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Research Article

Protocol for Economic Evaluation of a cRCT on Screen and Treat Strategy for Anemia Reduction in Rural India

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Abstract

Objectives: Anemia is a major public health problem in India. A cluster-randomized trial (cRCT) is undergoing in rural Telangana, India, to evaluate a 'Screen and Treat for Anemia Reduction (STAR)' approach using population-level screening for anemia using point of care diagnostic methods followed by appropriate treatment.

Methods: Here we describe the economic evaluation protocol of this approach, to be conducted alongside the cRCT. This will address the question of whether the approach will be a cost-effective intervention for increasing population mean hemoglobin and reducing the prevalence of anemia among pregnant women and children (6 months - 5 years age), as compared with the existing anemia control program alone. A cost-utility analysis (CUA) will be conducted to explore and quantify the costs per health gain using a societal perspective, considering costs and outcomes relevant to the public health department and the study population and quality of life (QoL) of the population in the intervention group using the EQ-5D-5L tool. The relative costs and outcomes will be assessed using the incremental cost-effectiveness ratio (ICER) in cost per percentage point reduction in anemia prevalence across the two approaches and cost per percentage point increase in the population mean hemoglobin, for the combined 6-month prevalence of anemia and cost per quality-adjusted life-years gained. Decision-analytic modelling to estimate cost-effectiveness beyond the trial period, will also be conducted.

Results and Conclusion: The results of this economic evaluation would help policymakers make an informed decision regarding this strategy for anemia reduction.

Keywords: *Anemia; cRCT; Health Economics; CEA; Protocol*

Abbreviations

cRCT: Cluster Randomized Control Trial; STAR: Screen and Treat Strategy; CUA: Cost Utility Analysis; QoL: Quality of Life; EQ-5D-5L: European Quality of Life Five Dimension; ICER: Incremental Cost-Effectiveness Ratio; NFHS: National family Health Survey; UT: Union Territory; MOHFW: Ministry of Health and Family Welfare; NIPI: National Iron Plus Initiative; IFA: Iron Folic Acid; QALY: Quality Adjusted Life Years; Hb: Hemoglobin; ASHA: Accredited Social Health Activist (ASHA); OOP: Out of Pocket Expenditure; ANC: Antenatal Care; WTP: Willingness to Pay Threshold; MCH: Maternal and Child Health; WHO CHOICE: CHOosing Interventions that are Cost Effective; DSMB: Data Safety Monitoring Board

Introduction

Anaemia is one of the most important nutritional public health problems across the world [1,2]. Anaemia affects almost all age groups in India with especially higher prevalence observed in preschool children, adolescent girls, pregnant women and lactating mothers [3,4]. Anaemia among adolescent mothers has a lasting impact, posing the risk of maternal mortality, low birth weight and higher risk of anaemia in the newborn [5]. As per previous NFHS reports, the prevalence of anemia among women (15 - 49 years) was reported to be around 52% in 1998-99 (NFHS-2) and 53% in 2015-16 (NFHS-4) [6].

The recent National Family Health Survey (NFHS)-5 (2019-20), has shown a rise in prevalence of anaemia in both children (6 - 59 months) and women (15 - 49y) [7]. A rise in percentage of children under five, affected by anaemia has been reported in 16 states/UTs of India [8]. In the state of Telangana, it has increased from 60.7% to 70%. Prevalence of anaemia in women of reproductive age (15 - 49 years) has also shown an increase in 16 states/UTs including Telangana, where the increase has been marginal from 66.6 to 67.6% [9].

National level programs like, the National Iron Plus Initiative (NIPI) started by the Ministry of Health and Family Welfare (MOHFW) in 2013 [10,11] has brought together the existing programs for prophylactic Iron-Folic Acid (IFA) supplementation (for pregnant and lactating women and children in the age group of 6 - 60 months), along with screening by frontline health workers for clinical signs of anaemia (mainly palmar pallor) and referral to health facilities for diagnosis and treatment. However, the coverage of the program is poor. Using clinical signs for population level screening has low sensitivity and several gaps in the supply chain and management of anaemia are known to exist [12].

It has been suggested that universal prophylactic IFA supplementation approach may not be adequate and providing appropriate treatment for anemia using point of care diagnostic methods may be useful (in addition to the current program of prophylactic IFA supplementation to vulnerable non-anemic groups) [11].

However, evidence on the feasibility, impact and cost effectiveness of the "Screen and Treat strategy for anaemia reduction (STAR)" is currently lacking. A cRCT (Cluster randomized Control Trial) is underway in Medchal district, Telangana [13].

This paper describes the protocol for the economic evaluation of the STAR strategy'. This is proposed to be conducted alongside the cluster-randomised trial, to evaluate the cost-effectiveness of the program. The evaluation will address the question of whether the 'screen and treat' approach is a cost-effective intervention for reducing the prevalence of anaemia among pregnant women and children (6 months-5 years age), and increasing population mean haemoglobin, compared with the usual IFA supplementation approach alone.

Methods

Design

The study is a community-based cluster-randomized open labelled trial to be carried out in rural parts of Telangana, a state in South India. The selected villages as part of the study would be randomly allocated to the intervention and control arms. The intervention arm will utilise the STAR approach for anaemia control, whereas the control arm will have the existing anaemia control program.

The economic evaluation will be conducted alongside the trial to examine the difference in costs and outcomes between the intervention and control arms. If the intervention is found to be both cost-saving and associated with equivalent or improved outcomes, then it is said to dominate the comparator. If (as is more likely) the intervention incurs additional costs, but provides additional health and/or utility gains, it is not immediately apparent whether the intervention would be preferred to the comparator. In such a scenario, an economic evaluation comparing costs and outcomes can be informative to the decision-makers [14].

We will conduct a cost-utility analysis (CUA) to assess the costs per quality adjusted life years (QALY) gained. Additionally outcomes will also be assessed in terms of clinical endpoints to represent incremental costs per unit rise in haemoglobin (Hb) levels.

The economic evaluation will be undertaken from a societal perspective, considering costs and outcomes relevant to the payer (public health department), and the population/study participants.

Study population

The study would be conducted in accordance with the protocol for the main cRCT [13]. The study population, sample size and allocation of population to intervention and control arms will be done based on the protocol of the main study. All eligible participants in the age group of 6 months to 50 years living in the selected villages would form the population for this evaluation. Two important subgroups will be assessed separately which include children (6 - 60 months) and pregnant women.

Sample size

The sample size for this study will be based on the results of the internal pilot study in 6 villages of Medchal district, Telangana (ongoing) [13].

The proposed sample size for collecting quality of life data is 216 per population subgroup (considering mean utility of anemia as 0.93, std. deviation of 0.1, type I error as 0.05 and power of 80% and non-response rate of 10%).

We will be collecting baseline data on QoL in the intervention village and will collect follow-up QoL data at 3 months and endline. No data will be collected from the control village as the QoL of any group of mild/moderate anemics will be the same and change after treatment.

While we do not explicitly propose subgroups of mild moderate and severe, random selection will provide us with a representative sample corresponding to the proportion of mild/moderate/severe anemia in the population.

Intervention and comparator

In the intervention arm, Hb levels will be assessed by a point of care test by portable autoanalyzer using capillary blood sample [16]. The Hb values of the participants will be integrated into the database with the software program developed for the study. This will form the basis for distribution of the appropriate doses of the iron folate tablets (according to grade of anemia) to the study participants in the intervention arm. All those diagnosed with severe anaemia will be referred for care to the appropriate health facility.

In the control arm after completing the baseline data collection, there would be no intervention by the research team and the existing anaemia control program would continue. The routine programme comprises of prophylactic iron supplementation to the target groups with an option of facility-based screening and anemia treatment when needed.

Results

Measures of outcome

The measures of outcome employed in the economic evaluation and the timing of their collection are presented in table 1. The data for outcome assessment will be collected using paper based, structured questionnaires and finger prick blood sample of pregnant women and young children. The baseline will be conducted before the delivery of the screen-and-test intervention, and the follow-up after 6-months of intervention period.

Measure	Means of collection	Timing of collection
Population mean Hb Prevalence of anemia	Finger prick blood sample of pregnant women and young children	Baseline: Prior to intervention Follow-sup: 6 months post-baseline assessment
Intervention compliance	Questionnaire via tablet-based interviews	Baseline: 1 month Follow-up: 2-month, and 3-month
Patient referral to health facilities by ASHA	Questionnaire via tablet-based interviews	Baseline: 1 month Follow-up: 2-month, and 3-month
Proportion of diagnosed anemic persons receiving adequate treatment with IFA	Questionnaire via tablet-based interviews	Baseline: Prior to intervention Follow-sup: 6 months post-baseline assessment
Proportion of anaemic persons who have complete recovery	Finger prick blood sample of pregnant women and young children	Baseline: Prior to intervention Follow-up: 6 months post-baseline assessment
Quality of life	EQ-5D-5L	Baseline: Prior to intervention Follow-up: 6 months post-baseline assessment

Table 1: *Overview of outcome measures.*

Population mean haemoglobin would be the primary outcome measure. In addition, anaemia prevalence in population sub-groups (6 - 60 months old children and pregnant women) in two arms will also be measured. The primary measure of outcome for CEA will be difference in prevalence of anemia from baseline to end-line (end of follow up at 6 months) and difference in quality adjusted life years gained.

Quality of life assessment will be conducted using the Euro Quality of Life-5 Dimensional-5 level (EQ-5D-5L) health survey (Annexure I) administered at baseline and end of 6 months to every participant [17]. Participants' health states will be captured using the 5 domains of the EQ-5D-5L namely mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

The EQ-5D-5L will be mapped to the Euro Quality of Life-5 Dimensional-5 level (EQ-5D-5L) using the crosswalk method. From the primary data we will obtain a health state for each of the five dimensions represented as 21232 or 11224 etc. with each digit representing the grade of problem for the five dimensions of health. This health state for each individual will be converted to a utility score ranging between < 0-1 where 1 means perfect health and 0 means death using the Indian value-set [18]. The average of the baseline and 6-month

utility score weights for the participants in both groups will be multiplied by the time period (6/12 months) to derive QALYs. Incremental QALYs will then be computed as the difference in mean QALYs (intervention group minus control group).

Measures of resource use and cost

We will be including direct medical, direct non-medical costs borne by the health system and the study population. An overview of resource use and cost measures to be employed in the cost-effectiveness analysis is presented in table 2.

Cost component	Means of collection	Timing of collection	Sources of data
Cost of tablet development for questionnaire	Interviews with program developers	After completion of development	Developers of tablet-based questionnaire
Cost of training of ASHA staff	Interviews with project team, administrative records	After completion of training	Trial team
Cost of intervention implementation	Interviews with project team, administrative records	After completion of intervention	Trial team
Health service use	Tablet-based questionnaire	6-months after baseline	Quantity-participant interview, including tablet-based questionnaire
Other service use	Tablet-based questionnaire	6-months after baseline	Quantity-participant interview, including tablet-based questionnaire

Table 2: *Overview of cost measures.*

A bottom up costing approach will be used to estimate health system costs of implementing the STAR strategy. This will include start-up costs and implementation costs that are likely to differ across the intervention and control groups, specifically the costs of developing the intervention, training of the ASHA workers, delivering messages by the ASHAs, materials used during the session, and use of health and other services by the participants during the follow-up period (Table 3).

Service type	Sources of unit cost
Health service visits by women	Trial team
Health service visits by children	Trial team
Training of ASHA	Trial team
Development of tablet-based questionnaire	Trial team
IFA tablet distribution	Tablets will be procured from company Cyanopharma
Other healthcare services	OOPE
Prescribed medicines	OOPE
Unmet need for any of the listed services and why not able to access the service	NA
Cost of the baseline survey (screen and treat)	Trial team
Cost of home visits by ASHA	Trial team
Cost of Screening test	Trial team
Cost of referral (when applicable)	Trial team
OOP during facility visit (when applicable)	Trial team
Loss of wages due to referral (when applicable)	Trial team
Cost of physician consultation at facility	Trial team
Cost of medicines other than in the NIPI Program	Trial team
Cost of travel	Trial team
Cost of other investigations (if any)	Trial team
Cost of the Endline survey	Trial team

Table 3: *Information to be gathered on reported service use and sources of cost data.*

The costs of developing the tablet-based questionnaire will be obtained from the developers. All capital costs will be annualized based on average life of the product. The cost of implementation of the intervention will include cost of staff salaries, equipment, drugs, and other consumables. Since, a large part of the intervention will be delivered by the ASHA workers, costs will be assessed based on additional performance based incentives paid to them. The costs of delivering the messages as part of the intervention will be affected by whether it would be additional to target pregnant women and children or it would replace some elements of the other services they offer. This will be established by asking ASHAs about the feasibility of integrating the training into future sessions and how the inclusion of the intervention would affect the program of sessions.

Data on OOP expenditure incurred for the diagnosis and treatment of anemia and anemia related complications will be elicited from the study participants in both the arms. Data will be collected during follow-up visits using a pre-structured questionnaire (Annexure 2). The participants will be asked about treatment sought, type of health facility (public or private) and expenditure on doctor consultation fee, diagnostics, drugs, transportation or any other charges.

All resources will be valued at 2020/2021 Indian rupees, and the 6-month trial follow-up means that there is no requirement to apply discounting.

Cost-effectiveness analysis

The total costs for the intervention and control groups, as well as the average cost per participant, incorporating the cost of development, training and delivery of screen and test for the intervention group will be calculated. Using regression analysis, we will control for differences in characteristics of participants (such as age, socio-economic status) in the two groups. This will also allow to better manage skewed data, which is likely to be the case, as we do not expect high proportion of participants to have high service costs (provision of IFA and ANC-Antenatal Care in public health facilities is free of cost) [19]. From these regression analyses, the average cost of participant, prevalence of anemia, utilization of health services, will be estimated for intervention and control groups. Costs and outcomes will be combined into a single measure, the incremental cost-effectiveness ratio (ICER), which is the difference between intervention and control groups in costs divided by difference in outcomes [19,20]. Results of the CEA will be expressed in cost per percentage point reduction in anemia prevalence across the two approaches, and cost per percentage point increase in the population mean hemoglobin, for the combined 6-month prevalence of anemia and cost per quality adjusted life year gained.

Addressing uncertainty

As we will have individual-level data on costs and outcomes for the period of trial follow-up, the uncertainty of the cost-effectiveness analysis will be evaluated using non-parametric bootstrapping [21]. Bootstrapping produces an estimate of the joint distribution of costs and effectiveness that does not rely on assumptions about the nature of this distribution. The decision uncertainty surrounding cost-effectiveness would be reported using cost-effectiveness acceptability curves [22]. These display the proportion of the estimates produced by bootstrapping that would be acceptable below a given -willingness to pay threshold (WTP), over a range of these WTP thresholds. We will also perform scenario analysis, incorporating different extremes of uncertain values in order to estimate a best case, and worst case scenarios and pother policy-relevant scenarios.

Modelling

The base case will have a time horizon of up to 6 months, the period of the intervention trial follow-up. If the intervention demonstrates clinical effectiveness in that period, a decision analytic modelling to estimate cost-effectiveness beyond the trial period will be parameterized in Microsoft excel. The model would incorporate long-term costs and effects of anemia in children and pregnant women. A reduction in prevalence of anemia due to STAR strategy will result in a reduction in prevalence of complications arising as a result of anemia. Primary literature review will be undertaken to estimate differences in complications in pregnant females (such as pre-

eclampsia, pre-term birth), neonates (low birth weight, neonatal illnesses) and children (cognition). A time horizon of 10 years will be considered since it is assumed that all the costs and benefits of the STAR intervention will be accrued during this time period. Additionally the complications arising as a result of anemia in the two groups- pregnant females and children (6 months-5 years) are unlikely to occur beyond a period of 10 years from baseline.

Additional cost analysis to inform implementation

Along with total costs of the intervention, other components such as costs of development, training and delivery of the intervention will also be reported. We will consider how costs of the intervention might differ if the 'screen and test' intervention approach were to be delivered in MCH services more broadly. This will include such factors as the need for refresher training, and training of new staff members. The costs will be analyzed using health systems and societal perspective.

Data entry and storage

Data pertaining to health system costs, OOP expenditure and quality of life will be collected using paper-based forms. The same will be entered and analyzed using Microsoft excel software.

Trial management

The trial would be overseen by a Data Safety Monitoring Board (DSMB), chaired by a Biostatistician and will have members with expertise in Epidemiology, Toxicology, Clinical Research and Bioethics.

Discussion

The value that a society places on prevention of anaemia is unknown nor is there an explicit Willingness to Pay (WTP) threshold for cost per QALY in India. As India does not have an explicit WTP per QALY threshold we will assume WHO CHOICE (CHOosing Interventions that are Cost Effective) parameters to measure against the results of our study [23]. However, this threshold many vary with other factors such as the value society places on the availability of treatments for particular conditions.

The perceived value of preventing a case of anaemia among pregnant women and children will depend on the decision makers' acceptance of the posited causal association between anaemia prevalence and long-term health impacts for pregnant women and children aged 6 months-5 years.

Conclusion

This economic evaluation conducted along with the cRCT will provide decision-makers with valuable data to inform any future implementation of this innovative intervention for primary prevention of anaemia among pregnant women and children aged 6 months to 5 years age. The results would be applicable not only to India but also other LMICs.

Approvals and Registration

Institutional ethics approval would be obtained from the ethics committee of National Institute of Nutrition, Hyderabad before the initiation of the participant enrolment in the main study.

Conflict of Interest

The authors declare that the research will be conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Volume 11 Issue 8 August 2022