysed using a linear mixed-effects model including treatment group, visit, anaemia severity, and all interactions to obtain an estimate of the treatment differences (IV iron vs placebo) in the change from baseline to 8 weeks post intervention for mild and moderate anaemia severity separately. Analysis of secondary continuous outcomes collected at baseline and 8 weeks post intervention will use the same model as the primary outcome, we will use logistic models for dichotomous outcomes. All treatment effects will be accompanied by two-sided 95% confidence intervals and p-values.

Recategorization of disability weights: We reason that the effect sizes for primary and secondary outcomes will be inversely associated with baseline haemoglobin concentration (i.e. women with more severe anaemia will have larger effects) (Figure 2). Treatment effects across the continuous baseline haemoglobin will be obtained using a linear mixed effects model, with allowance for non-linear relationships. We will then use a regression approach to formally evaluate the relationship between baseline haemoglobin (as a continuous variable and including individuals with severe anaemia) and treatment-related changes from baseline to 8 weeks in primary and secondary functional outcomes. We will finally use these results to determine the haemoglobin thresholds that most closely reflect relevant GBD health state descriptors corresponding to disability weights for mild, moderate and severe anaemia.

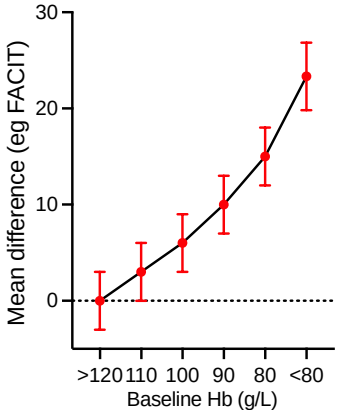

Figure 2: Modelling mean difference vs baseline haemoglobin to recategorise anaemia severity

Timeline

	Indicator	Timeline
Trial Set-up	Research agreements finalised	Y1, Q1
	Protocol submitted to ethics	Y1, Q1
	Study drug onsite	Y1, Q2
	Study field staff recruited and trained – Bangladesh	Y1, Q3
Study Database	CRFs finalised and trial database built	Y1, Q3
Ethics & Governance	Convening of governance groups[a]: first meeting and protocol review	Y1, Q2
	Governance group meetings (TSC[a], DSMC[a], TMC[a])	Y1–4
	Protocol approval – Ethics icddr,b and Ethics WEHI Australia	Y1, Q2
	Protocol approval – Drug Regulator Bangladesh	Y1, Q3
	Trial Registration (ANZCTR, WHO ICTRP)	Y1, Q3
Co-production with stakeholders	Co-design workshop with consumers to inform trial implementation	Y1, Q2
	Community sensitisation	Y1, Q3
Data Collection	Enumeration of potential participants	Y1, Q2-3
	Commence screening of participants	Y1, Q4
	First Subject First Visit	Y1, Q4
	Last Subject Last Visit	Y3, Q3
Data Cleaning and Analysis	Completion of statistical analysis plan	Y3, Q3
	Completion of data cleaning	Y4, Q2
	Database lock, trial unblinding and commence analysis	Y4, Q2
Derivation of new thresholds	Modelling to define the Hb[b] thresholds that align to functional impairments	Y4, Q2-3
Dissemination	Completion of trial analyses, draft report to donor	Y4, Q4
	Dissemination of results to stakeholders e.g. WHO	Y4, Q4
Publication	Completion and publication of protocol paper	Y2, Q3
	Completion and submission of final manuscript	Y4, Q4

[a]TSC: Steering Committee, TMC: Trial Management Committee, DSMC: Data Safety and Monitoring Committee, [b]Hb: Haemoglobin

The research team will provide regular progress updates at a cadence determined by the donor.

Impact of Research

Alleviating anaemia in women is a key global nutrition target and sustainable development goal indicator. Anaemia is considered the third leading cause of Years Lived with Disability in this

group. The key question remains how anaemia impacts, and reduction improves, wellbeing and health outcomes. Cost-effectiveness assessments of anaemia control solutions rely on the burden of anaemia as assigned by the GBD, based on disability weights for mild, moderate and severe anaemia which are based on clinical descriptors corresponding to the statistical thresholds for anaemia severity recommended by WHO. Our study will enable functional thresholds for severity that will enable improved assignment of anaemia disability weights. Enhanced understanding of the functional impact associated with anaemia severity will have critical value in defining the global and regional burden of anaemia, improving the rationale for and evaluation of cost-effective anaemia control interventions, and identifying key groups to whom interventions should be targeted. Overall, these data will unlock high quality cost-effectiveness analyses based on empiric data, enabling grant makers to make evidence-based decisions. For example, Open Philanthropy have provided >$8m to Fortify Health to strengthen food (iron) fortification programs. This study will strengthen or diminish the case for similar investments in the future.

Our team have strong links with WHO and led with development of updated WHO guidelines on haemoglobin thresholds to define anaemia.[39,40] SP leads the WHO Collaborating Centre for Anaemia Detection and Control. With approval of the donor, we will directly involve WHO secretariat in the strategic governance of this project, ensuring impact. SP is also a Subject Matter Expert for the IHME GBD Anaemia Estimates project. These partnerships along with partnerships with USAID, UNICEF and the Gates Foundation will ensure translation of results.

Human Subjects Research

The complete protocol and data collection tools will require approval from ethics committees in Bangladesh (icddr,b review will comprise an initial Research Review Committee to ensure scientific quality followed by the Ethics Review Committee to ensure appropriate ethical principles are upheld) and WEHI (Human Research Ethics Committee) prior to the commencement of any research. The trial will require drug regulatory approval from the DGDA in Bangladesh who will ensure the quality of the study drug and placebo and be publicly registered with ANZCTR and WHO ICTRP prior to opening for recruitment. Our team has successfully achieved ethics and regulatory approval for three interventional trials in Bangladesh. We will provide written education regarding the trial, after which receiving this information participants will provide written informed consent. All study staff will maintain Good Clinical Practice certification. Participants can withdraw from the trial at any time.

Governance: The trial will be governed under the following structure:
Trial Steering Committee (TSC): An international, independently chaired group of experts, will meet twice annually with investigators to supervise development of the protocol and trial implementation. The trial steering committee will include stakeholders e.g. WHO and government officers, and a representative for the donor as an observer, to ensure the trial meets policymaker and donor needs.
Trial Management Committee (TMC): Comprises co-investigators, statistician, and field supervisors who will meet at least weekly to ensure operations of the study and alignment with the trial timeline.
Data Safety and Monitoring Committee (DSMC): Comprised of three independent experts and a statistician, members will review the protocol and meet according to a pre-agreed charter.

Co-production with stakeholders: Our team will formally incorporate engagement with the community. We are highly experienced in engaging with consumers and communities through co-design e.g. for the EDIVA trial. icddr,b will lead co-design workshops before the start of the trial and will include consumers (women aged 18-45), community stakeholders (health workers, local leaders), and policy makers. Lessons from co-design will influence community sensitisation, participant information documentation, and health worker training. Our engagement strategies include meetings with consumers, elders, husbands, health workers, and Ministry of Health officials.

Alternate Funding Sources

Alternate funding sources: This project has been designed to align with GiveWell research priorities. If we do not receive Givewell funding, we may seek competitive grant funding from the Australian National Health and Medical Research Council (NHMRC) (success rate 8-9%). NHMRC typically does not fund global health research, and even if we were to successfully obtain funding, this project would not commence until 2027, delaying the development of knowledge that would advance progress towards the 2030 global anaemia targets and improve health for women.

References (Please see Appendix)