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Machine learning of blood haemoglobin and haematocrit levels via smartphone conjunctiva photography in Kenyan pregnant women: a clinical study protocol

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ABSTRACT

Introduction Anaemia during pregnancy is a widespread health burden globally, especially in low- and middle-income countries, posing a serious risk to both maternal and neonatal health. The primary challenge is that anaemia is frequently undetected or is detected too late, worsening pregnancy complications. The gold standard for diagnosing anaemia is a clinical laboratory blood haemoglobin (Hgb) or haematocrit (Hct) test involving a venous blood draw. However, this approach presents several challenges in resource-limited settings regarding accessibility and feasibility. Although non-invasive blood Hgb testing technologies are gaining attention, they remain limited in availability, affordability and practicality. This study aims to develop and validate a mobile health (mHealth) machine learning model to reliably predict blood Hgb and Hct levels in Black African pregnant women using smartphone photos of the conjunctiva.

Methods and analysis This is a single-centre, cross-sectional and observational study, leveraging existing antenatal care services for pregnant women aged 15 to 49 years in Kenya. The study involves collecting smartphone photos of the conjunctiva alongside conventional blood Hgb tests. Relevant clinical data related to each participant's anaemia status will also be collected. The photo acquisition protocol will incorporate diverse scenarios to reflect real-world variability. A clinical training dataset will be used to refine a machine learning model designed to predict blood Hgb and Hct levels from smartphone images of the conjunctiva. Using a separate testing dataset, comprehensive analyses will assess its performance by comparing predicted blood Hgb and Hct levels with clinical laboratory and/or finger-prick readings.

Ethics and dissemination This study is approved by the Moi University Institutional Research and Ethics Committee (Reference: IREC/585/2023 and Approval Number: 004514), Kenya's National Commission for Science, Technology, and Innovation (NACOSTI Reference: 491921) and Purdue University's Institutional Review Board (Protocol Number: IRB-2023-1235). Participants will include emancipated or mature minors. In Kenya, pregnant women aged 15 to 18 years are recognised as emancipated or mature minors, allowing them to provide informed consent independently. The study poses minimal risk to participants. Findings and results will be disseminated through submissions to peer-reviewed journals and presentations at the participating institutions, including Moi Teaching and Referral Hospital and Kenya's Ministry of Health. On completion of data collection and modelling, this study will demonstrate how machine learning-driven mHealth technologies can reduce reliance on clinical laboratories and complex equipment, offering accessible and scalable solutions for resource-limited and at-home settings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Unmodified smartphone cameras and machine learning approaches are used to non-invasively predict blood haemoglobin (Hgb) and haematocrit (Hct) levels from an easily accessible site—the conjunctiva.
- ⇒ Development and validation of the model are tailored to predict blood Hgb and Hct levels in a quantitative manner similar to clinical laboratory testing, rather than detecting anaemia as a binary outcome.
- ⇒ Study population is specifically designed to address healthcare disparities impacting Black African pregnant women.
- ⇒ Target gestation includes all three trimesters with approximately equal representation from each trimester.
- ⇒ Due to the observational nature of the study, there is no intervention administered.

INTRODUCTION

The prevalence of anaemia remains high, affecting nearly one-quarter of the global population (1.92 billion) in 2021.[1–3] It is especially predominant among women of reproductive age in low- and middle-income countries, impacting 45% of pregnant and

40% of non-pregnant women.[4 5] In East Africa, it is estimated that 42% of pregnant women are anaemic.[6] In Kenya, cases among pregnant women surged from 55 539 in 2016 to 295 642 in 2019.[7] At the country's largest maternity unit, 57% of women in their second and third trimesters were affected by anaemia.[8] Even in the USA, more than 40% of females aged 12 to 21 years are estimated to have iron deficiency or iron-deficiency anaemia.[9]

Anaemia is a major contributor to maternal and neonatal mortality. Moderate to severe anaemia exacerbates critical conditions such as haemorrhage and sepsis during pregnancy.[10 11] Anaemia-associated pregnancy complications include preterm labour, low birth weight, stillbirth and neonatal mortality, all of which increase the risk of adverse outcomes for both mothers and newborns.[10 11] Maternal anaemia during pregnancy can have long-term consequences on a child's neurocognitive development.[12] Importantly, interventions are available to address anaemia even in resource-limited settings, including dietary modifications with iron-rich foods, supplementation with iron, folic acid, vitamin B_{12}[13–16] and blood transfusion in cases of severe anaemia.[17]

Anaemia management during pregnancy relies on the ability to quantitatively assess blood haemoglobin (Hgb) and haematocrit (Hct) levels in a timely manner. The main challenge in resource-limited settings is that anaemia during pregnancy is often not detected or is detected too late. The World Health Organization (WHO) recommends at least one blood Hgb test per trimester. Unfortunately, women in these settings often lack access to recommended diagnostic testing. For instance, in Kenya, only 17% of women had access to minimally adequate delivery care with routine antenatal tests.[18] Other countries in sub-Saharan Africa and South Asia face similar challenges. However, there are only a limited number of studies using non-invasive or point-of-care (POC) blood Hgb tests specifically for pregnant women in general.[19–22]

The gold standard for diagnosing anaemia is a clinical laboratory blood Hgb test to measure Hgb content in the blood (grams per decilitre).[23–26] However, venous blood draw-based Hgb tests have several limitations, including the need for specialised equipment (haematology analyser), pain, discomfort, risk of haematoma, infection and iatrogenic blood loss.[27] Non-invasive and cost-effective blood Hgb testing technologies remain limited.[28–32] For example, Masimo and OrSense devices require expensive specialised equipment available only in advanced hospital settings.[33–35] Alternatively, POC blood analysers that use capillary blood sampling (finger-prick testing) (eg, Abbott i-STAT, HemoCue and VERI-Q) are commercially available, but require environmentally sensitive cartridges with short shelf lives.[36 37]

Non-invasive POC blood Hgb assessment technologies have received considerable attention,[38] including HemaApp,[39] fingernail mobile app,[40–42] fingertip devices,[43 44] lip mucosal imaging[45] and palpebral conjunctiva smartphone imaging.[46–59] Specifically, the palpebral conjunctiva, a common site for assessing paleness and anaemia, offers the advantages of easy, non-contact imaging without surface pressure.[60] Its underlying microvasculature is unaffected by skin pigmentation (eg, melanocytes), removing the need for personal calibration.[61] In addition, the conjunctiva may not be easily recognisable, providing enhanced privacy protection.[62 63]

Objectives and hypothesis

The primary objective of this study is to develop and validate a mobile health (mHealth) computational model using machine learning to accurately and precisely predict blood Hgb and Hct levels in Black African pregnant women using photos of the conjunctiva acquired by a smartphone camera. The central hypothesis is that blood Hgb levels can be reliably predicted from red-green-blue (RGB) images of the conjunctiva in a non-invasive manner with performance comparable to POC finger-prick testing. First, we will capture high-quality conjunctiva photos under diverse photo acquisition settings from pregnant women across all three trimesters, encompassing a broad range of Hgb and Hct levels. Second, we will refine the mHealth prediction model and compare the predictions with conventional blood Hgb and Hct testing methods. Given the physiological changes during pregnancy that vary by trimester, this study emphasises acquiring data from all stages to ensure reliable predictions.

METHODS: PARTICIPANTS, STUDY PROCEDURES AND OUTCOMES

Study design

This is a single-centre, non-interventional, cross-sectional and observational study involving the acquisition of photos of the conjunctiva alongside conventional blood Hgb and Hct tests. Relevant clinical data related to the participant's anaemia status will also be collected. The blood Hgb and Hct values computed from the mHealth prediction model will not be used to guide interventions or diagnostics. All data collection will take place during a single study visit. Thus, a retention plan is not required.

Setting and recruitment

Figure 1 outlines the setting, enrolment and data collection. The primary clinical setting is the Maternal Child Health (MCH) clinic at Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya, in collaboration with the Academic Model Providing Access to Healthcare (AMPATH). MTRH is the second-largest referral hospital in Kenya. The MCH clinic at MTRH has 20 obstetricians and over 40 residents who care for approximately 900 pregnant women per month. AMPATH also provides a framework for sustainable research and scalable healthcare access. AMPATH is a partnership between the Moi University School of Medicine, MTRH and a consortium of US institutions.

Study participants

Our study will recruit volunteer pregnant women receiving antenatal care at the MCH clinic, targeting

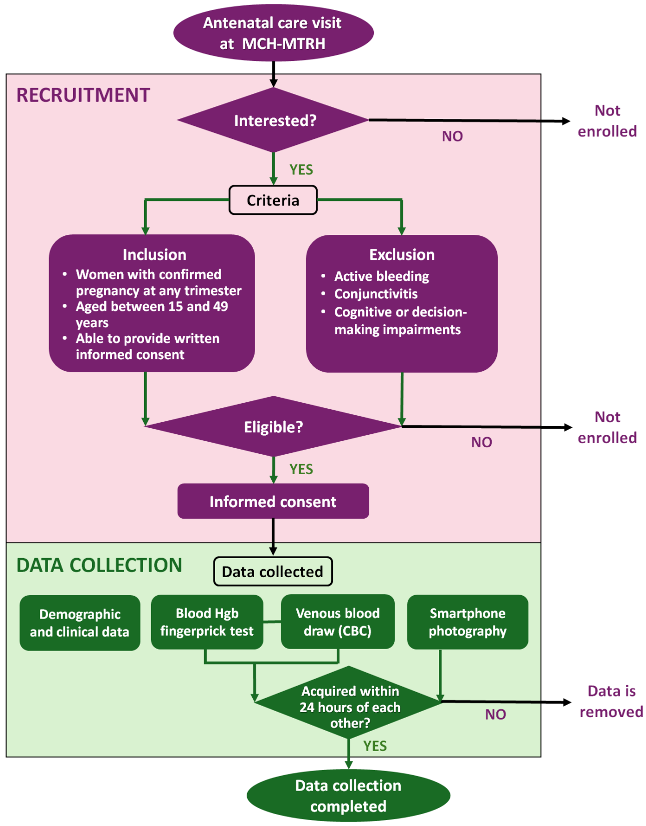

Figure 1 Flowchart of recruitment, enrolment and data collection. This single-centre, cross-sectional and observational study leverages existing antenatal care services for pregnant women aged 15 to 49 years at the Maternal Child Health (MCH) clinic at Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya. CBC, complete blood count; Hgb, haemoglobin.

600 participants, with approximately 200 women per trimester, aged 15 to 49 years. Because the mHealth prediction model for blood Hgb computation relies on machine learning, conventional statistical methods are not directly applicable for estimating power and sample size. However, our estimates are conservative based on the previous study at MTRH.[49] For 200 participants per trimester, the 95% confidence intervals (CIs) for the correlation coefficient between the mHealth and clinical laboratory blood Hgb levels are expected to range from 0.09 to 0.13, assuming a correlation coefficient of 0.85. Similarly, the 95% CI for the intraclass correlation coefficient (ICC) will range from 0.07 to 0.13, assuming an expected ICC of 0.85. To mitigate the risk of overfitting, a separate masked testing dataset comprising 30% of the total data will be used. This testing dataset will be independent of the training dataset, which consists of the remaining 70% of the data.

Inclusion and exclusion criteria

The study inclusion criteria (figure 1) are as follows:

1. Women with confirmed pregnancy at any gestational stage (first, second or third trimester).
2. Aged 15 to 49 years.
3. Able to provide written informed consent.

Participants will be excluded if they have hypotension, active or ongoing bleeding, conjunctivitis (or visible conjunctival inflammation), trauma or infection affecting the eyes or eyelids, or if laboratory blood Hgb and Hct testing may be delayed beyond 24 hours after photography.

Overall procedure

If the patient agrees to participate in this study, study personnel will provide simple instructions on how to gently pull down the inner eyelid using the participant's index finger. Then, the study personnel will hold a colour reference chart on the patient's forehead and capture photos of both the left and right eyes using three different smartphone models. The total time required for imaging is approximately 5 minutes. Clinical data will also be collected, including laboratory Hgb and Hct values from blood samples drawn within 24 hours before or after the conjunctiva photo timestamp. The study personnel will complete a clinical data collection sheet and attach the results of the clinical laboratory test. All photos and associated data will be submitted through a customised data collection application (app).

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Timepoints for data collection

All data collection for the study will take place during a single visit, lasting approximately 10 minutes, with no follow-up required. During the visit, consented participants' baseline demographic and clinical data will be recorded on a study form. Smartphone photography and venous blood draw and/or finger-prick testing will then be performed. To ensure data reliability, smartphone photography must occur within 24 hours of the blood draw. Once data collection is complete, all information will be uploaded to a customised data collection app linked to a Health Insurance Portability and Accountability Act (HIPAA)-compliant server, where it will be organised and processed for analysis.

Demographic and clinical data

Demographic data collected from participants will include date of birth, marital status and highest level of education completed. Clinical data will cover details of the current pregnancy, obstetric history, medical and surgical history (including blood pressure), family history and antenatal profile.

Clinical laboratory blood Hgb test and/or finger-prick test

We will assess the results of complete blood count (CBC) tests, specifically measuring clinical laboratory-based blood Hgb and Hct levels using the Beckman Coulter AcT 5diff or a similar device from samples collected on the same day. CBC tests will be conducted at a clinical reference laboratory certified by the College of American Pathologists' External Quality Assurance Program.

In addition, capillary blood sampling using VERI-Q will be performed either before or after photographing the conjunctiva.

Smartphone conjunctiva photographing

Photos acquired with a digital (or smartphone) camera exhibit different colours depending on smartphone models, image formats and light conditions.[64,65] To develop an mHealth prediction model that is accurate under diverse data acquisition conditions, the photo acquisition protocol will incorporate a custom-made colour reference chart,[54] different smartphone models (Google Pixel 5, Samsung Galaxy A52 and Samsung Galaxy S21) and file formats. The colour reference chart, roughly the size of a business card, is designed to support colour recovery with reduced dependence on photo acquisition settings by being physically captured within each photo. Instead of commercially available colour reference charts (eg, Macbeth ColorChecker, ColorChecker Classic Mini), we will use a custom-designed colour chart that can be mass-printed with a standard inkjet printer. Due to sanitation requirements and participant tracking, disposable colour charts are necessary. However, the high cost of commercially available options makes them impractical for single-use applications.

For Samsung Galaxy S21, both DNG (also known as RAW) and JPEG formats will be generated using Pro Mode. Google Pixel 5 and Samsung Galaxy A52 will use a third-party app (Adobe Lightroom or Halide Mark) to capture photos in DNG format. As a key specification of smartphone cameras, we evaluated the spatial resolution of the three different smartphone models using the edge method in a laboratory setting.[66] The measurements were conducted at a typical distance of 100–150 mm between the camera and the participant's eye. Google Pixel 5 has a spatial resolution of 137 µm, while Samsung Galaxy S21 has a spatial resolution of 172 µm. Despite being a lower-end smartphone, the Samsung Galaxy A52 has a spatial resolution of 108 µm.

Data collection mobile app

We developed a mobile app for Android to facilitate the collection and transfer of photos (figure 2). This app is specifically designed to ensure proper use of the colour reference chart during photo acquisition. It allows study personnel to upload photos taken with the smartphone camera, requiring them to complete form fields before selecting photos from the smartphone gallery for upload. All data, including the photos collected, are stored on a HIPAA-compliant cloud server and can be securely accessed through a high-security portal. Importantly, the data collection app is designed to efficiently handle large photo files in the DNG (RAW) format. The DNG format reduces non-linear rendering and image compression.[65] With a 10-bit colour depth in each RGB channel, DNG allows for $2^{10\times3}$ combinations of RGB values. In contrast, JPEG with an 8-bit colour depth ($2^{8\times3}\approx$16.77 million colours) involves non-linear filtering and image compression. As a result, DNG photos are substantially larger than JPEG photos. Recent smartphone models support direct access to the DNG format either in the default camera settings or through third-party applications (eg, Adobe Lightroom or Halide Mark). The app also enables photo uploads even when network connectivity is interrupted; it

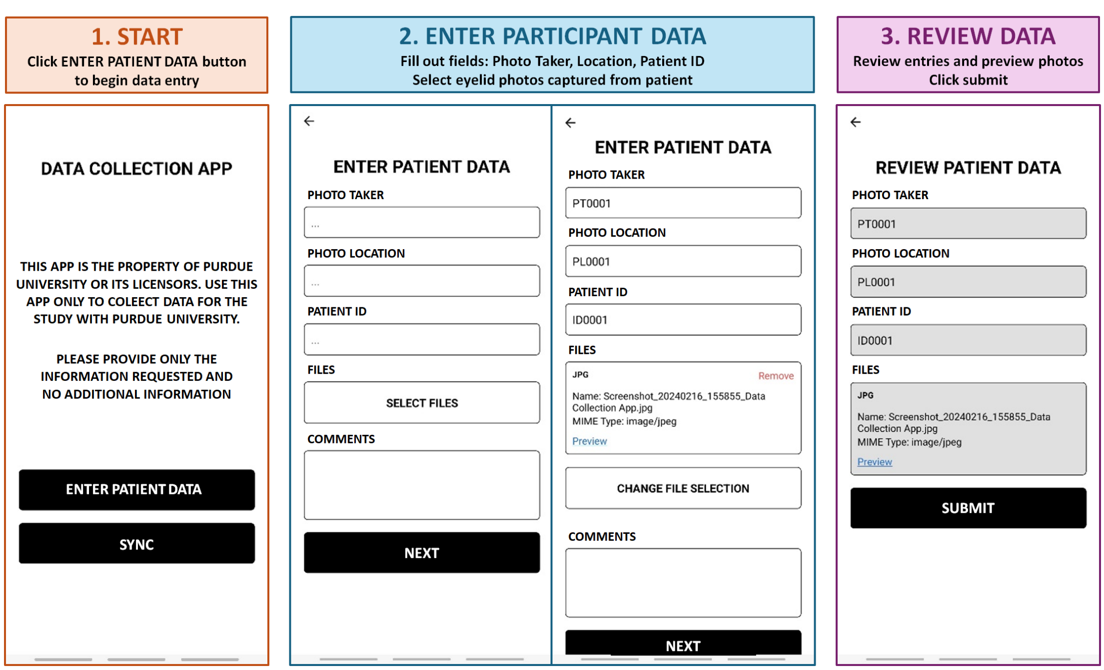

Figure 2 Representative screenshots of the customised data collection mobile app for Android smartphones. The app's flow and processes are designed to efficiently manage large photo files. The user interface enables study personnel to upload photos to a Health Insurance Portability and Accountability Act (HIPAA)-compliant cloud server, which can be securely accessed through a high-security portal.

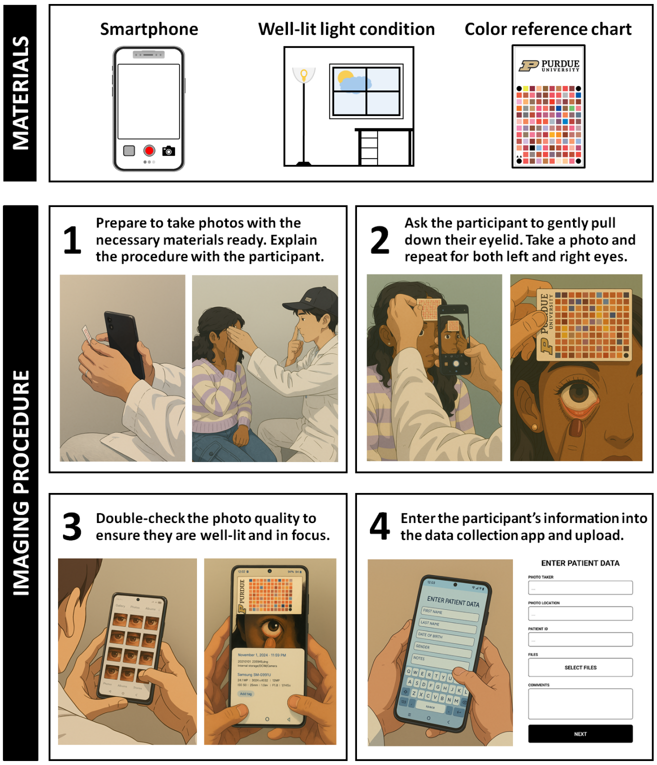

Figure 3 Photo acquisition instructions and procedure. Preparation materials and instructional examples guide study personnel in quickly capturing high-quality photos of the participant's conjunctiva. The original demonstration photos, featuring the authors performing the procedure, are further rendered using ChatGPT.

automatically uploads photos from a temporary folder in the background, one photo at a time, to reduce the data payload. Once all photos are uploaded, the temporary folder is deleted from the device.

Smartphone photographing procedure

Figure 3 summarises the photo acquisition protocol.

1. Direct the participant to sit facing the ceiling light source. Adjust the room brightness if necessary to ensure clear photos without shadows or glares.
2. Write the participant identifier (ID) and date on the colour reference chart to distinguish photos.
3. Ask the participant to remove glasses or any objects that may obstruct the forehead.
4. Rehearse pulling down the inner eyelid with the participant to ensure adequate and accurate exposure.
5. Hold the chart against the participant's forehead with one hand. Instruct the participant to use their fingertips to pull down the inner eyelid.
6. Ensure the colour reference chart is horizontally aligned with the participant's eye and visible in the camera view.
7. While holding the chart with one hand, use the other hand to operate the smartphone.
   a. Ask the participant to look up at the ceiling while exposing the conjunctiva.
   b. Include both the entire colour reference chart and the conjunctiva within the frame.
   c. The colour reference chart must remain horizontal.
   d. Avoid covering the chart with fingers or casting shadows on it.
   e. Keep the chart flat without bending.
   f. Ensure consistent lighting; the colour reference chart and conjunctiva should have similar brightness.
8. Use the smartphones in this sequence: Samsung Galaxy A52, Google Pixel 5 and Samsung Galaxy S21.
   a. Capture four photos of the left conjunctiva with each smartphone.
   b. Capture four photos of the right conjunctiva with each smartphone.
9. Input the participant's information and upload the photos to the data collection app (figure 2).

Model refinement and optimisation

The mHealth prediction model will be refined and optimised for the target population, as it has not yet been tailored to this group. The current version of the mHealth model comprises four submodules[47 49 52–54 67–69]:

1. Colour correction: extracts absolute colour values of the conjunctiva, ensuring consistency across different smartphone models and light conditions.[68]
2. Automated segmentation: automatically identifies and delineates the conjunctival region of interest.[67 69]
3. Hyperspectral learning (also referred to as spectral reconstruction, spectral super-resolution or spectral reflectance estimation): reconstructs high-resolution spectral data from RGB values of photos captured by smartphone cameras.[49 53]
4. Blood Hgb and Hct content computation: estimates blood Hgb and Hct levels using the reconstructed hyperspectral data.[47 49]

To mitigate the risk of overfitting in the blood Hgb and Hct content computation, photo data will be divided into training (70% of participants) and testing (30%) datasets based on participant IDs. The photos from the same participants will be assigned exclusively to either the training or testing datasets to prevent data leakage. Cross-validation will be conducted to evaluate the model's performance across different subsets of the data. It should be noted that colour correction, automated segmentation and hyperspectral learning are not subjected to training, as these processes were already completed using separate data from our previous studies.[47 49 52–54 67–69] This compound machine learning model integrates domain knowledge (eg, tissue optics and computer vision) into the learning process. Notably, this is designed to mitigate the constraints of relatively limited data. It allows the model to be trained effectively with a limited clinical dataset, addressing the limitations of purely data-driven methods.[70 71]

Performance evaluation

To assess the performance of the mHealth model compared with clinical laboratory blood Hgb, Hct and/or finger-prick blood Hgb values, we will perform the following analyses using a testing dataset or cross-validation methods.

1. Linear correlation analysis: Quantifies the strength of the relationship between mHealth and clinical laboratory blood Hgb and Hct values.
2. Bland–Altman analysis: Uses multiple measurement pairs to evaluate whether mHealth blood Hgb and Hct values align reliably with clinical laboratory results, returning bias and 95% limits of agreement.
3. ICC analysis: Assesses the reliability of mHealth blood Hgb and Hct values, focusing on reproducibility—the ability of different users to obtain consistent results. Given that multiple smartphones will be used to capture photos from the same participant, we will emphasise inter-reliability (reproducibility), which measures variation across different users evaluating the same group of participants.
4. Paired t-tests: Determines whether blood Hgb and Hct values obtained from the left and right conjunctivae are statistically identical.

In addition, we will follow the STARD (Standards for Reporting of Diagnostic Accuracy Studies) guideline[72 73] for assessing the diagnostic performance of our mHealth prediction model as well as the TRIPOD+AI (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis + Artificial Intelligence) guideline[74] for reporting our machine learning-based prediction study.

ETHICS AND DISSEMINATION

Ethics approval and consent

This study is approved by the Moi University Institutional Research and Ethics Committee (Reference: IREC/585/2023 and Approval Number: 004514), Kenya's National Commission for Science, Technology, and Innovation (NACOSTI Reference: 491921) and Purdue University's Institutional Review Board (Protocol Number: IRB-2023-1235). Our study involves recruiting participants from vulnerable populations, specifically pregnant women, including some who are emancipated or mature minors. In Kenya, pregnant women aged 15 to 18 years are considered emancipated or mature minors, allowing them to provide informed consent independently, without parental involvement. The informed consent form is available in both English and Swahili, the native and widely spoken language in Kenya. Study personnel responsible for communicating with participants are fluent in both languages to ensure clear and effective communication.

Confidentiality, data storage and security

All study data will be stored and accessed in compliance with HIPAA and the Kenya Data Protection Act, 2019.

Specifically, photos will be labelled with the participant ID, smartphone model and left/right. Demographic and clinical information recorded on paper forms by site personnel will be scanned using the smartphone. Data will be uploaded via a custom data collection app developed for this study. This app transmits data to a secure Amazon Web Services server, which is HIPAA-compliant. Access to the server is restricted to study investigators and authorised personnel. Computer records will be stored on password-protected systems, and paper records will be secured in locked cabinets accessible only to authorised study personnel.

Dissemination

We will disseminate results through publications in peer-reviewed journals and presentations at the participating institutions, including Moi Teaching and Referral Hospital, and Kenya's Ministry of Health. This study primarily focuses on developing a machine learning model for blood Hgb and Hct assessments. Our next steps are to scale the project towards developing a minimally viable product—a functional mobile app for bloodless, quantitative blood Hgb assessment—for larger clinical trials. Building on further collaboration with healthcare philanthropy organisations, we plan to evaluate the effectiveness and implementation of the mHealth prediction model through pilot studies and real-world applications.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

DISCUSSION

Digital health technologies have experienced rapid growth and are now widely adopted across various clinical settings. In particular, photos captured with mobile devices (eg, smartphones and tablets) have emerged as pivotal tools in digital health applications, including telemedicine and mHealth.[75–78] Clinical photos are instrumental in healthcare diagnostics, monitoring and management, especially in at-home healthcare and resource-limited settings where traditional equipment may be scarce. Consequently, healthcare professionals increasingly regard smartphones and tablets as indispensable components of modern healthcare practice. However, guidelines on conducting clinical studies using high-quality clinical photos from mobile devices are often not available.

This protocol paper outlines a clinical study exploring the use of smartphone cameras as diagnostic tools. Building on prior research demonstrating the diagnostic potential of clinical photography, this study leverages smartphone technology to improve access to high-quality clinical images. Furthermore, advancements in machine learning and artificial intelligence enhance the diagnostic accuracy of photo-based analyses. The protocols and procedures described here aim to extend the reach of diagnostic imaging in low-resource environments, where traditional diagnostic tools are often inaccessible. These methods may also be applicable to other clinical studies requiring high-quality imaging.

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Contributors HS, SMP, SK, JWL and YLK developed the data acquisition protocol and instructions and designed the mobile app for data collection. EK and EN provided feedback on the data acquisition process and collected data in the clinical setting. HS, SMP, SK, JWL, SGH and YLK reviewed data quality and provided feedback to the Kenya team. PJL and JWL assisted with study management and logistics. EOW, MCW and YLK obtained ethics approval. EOW led the clinical aspects, including subject enrolment, as the site PI for this study. MCW and YLK revised the protocol and study design. YLK conceptualised the study and provided mentorship and academic supervision. HS generated the figures. HS and YLK wrote the manuscript, with JWL, EOW and MCW providing feedback. YLK is the lead corresponding author and guarantor. For figure 3, the original demonstration photos, featuring the authors performing the procedure, are further rendered using ChatGPT. This is to follow the BMJ guideline on the usage of identifiable photos.

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Competing interests YLK is a founding member of HemaChrome LLC.

Patient and public involvement Patients and/or the public were not involved in the design or conduct of this research study.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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