SCHOOL OF PUBLIC HEALTH

COLLEGE OF HEALTH SCIENCES

UNIVERSITY OF GHANA

IMPACT OF PERIOPERATIVE MALARIA SCREENING AND TREATMENT ON SURGICAL OUTCOMES AT THE EASTERN REGIONAL HOSPITAL, KOFORIDUA: A SINGLE-BLIND RANDOMISED CONTROLLED TRIAL

BY

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Declaration

I, Forster Amponsah-Manu hereby declare that this trial was carried out by myself under the supervision of Dr Alexander Manu and Dr Samuel O. Sackey, with the exception of duly acknowledged references. I further declare that this work has not been presented elsewhere for any other degree.

…… Date: 15th December, 2023

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Date: 15th December, 2023

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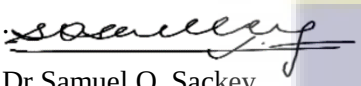

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Dedication

This work is dedicated to the Almighty God, my supervisors, mentors, house officers, the entire staff and clients of Eastern Regional Hospital, and the entire family and friends of Amponsah-Manu.

Acknowledgement

I humbly acknowledge the endless list of people and organizations who made it possible for this incredible dream to come to reality. I simply say “THANK YOU AND GOD BLESS YOU”.

Abstract

Background: Although there are suggestions that perioperative malaria infection affects surgical outcomes, screening and treatment is not done routinely in the practice of surgery in Ghana. This study examined the impact of perioperative malaria screening and treatment on surgical outcomes in the Eastern Regional Hospital, Koforidua.

Methodology: A single-blind randomised controlled trial was conducted. Patients admitted for various surgeries were randomised to either undergo perioperative screening for malaria and treatment if positive, or to a control arm where no screening was done. All participants were followed-up to 30 days' post-operation to document the incidence of adverse surgical outcomes. The differences in incidences of the outcomes were analysed by intention to treat.

Results: In total, 443 patients (226 interventions and 217 controls) with various indications for surgery were enrolled between August and November, 2022. Ten (4.4%) in the intervention arm screened positive and were treated for malaria. Overall, 20% (88/443) developed poor surgical outcomes. There was borderline evidence of a 27% risk reduction in the intervention compared to the controls, with a possible 50% reduction as well as 7% increase in the risk of poor surgical outcomes (RR=0.73, 95%CI: 0.50-1.07, p=0.1). After adjusting for residual confounding, there was a statistically significant 67% reduction in the risk of prolonged hospitalisation for participants in the intervention compared to the control arm (aRR=0.33; 95% CI: 0.12-0.85; p=0.022).

Conclusion: Prevalence of malaria among surgical patients at the Eastern Regional Hospital was low. However, there is suggestion that screening and treating malaria may improve surgical outcomes.

Keywords: Impact, Perioperative, Malaria, Screening, Treatment, Surgical Outcomes.

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Definition of terms

Surgical outcomes: Surgical outcomes refer to operation results, consequences or aftermath of a disease following a surgical intervention. These results may include complications (such as surgical site infection, hemorrhage and death), time taken to recover from the disease, number of days required to stay in the hospital and whether or not patient required re-admission during a specified post-operative period after discharge.

Surgical Site Infection: Is an infection that occurs at or near surgical incision within 30days of operative procedure, or within 90 days if foreign material is surgically placed at the site (Borchardt & Tzizik, 2018). The infection may be superficial, characterized by reddening of overlying skin, local warmth and/or unusual pains at the site of incision or may be deep where tissue beneath the skin is involved and/or the area of the organ(s) involved in the main procedure (Centers for Disease Control and Prevention (CDC), 2010).

Length of stay: The number of days a patient stays in a hospital after surgery. This does not include days' patient stays on account of difficulty in settling bills. If patient stays beyond the average length of stay for a specific surgery, **prolonged length of stay** is said to have occurred.

Readmission rate: The return of a patient to inpatient hospital care shortly after discharge (typically within 30 days of discharge).

Perioperative Malaria Screening: A blood test that is performed either before or during surgery on a patient undergoing surgery, to look out for the presence of malaria parasites. This may be done by the use of rapid diagnostic test (RDT) kit and/or by the use of microscope.

List of Abbreviations

ACT	Artemisinin-based Combination Therapy
ASA	American Society of Anaesthesiology
BCIH	BEIT CURE International Hospital
BF for MPs	Blood Film for Malaria Parasites
CDC	Centres for Disease Control and Prevention
DALYs	Disability Adjusted Life Years
ERHK	Eastern Regional Hospital, Koforidua
GHS-ERC	Ghana Health Service-Ethics Review Committee
ITT	Intention-to-treat
LOS	Length of Stay
PLOS	Prolonged Length of Stay
PMI	President's Malaria Initiative
RDT	Rapid Diagnostic Test
SSI	Surgical Site Infection
WHO	World Health Organisation

CHAPTER ONE

1.0 Introduction

1.1 Background

The essence of surgical care in global public health cannot be overemphasized and the need for surgery in the clinical setting has increased due to epidemiological transition of diseases. The global volume of surgery has risen substantially from 226.4 million in 2004 to 312.9 million operations in 2012 (Weiser et al., 2016). Surgery can treat up to 11% of the global disease burden, despite the challenge associated with underreporting in low- and middle-income countries (LMICs) (Debas et al., 2015). More importantly, the burden (in Disability-adjusted life years (DALYs) per 1000 people) of surgically treatable conditions is highest in Africa (Ozgediz et al., 2008).

Surgical outcomes refer to the results of a surgical operation and includes mortality and morbidity, as well as length of stay, readmission, recovery time, operative numbers, repeat rates, etc. (Chou et al., 2015). Factors such as type, timing and duration of surgery, comorbidities and infections may impact surgical outcomes (Peiffer et al., 2020). However, the determinants of postoperative outcomes may vary with socio-economic class (Peiffer et al., 2020). Low and middle-income countries have peculiar factors contributing to surgical outcomes.

In Ghana, among pediatric patients at the Eastern Regional Hospital, Peiffer et al. (2020) reported that malaria infection is linked to poor surgical outcomes. Complication rates, particularly poor surgical wound healing, were found to increase with preoperative malaria infection and they reported that malaria infection increased a child's risk of 90-day hospital readmission (Peiffer et al., 2020).

Malaria is an infectious disease that is endemic in sub-Saharan Africa, including Ghana. *Plasmodium falciparum* is associated with a severe form of the disease that results in high mortality and severe morbidity especially among children. Malaria is transmitted through the bite of an infected female Anopheles' mosquito. Rarely, it may be transmitted via blood transfusions, organ transplant and trans-placental from mother to child (in-utero).

Malaria symptoms include fever, chills, malaise, headaches, myalgia, nausea and vomiting and occur within a spectrum from mild (uncomplicated) to life-threatening disease. The mild symptom is often further classified as an uncomplicated form of malaria and is usually treated on an outpatient basis. Severe malaria involves severe symptoms and signs that require admission and are associated with high morbidity and mortality (Centers for Disease Control and Prevention (CDC), 2007). Currently, the 1st line treatment for uncomplicated malaria is a 3days course of oral artemisinin-based combination therapy (ACT). Parenteral artemisinin therapy, such as Artesunate, is reserved for severe cases (World Health Organization (WHO), 2015).

In surgical practice, it is recommended that acute episodes of symptomatic malaria should be resolved before any elective surgery (Bashford & Howell, 2017). It is, however, unknown if asymptomatic malarial parasitaemia has any impact on surgical outcomes (Soltanifar et al., 2015).

1.2 Problem statement

Burden of malaria is high in Ghana accounting for 2.1% of global malaria cases and 1.9% of global malaria deaths (https://www.severemalaria.org/). Malaria has severe effects on all body systems that includes the blood and circulation, renal, hepatic, respiratory, cardiovascular and nervous systems and therefore could pose challenges to outcomes of surgery and anaesthesia (Soltanifar et al., 2015).

Preoperative malaria infection is an actionable independent predictor of readmission in the pediatric surgical population in Ghana (Peiffer et al., 2020). Malaria's relationship with surgery is bidirectional: whilst malaria is a leading cause of perioperative hyperpyrexia, increases the rate of surgical site infections, prolongs postoperative recovery, surgery can also cause reactivation of dormant malaria (Eipe, 2004; Sundet et al., 2004).

Meanwhile, adverse surgical outcomes pose a significant socio-economic burden on patients, families, communities and health systems globally particularly in low-middle-income countries like Ghana. If perioperative malaria results in higher incidence of adverse surgical outcomes including complications and re-admissions, it will constitute a significant drain on the existing limited health infrastructure and resources which is avoidable by simple screening and treatment. However, malaria screening is not routinely done preoperatively.

There is biologic plausibility of substantial benefit in screening for malaria in the surgical patient based on the endemicity of the disease and the system wide effects on the infected person. Literature on the malaria and its effects on surgical outcomes were mainly from case reports and small sample observational studies carried out predominantly in the pediatric populations (Peiffer et al., 2020). These studies, by their design, provide poor quality scientific evidence and lack external validity and extrapolation to all surgical patients.

Therefore, the purpose of this study was to determine impact of perioperative malaria screening and treatment on surgical outcomes, and to contribute high quality evidence in support for the need for policy change in surgical practice.

1.3 Justification

Despite the enrolment of many interventions to improve surgical outcomes by WHO and its relevant stakeholders, more attention is required on some peculiar factors associated with poor surgical outcomes in sub-Sahara Africa.

Given that a link has been identified between parasitaemia of highly endemic disease (malaria) and poor surgical outcomes, further research is essential to establish strong evidence for action/intervention. The findings of this study may inform policymakers to formulate perioperative malaria screening policy when designing plans to improve surgical outcomes in Ghana and even Africa. This will go a long way to reduce the economic burden on patients and families, and there will be less stress on our limited health resources.

1.4 Conceptual framework

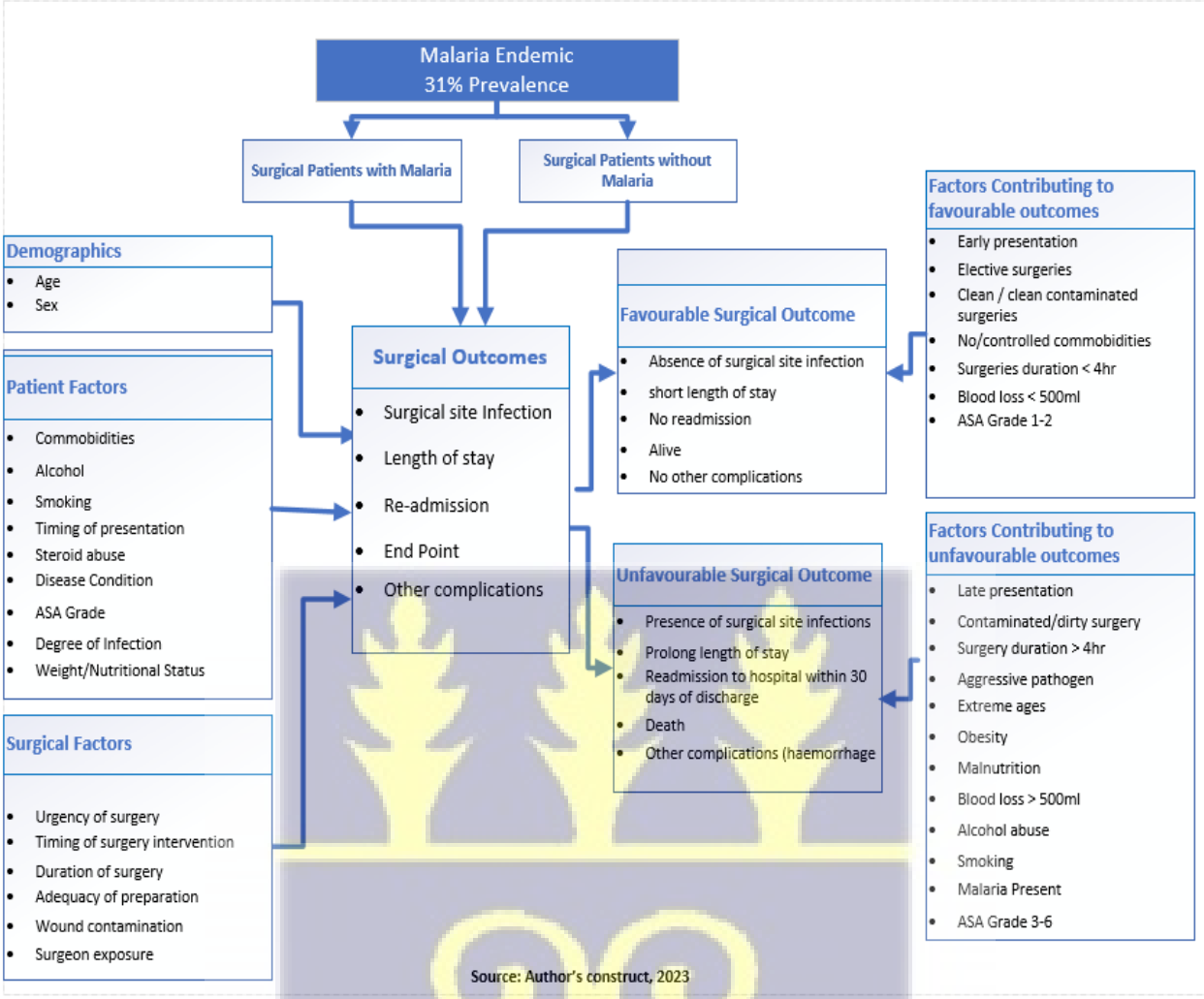

Figure 1.1: Conceptual framework on impact of malaria screening and treatment on surgical outcomes of patients undergoing surgeries

In the Eastern Region of Ghana, malaria prevalence is 31% of the general population (Ejigu & Wencheko, 2021). If samples of the population with surgical needs are screened and treated for malaria, it may impact on their surgical outcomes being it favourable or unfavourable. As listed in the above figure, patient's demography, patient factors and surgical factors, are each known to have an independent association with surgical outcomes.

1.5 Research hypothesis

The hypothesis tested in this study was that *perioperative malaria screening and treatment would lead to better surgical outcomes including less surgical site infection, short length of stay, low rate of re-admission and less mortality*.

1.6 Study objectives

1.6.1 General objective

The general objective of the study was to determine impact of malaria screening and treatment on surgical outcomes of patients undergoing surgeries at the Eastern Regional Hospital, Koforidua.

1.6.2 Specific objectives

The specific objectives were;

1. To determine proportion of surgical patients with malaria before surgery at the Eastern Regional Hospital, Koforidua.

2. To determine incidence of poor surgical outcomes (surgical site infection, prolonged length of stay, readmission, and death) among patients at the Eastern Regional Hospital, Koforidua.

3. To determine impact of perioperative malaria screening and treatment on the incidence of poor surgical outcomes at the Eastern Regional Hospital, Koforidua.

CHAPTER TWO

2.0 Literature review

The literature review has been organised in headings and sub-headings. The overall review of the literature has suggested that only few studies have explored this topic, and therefore the literature has been very limited.

Malaria is one of the leading causes of morbidity and mortality globally, contributing to significant health effects on adults and children. Over two million malaria cases with nearly 700,000 deaths, are recorded annually throughout the world (WHO, 2021). Over 90% of these deaths occur in Sub-Saharan Africa, with the most affected age group being children under-5 years (Roark, 2019). *Plasmodium falciparum* accounts for the vast majority of malaria disease burden, and the fatal form the world over (WHO, 2018). Recent data shows that malaria prevalence is 31% of the general population in the Eastern Region of Ghana (Ejigu & Wencheko, 2021).

Though malaria is primarily a medical condition, there are few reported cases of direct complications requiring surgical interventions. There is, however, a general scarcity of scientific information on the surgical aspect of malaria and its effects, directly or indirectly, on the surgical patient. Malaria related splenomegaly is the most common complication of the disease that requires surgical treatment (Gibney, 1990). Splenectomy is usually performed in this case for either hypersplenism or spontaneous rupture. Splenectomy, performed for any reason, increases susceptibility to pneumococcal infections and infections with *Haemophilus influenzae, Neisseria meningitides,* and many other bacteria (Shaw & Print, 1989). The effect of splenectomy on malaria causes more severe and fatal diseases even in people living in endemic regions (Garnham, 1970; Maharaj et al., 1982; Oster et al., 1980).

Acute pancreatitis has been reported in patients with severe *falciparum and vivax* malaria in India with a mortality rate of 20-30% (Abhilash et al., 2016; Mandal et al., 2011; Mohapatra & Gupta, 2011; Seshadri et al., 2008). These patients were found to have no other known risk factor for acute pancreatitis apart from malaria, and most of the reported cases had low parasite loads. Low immunity due to the non-resident in malaria-endemic regions and high parasitaemia in the immune patients have mainly been blamed for this rare but potentially fatal complication that may require a surgical intervention. The mortality associated with malaria-related acute pancreatitis has been linked with multi-organ failure in the reported cases (Abhilash et al., 2016; Mandal et al., 2011; Mohapatra & Gupta, 2011; Seshadri et al., 2008).

These rare surgical complications of malaria were reported in India's tropical geography, similar to Sub-Saharan Africa (Mandal et al., 2011). The most dominant Plasmodium species are *falciparum* and *vivax*, identical to those in Africa. However, India might have different endemicity patterns from that of Africa (Mandal et al., 2011). Therefore, the existence of those uncommon complications might not generally apply to the African environment. A local study might be conducted to ascertain if malaria can cause similar complications in our setting.

2.1 Prevalence of Malaria among Surgical Patients

In Malawi, a sub-Saharan African country with malaria endemicity, 14.7% of children admitted to BEIT CURE International Hospital (BCIH) for elective surgery between the years 2003 and 2010 had malaria parasitemia (Roca-Feltrer, et al., 2012). Twelve percent of pediatric surgery patients in the Eastern Region of Ghana had malaria in a retrospective comparative study conducted in 2020 (Peiffer, et al., 2020).

2.2 Incidence of Poor Surgical Outcomes

In a multicenter randomised controlled trial conducted in Ghana, Benin, Nigeria, Rwanda, South Africa, India and Mexico (FALCON trial), **Surgical Site Infection (SSI)**, the most common post-operative complication globally was reported to have occurred in 22.0% of all surgical patients (NIHR Global Research Health Unit on Global Surgery, 2021). Bediako-Bowan et al. (2020) reported a 10% incidence risk of surgical site infection among patients who had had a surgical procedure at the Korle-Bu Teaching Hospital.

In a study conducted in Ghana at the Komfo Anokye Teaching Hospital Kumasi, **death** was reported in 12% of all adult patients who underwent open abdominal operations on accounts of acute intestinal obstruction (Ohene-Yeboah, Adippah, & Gyasi-Sarpong, 2006). Post-operative death was also reported in 6.3% of patients who were operated for abdominal pain in Kumasi, Ghana (Ohene-Yeboah, 2006).

Hendriksen et al., (2018) reported 9.2% overall **30-day readmission rate** and 6.7 ± 5.5 days' average **length of stay** (LOS) following exploratory laparotomy procedures on adult and pediatric patients at the Eastern Regional Hospital Koforidua. In a study conducted in the Department of General Surgery, Worcester Hospital in South Africa, 2.87% unplanned readmission occurred within 30 days' post-op, and the median initial length of stay was 4days (Snyders et al., 2020). Tefera et al., (2020) defined **prolonged length of stay** (PLOS) as hospital stay above 75th percentile of expected length of stay for specific operations and 25.3% incidence of PLOS was reported in a prospective study conducted at the adult surgical ward of Jimma university medical center, Ethiopia.

In Nigeria, a study found postoperative complication rate among the participants to be 18.5% (95% CI 16.6–20.6) in the patient cohort, of which the commonest was infective complications (Osinaike et al., 2019).

2.3 Impact of Perioperative Malaria Infection on Surgical Outcomes

Preoperative malaria infection is an actionable independent predictor of readmission in the pediatric surgical population in Ghana (Peiffer et al., 2020). Malaria is a leading cause of perioperative hyperpyrexia, increases the rate of surgical site infections, prolongs postoperative recovery, and surgery can cause dormant reactivation of malaria (Eipe, 2004; Sundet et al., 2004).

2.4 Impact of Malaria Screening and Treatment on Surgical Outcomes

Perioperative fever with clinical signs and symptoms of malaria were reported in children with cleft lip and palate repairs, posing some diagnostic challenges (Roark, 2019). These children were tested and treated for malaria 3-to 4 weeks before their elective surgeries. There was a significant reduction in febrile episodes when the children were treated empirically for malaria 3- 7 days before surgery. The findings of this study cannot be generalized to all surgical patients because it was conducted in children under-5 years, with a small sample size of fewer than 40 patients. Also, the episodes of perioperative hyperpyrexia could have been due to other causes such as anaesthesia, drugs (Drugs.com (database online), 2018), postoperative infection and other tropical infections (Abba et al., 2011; WHO, 2015b).

2.5 Summary of Literature review

In summary, the prevalence of malaria among surgical patients in malaria endemic regions is significant. The incidence of poor surgical outcomes also remains significant especially in a low- to middle-income country like Ghana. Reports from few studies suggest that malaria has some

negative impact on surgical outcomes, and perioperative malaria screening and treatment may impact on the surgical outcome. However, these studies were limited to paediatric population with small sample size and limited scope of surgical outcome measured.

CHAPTER THREE

3.0 Methodology

3.1 Study design

This research was a single centre, single blind, parallel randomised controlled trial (RCT) where patients scheduled for surgeries at the Eastern Regional Hospital, Koforidua were randomly assigned (1:1) to intervention and control arms. The process flow diagram for the study is shown in figure 3.1.

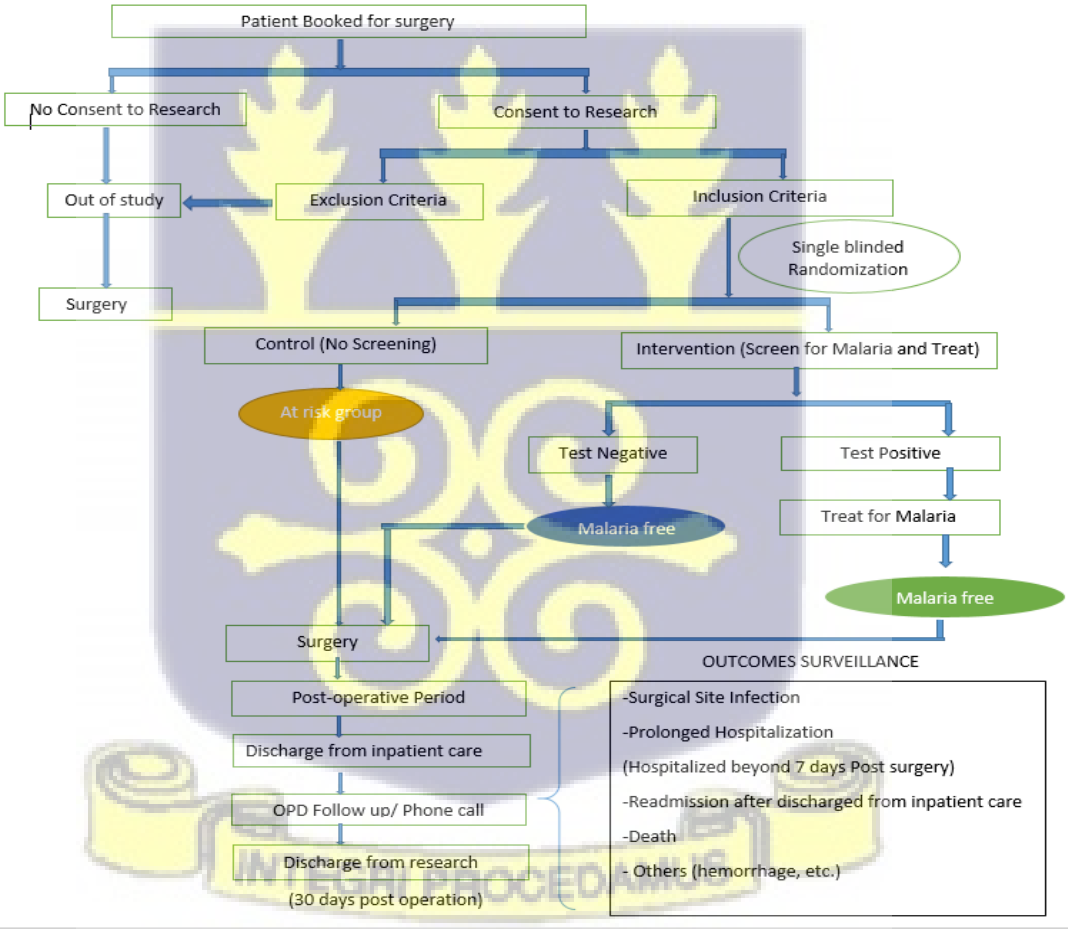

Figure 3.2: Flowchart showing the process of randomised controlled trial designed to assess impact of malaria screening and treatment on surgical outcomes

3.2 Study participants

Participants were patients who were prepared for both elective and emergency surgeries at the general surgery and obstetrics & gynaecology departments of the Eastern Regional Hospital, Koforidua between August and November 2022.

3.2.1 Inclusion criteria

- Patients who were 6 months old and above, since under 6 months and congenital malaria are rare.
- Patients who were prepared and underwent surgical operation involving ≥5cm skin incision.
- Patients who consented to participate in the trial.

3.2.2 Exclusion criteria

The following categories of patients were excluded from this study:

- Surgical patient with uncompensated comorbidities such as diabetic ketoacidosis, decompensated heart failure, hypertensive emergencies, sickle cell crisis among others.
- Patient who had previous surgery within 30days prior to recruitment. This helped to avoid reporting of surgical outcomes which may be from surgery performed prior to recruitment.
- Patient who had an active surgical site infection or any other surgical outcomes from procedures that took place before time of recruitment.

3.2.3 Study setting – Eastern Regional Hospital, Ghana

The study was conducted at the General Surgery and Obstetrics & Gynaecology departments of the Eastern Regional Hospital, Koforidua. The hospital was established in 1926 and serves as the referral centre for over 3 million inhabitants of 33 districts (mainly rural) in the Eastern Region of

Ghana (Ghana Statistical Service, 2021). Its catchment area includes adjoining districts in the Central, Greater Accra, Ashanti and Volta regions.

The Surgical Department is a 77-bed capacity unit with an average daily admission of 10 cases where on average, 188 cases are operated every month. The Obstetrics & Gynaecology department is a 115-bed capacity facility with an average daily admission of 20 cases, where 250 cases are operated on every month.

The hospital has five major operating theatres, four for both general surgeries and obstetrics-gynaecology operations, and the fifth is exclusively for obstetrics. Nurse anaesthetists administer anaesthesia for all surgeries in the hospital. There were three specialist general surgeons, one consultant surgeon, four obstetrician-gynaecologists as well as medical officers who performed the surgical operations in the hospital at the time of this study.

3.3 The Intervention

In the intervention group, participants underwent perioperative screening for malaria parasite(s) using microscopy. Participants who were found to have malaria parasitaemia received standard malaria treatment with artemisinin-based combination therapy (ACT) whether symptomatic or not in accordance with the standard treatment of malaria. The comparison (at risk) group were not screened at all for malaria and did not receive any malaria treatment.

3.4 Trial Outcome Evaluation

The screened-positive (and treated) and the screened-negative sub-groups (collectively known as intervention group) constituted malaria-free surgical patients. On the other hand, the unscreened (comparison) group assumed an equal risk of malaria parasitaemia as the general population. Thus,

the unscreened control group enabled the study to compare surgical outcomes between the general population and perioperative malaria free patients.

The primary surgical outcome measured in this study was the proportion of patients who developed surgical site infection within 30 days' post-operation. Other outcomes which were measured within the 30-day post-op follow-up were

- proportion of patients with prolonged length of stay during the index admission following surgery,
- proportion of patients who were readmitted after discharge from in-patient care following surgery,
- proportion of patients who died and
- proportion of patients with other post-operative complications such as haemorrhage, pneumonia, sepsis, urinary tract infection, seroma, etc.

Each patient was followed up weekly, for a period of 30 days' post-operation, during which the development of surgical site infections, length of stay, readmission, death and other complications were recorded. Questions about malaria symptoms were asked at each follow-up visit of participants in the intervention group to be sure they remained clinically free from malaria during the 30days post-operation.

3.5 Sample size determination

Surgical site infection involving binary data (i.e., present or absent within the 30days post-op) was considered as the primary outcome in determining the sample size. Thus, the minimum sample size for both arms, N for RCT is given by:

$$N = 2\,x\,(\boldsymbol{Z\alpha/2} + \boldsymbol{Z1} - \boldsymbol{\beta})2[p1(1 - p1) + p2(1 - p2)]/(p2 - p1)2$$ (Sakpal, 2010)

Where, N= Minimum sample size for both groups

p1= Proportion of outcome from the control group

p2= Proportion of outcome from the intervention group

α = Level of significance

1-β= Power of test

$Z_{\alpha/2}$= Z value corresponding level of significance

$Z_{1-\beta}$= Z value corresponding level of power

Using the worst scenario in the FALCON trial, incidence of SSI for contaminated or dirty stratum is 30.0% (NIHR Global Research Health Unit on Global Surgery, 2021). Therefore, p1=30% represents the incidence of surgical site infection among patients with no malaria screening. Assuming that malaria screening reduces incidence of SSI to 15%, p2= 15% represents incidence of SSI among participants with malaria screening. At a power (1-β) of 90%, level of significance (α) of 5%, minimum sample size 'N' required for both arms was calculated as: $N= 2 \times (\mathbf{1.96+ 1.285})^2[0.3(1- 0.3) + 0.15(1- 0.15)]/ (0.15-0.30)^2$ **= 316**

However, considering the possibility of losing patients to follow-up during the 30 days, a 10% (32) adjustment on the size was applied. Therefore, the study aimed to recruit **a minimum of 348** participants. The study aimed to recruit **174 participants each** into the control and intervention in 1:1 ratio. On average both the General Surgery and Obstetrics & Gynaecology departments conduct 50 surgeries per week. We anticipated an 80% consent rate and therefore with 40 patients' recruitment per week, we anticipated 3 months' recruitment period with one-month outcome surveillance.

3.6 Randomisation, Allocation Concealment and Sampling Procedure

General surgery and obstetrics-gynaecology constitute distinct surgical specialities. The sample size was equally reserved for each sub-group to ensure an adequate representation of the two different sub-groups. In each department, assigned assessors first evaluated each patient's eligibility to participate in the study.

After consent, each eligible participant was randomly assigned to either intervention or comparison group by a computer-generated randomisation scheme performed by independent information technology personnel. An excel randomization technique was adopted to randomly and evenly assign codes to patients targeted for malaria screening and treatment project. The randomization formula used in the Excel was: =RANDBETWEEN (1 and 348) indicating the numbering sequence and the total number of patients targeted which was 348. The formula indicates that there is specific ordering of these numbers. After this process was achieved, special CODES called the randomization code (M) was generated accordingly and mapped to the auto generated codes at different fields. Codes linked to either of the study arms were printed and put in an opaque envelope. Each participant was made to choose an envelope. The assessor then opened and checked the trial arm that the participant was assigned to. For minors, a parent or caretaker consented on their behalf whilst they assented to participate in the study.

The recruitment was done over a period of four months to allow for variability in the backgrounds of the patients enrolled into the trial.

3.7 Blinding

The content of each randomly chosen sealed envelope was made accessible only to the assessor. Blood samples for malaria screening were taken together with blood samples for routine

preoperative laboratory tests to ensure that participants remained blinded of the study arm to which they belonged.

3.8 Data collection

Informed consent: A written/thumb-printed informed consent was obtained from all participants prior to participation in the trial. A standard participant information sheet was read out to the participants in English or Akan which outlined the purpose of the trial and mentioned that "it is to know whether treating malaria prior to surgery may be beneficial". The information sheet also explained to the participant that if screening for and treatment of malaria before surgical procedures is found to have be beneficial in terms of positive surgical outcomes, then it would have important implications on how surgical patients in this country and elsewhere are prepared for surgery in malaria-endemic areas.

The benefits and risks of participation were also explained to the participant. The information sheet also explained to the participant that a small sample of their blood which was drawn for their routine preparation for the surgery will be used to assess whether they had malaria or not if they fell into the intervention arm.

They were assured that participation in the trial was entirely voluntary and that they were free to refuse to participate in the study without explanation or effect on the care they receive in the hospital or any other facility in the country. The time taken for responding to the questionnaires may also be discomforting but again the participants were assured that the case report forms (CRFs) took only approximately 20-40 minutes to complete. They were also encouraged to feel free and let the trial team know when they felt any discomfort. They were also assured of that they were free to refuse responding to any questions they deemed sensitive. They were also informed

that records on complications, admissions and mortality will be obtained from their folders to assess the impact of the intervention. Participants were assured of their freedom to refuse participation or withdraw from the study at the start, during data collection and at the end of the trial without any effects on the care they receive in any facility across the country.

Participants were assured that the data they provide will be anonymised, treated with utmost confidentiality and will only be accessible to the leadership team of the study. They were assigned unique study identification numbers (Trial ID) so that no data will be traceable to them. When their responses are to be reported, only aggregate figures will be presented and not individual responses traceable to them. Participants were allowed to ask questions or seek clarification on any aspects of the trial that they did not understand and the trial team explained to them until they were satisfied. Thereafter, they were invited to willingly consent to participate in the assessment and given time to ponder over the details of the trial that was presented. Consent for participation was indicated with a signature or thumbprint (in the presence of a chosen witness who counter-signed to confirm consent for respondent participation in the study). The forms were also signed, dated and initialled by the trial team member who obtained the consent.

Data collection: Upon consent, each participant's demographics and baseline clinical data were first taken using a pre-tested questionnaire. CRFs were filled for each patient to document the management they received during the operation and post-operatively.

At each week's post-operative follow-up, the patient was assessed for the occurrence of the predefined outcomes. A CRF including a checklist was used to elicit the signs and symptoms of complications. These patients' self-reported outcomes, clinical examination findings and hospital records were abstracted onto the CRFs and used to determine the occurrence of adverse surgical

outcomes in the trial. The date each outcome occurred was recorded accordingly, together with other important details about the outcome.

3.9 Data processing and storage

The completed trial case report forms (CRFs) were submitted to a central trial office for manual checking of the data for completeness, blanks, and data coherence and consistency before being passed on to trained clerks for the data entry. Double data entry was done independently by two clerks into Microsoft Excel 2016. The two streams of data were compared by a trained trial data manager and any clerical errors were corrected using the source documents. Range and consistency checks and inter-database checks were conducted on the data and photocopies of CRFs with any errors were sent to the clinical and field teams for correction, if the source CRFs could not be used to do so. The cleaned data were transferred into Stata statistical analysis software (Stata Corp, College Station, Tx, USA) and stored on a password-protected server. Only the principal investigator and senior trial management team members had access to the data on the server.

3.10 Statistical analysis

Trial results were presented using numerical, tabular, and graphical methods. A comparison of the baseline characteristics was made to check whether balance was achieved between the two arms of the trial from the randomization. Data were represented with percentages for categorical variables, and means or medians for continuous data depending on normality or otherwise of the data.

Analysis was primarily by intention-to-treat (ITT) where each subject was regarded as belonging to the arm to which he/she was initially randomized at enrolment, irrespective of the treatment he/she finally received.

Association for categorical data were tested using Chi-squared test of association or Fisher's exact test where the expected cell size was less than 5. Two sample t-test was used to assess the differences in the outcomes and baseline characteristics which are continuous data and for the data which were not normally distributed, a non-parametric alternative i.e. Wilcoxon rank-sum test was applied.

Bivariate analysis was conducted, involving the presence/absence of each surgical outcome across the two groups. Incidence of each outcome among the intervention and control groups were analysed, and incidence risk ratio determined.

For the purpose of inferential analysis, a multivariate log-binomial regression model was fitted to analyse the impact of the intervention on the risk of each poor surgical outcome, adjusting for baseline patient characteristics. Statistical significance was assessed at 5% level.

3.11 Ethical consideration

This trial received approval from the Ghana Health Service Ethics Review Committee (GHS-ERC) with protocol/serial number: GHS-ERC 021/05/22. The clearance for the conduct of the trial including the data collection was also obtained from the Medical Director of Eastern Regional Hospital, Koforidua, Ghana. The trial was registered with BioMed Central (BMC) registry with registration number: ISRNCTN15551514.

A written informed consent was obtained from each participant prior to participation in the trial. This involved giving them or reading out a standard written information sheet that explained the purpose of the trial, what will be expected of them if they agree to participate in the trial, the benefits and risks of participation, confidentiality around the trial and the data, their right to withdraw from participation at the start, during and at the end of the data collection, and inviting

them to sign or thumbprint in the presence of a witness to indicate their willingness to participate in the trial. No patient had their management delayed or denied during the course of this study, even if they do not agree to participate in the trial. They were assured that non-participation will have no effects on the treatment they received in the facility or any other facility in the country.

Respondents were interviewed in a secluded place to ensure auditory and visual privacy. Participants were assured of privacy and confidentiality around the processes of data collection and processing throughout the trial. All participants were identified with a unique study ID number so that no information was traceable to them. All processing and analysis were done and the results presented only in aggregate figures rather than those of individual participants.

3.11.1 COVID-19 precautions

The entire conduct of the study was in strict compliance with the national COVID-19 protocols as being implemented at the Eastern Regional Hospital. All data collectors were trained and provided personal protective equipment (PPE) and were trained to wear these throughout the data collection process. These PPEs included face masks and portable alcohol-based hand sanitizers in bottles to be hung on clothing to allow for easy access and regular use during the data collection. Social distancing (at least 2 metres) was observed in all interactions with all persons during the data collection. Researchers washed their hands with soap under running water and sanitized with alcohol-based hand sanitizers before entry into the premises of any facility for the study. All the data collectors were fully vaccinated against COVID-19 as per national guidelines.

During the interactions with the respondents, data collectors were trained to continuously hand-sanitize and educate the participants on the national COVID-19 protocols including regular handwashing, hand sanitizing, wearing of face masks and social/physical distancing. They carried

spare PPEs with them and gave out to participants who did not have any, teaching them how to wear and take them off safely.

3.11.2 Use of the findings

Findings from this trial will be submitted to School of Public Health, University of Ghana as a dissertation in partial fulfilment of the requirements for a Master of Philosophy in Applied Epidemiology & Disease Control degree. An initial debrief was held with the Medical Director of the ERHK after the end of the data collection to indicate successful completion of the data collection, appreciate staff co-operation and provide some feedback on the overall number enrolled and followed-up. A separate feedback session will be held with management and staff of the Hospital, the Ghana Health Service, Ghana Field Epidemiology and Laboratory Training (GFELT) Programme and National Malaria Control Programme to highlight the main findings of the study and the implications for the malaria control and management in the country. Manuscripts will be written from the work and submitted for publication in peer-reviewed journals.

3.11.3 Conflict of interest

The researcher declares that he is a consultant general surgeon at the Eastern Regional Hospital, Koforidua and hence has interest in the research but no conflict of interest.

3.11.4 Funding

The researcher was awarded a President's Malaria Initiative (PMI) scholarship for the degree study and the conduct of this trial. The trial was also partly funded by Precision Medicine for Aggressive Breast Cancer (PMABC), Henry Ford Cancer Institute, Michigan. The funders had no role in data collection, analysis or reporting.

CHAPTER FOUR

4.0 Results

A total of 443 patients with various indications for surgical procedures between August 2022 and November 2022 were enrolled into the trial. Figure 4.1 shows the participant flow through the study. Of these 443 participants, 226 were randomly assigned to the intervention arm and 217 to the control arm.

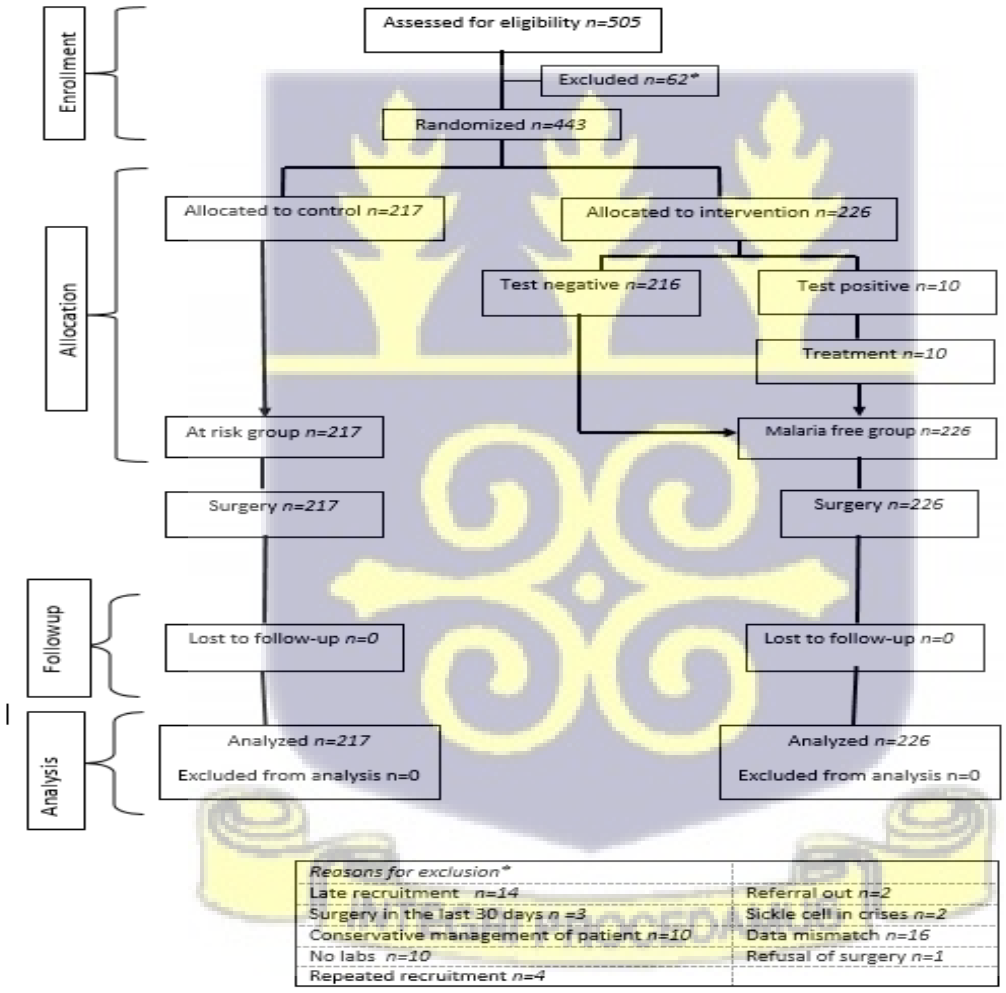

Figure 4. 1: Flowchart of the progress through the phases of a randomized controlled trial

4.1 Baseline characteristics of study participants

The baseline comparability of the two arms of the trial – an indication of the effectiveness of the randomization – is as shown in tables 4.1-4.5. There were no statistically significant differences between the intervention and control arms regarding socio-demographic characteristics including age, level of education and occupation. The median age of participants in intervention arm was (35 [28-47] years) and this did not significantly differ from the control arm (35 [28-44] years). There was equal proportion of males (21.7%) in both groups. There were, also no difference in the baseline mean-height, weight and BMI of respondents between intervention and comparison groups (Table 4.1).

Similarly, there was no differences in the lifestyle characteristics between the intervention and control groups. Majority of the respondents were non-smokers (95.6% intervention vs. 98.2% control) and close of 20% of participants in both groups were alcohol users. One-third (3.7.6% intervention vs. 38.2% controls) of respondents reported regular use of insecticide treated net. Also, a proportion of respondents in the intervention (18.1%) and control (16.1%) groups reported use of an antimalarial drug in the one-month period preceding the study (Table 4.2).

Table 4.1: Baseline sociodemographic characteristics of respondents in intervention and control arms

Variable	Intervention	Control	Chi-Squared test
	n=226(%)	n=217(%)	P-value
Sociodemographic Characteristics			
Age (years)			
Median, [IQR]	35 [28-47]	35 [28-44]	0.935[a]
10-29	72 (31.9)	60 (27.6)	0.147
30-49	107 (47.3)	121 (55.8)	
50-69	31 (13.7)	29 (13.4)	
70 and above	16 (7.1)	7 (3.2)	
Sex			0.995
Female	177 (78.3)	170 (78.3)	
Male	49 (21.7)	47 (21.7)	
Level of education			0.205
None/Primary	54 (23.9)	35 (16.1)	
JHS	96 (42.5)	100 (46.1)	
SHS/VOCTECH	36 (15.9)	40 (18.4)	
Tertiary	40 (17.7)	42 (19.4)	
Occupation			0.183
Government worker	34 (15.0)	38 (17.5)	
Artisan	56 (24.8)	63 (29.0)	
Trading	67 (29.6)	70 (32.3)	
Farmer	34 (15.0)	18 (8.3)	
Unemployed (include students)	35 (15.5)	28 (12.9)	
Anthropometrics, Mean (SD)			
Height (Cm)	159.1 (8.4)	159.1 (8.1)	0.988[&]
Weight (Kg)	77.1 (17.5)	78.5 (14.6)	0.482[&]
BMI (Kg/m^2)	30.2 (6.2)	31.0 (6.1)	0.351[&]

IQR-interquartile range, [a]P-value from 2-sample Wilcoxon rank-sum test, [&]t-test

Table 4.2: Baseline lifestyle characteristics of respondents in intervention and control arms

Variable	Intervention	Control	Chi-Squared test
	n=226(%)	n=217(%)	P-value
Lifestyle Characteristics			
Smoking			0.230[#]
Non-smoker	216 (95.6)	213 (98.2)	
Current smokers	6 (2.7)	1 (0.5)	
Ex-smokers	4 (1.8)	3 (1.4)	
Alcohol use			0.940
Non-alcohol user	186 (82.3)	178 (82.0)	
Alcohol user	40 (17.7)	39 (18.0)	
Steroid use			0.538[#]
Non-users	219 (98.2)	210 (97.2)	
Users	4 (1.8)	6 (2.8)	
Use of insecticide treated net			0.890
Non-user/non regular user	141 (62.4)	134 (61.8)	
Regular use (daily)	85 (37.6)	83 (38.2)	
Use of antimalarial medication in the preceding one month			0.574
Non-user	185 (81.9)	182 (83.9)	
User	41 (18.1)	35 (16.1)	

[#]P-value from Fisher's exact test

Tables 4.3-4.5 show the clinical characteristics of study participants. The intervention and control groups were similar in their baseline haematological parameters as well as presence of co-morbid illness and indication and type of surgical procedure.

Table 4.3: Baseline clinical characteristics of surgical patients

Variable	Intervention	Control	Fisher's exact test
	n=226(%)	n=217(%)	P-value
Previous surgery			0.280#
No history	146 (64.9)	130 (59.9)	
History of surgery	79 (35.1)	87 (40.1)	
Medical history/ Co-morbidities			
Immunology/allergies	4 (1.8)	4 (1.8)	1.000
Eyes, nose and Throat	1 (0.4)	1 (0.5)	1.000
Cardiovascular disease	47 (20.8)	42 (19.4)	0.723#
Endocrine disease	8 (3.5)	9 (4.1)	0.808
Respiratory disease	7 (3.1)	4 (1.8)	0.545
Gastrointestinal disease	4 (1.8)	3 (1.4)	1.000
Liver & biliary diseases	1 (0.4)	4 (1.8)	0.207
Genitourinary	2 (0.9)	3 (1.4)	0.680
Haematological	4 (1.8)	11 (5.1)	0.067
Musculoskeletal	2 (0.9)	3 (1.4)	0.680
Neurological	1 (0.4)	2 (0.9)	0.617

Chi-Squared Test P-value

Table 4.4: Baseline haematological parameters among intervention and control groups

Variable	Intervention (n=226)		Control (n=217)		t-test
	Mean (SD)	Range	Mean (SD)	Range	P-value
HB	11.7 (2.4)	3.4-21.0	11.9 (2.2)	5.4-19.9	0.415
WBC	8.8 (4.5)	2.8-28.2	8.5 (4.1)	2.0-26.4	0.423
Platelet	224.3 (90.7)	27.7-570.0	228.2 (93.4)	10-648.0	0.661
Neutrophil	6.1 (4.5)	0.6-25.9	5.7 (3.9)	0.8-22.4	0.342
Creatinine	91.0 (82.9)	28-1098.0	86.2 (50.7)	34.0-550.0	0.484
Potassium	4.1 (0.5)	2.2-8.5	4.2 (0.4)	3.0 –6.0	0.393
Sodium	144.2 (4.6)	103 -159.0	143.8 (4.3)	118-150.0	0.354

SD-standard deviation

This study revealed that out of a total of 242 participants who had obstetrics and gynaecology procedures, 46.0% of the intervention arm and 47.9% of the control arm had obstetric conditions (Table 4.5a). A total of 198 general surgery cases were identified, with gastrointestinal surgery accounting for 15.5% in the intervention arm and 19.4% in the control arm (Table 4.5a).

Approximately three-quarters of the intervention (73.0%) and control (76.5%) arm participants were in ASA category 1, whilst two-thirds of the intervention arm (67.7%) and the control arm (68.2%) involved spinal anesthesia (Table 4.5a). Again, this study showed that majority of the participants in the intervention (97.8%) and control (97.2%) groups underwent major surgeries (Table 4.5b). Concerning surgeon grade, medical officers performed surgeries for 42.5% of the intervention groups and 44.7% of the control groups, respectively. Of the procedure category, 44.7% of the intervention group and 46.1% of the control group involved caesarian sections (Table 4.5b).

Table 4. 5a: Indication, types and characteristics of surgical procedures among intervention and control arms.

Variable	Intervention	Control	Chi-Squared test
	n=226(%)	n=217(%)	P-value
Indication for surgery			0.738#
OBS and GYN(n=242)			
Obstetric diseases	104 (46.0)	104 (47.9)	
Gynecological diseases	18 (8.0)	18 (8.3)	
General surgery (n=198)			
Gastrointestinal	35 (15.5)	42 (19.4)	
Genitourinary	3 (1.3)	1 (0.5)	
Musculoskeletal	6 (2.7)	5 (2.3)	
Hernia	47 (20.8)	34 (15.7)	
Endocrine	13 (5.8)	13 (6.0)	
Urgency of surgery			0.560
Elective	126 (55.8)	115 (53.0)	
Emergent	100 (44.2)	102 (47.0)	
ASA			0.398
1	165 (73.0)	166 (76.5)	
2	61 (27.0)	51 (23.5)	
Type of Anaesthesia			0.336
Local	8 (3.5)	3 (1.4)	
Spinal	153 (67.7)	148 (68.2)	
General	65 (28.8)	66 (30.4)	

#Fisher's exact test P-value, ASA -American Society of Anaesthesiologists.

Table 4. 6b: Indication, types and characteristics of surgical procedures among intervention and control arms.

Variable	Intervention	Control	Chi-Squared test
	n=226(%)	n=217(%)	P-value
Type of surgery			0.709
Minor	5 (2.2)	6 (2.8)	
Major	221 (97.8)	211 (97.2)	
Surgeon grade			0.245
Medical Officer	96 (42.5)	97 (44.7)	
Specialist	56 (24.8)	39 (18.0)	
Senior Specialist	28 (12.4)	37 (17.1)	
Consultant	46 (20.4)	44 (20.3)	
Procedure Category			
Laparotomy	40 (17.7)	42 (19.4)	0.654
Salpingectomy	8 (3.5)	6 (2.8)	0.641
Hernia repair	45 (19.9)	32 (14.8)	0.152
Caesarian section ± BTL	101 (44.7)	100 (46.1)	0.769
Appendectomy	13 (5.8)	9 (4.2)	0.437
Myomectomy	12 (5.3)	10 (4.6)	0.734
Hysterectomy ± SO	7 (3.1)	8 (3.7)	0.732
*Others	25 (11.1)	23 (10.6)	0.875
Surgical wound type			0.766
Clean	44 (19.5)	34 (15.7)	
Clean-contaminated	128 (56.6)	129 (59.4)	
Contaminated	35 (15.5)	36 (16.6)	
Dirty	19 (8.4)	18 (8.3)	

BTL-Bilateral tubal ligation. SO-Salpingo-Oophorectomy. *Others include mastectomy, thyroidectomy, hemorrhoidectomy, amputation, excision, cholecystectomy, ovarian cystectomy, fistulotomy and orchidopexy.

4.2 Proportion of surgical patients with malaria before surgery

Ten (representing 4.4%) out of the total of 226 patients in the intervention arm tested positive for malaria and were treated during the trial. All the 226 in the intervention arm were further monitored for malaria signs and symptoms (and tested where required) until the 30th day after the surgical operation.

4.3 Proportion of patients with poor surgical outcomes

Eighty-eight (20%) of all 443 participants developed at least one poor surgical outcome (Table 4.6). About 16.8% of the intervention arm compared with 23.0% of control arm developed at least one poor surgical outcome (Figure 4.2).

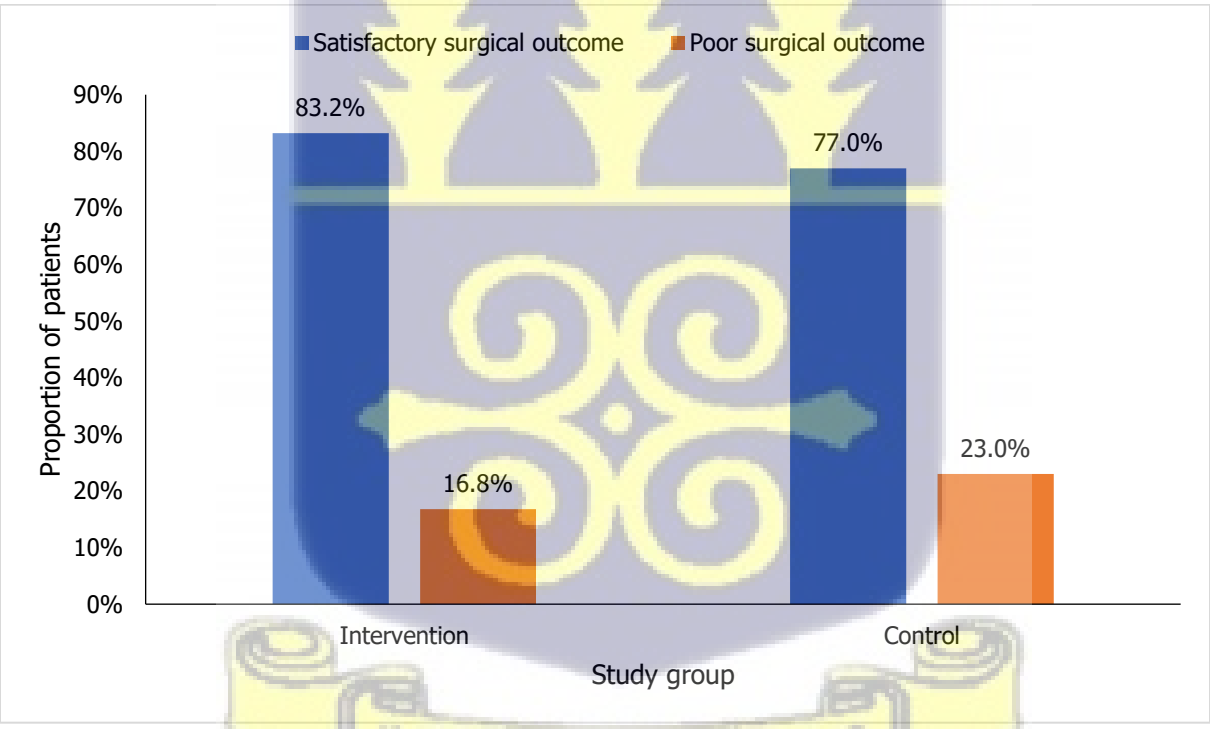

Figure 4.2: Incidence of poor surgical outcomes among intervention (n=226) and control (n=217) surgical groups

In table 4.6, prolonged length of stay (13.8%) and surgical site infection (9.7%) were the two leading poor surgical outcomes recorded among the participants. Of 61 patients with prolonged length of stay, majority 35 (57.4%) were in control arm, though the difference was not statistically significant. Similarly, of 43 patients with surgical site infection, 27 (62.8%) were in control arm. Also, 12 (63.2%) of the 19 patients with pathological post-surgical complications including deep vein thrombosis, urinary tract infection, pneumonia, sepsis, post-partum haemorrhage, seroma, wound dehiscence (gaped wound), pulmonary embolism, pleural effusion and lymphedema were in control arm. However, incidence of re-admission was higher in intervention group (6, 2.7%) than control group (1, 0.5%) but the events were rare with very wide confidence intervals including evidence of no difference between the intervention and control arms.

The overall median length of stay of participants following surgery was 2 (IQR=2, 4) days; 3 (IQR= 2, 4) days for participants in the intervention arm and 2 (IQR=2, 4) days among those in the control arm. However, results from Wilcoxon rank-sum test did not show statistically significant difference in the median length of stay between the two arms (p=0.743). Furthermore, there were no significant differences between the two arms of the trial with respect to prolong length of stay, surgical site infection, readmission, death, or other post-operative complication (p>0.05 for each).

Table 4.7: Surgical outcomes among intervention and control groups

Surgical outcomes	Total	Intervention	Control	Chi-Squared test
	N=443(%)	n=226(%)	n=217(%)	P-value
Length of stay (LOS)				
Median [IQR]	2 [2-4]	3 [2-4]	2 [2-4]	0.743[b]
Prolonged LOS (>7 days)	61 (13.8)	26 (11.5)	35 (16.1)	0.158
Surgical site infection (SSI)	43 (9.7)	16 (7.1)	27 (12.4)	0.057
Re-admission within 30 days	7 (1.6)	6 (2.7)	1 (0.5)	0.123[#]
Mortality within 30 days	9 (2.0)	5 (2.2)	4 (1.8)	1.000[#]
***Other post-op complication**	19 (4.3)	7 (3.1)	12 (5.5)	0.206
Any poor surgical outcome	88 (19.9)	38 (16.8)	50 (23.0)	0.101

#Fisher's exact test P-value, [b]P-value from Wilcoxon rank-sum test, *Other post-op complications include deep vein thrombosis, urinary tract infection, pneumonia, sepsis, post-partum hemorrhage, seroma, gaped wound, pulmonary embolism, pleural effusion and lymphedema.

The risk of developing any poor surgical outcome was 16.81% in the intervention group and 23.04% in the control group with a relative risk of 0.76 (Table 4.7).

Table 4.8: Risk of any poor surgical outcome

Trial arm	Surgical outcome		Total	Risk (95% CI)	RR (95% CI)	p-value
	Any	None				
Intervention	38	188	226	16.81% (11.94-21.69)	0.73 (0.50-1.07)	0.101
Control	50	167	217	23.04% (17.44-28.64)		
Total	88	355	443			

RR- relative risk

The risk of surgical site infection among the intervention group was 7.08% and 12.44% in the control group with a relative risk of 0.57 (Table 4.8).

Table 4. 9: Risk of surgical site infection

Trial arm	Outcome (SSI)		Total	Risk (95% CI)	RR (95% CI)	p-value
	Present	Absent				
Intervention	16	210	226	7.08% (3.74-10.42)	0.57 (0.32-1.03)	0.057
Control	27	190	217	12.44% (8.05-16.83)		
Total	43	400	443			

RR- relative risk

Risk of prolonged hospital stay among the intervention group was 11.50% and 16.13% among the control group, with a relative risk of 0.71 (Table 4.9).

Table 4. 10: Risk of prolonged hospital stay

Trial arm	Outcome (Prolonged hospital stay)		Total	Risk (95% CI)	RR (95% CI)	p-value
	Present	Absent				
Intervention	26	200	226	11.50% (7.34-15.66)	0.71 (0.44-1.14)	0.158
Control	35	182	217	16.13% (11.24-21.02)		
Total	61	382	443			

RR- relative risk

Risk of re- admission was 2.65% in the intervention group and 0.46% in the control group with a relative risk of 5.76 (Table 4.10).

Table 4. 11: Risk of re-admission

Trial arm	Outcome (Re-admission)		Total	Risk (95% CI)	RR (95% CI)	p-value
	Present	Absent				
Intervention	6	220	226	2.65% (0.56-4.75)	5.76 (0.70-47.46)	0.064
Control	1	216	217	0.46% (0-1.36)		
Total	7	436	443			

RR- relative risk

The risk of other post-op complication in the intervention arm was 3.1% and 5.5% in the control arm with a relative risk of 0.56 suggesting a non-significant 44% reduction in the risk between intervention and control arms (Table 4.11).

Table 4. 12: Risk of other post-op complication

Trial arm	Outcome (*other post-operative complication)		Total	Risk (95% CI)	RR (95% CI)	p-value
	Present	Absent				
Intervention	7	219	226	3.10% (0.84-5.36)	0.56 (0.22-1.40)	0.207
Control	12	205	217	5.53% (2.49-8.57)		
Total	19	424	443			

RR- relative risk; *Other post-op complications include deep vein thrombosis, urinary tract infection, pneumonia, sepsis, post-partum hemorrhage, seroma, gaped wound, pulmonary embolism, pleural effusion and lymphedema.

The risk of mortality was 2.21% among the intervention group and 1.20% among the control group with a relative risk of 1.20 (Table 4.12).

Table 4. 13: Risk of mortality

Trial arm	Outcome (Mortality)		Total	Risk (95% CI)	RR (95% CI)	p-value
	Present	Absent				
Intervention	5	221	226	2.21% (0.29-4.13)	1.20 (0.32-4.41)	0.783
Control	4	213	217	1.84% (0.05-3.63)		
Total	9	434	443			

RR- relative risk

4.4 Impact of perioperative malaria screening and treatment on surgical outcomes

After adjusting for the majority of participants' baseline characteristics, there was 67% reduced risk of prolonged hospitalisation among participants who received the intervention compared to the control group (aRR=0.33; 95% CI=0.12-0.85; p=0.022). Although, the intervention did not show statistically significant impact on the risk of surgical site infection, readmission, death, and other post-op complications (Table 4.13), there was borderline evidence of a 27% reduction in the risk of poor surgical outcomes in the intervention group compared to the controls with the 95% confidence interval suggesting that the data were consistent with a possible 50% reduction in the risk of poor surgical outcomes as well as a 7% increase (RR=0.73; 95% CI= (0.50, 1.07), p=0.1).

Table 4. 14: Multivariate log-binomial regression analysis of impact of intervention on surgical outcomes

Surgical outcome	cRR (95% CI)	P-value	aRR (95% CI)	P-value
Any surgical outcome	0.73(0.50-1.07)	0.103	0.67(0.36-1.27)	0.225
Surgical site infection	0.57(0.32-1.03)	0.061	0.48(0.17-1.38)	0.173
Prolonged length of stay	0.71(0.44-1.14)	0.161	0.33(0.12-0.85)	**0.022**
Readmission within 30days	5.76(0.70-47.46)	0.104	5.32(0.64-44.52)	0.123
Death within 30 days	1.20(0.33-4.41)	0.783	1.14(0.22-6.08)	0.874
*Other post-op complication	0.56(0.22-1.40)	0.214	0.40(0.08-1.97)	0.260

cRR, crude risk ratio; aRR, adjusted risk ratio; CI, confidence interval

P-value highlighted in bold was considered statistically significant (p<0.05)

*Other post-op complications include deep vein thrombosis, urinary tract infection, pneumonia, sepsis, post-partum hemorrhage, seroma, gaped wound, pulmonary embolism, pleural effusion and lymphedema

CHAPTER FIVE

5.0 Discussion

This randomised and blinded trial is the first of its kind in Ghana, especially conducted within programme settings to assess the impact of perioperative malaria screening and treatment on surgical outcomes among surgical patients of all age groups. We found borderline evidence that screening for and treating malaria before surgery in asymptomatic patients may reduce the incidence of adverse surgical outcomes by more than a quarter (27%). Data were also consistent with a possible halving of the risk of adverse surgical outcomes as well as a 7% increase in the risk. The retrospective study by Peiffer, et al. (2020) was limited to paediatric surgery and only described how malaria infection predicted poor surgical outcomes. Outside Ghana in Malawi, Roca-Feltrer, et al. (2012) also focused on childhood malaria rather than in the general population.

Comparisons of the current study results with existing literature was limited by the relative lack of studies investigating the same topic. This discussion focused on the findings from this study and their implications for future research, policy, and practice.

5.1. Baseline characteristics of study participants

The analysis of the data provided showed that the intervention and control groups were well-matched in terms of socio-demographic, lifestyle, clinical, and haematological characteristics, as well as surgical procedure types.

The intervention and control groups displayed similar socio-demographic characteristics such as age, sex, level of education, and occupation. This is important as it ensures that any potential confounders related to these factors are minimized, allowing for a more valid comparison of the intervention's effectiveness.

The lifestyle factors examined, including smoking, alcohol use, steroid use, and use of insecticide-treated nets, were also similar between the groups. This further strengthens the internal validity of the study.

The baseline clinical characteristics of the participants were also well matched, with no significant differences in previous surgery history or co-morbidities. This is particularly important, as these factors could potentially influence surgical outcomes, and their balance between the groups ensures that the comparison of the intervention's effectiveness is more accurate.

The baseline haematological parameters showed no significant differences between the intervention and control groups. This is important as it eliminates any potential bias in the comparison of surgical outcomes, ensuring that any observed differences are more likely to be due to the intervention itself rather than differences in participants' health status.

The indication for surgery, urgency of surgery, ASA, type of anesthesia, type of surgery, surgeon grade, procedure category, and surgical wound type were all similar between the intervention and control groups. This is crucial for comparing the intervention's effectiveness, as it minimizes the potential confounding effects of different surgical procedures and ensures that any observed differences in surgical outcomes can be more confidently attributed to the intervention.

This study revealed that out of a total of 242 participants who had obstetrics and gynaecology procedures, 46.0% of the intervention group and 47.9% of the control group had obstetric conditions. A total of 198 general surgery cases were identified, with gastrointestinal surgery accounting for 15.5% in the intervention group and 19.4% in the control group. A similar study found obstetrics as the commonest surgical procedure and hypertension being the commonest comorbidity (Osinaike et al., 2019).

5.2 Proportion of surgical patients with malaria before surgery

About 4% (10/226) of participants in the intervention group tested positive and were treated for malaria. This finding was relatively lower compared to the finding by researchers who reported an incidence of 12% and 14.7% among pediatric surgical patients in the Eastern region of Ghana and in Malawi respectively (Roca-Feltrer et al., 2012; Peiffer et al., 2020). The relatively lower test positivity rate and incidence in this study could be due to the focus on asymptomatic surgical patients who present for surgery other than malaria infection as well as a possible higher activation of B cells during infection and higher induction of antibodies after malaria in adults compared to children (Oyong et al., 2022).

5.3. Incidence of poor surgical outcomes

The primary outcomes examined in the study were length of stay (LOS), prolonged LOS (>7 days), surgical site infection (SSI), re-admission within 30 days, mortality within 30 days, other post-op complications, and any poor surgical outcome.

Among all participants in this trial the incidence of developing a poor surgical outcome was approximately 20%, which does not differ much from postoperative complication rate of 18.5% reported in a study conducted in Nigeria (Osinaik et al., 2019). However, in the present study prolonged length of stay was the poor surgical outcome with the highest incidence, unlike the aforementioned study where infective complications predominated. In fact, the incidence of surgical site infection in this trial (9.7%) is lower than 22% which was reported in the FALCON trial by NIHR Global Research Health Unit on Global Surgery (2021). The finding in this study is rather consistent with 10% incidence risk of surgical site infection reported by Bediako-Bowan et al. (2020) in a study conducted purely in Ghana (Korle-Bu Teaching Hospital).

Proportion of patients with poor surgical outcomes was higher in control group (23.0%) than intervention group (16.8%). In other words, participants who were screened and freed from malaria parasites prior to surgery had less incidence of poor surgical outcomes. In a similar study, Sundet et al. (2004) found that the rate of infections was significantly higher among participants with malaria (malaria group) compared with the non-malaria group (36.1% vs. 10.0%) (Sundet et al., 2004). One of the reasons for the higher rates of complications among surgical patients with malaria was due to weakened immune systems caused by malaria, which increases patient's susceptibility to other post-surgical bacterial infections and longer recovery times (Ssentongo, 2020; Sundet et al., 2004).

Majority of patients with either prolonged length of stay, surgical site infection or other post-surgical complications were in control group compared to intervention group. This results corroborates findings of a study which indicated that post-injury malaria adds to the burden of trauma by increasing the risk of postoperative wound infections and delaying recovery (Sundet et al., 2004).

The lower rate of SSIs in the intervention group, although not statistically significant, suggests a potential positive effect of the intervention. The clinical importance of reducing SSIs cannot be overstated, as SSIs are associated with increased morbidity, prolonged hospital stay, and higher healthcare and economic costs for both the patient and the health system. Further research with larger sample sizes may be needed to confirm whether the intervention indeed has a significant impact on reducing SSIs.

In the bivariate analysis, the lack of significant differences in prolonged LOS, re-admission rates, other postoperative complications, and death suggests that the study is underpowered to detect small differences, especially in a rare event like mortality after surgical procedures.

The incidence of re-admission was higher in intervention group (6, 2.7%) than control group (1, 0.5%) but very little can be deduced from these results as the outcome was very rare and the study is too underpowered to detect any important differences worth discussing. Indeed, literature suggests that perioperative malaria infection is an actionable independent predictor of readmission in the pediatric surgical population in Ghana (Peiffer et al., 2020). Testing this hypothesis in a larger study will demonstrate whether the results will vary between paediatric and adult populations.

5.4. Impact of perioperative malaria screening and treatment on surgical outcomes

There was a borderline evidence of difference in the proportion of patients with poor surgical outcomes between the intervention and control groups at the bivariate level, which then suggest no or minimal impact of the malaria screening and treatment on surgical outcomes. However, at a higher level of analysis where majority of participants' characteristics including age, sex, smoking status, alcohol use , steroid use, BMI, preoperative serum creatinine, serum potassium, type of surgery, urgency of surgery, class of wound, grade of surgeon, ASA score and type of anaesthesia were controlled in a log-binomial regression analysis the intervention group was associated with a 67% reduction in the risk of prolonged length of stay (aRR=0.33; 95% CI=0.12-0.85; p=0.022). This implies, patients who were screened and treated for malaria prior to surgery had 67% lower incidence of prolonged hospitalisation following surgery. The higher incidence of prolonged hospitalisation among the control group (16.1%) could perhaps be as a result of the higher incidence of surgical site infection that was recorded in the controls (12.4%) compared to the intervention (7.1%), even though it did not reach statistical significance. In previous studies hyperpyrexia was found as one of the reasons for prolonged hospitalisation among paediatric population with malaria (Eipe, 2004; Sundet et al., 2004; Roark, 2019).

5.5. Strengths of the study

This study has many strengths:

1. Firstly, the use of a randomised controlled trial design provides a robust design for very strong evidence to inform programme decisions.
2. Secondly, the study was implemented in a large facility with substantial numbers of participants in spite of the limited time for the data collection.
3. Thirdly, the study was conducted within health systems settings and the findings can easily be generalizable to similar settings at least in Ghana.
4. Fourthly, the data collection procedures were robust and had multiple internal validations to ensure accuracy.

5.6. Limitation of the study:

Despite the many strengths, this study had a few limitations as follows:

1. Small sample size: The relatively small sample size may have limited the power to detect significant differences in surgical outcomes between the intervention and control groups. This is particularly relevant for the observed borderline significant reduction in SSIs, which may have reached statistical significance with a larger sample. Future research with larger samples is needed to confirm the effectiveness of the intervention in improving surgical outcomes. Potential for type II error: The lack of statistically significant differences for most outcomes between the intervention and control groups could be due to type II error (i.e., failing to detect a true effect). Larger studies with increased statistical power are necessary to confirm the absence of an effect or to identify any small but significant differences in surgical outcomes between the groups. A larger study could only mean

extending the data collection period or recruiting more facilities both of which could not be accommodated within the tight schedules of the University's academic calendar.

2. Generalizability: The present study was conducted in a single centre. The study population and intervention may not be representative of all surgical populations or interventions, limiting the generalizability of the findings to other settings. However, as mentioned earlier, many of the findings could be generalizable to similar settings and might have at least generated hypothesis that are worth testing in better-powered studies and more representativeness.

CHAPTER SIX

6.0 Conclusion and Recommendations

6.1. Conclusion

The prevalence of malaria among surgical patients at the Eastern Regional Hospital was low. Poor surgical outcomes are not rare - affects one out of every five patients - and the two leading poor surgical outcomes were prolonged hospitalisation and surgical site infection. Providing perioperative malaria screening and treatment reduced patient's length of hospital stay after surgery but had no significant impact on surgical site infection, readmission rate, death, and other post-op complications due to low power of the study. Screening and treatment of malaria perioperative, may reduce poor surgical outcomes.

6.2. Recommendation

To the Eastern Regional Hospital and the National Malaria Control Programme-Ghana Health Service:

1. It is recommended that, in the clinical assessment of patients for surgical procedures, malaria screening and treatment preoperatively should be considered. This is a recommendation for the short to medium term (within the next 2 years).

To the Ministry of Health, Ghana and the National Malaria Control Programme-Ghana Health Service:

2. Further studies should be coordinated and powered to conclusively determine the outcomes of surgery after screening and treatment of asymptomatic malaria as can be hypothesized in this study. This should be a medium to long term (2-5 years) project to be coordinated by the Ghana Health Service and the Ministry of Health, Ghana.

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APPENDICES

Appendix A: Field Pictures

Appendix B: Letter of permission to conduct study at the ERHK

In case of reply the number and the date of this letter should be quoted.

GHANA HEALTH SERVICE
Your Health*Our Concern

EASTERN REGIONAL HOSPITAL
P.O. BOX 201
KOFORIDUA, E/R
GHANA-WEST AFRICA.
WEBSITE: www.erhk.org
EMAIL: info@erhk.org
eastern.rh@ghs.gov.gh
TEL. 03420-23011 FAX 03420-25296

My Ref. No.: GHS/ERHK/HR/PF/MP 7
Your Ref. No.:

28TH APRIL, 2022

DR. FORSTER AMPONSAH-MANU
P.O.BOX 201
KOFORIDUA

RE; PERMISSION TO CONDUCT RESEARCH

Your letter dated 25th April, 2022 in respect to the above subject matter refers.

This is to inform you that approval has been given to you (Dr. Forster Amponsah-Manu with Student ID: 10876950) a resident of the MPhil. in Applied Epidemiology and Disease Control programme at the School of Public Health, University of Ghana, Legon to conduct a research at the Eastern Regional Hospital, Koforidua on the topic **"Impact of Peri-operative Malaria Screening and Treatment on Surgical Outcomes at the Eastern Regional Hospital, Koforidua- a single blind randomized control trial" .**

You are therefore requested to submit copies of research report to the office of the Medical Director upon completion of the study or research.
Thank you.

DR.ARKO AKOTO-AMPAW
MEDICAL DIRECTOR

Cc: The Dean
School of Public Health
University of Ghana, Legon

Appendix C: Letter of ethical approval from the GHS-ERC

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this Letter should be quoted.

Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra
Digital Address: GA-050-3303
Mob: +233-50-3539896
Tel: +233-302-681109
Email: ethics.research@ghsmail.org

My Ref. GHS/RDD/ERC/Admin/App 122/269
Your Ref. No.

18th July, 2022

Dr. Forster Amponsah-Manu
University of Ghana,
School of Public Health

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol.

GHS-ERC Number	**GHS-ERC: 021/05/22**
Study Title	Impact of Peri-operative Malaria Screening and Treatment on Surgical Outcomes at the Eastern Regional Hospital, Koforidua: A Single-blind Randomised Controlled Trial
Approval Date	18th July, 2022
Expiry Date	17th July, 2023
GHS-ERC Decision	**Approved**

This approval requires the following from the Principal Investigator

- Submission of a yearly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months,
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report after completion of the study
- Informing ERC if study cannot be implemented or is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

You are kindly advised to adhere to the national guidelines or protocols on the prevention of COVID -19.

Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol

SIGNED.....
Mr. Kofi Wellington
(GHS-ERC Vice Chairperson)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra

Appendix D: Participant information sheet

INFORMATION SHEET (for all participants)

Title: Impact of Perioperative Malaria Screening and Treatment on Surgical Outcomes at the Eastern Regional Hospital, Koforidua

Principal Investigator: Forster Amponsah-Manu

Address:

FORSTER AMPONSAH-MANU

DEP'T. OF GENERAL SURGERY

EASTERN REGIONAL HOSPITAL

P.O.BOX 201.

KOFORIDUA- EASTERN REGION

GHANA

TEL: +233 24 4655108

Email: foster_amponsah@yahoo.com

This is research entitled '**Impact of Peri-operative Malaria Screening and Treatment on Surgical Outcomes at the Eastern Regional Hospital: A Single-blind Randomised Controlled Trial**'. The objective of the research is to determine impact of malaria screening and treatment on surgical outcomes of patients undergoing elective surgeries at the Eastern Regional Hospital, Koforidua. This study will help us get data to standardize surgical care and to improve surgical outcomes. Supposing screening and treating patient undergoing planned surgery for malaria provides better results following surgery, it can serve as a new way of surgical practice for better and satisfactory results to patients.

You will be asked to give informed consent to enroll in the study. A minimum of 348 persons being planned for surgery will be enrolled into this study. Enrollment into the study will take place for a period of three months. Each participant will be enrolled into one of two arms of the research. Participants in one arm will be tested for malaria, and treatment using 3 days course of antimalarial drug will be offered to those who test positive. On the other hand, participants in the 2nd arm will not be tested for malaria and will not be given antimalarial drug. The selection will be made by balloting. The research is for the whole duration of your hospital admission and up to thirty days after surgery.

Some information from your medical records will be used in filling out a questionnaire and subsequent information recorded during the course of follow-up. **It would take about 20-40 minutes during administration of questionnaire**. Blood sample (**two teaspoonful of blood**

maximum) would be taken for laboratory tests, which will include malaria test in case you are enrolled into that arm of the study**. If you are enrolled in the other arm of the study which would not require malaria screening, two teaspoonsful (10mls) of blood would be taken to perform routine tests prior to surgery but no malaria test would be performed on the sample**. A tiny needle will be used to puncture a vein through the skin on your forearm to draw blood for the laboratory tests. After the tests, blood sample shall be discarded immediately. All the information collected will be confidential and your identity will be anonymous.

You will continue to receive the standard surgical care provided by the hospital. Additionally, you will be required to report to the hospital weekly after discharge until post-op day 30 during which some questions will be asked and you will be physically examined to look out for certain results. In the case where you are not able to report for follow-up, a phone call interview will be done as an alternative.

Suppose you find yourself among unscreened group, and you develop symptom(s) suggestive of malaria you will be screened and treated immediately, if it comes out positive.

The risks associated with this study are needle pricks during blood sampling and frequent than usual visits to the hospital. However, these risks are not much different outside the study or during routine surgical care. You can stop participating at any time if you feel uncomfortable. No one will be angry with you if you do not want to participate. You will not be denied treatment in the hospital in case you decide not to participate; you will receive standard surgical treatment and care anyway.

If screening and treatment for malaria before operation is found to have positive impact on surgical outcomes then it would have been of benefit to participants in the intervention arm of the study. Findings of the study will be used to improve services in the facility for future care provided by health workers.

Cost of laboratory tests and antimalarial drug will be paid for with or without National Health Insurance. For each follow up visit, you will be given a fixed amount of ghc 20.0 to compensate for your cost of transport. There will be no other compensation for your participation. Cost of surgery and hospital admission(s) will not be absorbed by this study.

As stated above, your name or identity will be kept anonymous during data processing and analysis. All information taken from you for the purpose of this study shall be kept safe under a lock and key drawer. Data will be analyzed and final report will be presented to the School of Public Health, University of Ghana for the purpose of attaining master's degree. Findings will also be shared with the Eastern Regional Hospital, to help inform policy in the hospital.

The study is being funded by President's Malaria Initiative, a USAID program in collaboration with Ghana Malaria Control Program.

By signing the attached consent form, it means that you understand and know the issues concerning this study. If you do not want to participate in this study, please do not sign the consent form. You will be given a copy of the Information sheet and Consent form after it has been signed or thumb-printed to keep.

You may contact me (as the Principal Investigator) by using the following information in case of any concern with regards to this study.

Forster Amponsah-Manu

Department of Surgery, Eastern Regional Hospital, Koforidua

Tel: 0244655108

Email address: foster_amponsah@yahoo.com

If you have any questions about your rights as a research participant or you require further clarification on ethical issues, you can contact the ERC via the under stated information.

Nana Abena Apatu

Administrator, GHS-ERC

Tel: 0503039896

Email address: ethics.research@ghsmail.org

Appendix E: Consent form

CONSENT FORM (for all adult participants)

STUDY TITLE: Impact of Peri-operative Malaria Screening and Treatment on Surgical Outcomes at the Eastern Regional Hospital, Koforidua: a Single-blind Randomised Controlled Trial

PARTICIPANTS' STATEMENT

I acknowledge that I have read or have had the purpose and contents of the Participants' Information Sheet read and all questions satisfactorily explained to me in a language I understand (Twi, Ewe, Ga, Krobo, Hausa). I fully understand the contents and any potential implications as well as my right to change my mind (i.e. withdraw from the research) even after I have signed this form.

I voluntarily agree to be part of this research.

Name of Participant……..

Participants' Signature ……...OR Thumb Print……

Date: …….

INTERPRETERS' STATEMENT

I interpreted the purpose and contents of the Participants' Information Sheet to the aforementioned participant to the best of my ability in the (Twi, Ewe, Ga, Krobo, Hausa) language to his proper understanding.

All questions, appropriate clarifications sort by the participant and answers were also duly interpreted to his/her satisfaction.

Name of Interpreter……

Signature of Interpreter…….. OR Thumb Print …….....

Date: ……

STATEMENT OF WITNESS

I was present when the purpose and contents of the Participant Information Sheet was read and explained satisfactorily to the participant in the language, he/she understood (Twi, Ewe, Ga, Krobo, Hausa).

I confirm that he/she was given the opportunity to ask questions/seek clarifications and same were duly answered to his/her satisfaction before voluntarily agreeing to be part of the research.

Name: ……

Signature……... OR Thumb Print …….....

Date: ……

INVESTIGATOR STATEMENT AND SIGNATURE

I certify that the participant has been given ample time to read and learn about the study. All questions and clarifications raised by the participant have been addressed.)

Researcher's name…….

Signature …….

Date…….

Appendix F: Child assent form

CHILD ASSENT FORM (for children above 7 years)

My name is Dr. Forster Amponsah-Manu, a medical doctor who has specialized in treating ill-person through operation. I work here at the department of surgery of the Eastern Regional Hospital, Koforidua. My interest now is to conduct research entitled IMPACT OF PERI-OPERATIVE MALARIA SCREENING AND TREATMENT AT THE EASTERN REGIONAL HOSPITAL, KOFORIDUA: A SINGLE-BLIND RANDOMISED CONTROLLED TRIAL. I am asking you to take part in this research study because I am trying to learn more about how we could improve on the results of patients undergoing surgery. This research will help us know if testing and treating people like you for malaria before operation will make you heal better after the operation or not.

This will take as long as the total period of your admission into hospital and outpatient follow ups either in person or on phone after discharge. If you agree to be in this study, you will be selected in either one of two groups of people in the study by balloting. First group will be tested for malaria before operation, and if malaria is present, the person will be given malaria drug for 3days. The second group will not be tested for malaria and as such will not be given malaria drug. You would be asked some questions and your guardian(s) (mother, father, brother, sister, etc.) will help us with the ones you do not know about yourself. We would keep your answers private; only people working on the research will see them. Before the day of your operation, we will take small amount (maximum 2 teaspoonful) of blood for test by sticking a tiny needle on your forearm. However, if you find yourself in the 2nd group mentioned above, malaria test would not be performed on your blood sample. The blood taken would be used to run tests usually performed before every operation in the hospital.

We do not think that any big problems will happen to you as part of this study, but you might feel discomfort when we prick you for your blood sample. You might also not feel comfortable with some questions we will ask you during the study. On the other hand, you can feel good about helping us to learn more about how we could improve on patients care when you take part in this research.

You do not have to be part of this research if you do not want to. You are also free to withdraw from the research at any time if you so wish. No one will be angry with you if you do not want to participate. Your information will be kept confidential. No one will be able to know how you responded to the questions.

You may ask me any questions about this study. You can call me at any time (tel. 020 6301696 or 0244 655108) or talk to me the next time you see me. Please talk about this study with your parents before you decide whether or not to participate. I will also ask permission from your parents before you are enrolled into the study. Even if your parents say “yes” you can still decide not to participate.

By signing below, it means that you understand and know the issues concerning this research study. If you do not want to participate in this study, please do not sign this assent form. You and your parents will be given a copy of this form after you have signed it.

CHILD'S STATEMENT

I acknowledge that I have read or have had the purpose and contents of the Child Assent Form above and all questions satisfactorily explained to me in a language I understand (Twi, Ewe, Ga, Krobo, Hausa). I fully understand the contents and any potential implications as well as my right to change my mind (i.e. withdraw from the research) even after I have signed this form.

I voluntarily agree to be part of this research.

Child's Name: …….. Parent: ……

Child's Signature/thumbprint: …… Date: ……

INTERPRETERS' STATEMENT

I interpreted the purpose and contents of the Child Assent Form to the aforementioned child to the best of my ability in the (Twi, Ewe, Ga, Krobo, Hausa) language to his/her proper understanding.

All questions, appropriate clarifications sort by the participant and answers were also duly interpreted to his/her satisfaction.

Name of Interpreter……

Signature of Interpreter…….. OR Thumb Print …….....

Date: ……

STATEMENT OF WITNESS

I was present when the purpose and contents of the Child Assent Form was read and explained satisfactorily to the participant in the language, he/she understood (Twi, Ewe, Ga, Krobo, Hausa).

I confirm that he/she was given the opportunity to ask questions/seek clarifications and same were duly answered to his/her satisfaction before voluntarily agreeing to be part of the research.

Name: ……

Signature…….... OR Thumb Print …….....

Date: ……

INVESTIGATOR STATEMENT AND SIGNATURE

I certify that the participant has been given ample time to read and learn about the study. All questions and clarifications raised by the participant have been addressed.

Researcher's name…….

Signature …….. Date …….

Appendix G: Parental information sheet and consent

PARENTAL INFORMATION SHEET AND CONSENT FORM

Title: Impact of Peri-operative Malaria Screening and Treatment on Surgical Outcomes at the Eastern Regional Hospital: A Single-blind Randomised Controlled Trial.

Principal Investigator: Dr Forster Amponsah-Manu

Address:

DEP'T. OF GENERAL SURGERY

EASTERN REGIONAL HOSPITAL

P.O.BOX 201.

KOFORIDUA- EASTERN REGION

GHANA

TEL: +233 24 4655108

Email: foster_amponsah@yahoo.com

General Information about Research

I am inviting your child to take part in this research because I am trying to learn more about how we could improve on the results of patients undergoing surgery. This research will help us know if testing and treating people like your child for malaria before operation will make them heal better after the operation or not.

The study will take as long as the total period of your child's admission and follow ups either in person or on phone after discharge. If you agree to let your child participate in this study, he/she will be selected in either one of two groups of people in the study by balloting. First group will be tested for malaria before operation, and if malaria is present, the person will be given malaria drug for 3days. The second group will not be tested for malaria and as such will not be given malaria drug. Your child would be asked some questions written on a sheet about him/herself during this study. You may be required to help us with some information if he/she doesn't know about him/herself. We would keep the response from both of you private; only people working on the research will see them. Before the day of your child's operation, we will take small amount (maximum 2 teaspoonful) of blood for test by sticking a tiny needle on his/her forearm. However, if your ward finds him/herself in the 2nd group mentioned above, malaria test would not be performed on his/her blood sample. The blood taken would be used to run tests usually performed before every operation in the hospital.

After the child has been operated, he/she will regularly be examined for how well he/she is doing. Any result that comes after surgery will be recorded. The result information will be collected every week until 30days after operation. This information gathered for each and every individual in each

group of the research would be studied to understand if those who would be tested for malaria before operation have better results or not. If the finding becomes clear that malaria testing helps to improve results of operation, then it would be added to the hospital practice to test every person for malaria before operation.

Possible Risks and Discomforts

We do not think that any big problem will happen to your child as part of this study, but he/she might feel discomfort when we prick him/her to draw blood sample. You or/and your kid might also not feel comfortable with some questions we will ask you during the study.

Possible Benefits

You and your participating child can feel good about helping us to learn more about how we could improve on patients care when your child take part in this research. Moreover, if test and treatment for malaria before operation is found to have positive results on surgical outcomes then it would have been of benefit to your child in case, he/she gets enrolled in the group tested for malaria**.** Generally, this study would help improve services in the facility provided by health workers.

Confidentiality

We will protect information about your child to the best of our ability. Your child will not be named in any reports. Only hospital staffs trained to collect information during this study may sometimes look at your child's research records.

Compensation

Cost of laboratory tests and antimalarial drug will be paid for with or without National Health Insurance. For each follow up visit to the hospital, your child would be given an amount of ghc 20.0 to compensate for cost of transport. There will be no other compensation for your child's participation. Cost of surgery and hospital admission(s) will not be absorbed by this study.

Voluntary Participation and Right to Leave the Research

Your child does not have to be part of this research if he/she does not want to. He/she is also free to withdraw from the research at any time if he/she or you so wish. No one will be angry with him/her if he/she does not want to participate.

Contacts for Additional Information

You may contact me (as the Principal Investigator) by using the following information in case of any concern with regards to this study.

Forster Amponsah-Manu

Department of Surgery, Eastern Regional Hospital, Koforidua

Tel: 0244655108

Email address: foster_amponsah@yahoo.com

If you have any questions about your child's rights as a research participant or you require further clarification on ethical issues on behalf of your child, you can contact the ERC via the under stated information.

Nana Abena Apatu

Administrator, GHS-ERC

Tel: 0503039896

Email address: ethics.research@ghsmail.org

Appendix H: Research questionnaire/ Case report form

QUESTIONNAIRE

IMPACT OF PERI-OPERATIVE MALARIA SCREENING AND TREATMENT ON SURGICAL OUTCOMES AT THE EASTERN REGIONAL HOSPITAL, KOFORIDUA: A SINGLE-BLIND RANDOMISED CONTROLLED TRIAL

Folder no _____ Department_____

Initials _____

INCLUSION / EXCLUSION

Mark the box with a √ or X for each question. The patient is excluded from participating in the study if any of the exclusion boxes are marked

		Yes	No
1	Patient undergoing surgical operation involving ≥5cm skin incision		Exclude
2	Understands written and oral information or has been explained in vernacular		Exclude
3	Patient or parent authorisation of informed consent effected/signed		Exclude

4	Patient will require a referral immediate post-op	Exclude	
5	Receiving or will receive in-patient care for a medical condition that may prolong patient's hospital stay	Exclude	
6	Has an active surgical site(abdomen) infection	Exclude	
7	Had abdominal surgery in the last 30days	Exclude	
8	Hypertensive crisis evidence by BP ≥180/120mmhg + end organ dysfunction	Exclude	
9	Uncontrolled blood sugars within 24hrs pre-op or evidence of DKA	Exclude	
10	Crisis in a sickle cell diseased	Exclude	
11	Acute severe asthmatic attack pre-op	Exclude	

12	Decompensated heart failure	Exclude	

RANDOMISATION

Arm Assignment /Randomisation

Enrolled subjects will be equally randomised into two arms Control – "No malaria screening" and Intervention – "Screening & treatment for malaria" based on an alternate randomisation scheme into two arms.

Randomisation will take place after verification that the subject does not meet the exclusion criteria above.

The sealed randomisation envelope may now be opened and the subject randomised to one of the study arms.

Patient was randomised to Malaria screening (Intervention) □

No malaria screening (comparison) □

Randomisation Code_____

DEMOGRAPHICS

Where does patient live_____

Residential address_____

Mobile telephone number_____/ house no_____

Sex: Man □ Female □ Age: _____ years

Level of education _____ Occupation _____

Average monthly income _____

Regular use of Insecticide Treated Net: Yes □ No □

Intake of antimalarial medication in the last 1 month Yes □ No □

Weight _____kg Height _____cm

Is the patient a smoker? Yes □ No □ ex-smoker □

If yes, on a daily basis? Yes □ No □

How many cigarettes / cigars / tobaccos per day _____

Dose the patient drink alcohol? Yes □ No □

If yes, on a daily basis? Yes □ No □

What type alcohol _____ Bottles/tots per day _____

Steroid use Yes □ No □

If yes, what type? Topical _____ Systemic _____

HISTORY / PHYSICAL EXAMINATION

Please note specific information below

Key symptom(s): _____

Duration of symptoms _____days _____hours

History and year of any previous surgery Yes □ No □

If yes, please specify_____

_____

Does the patient have any other **RELEVANT** medical history and / or diseases?

Yes □ Please specify below No □

Diseases or symptoms	**System code**	**Yes**	**No**
		□	□
		□	□
		□	□
		□	□

		☐ ☐
		☐ ☐
		☐ ☐
		☐ ☐
		☐ ☐
		☐ ☐
		☐ ☐
		☐ ☐

System code:

1=Allergies	6=Gastrointestinal	11= Hematological
2=Eyes, ears, nose and throat	7= Genito-Urinary	12=Dermatological
3=Cardiovascular	8=Musculoskeletal	13=Immunological
4=Respiratory	9=Neurological	14=Psychiatric
5=Liver and biliary	10=Endocrine	99= Other

MEDICATION

Has the patient been using any medication prior to admission / surgery?

Yes □ Please fill in the Medication form below No □

MEDICATION FORM

Generic name	Dose	Duration
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

OBS & GYN DATA (If applicable)

Parity _____

Pregnancy Yes □ No □

If yes, gestational age _____

Date of last SP received _____

KEY EXAMINATION

GCS Normal □ Abnormal □ _____

Temperature Normal □ Abnormal □ _____

Blood pressure Normal □ Abnormal □ _____

O2 saturation Normal □ Abnormal □ _____

Heart disease Normal □ Abnormal □ _____

Lung disease Normal □ Abnormal □ _____

Palpation of abdomen Normal □ Abnormal □ _____

BLOOD WORKUP

	Pre op	**Week 1**	**Week 2**	**Week 3**	**Week 4**
Date (dd-mm-yyyy)					
Hbg					
WBC					
Neutrophils					
Platelets					

Urea					
Creatinine					
Sodium					
Potassium					
Serum protein					
Serum albumin					
ALT					
ALP					
GGT					
INR					
aPTT					
BF for MPs					
Parasite count					
Parasite type					

SURGICAL FACTORS

Disease condition(s)/Indication for surgery _____

Type of Surgery - laparotomy_____ with_____

Hernia Repair_____

Appendectomy_____

Salpingectomy_____

Caesarean section_____

Myomectomy_____

Hysterectomy_____

Others (specify)_____

Wound classification Clean_____

Clean contaminated_____

Contaminated _____

Dirty_____

ASA grade 1_____2_____3_____4_____

Urgency of surgery Elective_____ Emergency_____

Surgeons grade House officer_____

Medical officer_____

Resident _____

Specialist _____

Snr Specialist_____-

Consultant _____

Type of anaesthesia Spinal_____ General_____

Pre-op diagnosis_____

Intra-op diagnosis_____

Post-op diagnosis_____

Pharmacological treatment received: _____

_____

_____

_____

STUDY VARIABLES

Screened for malaria_____ Not screened for malaria_____

If screened results Positive _____

Negative _____

If positive complete treatment taken yes_____ No_____

Negative who later became symptomatic and positive for malaria?

Yes_____ No_____

If yes how many days post op_____

Not screened who later became positive Yes_____ No_____

If yes, how many days post op_____-

FOLLOW-UP DATA

SURGICAL OUTCOMES

Surgical site infection Yes_____ No_____

If yes, what type superficial _____

Deep_____

Organ space_____

On what day post-op did SSI develop _____

Other post-operative complication Yes_____ No_____

If yes, what type? Tick as applicable Haemorrhage_____ POD_____

Pneumonia_____ POD____

Pleural effusion_____ POD____

UTI_____ POD_____

DVT_____ POD_____

Others (specify)_____

Surgical re-intervention Yes_____ No_____

If yes, how many days post op _____

30-day readmission Yes_____ No_____

If yes, how many days post op _____

Death within 30 days Yes_____ No_____

If yes, how many days post op _____

Number of days on admission before discharge_____

Appendix I: Standard operating procedure for data collectors

IMPACT OF PERI-OPERATIVE MALARIA SCREENING AND TREATMENT AT THE EASTERN REGIONAL HOSPITAL, KOFORIDUA: A SINGLE-BLIND RANDOMISED CONTROLLED TRIAL

Standard Operating Procedure (For Data Collectors)

1. Approach client reporting for surgery
2. Pick one transparent envelop containing all research documents
3. Provide client with a little background of the study
4. Make client aware of ethical clearance by Ghana Health Service
5. Make client aware that not being part of the study would not affect the quality of his/her care in the hospital
6. Provide client with participant information sheet
7. If client is a minor:
    i. Involve parent/guardian and provide parental information sheet
    ii. Provide child assent form to a child who is 7years and above
8. If client is unable to read/understand what is on the information sheet involve an appropriate interpreter
9. Obtain informed consent and make client endorse (either by signing or thumbprinting) on the consent form
10. Apply inclusion/exclusion criteria on page 1 and 2 of the questionnaires
11. If client qualifies, apply randomization procedure as follows:
    i. Randomly pick a white coded envelop

ii. Open envelop and place participant according to the study arm inscribed on the enveloped sheet i.e., either malaria screening and treatment or no malaria screening

12. Complete questionnaire accordingly

Appendix J: Standard operating procedure for medical laboratory scientists

Collection of blood sample by:

A. Venipuncture

Step	Action
1	Verify the patient's identity and give assurance.
2	Perform hand hygiene and wear examination gloves.
3	Select the appropriate site for venipuncture. Apply a tourniquet on the upper arm of the patient and look for large minimally moveable vein.
4	Clean the site the alcohol, and alcohol, and allow to air dry.
5	Insert the needle (attached to a syringe or vacutainer tube), and steadily draw blood.
6	Release the tourniquet, remove needle and the press firmly on the venipuncture site with piece of dry cotton.
7	Transfer the blood to the EDTA-containing tube, and mix gently by inverting the tube six to eight (6-8) times.
8	Label the EDTA-containing tube with the patient's name, date and time of collection.

B. Finger-prick

Step	Action
1	Verify the patient's identity and give assurance.
2	Perform hand hygiene and wear examination gloves.
3	Clean the third finger from the thumb (Ringer finger) with 70% ethanol or alcohol swab; allow to dry.
4	Prick the side of the finger ball with new sterile lancet.
5	Wipe off the first drop of blood with a clean dry cotton.
6	Gently squeeze finger to express blood as a ball and collect blood using micropipette or inverted cup.

Preparation of thick and thin blood films for malaria microscopy.

Step	Action
1	Gently mix the blood in the EDTA-containing tube before use, or use capillary blood.

2	Place a clean, labeled microscope slide on a standardized thick (1.2 cm or 12mm in diameter) and thin blood film-slide preparation template.
3	Collect 2µl of blood with a micro pipette and, and transfer the blood onto the small circle of the slide on the template.
4	To prepare the thin film, place the edge of the clean "spreader" slide at an angle of 45˚ in front of the blood drop intended for the thin film.
5	Slowly pull the "spreader" back until it touches the drop of the blood and allow the blood to spread along the edges of the spreader but not the end of the slide.
6	Rapidly push the spreader forward (away from the centre) in a smooth, continuous motion, until the spreader leaves a "feathery or tongue-shaped" end for the thin film.
7	To prepare thick film, transfer 6µl of blood with a micro pipette onto the large circle of the slide on the template. Using the tip of the micro pipette tip, cover slip, or the corner of a glass slide swirl the blood making a circle of about 1.2 cm or 12mm in diameter as per the template.
8	Dry the prepared slides horizontally in a slide folder with a cover. If rapid drying is required, dry the films with lower heat from a hair-dryer at 30cm distance for 5 seconds or a warmer set at 37˚c and below.

Procedure for staining blood smears using giemsa stain

Step	**Action**
1	Prepare 10% Giemsa stain working solution, and place it in a small container
2	Fix the thin film by using a Pasteur pipette to carefully drop methanol unto thin film only. **OR** Dip the thin film in to a small container or beaker containing methanol for 2 seconds.
3	Allow the blood film to air dry placing it flat on the drying rack or tray.
4	Place the slides flat on the staining rack or tray with the film blood facing upward.
5	Using a Pasteur pipette gently drop about 3ml of Giemsa stain working solution per slide onto the blood films within 15 minutes of preparation.
6	Set the timer to 10-15 minutes for the staining.
7	Gently flood the slides by dropping buffered water at the labelled end to float off iridescent scum on the stain.
8	Place the slides laterally in a drying box and allow to air-dry.

9	Discard the remaining 10% Giemsa solution

Examining the stained blood film

Step	Action
1	Place a drop of immersion oil on the Giemsa-stained blood film.
2	Place the-stained blood film on the microscope stage with the label to the right.
3	Place the thick film under the 10x objective lens and focus
4	Switch to the 100x oil immersion objective lens to touch the oil. Using the fine adjustment, focus on the blood film.
5	Scan and select a well-stained, even portion of the blood film.
6	Start with the field on the bottom right part of the film, and then move the slide to the left, field by field.
7	When the other end of the film is reached, move the slide upwards, then to the right, field by field.
8.	Repeat steps 6 and 7 till examination is completed in about 10 minutes

Determining whether a thick film contains malaria parasites and identifying the species.

Step	Action
1	Examine the thick film under the oil immersion objective, field by field , horizontally or vertically
2	Read a minimum of 100 fields before declaring that no malaria parasites were seen
3	If parasites are found, scan additional fields to increase the chance of identifying mixed infection
4	The thin blood film should always be examined to confirm malaria parasites when parasites are seen in the thick film
5	Determine all species and stages observed, and record them on worksheet

Examining the thin film to confirm species and mixed infections

Step	Action
1	The thin blood film must be examined to confirm species and mixed infections.
2	Place a drop of immersion oil on the feathery edge of the film
3	Move from the 10x lens to the 100x oil immersion lens, and focus on the thin film.
4	Read the thin or feathery edge of the film, moving from one field to the next, vertically first and horizontally.

5	Scan the film until all the species have been confirmed.

Performing parasite count on a thick film and calculating parasite density

Step	Action
1	Place the glass slide on the microscope with the label to the right
2	Determine the presence of malaria parasites, identify species and stages, and record
3	Starting at the bottom right of the film, look for a typical field with both parasites and white Blood Cells (WBC). Start counting.
4	Click the assigned tally counter for each parasite or WBC observed.
5	After counting all the parasites and WBC in one field, move to the next, and repeat the counting procedure.
6	Depending on the number of parasites observed, stop counting after you have counted 200-500 WBCs. Thus, If you have counted ≥100 and more parasites in 200 WBCs , stop counting, perform calculation and record the results as parasites per microliter (p/µL) If you have counted <100 parasites in 200 WBCs , continue counting until 500 WBCs, stop counting perform calculation and record the results as parasites per microliter (p/µL)
7	Count all parasites and WBCs in the final field.
8	Record the actual numbers of parasites and WBCs counted on an appropriate worksheet.
9	Calculate and record the parasite density in the worksheet/ logbook using the formula below:

Performing parasite count using thin when more than 100 parasites per field is counted in the thick film and calculating parasite density

Steps	Action
1	If more than 100 parasites per field is counted on the thick film, the thin film is used for parasites quantification.
2	Locate a field where RBCs are evenly distributed (single layer). Start counting from lower edge of the thin film moving up and down along the vertical axis
3	if infected Red Blood Cells (RBCs), are present, count all parasitized RBC, and record

4	Using two tally counters, count parasitized and non- parasitized RBC until a total of 5000 RBCs is reached Alternatively select area of approximately 250 RBCs per field, count parasitized RBCs in 20 fields (5000 RBCs)
5	After counting all the parasitized and non-parasitized RBCs in one field, record the result, move to the next field, and continue the same counting procedure
6	After counting, when 5000 RBCs have been reached, count all parasitized and non- parasitized RBCs in the last field
7	Calculate the parasite density from patient's actual RBC count, If this is not available, use an estimated average RBC of 5,000,000/µL. Calculate the parasite density from the formula: Parasite Density= Number of parasitized RBCs × 5,000,000 RBCs/µL Number of RBCs counted

Recording and reporting malaria microscopy

1. Record in the microscopy section of the laboratory register the patient's identification number, the date of examination, presence or absence of parasites, species, stages and density.

Malaria microscopy daily log sheet

Patient ID	Sex	Age	Result	Species	Stage	Density (p/µl)	Initials

2.Record time of release of results in the dispatch book

3.Prepare a report for the clinician and/or patient as follows
*For negative results, record as " No Malaria Parasites seen"
('No parasites seen' should be used rather than "Negative").

*For positive results report in the following order: species, stage and density. For example *p.falciparum* trophozoites = 42000 parasites/µL.