STUDY PROTOCOL

Cost-effectiveness of invasive devices versus non-invasive devices for screening of anemia in field settings in India: A study protocol [version 1; peer review: 1 not approved]

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Abstract
In India, an estimated 53\% of women and 58\% of children are anemic. The accuracy of Sahli’s hemoglobinometer, commonly used for detecting anemia in public health settings, is questionable. This study presents the protocol for assessment of cost and cost effectiveness of devices for screening of anemia using invasive devices (HemoCue 301 and True Hb), and non-invasive devices (AJO Spectroscopic Test and Masimo Pulse Oximetry test) compared to automated auto-analyser (reference test). The study population will include all adult patients attending the outpatient department in urban/rural health centres for routine investigations. Each included patient will undergo either one or two index tests apart from the reference test, on a predefined weekly schedule to avoid bias. The total and incremental costs of the intervention will be measured prospectively by measuring both screening and provider costs. Since the priority of the national program is detection of severe anemia, detection rates of anemia and severe anemia will be considered to calculate effectiveness. Cost comparisons of median, average and range of costs across the invasive and non-invasive devices will be calculated. Cost-effectiveness analysis will be compared for four devices within time horizon of 1 year. Ethics approval for the study has been obtained from the institutional ethics committees of the hospitals. The study protocol will generate evidence on the use of cost effectiveness of medical devices to influence policy decisions.

Keywords
anemia, invasive, non-invasive, costs, cost-effectiveness, India
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Background
Anemia is a public health problem that affects women and children, especially in low- and middle-income countries (LMICs). It affects nearly 53% of women and 58% of children in India. The most commonly used parameter to diagnose and detect anemia is by measuring hemoglobin (Hb). Several methods have been tested to ascertain an accurate value of Hb that can guide the course of management.

In India, Sahli’s hemoglobinometer has been in use extensively in public health settings. Its accuracy is being questioned, and hence there is a felt need to replace this device by a more accurate and easier-to-use method. Currently, several invasive and non-invasive devices are available for detecting anemia. These have been evaluated in diverse settings and population groups with mixed findings. In the absence of a concrete evidence, there is a need to examine the devices that have the potential to be included in public health programs. Given the fact that most of the screening happens in community and outreach settings where provision for a laboratory support seems difficult, the device ought to be tested in field settings with health workers (Auxiliary Nurse Midwives or ANMs) as end users.

Currently four such devices have been identified that have the potential to be used in public health settings, namely, digital hemoglobinometers (True Hb and Hemocue), and non-invasive devices, i.e. Masimo Pulse Oximetry test and AJO spectroscopic device test. There is a need to evaluate them in order to identify the most cost-effective device suitable for use in Indian and similar settings.

Rationale for the study
For the national Anemia Mukt Bharat (translated as ‘Anemia Free India’) program, diagnosis of anemia remains the mainstay for adequate and appropriate management. Public health programs require devices that are accurate, user friendly, and cost effective. A systematic approach using the principles of Health Technology Assessment (HTA) is required to identify the device that meets the requirements of health system. A multi-disciplinary approach encompassing analytical frameworks, economic assessments and outcomes research forms the basis of HTA. Until recently, few studies on HTA of medical devices have been conducted in LMICs. In India, use of HTA for priority setting and decision making has been adopted recently. The current study protocol aims to compare costs, and cost-effectiveness of different hemoglobinometers in field settings.

Aims and objectives
The aim of the study is to compare the costs and cost-effectiveness of invasive (True Hb and Hemocue) and non-invasive devices (Masimo and AJO Spectroscopic) to detect anemia in normal adults in field settings.

Primary objective. To estimate the cost-effectiveness of devices by evaluating the incremental cost per case detected from a health system perspective over a year’s time horizon based on the detection rate of anemia cases examined by invasive and non-invasive medical device methods for anemia in India.

Secondary objectives.

a) To measure the health-related quality of life (HRQoL) using EQ-5D tool across invasive and non-invasive devices for testing anemia.

b) To assess the user friendliness of the device for detection of anemia in field settings.

Methods

Study design
This is a prospective diagnostic accuracy study conducted across two tertiary care hospitals India- Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Puducherry, and Calcutta Medical College, Kolkata, West Bengal.

Study setting
The study will be conducted in field settings of two sites in India in 2019. These sites will be Medical Colleges with a facility for performing the gold standard test and having a field practice area. The sites will be considered depending on the willingness of the Head of the Institution/ Department of Community Medicine.

Diagnostic tests
Reference test (Gold standard). A hematological auto-analyzer will be selected as the reference test. These pieces of equipment are kept in Medical Colleges and are subjected to quality assessments through an internal and external quality checks for best results. Venous samples will be used for the tests.

Index tests. For invasive tests, Hb will be tested using both capillary and venous blood. The devices to be tested include HemoCue 301 and True Hb version. Non-invasive devices include AJO Spectroscopic Test and Masimo Pulse Oximetry Test. The details about these devices are described elsewhere. Standardized methods will guide the performance of tests using these methods.

Study participants
The study population will include consecutive adult patients attending the outpatient departments (OPD) of urban and rural field practice areas attached to the select Medical Colleges. Children, pregnant women and patients suffering from bleeding disorders will be excluded from the study. All the patients will be recruited face to face at the clinics. Only those patients who are advised Hb estimation as part of the routine investigations will be screened for their eligibility for the study. They will undergo the reference (Gold standard) test. In addition, each patient will be subjected to one or two index tests. Allocation of participants to different index tests will be based on a predefined weekly schedule.

A sample of size of 600 is required to assess the diagnostic accuracy of each device based on a 50% prevalence of anemia,
sensitivity = 82% (TrueHb) and 82% (HemoCue, at 5% level of significance. Details of the calculation have been mentioned elsewhere1.

Data collection
Individual level data on Hb readings of autoanalyzer and other devices will be collected electronically. Data from field workers will be collected on paper forms. Data pertaining to every participant will be linked using a unique identification number given at the time of recruitment. Blinding will be ensured by allowing users to upload the data real time that will be merged at the central level using unique identification number. This will help maintain the validity of the study. Missing data or indeterminant data of the index test or reference standards will be excluded from the analysis.

Cost assessment
We will capture the costs using a step-down costing methodology on paper forms, that will be transferred to a customized tool created in MS Excel, available as Extended dataa1.

Unit costs of all resources used in the different activities occurring in the in OPDs for the purpose of screening will be collected. The cost of ANM time will be calculated based on the time they would devote for testing for anemia including noting down patient details and test results. The costs will include full salary including fringe benefits.

The life-cycle of each medical device, considered as capital equipment in the study, will be 2.5 years. Annual maintenance cost of all diagnostic equipment will be assumed to be 10% of the annual rental value. Costs of other equipment such as syringe, needle, cotton swab and other consumables for conducting each test will also be accounted for.

The rental value of clinics (urban and rural health centers) will be captured based on present value as per the local information. Contribution of rental values of clinics and capital equipment towards each test will be calculated based on the time required to perform the test11.

To determine the examination cost, we will prepare the list of equipment needed to conduct each test. At the hospital, the examination cost will include both direct and overhead costs. Direct costs will include labor, capital and material costs. Labor cost will be the cost of ANM time, calculated based on the time they would devote for testing for anemia including noting down patient details and test results. Average time taken by ANMs to perform the test based on real-time observations of at least 30 patients would be captured. The costs will include full salary including fringe benefits. Capital costs will include annualised discounted depreciation cost of furniture, equipment and instruments used in the OPDs for screening. The material costs will include the actual usage of drugs, medical supplies, and office supplies for performing each test. Any wastage of resources incurred in the process will be accounted for. These costs to the public health system will be elicited from the records/publications.

Overhead costs will not be considered as both the facilities being large public hospitals, are managed through government funding; it will be difficult to identify budgetary allocations, and expenditure heads for allocation towards examination cost for each test.

The cost data will be collected in a MS-Excel divided into eight sections named as under:

i. Information about the facility: basic details of the facility will be collected.

ii. General information: which include data about working hours of the health facility

iii. Salary structure of the ANM as reported

iv. Details of Equipment: The cost of devices will be directly obtained from the manufacturers in the prescribed format. The format will include name of the device, unit price and expected life of the equipment. This data will be collected across the sites in Kolkata and Puducherry. The prices provided by the manufacturer will be considered for cost of screening.

v. Consumables: Under this section, details of consumables which includes materials and supplies issued, consumed, quantity used per test, and price per unit for every device will be collected in the facility.

vi. Details of the physical infrastructure: Under this section area, monthly rental price of 100 square feet place where the center is located and expenditure (if any) on renovation or construction of accessory items will be collected.

vii. Details about non-medical items: Name and quantity of functional non-medical items in each room will be physically observed by the researcher and reported.

viii. Activity time: Under this the respondents will be asked to report the activities which they perform and the time they spend routinely for the same. At both the sites the time which the ANM take for conducting the test will be estimated.

The costs will be presented as average values across each medical device. The proportion of cost distribution across human resources (ANM), equipment (device, charger and adapter), accessories (microcuvettes/strips), consumables (items used in the test), non-medical (items in examination room) and examination room (rental value) will also be presented.

Measurement of cost-effectiveness
Cost-effectiveness analysis will assess the relative efficiency of the invasive and non-invasive methods for detecting anemia. Standard protocols for conducting such evaluation of diagnostic tests would be used11. This will be reported as ‘correct diagnosis’ as the outcome measure. Correct diagnosis would be defined as ‘agreement of the result of the particular diagnostic
method with the gold standard’ or detection rate\(^5\). The detection rate will be the sensitivity of the devices i.e. ability of the devices to identify true positives. Since the priority of the national program is detection of severe anemia, we will consider the detection rates of anemia and severe anemia to calculate effectiveness.

The health-related quality of life (HRQoL) of patients will be measured at the time of enrolment into the study using the EQ-5D-5L questionnaire\(^1\).

Additionally, the user friendliness across key attributes (ease of use, efficiency in daylight, scope of subjective errors, portability, convenience to patient, interpretation of Hb results, need for power/battery, average time taken for performing one test, and expertise required) will also be analyzed.

General principles of cost-effectiveness will be applied to the results of costs and detection rate of each device\(^4\). The device with best accuracy results (sensitivity in this case) will be taken as the reference. Then it will be determined if this device was dominated by other devices. A dominated device is more costly, but less effective than another device. For non-dominated devices, the cost-effectiveness analysis will combine the unit costs per detection rate, i.e. the incremental cost effectiveness ratio (ICER).

The ICER will be calculated as: \([\text{Mean cost per test}} \times \text{device A} – \text{Mean cost per test}} \times \text{device B}] / [(\text{Detection rate}} \times \text{device A} – \text{Detection rate}} \times \text{device B}]\).

ICER values will be presented using costs and detection rates of each device, and separately for detection of anemia and severe anemia.

The results of cost-effectiveness analysis would be presented as incremental cost per detection rate of one method compared to the other. Results would be presented in a manner enabling easy comparison between all diagnostic techniques to assess relative efficiency.

**Long-term benefits of anemia screening**

The long-term benefits and cost-effectiveness of early detection of anemia comparing invasive and non-invasive methods will be analysed using decision analytical model, by quantifying the contribution of screening in preventing morbidities using data from Indian studies.

**User friendliness**

Laboratory technicians and ANMs will independently rate each of the following criteria: ease of use, efficiency in daylight, scope of subjective errors, portability, convenience to patient, interpretation of Hb results, need for power/battery, average time taken for performing one test, and expertise required, on a scale of 1 (very poor) to 5 (excellent) for each device method. The total score across each of these parameters for laboratory technicians and ANMs will be used to identify user friendliness for each method (maximum score for each method).

**Sensitivity analysis**

One-way and probabilistic sensitivity analysis will be conducted using lower and upper bound of sensitivity values of each device, and other cost parameters (e.g. accessories, consumables etc.). Sequential tornado analysis will be presented using ICER values from the sensitivity analysis in order to rank-order the different variables that influence the cost per detection rate values\(^11\). Scenario analysis will be conducted for detailing the annual costs conducted by 1 ANM in a health facility for detecting anemia and severe anemia.

**Conclusion**

This paper constitutes a protocol for the costs and cost effectiveness of medical devices in a LMIC. The evidence generated will contribute significantly by lending evidence on the use of cost effectiveness to influence decisions.

**Data availability**

No underlying data are associated with this study.

**Extended data**

This project contains the following extended data:

- Annexure 1.xlsx (step-down costing methodology).
- Annexure 2.xlsx (parameters proposed to be used in data analysis).

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Grant information

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References

Open Peer Review

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The study protocol is written well. However, authors need to mention clearly how this protocol is different from the one published in 2018. This has been referred as: Neogi S, Negandhi H, Sharma J, et al.: Diagnostic efficacy of digital hemoglobinometer (TrueHb), HemoCue and non invasive devices for screening patients for anemia in the field settings-a proposal. Indian J Comm Health. 2018; 30(Supp): 86–88.1 Beside comparing three devices in previously published protocol, what other generic features are included in this protocol. Currently, to me, its just an updated version of previously published protocol and thus should not be indexed again. Instead authors should have mentioned what progress they have made since publishing their previous protocol and how many individuals have been screened until now.

In the methods section, canvassing of EQ-5D questionnaire is mentioned but in cost-effectiveness analysis this information has not been used. It is not clear to me why this instrument is required (to measure changes in HRQoL or QALYs between individuals screened by invasive and non-invasive methods, which doesn't make any sense to me when individuals who are screened are not going to be followed-up).

More importantly, the very generic concept of Incremental Cost-Effectiveness Ratio (ICER) can't be applied here due to absence of follow-ups (i.e. no data is collected at two points in time). Authors can only compare cost per correctly detected screening outcome between four types of method/equipment instead of computing ICER.

Authors have not included details of costing information for enhanced training to field workers/ANMs to be used for various screening equipment in the clinical/community setting.

Finally, there is a huge difference in purchase prices between equipment and how these will be used in cost-effectiveness analysis is not clear to me. For instance within invasive method, the cost of Tru Hb equipment is 8-10 times higher than HemoCue. And if one is just comparing the purchase cost per correctly detected screening outcome within invasive method would be a terrible blunder. Therefore, one needs to account for the case loads as well as the mixed-use for varied purposes for an equipment during its lifetime or becoming obsolete.
I think these are serious issues in the published protocol and most things are replicated from the previously published protocol.

References

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Economic Evaluation of health intervention/service/program

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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