SCHOOL OF PUBLIC HEALTH

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UNIVERSITY OF GHANA

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

BY

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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).

Post-operative Hemorrhage: Bleeding after surgery that occurs at or near body tissue or organ where operative procedure was carried on. This ranges from bleeding that occurs at the skin incision to bleeding that occurs in a deep tissue or organ involved during the operation. Bleeding may occur immediately or delayed upto 3 to 4 weeks after surgery.

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 hospitalisation** is said to have occurred. For the purpose of this study any stay beyond 7days post-op will be regarded as prolonged hospitalization.

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

Peri-operative 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 Anesthesiology
BCIH	BEIT CURE International Hospital
BF for MPs	Blood Film for Malaria Parasites
CDC	Centers for Disease Control and Prevention
DALYs	Disability Adjusted Life Years
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

Abstract

Background: Peri-operative malaria screening and treatment is not done routinely in the practice of surgery in Ghana. However, there have been reports from few cross-sectional studies revealing a link between peri-operative malaria infection and poor surgical outcomes in Ghana and other parts of the world. Meanwhile adverse surgical outcomes continue to pose significant socio-economic burden on patients, families, communities and health systems globally particularly in low-middle-income countries like Ghana. We seek to determine impact of peri-operative malaria screening and treatment on outcomes of patients who undergoes elective surgeries at the Eastern Regional Hospital, Koforidua.

Methods: This research would be a single-blind randomised controlled trial (RCT) where patients scheduled for elective surgeries would be randomly assigned to intervention and comparison groups. Participants in the intervention arm will undergo perioperative screening for malaria parasite(s) and will be treated before surgery, if found to have the parasite(s). The control arm will not be screened at all for malaria and would not receive any malaria treatment. These two groups of participants would be followed-up to 30 days post-operation while outcomes including surgical site infection, haemorrhage, prolonged hospitalisation, readmission and death will be assessed and recorded. The difference in incidences of these outcomes across the two arms will be analysed by intention to treat using Stata 16 statistical software, and findings would be presented to the School of Public Health, University of Ghana.

Expected Outcome: This study is expected to show relevant results or findings to help inform policy change in surgical practice in Ghana and all other malaria-endemic countries.

Keywords: Impact, Peri-operative, Malaria, Screening, Surgical Outcomes, Single-blind

CHAPTER ONE

1.0 Introduction

1.1 Background

The essence of surgical care in global public health cannot be overemphasized. The need for surgery in the clinical setting has increased due to epidemiological transition of diseases. The global volume of surgery has seen a significant rise 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 (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, Jamison, Cherian & McQueen, 2008).

Public health intervention, including surgery, should be able to significantly make a positive impact on the quality of life of the population. Monitoring and evaluation involving outcome measures are the best ways of assessing impact.

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,

increases with preoperative malaria infection. It was found that "malaria infection may increase 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 transplacentally from mother to child (in-utero).

Malaria is typically characterized by fever, chills, malaise, headaches, myalgia, nausea and vomiting. Symptoms of malaria are in a spectrum from mild (uncomplicated) to life-threatening. 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 uses a 3days course of oral artemisinin-based combination therapy (ACT). Parenteral artemisinin therapy, such as artesunate, is reserved for severe cases (World Health Organisation (WHO), 2015).

In surgical practice, it is recommended that acute episodes of malaria should be resolved before any elective surgery (Bashford & Howell, 2017). In some malaria-endemic areas, routine screening before surgery is undertaken. It is, however, unknown if asymptomatic malarial parasitaemia has impact on surgical outcomes (Soltanifar, Carvalho & Sultan, 2015).

1.2 Problem statement

Burden of malaria is high in Ghana. Malaria has severe effects on all body systems that includes the blood and coagulation, renal, hepatic, respiratory, cardiovascular and nervous systems and

therefore could pose challenges to anaesthesia (Soltanifar et al., 2015) which could in turn affect 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, Heger & Husum, 2004). However, in our setting malaria screening is not routinely done pre-operatively.

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 peri-operative 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.

There is biologic plaucibility of substantial benefit in screening for malaria in the surgical patient based on the endemicity of the disease and the systemwide effects on the infected person. Literature on the malaria and its effects on surgical outcomes are 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 is to determine impact of peri-operative 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. Suppose it becomes well established that malaria screening and treatment significantly impacts surgical outcomes, it may inform policymakers to include such programmes 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 Research Hypothesis:

There will be no difference between the surgical outcomes of patients who are screened and/or treated for malaria peri-operatively and those who are not screened or treated for malaria.

1.5 Objectives

1.5.1 Main objective: To determine impact of malaria screening and treatment on surgical outcomes of patients undergoing elective surgeries at the Eastern Regional Hospital, Koforidua.

1.5.2 Specific objectives

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

2. To determine incidence of poor surgical outcomes (surgical site infection, post-op hemorrhage, readmission, and death) among patients at the Eastern Regional Hospital, Koforidua.

3. To determine incidence of prolonged hospitalisation among post-surgical patients at the Eastern Regional Hospital, Koforidua.

4. To determine impact of peri-operative malaria screening and treatment on the incidence of poor surgical outcomes at the Eastern Regional Hospital, Koforidua.

CHAPTER TWO

2.0 Literature review

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, McDonald & Dobbie, 1982; Oster, Koontz & Wyler, 1980).

Acute pancreatitis has been reported in patients with severe *falciparum and vivax* malaria in India with a mortality rate of 20-30% (Abhilash, Ahmed, Sathyendra & Abraham, 2016; Mandal et al., 2011; Mohapatra & Gupta, 2011; Seshadri, Dev, Viggeswarpu, Sathyendra, & Peter, 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.

These rare surgical complications of malaria were reported in India's tropical geography, similar to Sub-Saharan Africa. 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. 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 randomided 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% overral **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, Swart, and Duvenage, 2020). Tefera, Feyisa, Umeta, & Kebede (2020) defined **prolonged length of stay** (PLOS) as hospital stay above 75^{th} 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.

2.3 Impact of Peri-operative 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, Heger & Husum, 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).

CHAPTER THREE

3.0 Methods

3.1 Study design

This research would be a randomised controlled trial (RCT) where patients scheduled for elective surgeries would be randomly assigned to intervention and comparison groups.

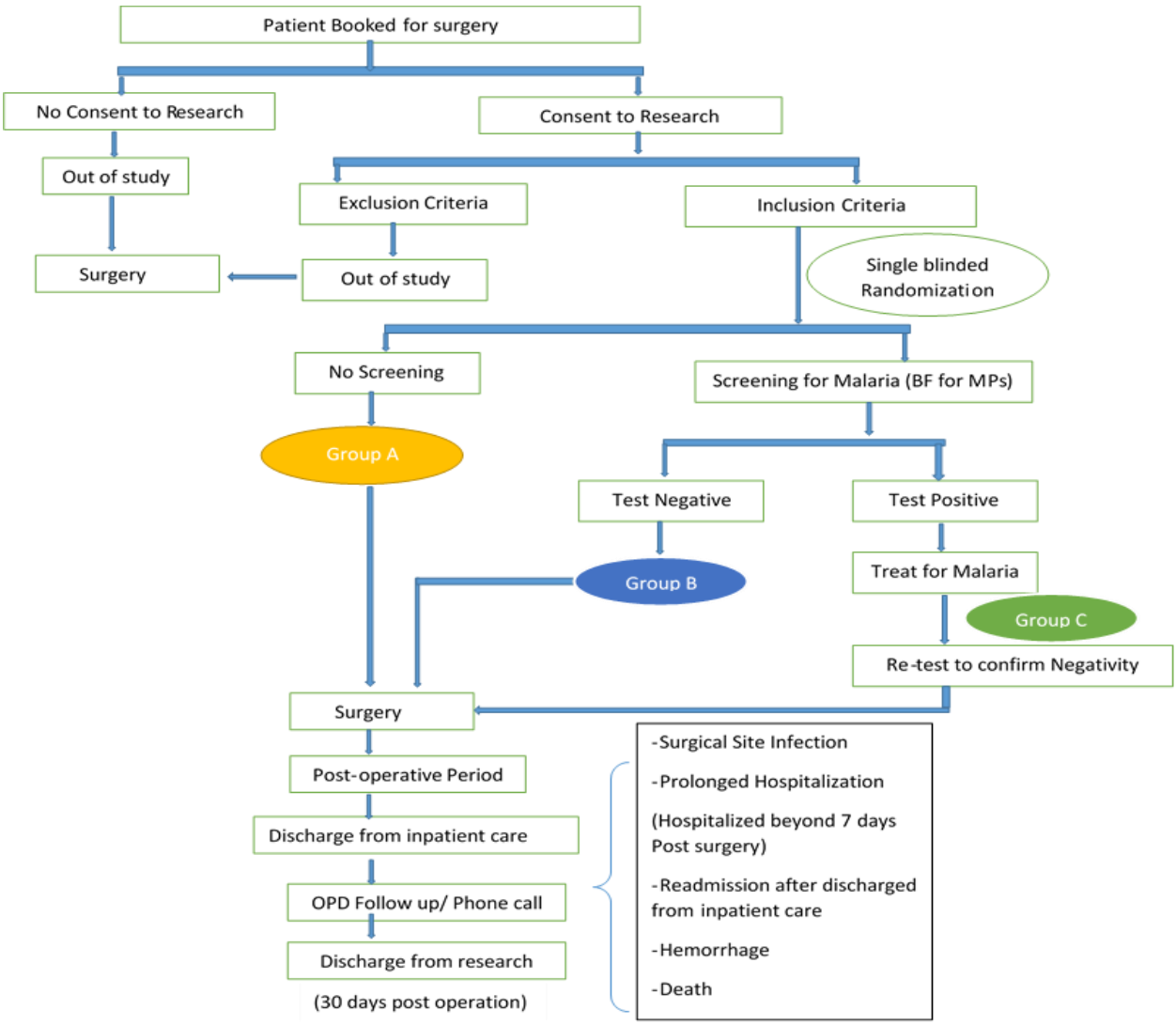

Figure 1: Flowchart showing randomised controlled trial designed to assess impact of malaria screening and treatment on surgical outcomes

3.1.1 The intervention

In the intervention group, participants will undergo perioperative screening for malaria parasite(s) using microscopy. Participants who are found to have malaria parasitaemia will receive standard malaria treatment with artemisinine combination therapy (ACT) whether symptomatic or not in accordance with the standard treatment of malaria. The comparison group will not be screened at all for malaria and would not receive any malaria treatment.

3.1.2 Trial Outcome Evaluation

The screened-positive (and treated) and the screened-negative sub-groups (intervention group) will make up known malaria-free surgical patients. On the other hand, the unscreened (comparison) group will be assumed to have an equal risk of malaria parasitaemia as all the participants before the screening and similar general population. Thus, the unscreened control group will enable the study to compare surgical outcomes between people who truly do not have malaria parasitatemia and the general population.

3.1.3 Follow-up of study participants

Each patient would be followed up weekly, for a period of 30 days post-op, during which the length of hospital stay, development of surgical site infections, hemorrhage, readmission and death data will be collected. Questions about malaria symptoms would be asked at each follow-up visit of participants in the intervention group to be sure they remain free from malaria during the 30days post-op.

3.2 Study setting – Eastern Regional Hospital, Ghana

The study would be conducted at the Surgical and Obstetrics-Gynecology 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. 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 general surgeries and obstetrics-gynaecology operations, and the other is mainly for obstetrics. Nurse anaesthetists administer anaesthesia for all surgeries in the hospital. There are three specialist surgeons, one consultant surgeon, and four obstetrician-gynaecologists who operate the majority of the surgical cases in the hospital. These specialists are being assisted by residents and medical officers in each department who have basic surgical skills.

3.3 Study population

The study will be made up of patients booked for elective surgeries at both the surgical and obstetrics-gynaecology departments of the Eastern Regional Hospital, Koforidua.

3.3.1 Inclusion criteria

- Patient must be at least 6 months old, since under 6 months and congenital malaria are rare.
- Patient must undergo an elective surgical operation involving ≥5cm skin incision.
- Patients who consent to participate in the trial.

3.3.2 Exclusion criteria

The following categories of patients shall be excluded from this study:

- Surgical patient with uncompensated comorbidities.
- Patient is undergoing surgery but has had previous surgery in the last 30days and before time of recruitment. This will help avoid reporting of surgical outcomes which may be from surgery performed prior to recruitment.
- Patient is undergoing surgery but has an active surgical site infection or any other surgical outcome from procedure that took place before time of recruitment. Recruitment must preceed the onset of surgical outcomes.

3.4 Sample size determination

Assuming the primary outcome is surgical site infection involving binary data (i.e., present or absent within the 30days post-op), the miniumum sample size for both arms, N for RCT is given by:

$$N= 2 \times (\mathbf{Z_{\alpha/2}+ Z_{1-\beta}})^2[p_1(1- p_1)+ p_2(1- p_2)]/(p_2-p_1)^2$$ (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

$1-\beta$= 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 will help reduce 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 significanc (α) of 5%, minimum sample size 'N' required for both arms is 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) increment on the size will be applied. Therefore, **a minimum of 348** participants would be recruited for this study. This will include **174 participants each** for control and intervention groups.

3.5 Sampling procedure

General surgery and obstetrics-gynaecology constitute distinct surgical specialities. The sample size will be equally reserved for each sub-group to ensure an adequate representation of the two different sub-groups. Thus, 174 participants comprising 87 screened and 87 unscreened would be sampled from each department.

In each department, assigned assessors would first evaluate each patient's eligibility to participate in the study. After consent, an eligible participant would be randomly assigned to either screening or comparison group by a computer generated randomisation scheme. Numbers will be generated randomly and put in an opaque envelope. The potential participant will be made to choose an envelope and then open to show the number in the envelope to a study coordinator. The coordinator will then check the trial arm that the participant has been assigned to and will then take the

participant through either screening and treatment or to continue their preparation for the surgery. For minors, a parent or caretaker will consent on their behalf whilst they give an assent to participate in the study. Also, any patient who falls in the unscreened category and develops sign(s)/symptom(s) of malaria pre-op or during follow-up shall be screened and treated if positive. The recruitment will be done over a period of three months to allow for variability in the backgrounds of the patients enrolled into the trial.

3.6 Data collection

Informed consent: All participants will be consented for participation of the study. A participant information sheet will be read out to the participants which will outline the purpose of the study and mention that it is to know whether treating malaria prior to surgery may be beneficial. The information sheet will also explain to the participant that **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.** It will further be noted that the findings of the study will be used to improve services in the facility for future care provided by health workers. It will help to improve the care experiences of future surgical clients across the country. As part of the information sheet, it will be explained to the participant that there may be the possibility of pain, infection at the site or bleeding during the blood collection but doctors will be on alert to support in the management whenever bleeding occurs. Participants will be assured that the blood draw will be made as painless as possible. Sterile procedures will be used for the sample collection to prevent infections and where they occur, they will be treated promptly. They will be assured that they are free to refuse to participate in the study without explanation or effect on the care they receive in the hospital. The time taken for responding to the questionnaires may also be discomforting but again the participant will be assured that they should let the team know

when they felt any discomfort and are free to refuse to respond to any questions they deem sensitive. The questionnaires on the facilities will take approximately 20-40 miuntes to complete. Where data are available, abstraction of facility records on complications, admissions and mortality will be obtained from the participants folders. Participants will be assured of their freedom to refuse participation or withdraw from the study at the start, mid-way through the data collection and at the end without any effects on the care they receive in any facility across the country. Respondents will be assured that the data they provide will be treated with utmost confidentiality and will only be accessible to the leadership team of the study. Where their responses are to be reported, only aggregate figures will be presented, and no data will be traceable to the respondent. Participants will be allowed to ask questions or seek clarification on any aspects of the assessment they do not understand. Thereafter, they will be invited to willingly consent to participate in the assessment. Consent for participation will be indicated with a signature or thumbprint (in the presence of a chosen witness who will counter-sign to confirm consent for respondent participation in the study). Upon consent, each participant's demographics and baseline clinical data will be first taken using questionnaire which has been pre-tested in a similar facility.

At each post-operative follow-up, patient would be assessed for the occurance of predefined outcomes. A checklist will be developed to elicit the signs and symptoms of complications and both patients' self-reported outcomes and clinical examination findings as well as hospital records will be used to determine the occurrence of adverse surgical outcomes in each arm of the trial. The date each outcome occurs will be recorded accordingly together with other important details about the outcome.

3.7 Data processing and analysis

Folder numbers and codes will identify respondents to facilitate follow up. The data will be thoroughly inspected; irrelevant, missing or inaccurate observations would be dealt with accordingly. Data will be entered into Microsoft Excel 2010 and exported to Stata version 16 for statistical analysis.

Research findings will be presented in texts, tables, and charts. Baseline characteristics would be described by percentages for categorical variables, and by means or medians for continuous data.

Analysis will primarily be by intention-to-treat (ITT) where a subject will be regarded as belonging to the arm to which they were initially randomized at enrolment irrespective of the treatment they received. A sub-analysis will be done per protocol where the participant will be regarded as belonging to the arm they actually experienced -whether screened and treated or not irrespective of the arm they were randomized to at enrolment.

A bivariate analysis will be conducted by way of 2x2 table, involving the presence/absence of each surgical outcome across the two groups. Incidence of each outcome among the intervention and control groups will then be analysed, and incidence risk ratio will be determined.

Confounders are going to be equally distributed to each arm of the trial. A baseline comparison of the characteristics of the respondents will be made to ensure the randomization obtained a balance on key confounders. Where there are statistically significant differences between the two arms of the study on a confounder, it will be adjusted for during the analysis.

Length of stay (LOS) will be used to derive prolonged length of stay (PLOS), in other words prolonged hospitalisation which occurance will be ticked when the length of stay exceeds 7 days before discharge from inpatient care.

Statistical significance will be assessed at 5% level.

3.8 Ethical consideration

The proposal would be used to seek the Ghana Health Service Ethics Review Committee's (GHS-ERC) approval.

Prior to that, clearance will be obtained from the medical director or any person appointed to represent them at the management level of the hospital for the conduct of the data collection. Respondents will be interviewed in a secluded place to ensure auditory and visual privacy for the interviews. As explained in earlier sections, all participants will provide written informed consent prior to participation in the study. Privacy and confidentiality of the process of data collection and data handling will be assured to all participants. All participants will be assured of confidentiality around the data they provide and that no information will be traceable to them when they participate in the study. They will be assured that the report will present only aggregate figures and percentage responses rather than those of individuals.

No patient would be denied or given delayed treatment for any condition during the course of this study.

All study activities will be conducted in strict compliance with national COVID-19 protocols including wearing of personal protective equipments (PPEs), handwashing, social distancing with participants and regular hand sanitization throughout, although the study is going to be facility-based (as outlined in section 3.9).

3.9 COVID-19 precautions

The entire conduct of the study will be in strict compliance with the national COVID-19 protocols as being implemented at the Eastern Regional Hospital. All data collectors will be provided full personal protective equipment (PPE) and will be trained to wear these throughout the data

collection process. These PPEs will include face masks and portable alcohol-based hand sanitizer bottles to be hang on clothing to allow for easy access and regular use during the data collection. Social distancing (at least 2 metres) will be observed in all interactions with all persons during the data collection. Researchers will also wash their hands with soap under running water and sanitize with alcohol-based hand sanitizers before entry into the premises of any facility for the study. It would be ensured that all assessors have received at least two jabs of the COVID-19 vaccines before participating in this study.

During the interactions with the respondents, assessors will be trained to constantly hand-sanitize and during the process educate the respondent on the national COVID-19 protocols including regular handwashing, hand sanitizing, wearing of face masks and social/physical distancing. In the unlikely event that a participant does not have a face mask, extra disposable face masks will be provided to the assessors to hand out to the participant free of charge and teach them how to wear and take it off safely.

3.10 Limitations

It may be difficult to generalise study findings, as this study would involve only one center. The limitted timelines required to submit final dissertation to the School of Public Health may not allow a multicenter study.

Direct effect of malaria parasitemia on surgical outcomes would not be studied due to the ethical obligation on the researcher to treat for malaria when detected. This study would only therefore look at the surrogate effect of malaria on surgical outcomes to inform policy change.

3.11 Funding

The student has been awarded a President's Malaria Initiative (PMI) scholarship.

3.12 Timelines

The study will be conducted between March 2022 to November 2022 accrding the the Gantt chart presented in table 1. This will include time from the development of the study protocols to the final submission to the University of Ghana School of Public Health. Disemination of the findings will then follow after the submission even though preliminary findings will be presented to stakeholders of the Eastern Regional Hospital where the study was conducted.

Table 1: Gantt Chart showing the timelines to the research study.

Study Activity	Mar	April	May	Jun	Jul	Aug	Sep	Oct	Nov
Proposal development									
Ethical submission/approval									
Data collection									
Data analysis and writing									
Supervisor's final approval									
Submission									

3.13 Budget

In total, an amount of **Eighty-six thousand six-hundred and eight Ghana cedis (GHS 86,608)** is the estimated budget for the study. The line item-by-item breakdown of the costs are as shown in table 2.

Table 2: Estimated budget for the study and justification

Budget items	Cost (GHS)	Justification
Internet bundle (DATA)	200.0	Online literature search and mails
Transportation/fuel	1,500.0	Travelling and meeting with mentors and supervisors

Training of data collectors	500.0	Per diem per head for 2 data collectors
Data collectors allowance	6,000.0	1000ghs per head per month for 2 data collectors, for 3 months
Participants compensation	6,960.0	Cost of travel during follow-up_ ghc20 per head
Ethical approval	50.0	Processing fee
Stationary/printing and comb binding	120.0	For three final copies of a manimum of 80 pages/leaves
Stata software for analysis	634.0	Robust and more efficient software for data analysis
Laboratory investigations	70,644.0	FBC@ghs25, BUE&CR@ghs60, Bf@ghs8, LFTs@ghs50, clotting@ghs60 per head
TOTAL	**86,608.0**	

REFERENCES

Abba, K., Deeks, J.J., Olliaro, P., et al. (2011). Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. Cochrane Database Syst Rev. 2011;(7):CD008122.

Abhilash, K.P., Ahmed, A.S., Sathyendra, S., & Abraham, O.C. (2016). Acute pancreatitis due to malaria: A case report of five patients and literature review. J Family Med Prim Care 2016; 5:691-4.

Bashford, T. & Howell, V. (2017). Tropical medicine and anaesthesia 1. BJA Education, 18(2): 35e40 (2018) doi: 10.1016/j.bjae.2017.10.004

Bediako-Bowan, A., Owusu, E., Debrah, S., Kjerulf, A., Newman, M.J., Kurtzhals, J. A. L., & Molbak, K. (2020). Surveillance of surgical site infection in a teaching hospital in Ghana: a prospective cohort study. J Hosp Infect. 104(3):321-327. Doi: 10.1016/j.jhin.2020.01.004

Borchardt, R. A., & Tzizik, D. (2018). Update on surgical site infections: The new CDC guidelines. JAAPA : official journal of the American Academy of Physician Assistants, 31(4), 52–54. https://doi.org/10.1097/01.JAA.0000531052.82007.42

Centers for Disease Control and Prevention. (2007). CDC and malaria

Centers for Disease Control and Prevention. (2010). Healthcare-associated infections: surgical site infection. Retrieved online on the 30th April 2022 at https://www.cdc.gov/hai/ssi/ssi.html

Centers for Disease Control and Prevention. (2014). Morbidity and mortality weekly report. Available from URL: http://www.cdc.gov/malaria/references_resources/mmwr.html#surveillance (accessed October 2014).

Debas, H. T., Donkor, P., Gawande, A., Jamison, D. T., Kruk, M. E., & Mock, C. N. (Eds.). (2015). Essential surgery. Disease control priorities (3rd ed., volume 1). Washington, DC: World Bank. doi:10.1596/978-1-4648- 0346-8. License: Creative Commons Attribution CC BY 3.0 IGO

Drugs.com (database online). (2018). Artemether and Lumefantrine. C1996-2018. Updated November 15, 2018. Available at: https://www.drugs.com/ppa/artemether-and-lumefantrine.html. Accessed December 21, 2018

Eipe, N. (2004). Malaria and postoperative fever 3] Acta Anaesthesiol Scand 481217 https://doi.org/10.1111/j.1399-6576.2004.00494

Garnham P.C.C. (1970). The role of the spleen in protozoal infections with special reference to splenectomy. Acra Trop 1970; 27: 1-14

Gibney, S.E.J., (1990). *Surgical aspects of malaria*: Br. J. Surg. 1990, Vol. 77, September, 964-967

Hendriksen, B. S., Morrell, D., Keeney, L., Candela, X., Oh, J., Hollenbeak, C.S., Arkorful, T. E., Newton, C., & Amponsah-Manu, F. (2018). Risk factors for readmission and length of inpatient stay in rural ghana following exploratory laparotomy. *Journal of the West Africa College of Surgeons*, 8(4), 24-44.

Maharaj D., McDonald G.A., Dobbie J.W. (1982). Splenectomy and Blackwater Fever. Br J Haematol 1982; 51: 6634

Mandal, B., Das, B.K., Chatterjee, S.K., Guh, P., Shai, S., Sharma, A., … et al. (2011). Acute pancreatitis in a case of falciparum malaria: A rare presentation. J Assoc Physicians India

2011; 59:731-3

Mohapatra, M.K., & Gupta, M.P. (2011). Falciparum malaria complicated with acute pancreatitis: A report of case series. J Vector Borne Dis 2011; 48:177-9.

NIHR Global Research Health Unit on Global Surgery (2021). Reducing surgical site infections in low-income and middle-income countries (FALCON): a pragmatic, multicentre, stratified, randomised controlled trial. Lancet (London, England), 398(10312), 1687–1699. https://doi.org/10.1016/S0140-6736(21)01548-8

Ohene-Yeboah, M., Adippah, E., & Gyasi-Sarpong, K. (2006). Acute intestinal obstruction in adults in kumasi, Ghana. *Ghana medical journal*, 40(2), 50-54, https://doi.org/10.4314/gmj.v40i2.36017

Ohene-Yeboah, M. (2006). Acute surgical admissions for abdominal pain in adults in kumasi, Ghana. *ANZ journal of surgery*, 76(10), 898-903, https://doi.org/10.1111/j.1445-2197.2006.03905.x

Oster, C.N., Koontz L.C., & Wyler, D.J. (1980). Malaria in asplenic mice: effects of splenectomy, congenital asplenia, and splenic reconstruction on the course of infection. Am J Trop Med Hyg, 1980; 29: 113842

Ozgediz, D., Jamison, D., Cherian, M., & McQueen, K. (2008). The burden of surgical conditions and access to surgical care in low- and middle-income countries. Bulletin of the World Health Organization, 86(8).

Peiffer, S., Ssentongo, A.E., Keeney, L., Amponsah-Manu F., Yeboako R., Ofosu-Akromah, R., … Ssentongo, P. (2020). Predictors of poor postoperative outcomes in pediatric surgery patients in rural Ghana. BMC Surg 20:211. Retrieved from https://doi.org/10.1186/s12893-020-00867-9

Public Health Agency of Canada. (2014). Canadian recommendations for the prevention and treatment of malaria. An Advisory Committee Statement (ACS) Committee to Advise on Tropical Medicine and Travel (CATMAT). Available from URL: http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40- 102-2014-eng.pdf (accessed October 2014).

Roark, G.L. (2019). *Retrospective comparison of 2 management strategies for perioperative malaria episodes in pediatric patients in a limited-resource setting.* Anesth Analg 129 515 519 https://doi.org/10.1213/ANE.0000000000004186.

Roca-Feltrer, A., Kwizombe, C.J., Sanjoaquin, M. A., Sesay, S. S., Faragher, B., Harrison, J., Geukers, K., Kabuluzi, S., Mathanga, D. P., Molyneux, E., Chagomera, M., Taylor, T., Molyneux, M., & Heyderman, R. S. (2012). Lack of decline in children malaria, Malawi, 2001-2010. *Emerging infectious diseases*, 18(2), 272-278. https://doi.org/10.3201/eid1802.111008

Sakpal, T. V. (2010). Sample size estimation in clinical trial. Perspect Clin Res. 1(2), 67-69. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3148614/#__ffn_sectitle

Seshadri, P., Dev, A.V., Viggeswarpu, S., Sathyendra, S., & Peter, J.V. (2008). Acute pancreatitis and subdural haematoma in a patient with severe falciparum malaria: Case report and review of literature. Malar J 2008;7:97

Shaw, J.H.F., Print, C.G. (1989). Posts-splenectomy sepsis. Br J Surg 1989; 76: 1074-81.

Snyders, P.C.S., Swart, O., & Duvenage, R. C. (2020). Thirty-day readmission rate: A predictor of initial surgical severity or quality of surgical care? A regional hospital analysis. *SAMJ: South African Medical Journal , 110*(6), 537-539. https://dx.doi.org/10.7196/SAMJ.2020.v110i6.14355

Soltanifar, D., Carvalho, B., & Sultan, P. (2015). Perioperative considerations of the patient with malaria. Can J Anesth/J Can Anesth 62, 304–318. https://doi.org/10.1007/s12630-014-0286-7

Sundet, M., Heger, T., & Husum, H. (2004). Post-injury malaria: A risk factor for wound infection and protracted recovery. Tropical Med Int Health 9 238 24. https://doi.org/10.1046/j.1365-3156.2003.01190.x.

Tefera, G. M., Feyisa, B. B., Umeta, G. T., & Kebede, T. M. (2020). Predictors of prolonged length of and in-hospital mortality among adult patients admitted at the surgical wards of Jimma University medical center, Ethiopia: prospective observational study. *Journal of pharmaceutical policy and practice,* 13, 24. https://doi.org/10.1186/s40545-020-00230-6.

Weiser, T.G., Haynes, A.B., Molina, G., Lipsitz, S.R., Esquivel, M.M., Uribe-Leitz, T., … Gawande, A.A. (2016). Size and distribution of the global volume of surgery in 2012. Bull World Health Organisation, 94:201–209F | doi: http://dx.doi.org/10.2471/BLT.15.159293.

World Health Organization. (2015). Guidelines for the treatment of malaria (3rd ed.). Geneva, Switzerland: WHO Press.

World Health Organisation. (2021). World malaria report. Geneva.

World Health Organization. (2018). *World malaria report*. Geneva.