EFFICACY AND COST OF POST CESAREAN PAIN MANAGEMENT USING THE WORLD HEALTH ORGANISATION RECOMMENDATIONS VERSUS ROUTINE CARE AT NYERI COUNTY REFERRAL HOSPITAL
A RANDOMIZED CONTROLLED TRIAL

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2021

SECTION 1.1 DECLARATION

This dissertation is my original work and has not been presented elsewhere. This research project is my original work and has not been presented for academic award in any other university. References to work done by others have been clearly indicated.

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May God bless you all.

SECTION 1.4 DEDICATION

This thesis is dedicated to my mother, a strong and gentle soul who taught me to trust in God, believe in hard work and that much could be done with little.

To my siblings who have always been a source of inspiration, encouragement and stamina to undertake my higher studies and to face the eventualities of life with enthusiasm.

God bless you all.

SECTION 1.5 LIST OF ABBREVIATIONS

ACOG	American college of Obstetrics and Gynecologists
AE	Adverse effects
ANC	Antenatal clinic
APS	American pain society
DSMB	Data and safety monitoring board
ERC	Ethical review committee
GCP	Good clinical practice
ITT	Intention to treat
KNH	Kenyatta national hospital
NCRH	Nyeri county referral hospital
NRS	Numeric rating scale
NSAIDS	Nonsteroidal anti-inflammatory dugs
PCA	Patient controlled analgesia
RCT	Randomized controlled trial
SAE	Severe adverse effects
SOP	Standard operating procedure
UON	University of Nairobi
VAS	Visual Analog scale
VRS	Verbal categorical rating scale
WHO	World health organization

DEFINITION OF OPERATIONAL TERMS

Cesarean section: A surgical procedure for the delivery of a fetus through surgical incisions made through a woman's abdominal wall (laparotomy) and uterine wall (hysterotomy)

Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage (The international association for the study of pain, 1979)

Pain management: The process of providing medical care that alleviates or reduces pain.

WHO recommended Care: The WHO analgesic ladder for cancer pain adopted to guide the pharmacological treatment of acute post-operative pain.

NCRH Routine post-operative care: The current post cesarean medications offered at Nyeri County Referral hospital.

Efficacy: The ability of a drug to produce the desired beneficial effect.

Satisfaction: Difference between expectation of level of care (pain relief) and perception of actual care received. ('Expectation-performance theory')

Visual analog scale: A psychometric unidimensional measure of pain intensity ranging from mild to severe pain.

Immediately post operation: Time period from 1 to 60 minutes after patient has arrived from operating room.

Postpartum: Period after delivery. In this study it refers to the first 72 hours after delivery.

Adequacy: State of sufficieny.in this study state of sufficient pain control.

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ABSTRACT

Background: Adequate postoperative pain control after cesarean section is important because the postoperative mothers need enhanced recovery to effectively take care of their newborns. Effective pain control in the acute period aids early patient mobility and thus reduces the risk of postoperative venous thromboembolism. In addition, adequate postoperative pain control facilitates mother-child bonding and breastfeeding and can shorten hospital stay. Suboptimal acute post-operative pain management usually leads to persistent intermediate plus long post-operative pain, delayed functional recovery and postpartum depression. The World Health Organization (WHO) has issued guidelines/ recommendation on pain management. Pharmacologic management of acute pain is based on the World Health Organization analgesic ladder. Nyeri County Referral Hospital (NCRH) just like the national Ministry of Health in Kenya has not adopted these recommendations. In this study we sought to evaluate the efficacy and cost of WHO recommended versus the current routine post cesarean pain management at NCRH to inform practice decisions.

Objective: To evaluate the efficacy and cost of WHO recommended versus the routine care for post cesarean pain management at NCRH.

Methodology: This was a single blind Randomized controlled trial that was conducted in NCRH maternity theater and post-natal wards. Patients were randomized into two groups, either the WHO recommended pain management or the routine NCRH care with each having 193 participants. The primary outcomes were adequacy of pain control using the visual analog scale at immediately post-operatively, at 6,12,24 and 72 hours, patient satisfaction on pain control after 72 hours post-operation and cost of medications in each group. Descriptive statistics were used to describe the socio demographic characteristics of the study participants. Adequacy of pain control from the visual analog scale was compared between the two groups using independent T-test. Proportion of pain satisfaction 72 hours post-operatively was done using chi-square test. All statistical tests were performed at 5% level of significance p value<0.05. Cost analysis was done by multiplying the average cost of each medication with the total medications used by patients in each group. This was presented as total cost of pain management in each group. Intention-To-Treat (ITT) analysis was used. Data was analyzed using STATA® analytical package version 13. This study was approved by Kenyatta National Hospital-University of Nairobi Ethics and research committee under

protocol number P766/11/2018 and was submitted for trial registration at the Pan African Clinical Trial Registry.

Results: Between June and September 2019 a total of 400 patients were screened and 387 participants (96.8%) enrolled to the study. The baseline characteristics were similar between the two arms. The mean VAS scores were lower in the WHO group (mean 0.93, SD 1.3) than the NCRH group (mean 1.56, SD 1.9) in the immediate postpartum period (p value <0.001). At six hours postpartum, the mean VAS scores were also significantly lower (p=0.006) in the WHO group (mean 4.71, SD 2.1) than the NCRH group (mean 5.27, SD1.9). More participants were satisfied with pain control in the WHO group at 81% compared to NCRH group at 76% but was not statistically significant. The actual and projected total cost of medications administered was 4.98 and 5.28 times higher respectively in the WHO group than the NCRH group.

Conclusion: WHO recommended pain control regimen had reduced mean VAS scores immediately post-operatively and at six hours postpartum and the cost was 4.98 times higher than in the NCRH group.

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Recommendations:

- We advocate use of the WHO recommended regimen to control post-operative pain in the first six hours postpartum
- The cost of WHO recommended pain control regimen should be revaluated and lowered to make them available for patients

Key words: pain control, cesarean section, post-operative

2.0: INTRODUCTION

2.1: Background of the study

A cesarean section is defined as a surgical procedure done to deliver a fetus through a woman's abdominal wall (laparotomy) and uterus (hysterotomy) (1). With cesarean sections becoming more common in both developed and developing countries, the ideal cesarean section rate has been set as 10-15% internationally. Rates of cesarean sections done in a country can be used to measure the level of access to and use of this intervention. Cesarean section rates can also be used to track progress in mother and child health care, practical guide in policy making and in monitoring obstetrics emergencies and resource use (2). Jacob Nufer carried out the first successful cesarean in the year 1500 on his wife who later gave birth to more children after the cesarean section.

2.2: Post-Operative Pain Management

According to The International Association for the Study of Pain (IASP), pain refers to an uncomfortable emotional and sensory experience that is associated with tissue damage. Poorly managed post cesarean section pain can have debilitating effect on the physical and emotional well-being of a woman during the post-operative period affecting nursing and recovery process. Since the olden days, herbs and opium have been used to manage pain. Laudanum, invented in 17th century, is made by dissolving opium and alcohol and consists most of the opium alkaloids (1)(2). Pain relief is universally considered a human right and to achieve adequate pain control, it requires use of both safe and effective analgesic combinations(3). Currently, there lacks a gold standard for post-cesarean section pain control. The available options are valid because choice of pain control is dependent on the availability of pain control medication, facility protocols, available resources, personal preferences, and financial determinants(4).

2.3: Adverse effects of suboptimal treatment of severe acute pain

Pain has various effects on the cardiovascular system like increased pulse rate, blood pressure, increased peripheral vascular resistance which may lead to increased myocardial oxygen consumption leading to myocardial ischemia(5).

Uncontrolled pain in the Respiratory system causes a decrease in the cough reflex and decreased lung volumes due to shallow rapid breathes, which lead to atelectasis, sputum retention, hypoxemia predisposing one to infections. In the Gastrointestinal system patients experience decreased gastric and bowel motility as well as urine retention leading to urinary tract infection.

Pain increases the production of catabolic hormones such as growth hormones, glucagon, aldosterone, angiotensin, renin, and vasopressin. Catabolism leads to high blood sugar, negative nitrogen balance, and degradation of proteins, which can impair wound healing and cause muscle wasting. Immobility in the recovery period due to pain increases risk of thromboembolism, muscle wasting and spasm which prolonged the recovery period. Via the Central nervous system (CNS), pain can induce fear, anxiety, insomnia, or helplessness, and other debilitating long-term psychological effects(5)(6).

Adequate pain management after a cesarean section has increased benefits, to the mother, her family and the hospital. It is important to aid in mobilization of the mother to reduce the risk of postoperative venous thromboembolism and thus allowing the mother to give her new infant optimal care (increased mother-child bonding time and breastfeeding) and can shorten hospital stay (4).

2.4: WHO Guidelines on Pain Management

The World Health Organization (WHO) has issued recommendations on pain management. Pharmacologic management of acute pain, for instance, should be conducted in line with the WHO Analgesic ladder. The WHO ladder has a stepwise algorithm. Step 1 champions for the use of non-opioid analgesia to manage mild pain. Step 2 advocates for the use of weak opioids with or without non-opioids for the management of moderate pain, while step 3 advocates for strong opioids with or without non-opioids to manage severe pain. Typically,

recommended non-opioids drugs entail acetaminophen (paracetamol) and nonsteroidal anti-inflammatory drugs (NSAIDS). Administration of NSAIDs and opioid can be through the intramuscular, intravenous or the oral route.

2.5: Nyeri County Referral Hospital Pain Management Approaches

This study took place in Nyeri County Referral hospital due to its high inflow of obstetrics cases, convenience to the investigating team as pertains to access to data records and cost and the lack of a post-operative pain protocol at the hospital. Nyeri County Referral Hospital also lacks any personnel specialized in post-operative pain management and therefore data collected will be useful in protocol development. The routine care at NCRH for post cesarean pain includes 10mg intramuscular morphine, 8hourly on day one followed by 1gram paracetamol and 50mg diclofenac oral on subsequent two days 8 hourly.

2.6: Efficacy of Pain Management and Assessment

Pain measurement is complex because of its subjective nature, which can be modulated by environmental, psychological, and physiological factors. Such factors can be from previous painful events, different cultures, coping strategies, prognosis, anxiety or fear. These are often self-reported but if evaluated properly can lead to sensitive and consistent results(4). There is currently no objective way to measure pain but associated factors such as increased sensitivity to pain (mechanical withdrawal threshold), behavioral responses or physiological responses, and stress response (such as cortisol concentrations), may provide additional information.

The most used tools in pain assessment are the visual analogue scale (VAS) and numeric rating scale (NRS) – both found to be able to assess acute post-surgical pain accurately. These tools are also better than the four-point verbal categorical rating scale (VRS). They deliver the best results when patients use it to assess present pain intensity, but are also suitable for assessing pain intensity over a 24-hour period, or the preceding week to a limited extent because most people do not have an accurate memory of pain. Changing context factors can also affect its accuracy. The VRS scale on the NRS uses approximate ranges of its categories, which have been found to vary significantly between individuals/ patients sampled at different time points.

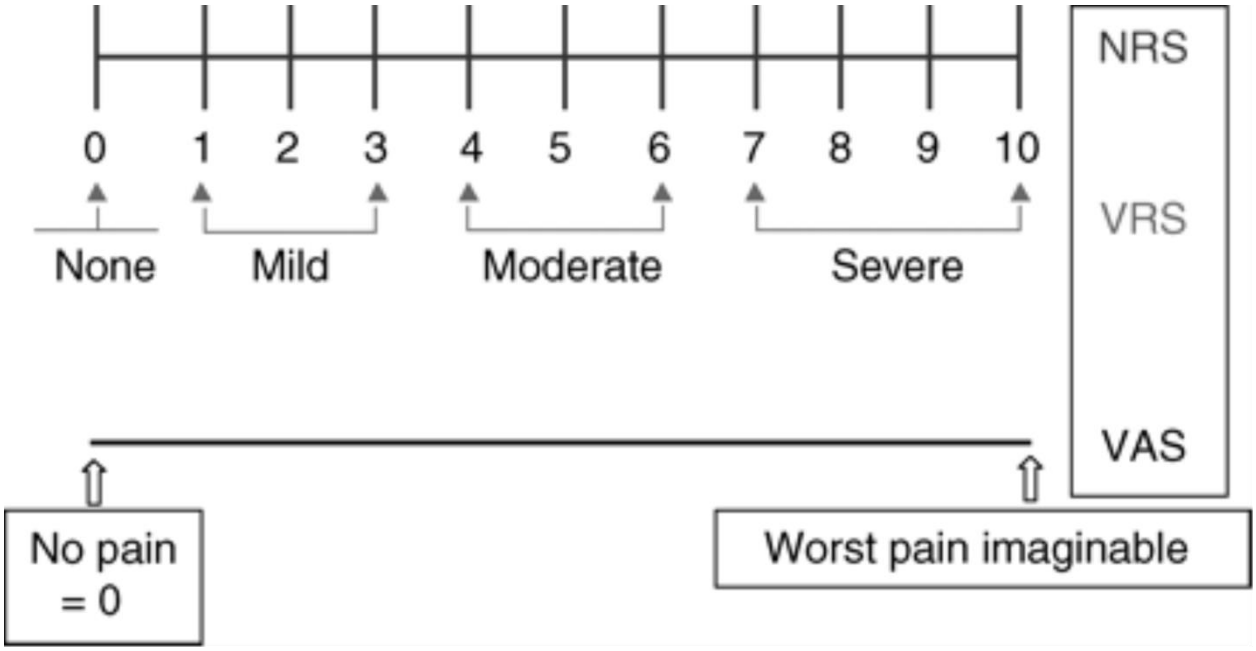

Figure 1: Visual analog scale for pain assessment.

3.0: LITERATURE REVIEW

Current pain management involves use of a cocktail of drugs with different modes of action with the aim of providing maximum pain control and reducing side effects through synergistic drug actions(7). Reviews done in various studies report the best way to achieve control of post cesarean section pain is by systematic and/or neuraxial morphine. The reviews recommend the use of multiple analgesics with synergistic mechanism of action to achieve an adequate and effective pain control with few adverse effects (7).

3.1: Control of post cesarean section pain

Various methods have been used to help reduce cesarean section pain pre, intra and post operatively. A multi-modal approach to pain control is the ideal practice in order to target the various pain pathways. Adequate post cesarean section pain management has many advantages to the new mother, her family and the hospital. It's vital in aiding patient mobilization to reduce the risk of post-surgical thrombo-embolism, thus allowing the mother to give her new infant optimal care (increased mother-child bonding time and breastfeeding) and can shorten hospital stay (11).

3.1.1: Opioids

Opioids bind to receptors in the peripheral tissue and CNS to modulate the effect of nociceptors. They are administered via oral, parenteral, transdermal, rectal, and neuraxial routes. Morphine, hydromorphone and fentanyl are the most used intravenous agents for the management of post-surgical pain with morphine being the gold standard. Morphine has a rapid acting formulation whose effect peaks at 1 to 2 hours. Tramadol is a weak opioid that is readily available in the public sector. In a randomized, double blinded study conducted in a South African academic hospital, Wilder-Smith et al (2003) showed that a single combined dose of intramuscular dose of 100mg tramadol and 75mg of diclofenac provided superior analgesia to either drug alone or to the placebo.

3.1.2: Local Anesthetics

Local anesthesia is a relatively easy and efficient tool for pain management that is used to infiltrate a surgical wound. It decreases opioid related side effects by having an opioid sparing effect and will also contribute to pain control in the immediate postoperative period.

It also decreases the risk for drugs crossing over to the infant(8)(9). Trotter et al. found that weight adjusted bupivacaine infiltration to a surgical site post cesarean section reduced the amount of rescue morphine used in women operated in general anesthesia (10). However, use of local anesthesia is not routinely used in our local setup specifically NCRH

3.1.3: NSAIDS

NSAIDS are efficient in treatment of visceral pain by decreasing post-surgical inflammation and affecting the nociceptive responses associated with acute pain. NSAIDs inhibit activity of cyclooxygenase (COX) enzyme with subsequent reduction of prostaglandin production, thereby causing an anti-inflammatory response. NSAIDs can be non-selective COX inhibitors or selective COX 2 inhibitors. NSAIDS have an opioid sparing effect, decreasing opioid related side effects by improving the effects of systematically or neuraxially given opioid (7). Cardoso *et al* (1998) combined intrathecal morphine (at three different doses) with 75mg IM diclofenac and found that the addition of IM diclofenac enhanced the analgesic effect of the intrathecal morphine, to such an extent that the authors recommended that there was no advantage to using intrathecal doses of morphine larger than 25μg if this is used in combination with systemic diclofenac.

This combination proved to be as effective as higher intrathecal morphine doses with and without NSAIDS. Paracetamol is commonly used synergistically with morphine and/or NSAID and is believed to act at both central and peripheral levels of the nociceptive paths(7). Paracetamol does not hinder with platelet function and it can therefore be used safely in patients with peptic ulcers or asthma which is a major advantage over NSAIDs. Intravenously used paracetamol has opioid-sparing effects (11). A comparative mixed trial found a reduction in 24-hour morphine use and a decrease in morphine related side effects when NSAIDs, paracetamol, or COX-2 inhibitors were administered with PCA morphine post-surgery. However, the three non-opioid agents were comparable as per the study (11).

A systematic review of 21 studies evaluating the effect of paracetamol alone compared to combination therapy (paracetamol and other NSAIDS) found an increase in the efficacy of pain management with combination therapy than when agents were used alone. A study done by Vyankatesh et al concluded that for post cesarean section pain control, rectal suppository

of diclofenac and tramadol can be used but tramadol had side effects like nausea and vomiting and therefore diclofenac suppository was viewed as a better analgesic.(12)

3.2: Cost-effectiveness and efficacy

Economic evaluation of analgesics is a common clinical practice which has been used to gauge the efficiency of health system services. Cost estimation of therapeutic schemes involves unitary costing and costing of consumables such as alcohol pads, needles, and syringes. Unitary cost involves direct costing of the analgesics. Merrikhihaghi et al 2015, demonstrated that analgesic effect of diclofenac is 3.21 times more cost-effective than tramadol with the same efficiency and for post cesarean pain. Therefore, a single dose therapy of diclofenac suppository can be a proper choice of pain management for postpartum women.

Chang et al. in 2004 measured efficacy and cost-effectiveness of morphine intravenous patient-controlled analgesia (PCA) against discontinuous morphine IM injection in Chinese women after elective gynecological operation. It has been concluded that intravenous PCA induces considerably better pain relieving effect on postoperative pain in comparison to discontinuous morphine IM injection(13). Also, the cost-effectiveness study showed intravenous PCA is more costly than discontinuous IM injection(13) . Vercauteren et al. in 2002 compared cost-effectiveness of intrathecal morphine with epidural PCA. The research demonstrated that epidural PCA has better analgesic effect with less nausea and vomiting, but it is more costly. Contreras-Hernandez et al. in 2008 compared cost-effectiveness of NSAIDs to cyclooxygenase-2 selective inhibitors. It has been concluded that cyclooxygenase-2 inhibitors such as celecoxib, is the most cost-effective in the treatment of joint pain.

3.3: Healthcare professionals' knowledge on pain management

Effective pain management is important to health care professionals and an accurate evaluation of pain is paramount, therefore, healthcare providers must be well-educated and knowledgeable about pain (14)(15). The American Pain Society (APS) stated pain as the "fifth vital sign" making screening of pain part of routine care. Worldwide, surveys of healthcare professionals' practices continue to reveal a deficit in their knowledge. Furthermore, many authors have reiterated the need for education of healthcare personnel on

pain management options through training programs to improve the provision of care and therefore the quality of life of patients.

Lack of knowledge on pain management is one of the predisposing factors for poor patient care and wellbeing. Other common hindrances to effective pain management by health care providers include respiratory depression and the fear for opioid addiction among many others. Such myths and misconceptions about pain and pharmacological pain control have been blamed for poor pain management(16)(17). Nurses' perception of pain and their satisfaction with pain management protocols were found to be poor is a study conducted in Iran (18)**.**

3.4: Global guidelines on postoperative pain management

According to World Health Organization (WHO), countries should maintain a C-section rate less than 15%. Cesarean sections have been on the rise recently and is now the most performed abdominal surgery in the United States(19). C-sections exceeded 32% in the USA in 2008, while prevalence in Colombia increased from 24.9% in 1988 to 45.7% in 2013 (20).

The American Society of Anesthesiologists (ASA) Task Force on Obstetric Anesthesia published Practice Guidelines for Obstetric Anesthesia in 2016 (Apfelbaum *et al*., 2016). These comprehensive guidelines addressed the pre-, intra- and post-operative anesthetic management of the obstetric patient in detail, basing recommendations on scientific evidence and expert opinion. These guidelines state that the choice of a particular anesthetic technique for a caesarean section must be individualized and based on the circumstances of each patient. However, the document does indicate that neuraxial techniques are preferred over general anesthesia in most cases.

Moreover, the ASA guidelines advise that for patients who have a neuraxial anesthetic for their caesarean section surgery, neuraxial opioids should be used preferentially over intermittent injections of parenteral opioids to manage post-operative pain. The guidelines are clear that there is evidence for better analgesia with epidural opioids as opposed to intermittent IV or IM opioids (Apfelbaum *et al*., 2016). According to Altenau et al in 2017 involving use of IV acetaminophen after cesarean delivery, IV acetaminophen was found to

be an effective addition to multimodal analgesia among patient who delivered via caesarian sections. It reduced the need for oral narcotic drugs for management of surgical pain compared to other multimodal agents at their institution (21).

The National Institute of Clinical Excellence (NICE) updated its 2004 guidelines on caesarean section in November 2011(Griffiths *et al*., 2011) which recommend women to be offered intrathecal or epidural diamorphine for intra and post-operative analgesia as this reduces the need for supplemental analgesia after delivery via a caesarean section. In the absence of the neuraxial option, patient-controlled analgesia opioids are recommended. In addition, NSAIDs should be used as an adjunctive analgesic agent because of their opioid sparing effects. The guideline also indicates that wound infiltration or ilioinguinal nerve blocks have also been found to be effective alternatives to systemic analgesics following caesarean section surgery.

According to the American College of Obstetricians and Gynecologists, the recommended target of post-operative pain control is to reduce the amount of narcotics used which can be achieved by multimodal pain management, using a combination of medications with different modes of action (22)(23). The approach is beneficial in both pre- and postoperative settings for its ability to deliver optimal symptomatic surgical pain relief (23)(24).Currently, this is used in the United States for managing post cesarean section pai and entails the usage of regional anesthesia plus a cocktail of intravenous (IV), intramuscular, and oral nonsteroidal anti-inflammatory drugs (NSAIDs) and oral narcotics and oral acetaminophen.

The South Africa guidelines recommend a neuraxial anesthetic technique for all women having caesarean sections unless there is a contraindication to this technique. The rationale is that this anesthetic technique will provide analgesia for the surgery and for a period after surgery as well. The guidelines provide details on the use of intrathecal bupivacaine with or without the addition of fentanyl (12.5 – 20μg). The guideline specifically does not recommend intrathecal morphine for these patients, despite overwhelming evidence in the international literature regarding the superior efficacy of this mode of analgesia for patients having caesarean sections. For those patients, where general anesthesia is necessary, the

guideline provides recommendations on the use of drugs to blunt the intubation response and on the use of opioids during the procedure.

Despite the availability of clinical practice guidelines by WHO and ACOG, post-operative pain management is still a problem and unsatisfactory. There are currently no Kenyan national guidelines on postoperative pain management. Different hospitals have adopted different guidelines or protocols.

4.0 JUSTIFICATION

The IASP defines pain as an unpleasant emotional and sensory experience linked with potential or actual tissue damage with reference to the 1964 definition by Harold Merskey.

Despite advances in analgesic therapy there is still inadequate management of acute pain. Karlstrom A, et al demonstrated that poorly controlled pain following cesarean section can have debilitating effect on the physical and emotional well-being of a woman during the post-operative period and affect nursing and recovery process.

In patients who have undergone surgical procedures, more than 80% report to experience acute post-surgical pain with approximately 75% of those reporting of moderate or severe post-surgical. Inadequately treated pain can have a negative bearing on quality of life, functional recovery and increase the risk of developing postsurgical complications and risk of chronic postsurgical pain (10). In a prospective descriptive study done by Ocitti and Adwok in 2000 over a period of three months, among 106 adult patients at Kenyatta National Hospital undergoing thoracotomy and/or laparotomy, 60% of the patients were not able to achieve adequate pain relief in first three days after the surgery.

J Obstet Gynecol and Neonatal Nurs in a descriptive patient survey, among 60 women undergoing cesarean birth at Central Swedish County Hospital, reported that women in their study who experienced higher than expected post cesarean section pain were more likely to have a negative birth experience and significant negative impact on breastfeeding and infant care. This can lead to impaired bonding between mother and baby. Sixty-two percent of women in their study reported that post-operative pain adversely affected their ability to take care of their babies significantly in the first 24hrs after delivery. Effective pain management after a cesarean section has many benefits to the new mother, her family and the hospital. It's vital in aiding patients' mobilization, reducing the risk of postoperative thrombo-embolism, and allowing the mother to give her new infant optimal care (increased mother-child bonding time and breastfeeding) and can shorten hospital stay (11).

Nyeri County Referral Hospital (NCRH) serves a large population especially in the obstetrics unit with a cesarean section rate of 12% (2015 survey at NCRH). Current WHO guidelines on post-operative pain management include the use of parenteral opioids, non-steroidal anti-

inflammatory drugs and acetaminophen which have not been adopted at NCRH. Currently, there are no Kenya National guidelines on post cesarean pain management despite the increasing number of cesarean section rates. The routine post-operative pain management at NCRH involves use of 10mg intramuscular morphine 8 hourly on day one followed by 1-gram oral paracetamol and 50mg oral diclofenac on subsequent days. No study has been done at the facility to determine the effectiveness and cost of the above routine practice on post-operative pain management.

This study compared the efficacy and cost of the WHO guidelines versus the current routine care at NCRH on post cesarean pain management**.**

5.0 STUDY OBJECTIVES

5.1 Research question

What is the efficacy and cost of World Health Organization recommended versus the current routine care for post cesarean pain management regimens at Nyeri County Referral Hospital?

5.2 Null hypothesis

There is no difference in mean VAS score for pain control between the World Health Organization recommended versus the routine Nyeri County Referral Hospital post cesarean pain management regimens.

5.3 Broad objective

To evaluate the adequacy and cost of the World Health Organization recommended versus the routine Nyeri County Referral Hospital post cesarean pain management regimens.

5.4 Specific Objectives

Among women who have undergone cesarean section at NCRH, who are randomized to World Health Organization recommended versus routine Nyeri County Referral Hospital post cesarean pain management regimens

1. To compare the efficacy of pain control using the differences in mean VAS pain score.
2. To compare the pain control satisfaction of WHO recommended versus the current routine care for post cesarean pain management.

3. To compare the cost of WHO recommended versus the current routine care for post cesarean pain management.

6.0 CONCEPTUAL FRAMEWORK

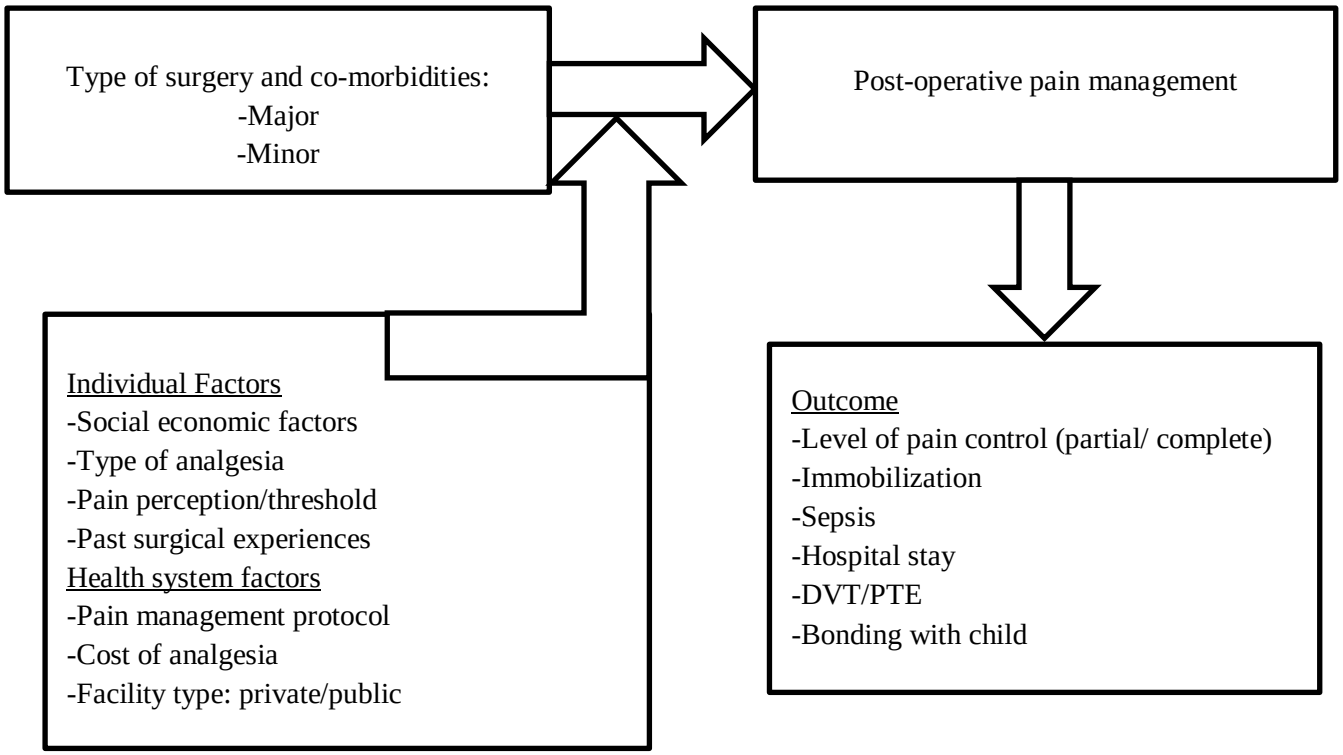

Figure 2: conceptual framework

7.0 RESEARCH METHODOLGY

7.1: Study site

The study took place at Nyeri County referral hospital. Nyeri County is in the central region of Kenya, southwest flank of Mount Kenya. Nyeri county referral hospital receives patients from Nyeri and referrals from surrounding hospitals. Its post-natal ward has a bed capacity of 50 patients. It reports approximately 400 deliveries every month. The deliveries occur amongst mothers with varying socioeconomic characteristics. Out of the 400 deliveries, about 10% are due to Cesarean section. On average, a total of 2 women undergo Cesarean section operation per day. Post operatively, patients are admitted in the post-natal ward for pain management for a period of 3 days before discharge to continue with oral pain medications at home. The routine care at NCRH for post cesarean pain includes 10mg intramuscular morphine 8 hourly on day one followed by 1-gram oral paracetamol and 50mg oral diclofenac 8 hourly on the subsequent two days.

7.2 Study Design

Single blind Randomized Controlled Trial (RCT) in which post cesarean patients were randomized to either the intervention, WHO post cesarean pain management regimen or the control, routine NCRH post cesarean pain management regimen. The WHO post cesarean pain management comprised of I.M Morphine 10mg 4hrly, I.V paracetamol 1 g 8hrly, I.M diclofenac 75mg 8hrly on day one, I.V tramadol 100mg 8hr, P.O paracetamol 1 g 8hrly, P.O diclofenac 50mg 8hrly on day two and P.O diclofenac 50mg 8hrly, P.O paracetamol 1g 8hrly on day three. The routine post-operative pain management at NCRH comprised of 10mg intramuscular morphine 8 hourly on day one followed by 1-gram oral paracetamol and 50mg oral diclofenac 8 hourly on subsequent two days.

7.3 Study Population

The study population were women who had undergone cesarean section at NCRH who were admitted for observation and recovery in the post-natal ward.

7.4 Sample Size Calculation

The sample size was determined using the Vyankatesh S et al. 2013 study where 193 patients in each group of the study was used.

$$n = 2 \times \frac{(Z_{1-\propto} + Z_{1-\beta})^2}{\Delta^2} \times SD^2$$

n = Desired sample size per group

$Z_{1-\propto}$ = value from standard normal distribution corresponding to desired confidence level - two tail (Z=1.96 for 95% CI)

$Z_{1-\beta}$ = value from standard normal distribution corresponding to 80% power (0.842)

Δ^2 = difference between treatment i.e. 0.30 (the difference from the two arms from the Vyankatesh S. et al (2013) study which had a VAS mean scores of 2.93 and 2.63 at 6 hours)

SD = the approximate standard deviation reported in the study for VAS scores at 6 hours by Vyankatesh S. et al i.e. 1.00

$$n = 2 \times \frac{(1.96 + 0.842)^2}{(0.30)^2} \times 1.0^2 = 175$$

A sample of 175 women will be required for each group, adding 10% of participants lost follow up or missing records brings 193 per group.

7.5 Inclusion and Exclusion Criteria

7.5.1 Inclusion Criteria

- Females 18 years of age and older at screening.
- All patients who had undergone a cesarean section.
- Participants able to provide informed consent both verbal and written.

7.5.2 Exclusion criteria

- Post cesarean patients having concurrent pain-causing condition e.g. arthritis, neuropathy, multiple sclerosis.
- Allergy, hypersensitivity, intolerance or contraindication to any of the study medication.
- Vulnerable population such as prisoner, mentally unstable to provide direct consent etc.
- Suspected or known addiction to drugs of abuse, prescription medicines or alcohol in the past five years through history taking and corroboration with next of kin.
- Clinically unstable post cesarean patients in intensive care unit.
- Patients on chronic use of pain medications prior to the cesarean section.

7.6 Consenting and study enrollment

Once identified, the principal investigator or research assistant briefed the patients on the purpose and method of the study and attained verbal consent. Thereafter, written informed consent was administered. The informed consent form provided information about the aims/ objectives of the study, recruitment and data collection procedures, and the potential risks and benefits to participants. Pertinent questions on study procedures or goals were answered to the satisfaction of the parent/guardian before signing consent forms. This process was free from coercion and was explicitly voluntary.

Those who accepted to be participants appended signatures or thumb prints on consent forms which was counter-signed by the PI. Records on the reasons for declining participation were recorded if a respondent was eligible. The investigator or research assistant then countersigned the consent form. A copy of the signed consent form was given to the participant. A log of the principal investigators, research assistants and enrolled patients was available in the labor ward. Data was collected from the eligible patients and every entry signed in the logbook.

7.7 Recruitment Procedures

Patients were blinded and assigned randomly in a 1:1 ratio into each group (either WHO group or NYCRH group) at the triage area or labor ward once they met the inclusion criteria. The intervention and controls were WHO recommended and NCRH routine postoperative pain management respectively.

7.8 Study Procedures

7.8.1 Randomization

Computer-generated random numbers with a study group, either WHO or NCRH assigned to each number were placed in sealed envelopes. All the envelopes were kept in a large sealed clear container. Once a patient was found to be qualified for the study, the patient randomly picked an envelope from the provided container after obtaining informed consent. The envelope was given to the un-blinded surgical team (operating surgeon, anesthesiologist, and post-natal primary nurse) which was opened after delivery of the fetus to identify the kind of intervention that would be provided to the blinded patient for post cesarean pain management. This was either the WHO recommended pain management or the routine care at NCRH. Pain assessment was done by the patients using the visual analog scale at rest, 6, 12, 24 and 72 hours.

In both groups, the cesarean section technique used was Pfannensteil incision on the lower abdominal wall, blunt dissection of the peritoneum and the transverse Monroe-Kerr uterine incision. Upon delivery of the fetus, the low transverse uterine incision was repaired in a 2-layer fashion closure technique with non-closure of the peritoneum. Fascia was closed with running non-locking stitch before closure of the skin. Both groups had detailed post-surgical notes with all the techniques explained.

7.8.2 Study Arms

Intervention

The WHO recommended pain management regimen started from day one to 3rd day post cesarean section as follows:

Day 1: I.M Morphine 10mg 4hrly, I.V paracetamol 1 g 8hrly, I.M diclofenac 75mg 8hrly.

Day 2: I.V tramadol 100mg 8hr, P.O paracetamol 1 g 8hrly, P.O diclofenac 50mg 8hrly.

Day 3: P.O diclofenac 50mg 8hrly, P.O paracetamol 1g 8hrly

Control

The routine NCRH post-operative pain management regimen also started from day one to 3rd day post cesarean section as follows:

Day 1: I.M Morphine 10mg 8 hrly

Day 2: P.O diclofenac 50mg 8hrly, P.O paracetamol 1g 8hrly

Day 3: P.O diclofenac 50mg 8hrly, P.O paracetamol 1g 8hrly

All drugs used in both the control and intervention groups were procured from the Nyeri County Referral Hospital pharmacy. Opioid drug accountability was done through a locked cabinet in a locked room accessible only to study staff with an entry and exit logbook. All vials were recounted and stocks taken daily.

7.8.3 Training of research team

The research team, comprising the principal investigator, 2 research assistants (two nurses), one data manager, and two data clerks undertook training in Good Clinical Practice (GCP) using the online portal from globalhealthtrainingcentre.org/elearning. In addition, they underwent a two-day training to review the study protocol, data collection and quality control procedures.

On job training of the research assistants took place over duration of one week. Initially they observed the process of obtaining informed consent and filling of the questionnaires. Thereafter they worked under supervision until the principal investigator was satisfied. The principal investigator constantly reviewed the questionnaires for completion.

7.9 Study Variables

Table1: Table of variables

Objective	Exposure variable	Outcome variable	Sources of data
Adequacy of pain control between WHO vs NCRH.	-WHO recommended pain medication from hospital pharmacy. -NCRH pain medication from hospital pharmacy	Adequacy of pain control using visual analog scale	-Patients files -Visual analog scale for pain.
Pain control satisfaction using WHO vs NCRH	-WHO recommended pain medication from hospital pharmacy -NCRH pain medication from hospital pharmacy	-Pain control satisfaction after 72 hours using the Likert scale	-Patients files -Likert scale
Cost of medication	-WHO recommended pain medication from hospital pharmacy -NCRH pain medication from hospital pharmacy	-Cost of WHO recommended regimen -Cost of NCRH analgesics	Patients files and pharmacy records

7.10 Data Collection Procedure

Questionnaires were filled by the health care provider after the 72 hours of pain management to assess their perception and attitude towards pain management. The questionnaire was administered either by the principal investigator or by specially trained research assistants. Training of research assistants on the principles of conducting RCTs and in good clinical practice took place over duration of one week; initially they observed the process of obtaining informed consent and filling of the questionnaires. Thereafter they worked under supervision until the principal investigator was satisfied. The principal investigator constantly reviewed the questionnaires for completion. Data monitoring was continuous, and the data manager alerted the principal investigator of any overt differences in the two groups.

Data on cost was collected from the revenue department. This included cost of administering individual drugs and for the period that the patient was on pain management in the immediate post -operative period.

7.11 Quality Control Measures

To reduce errors during data collection and analysis, the following quality control measures were implemented. The research assistants were trained on the procedures of the study such as how to conduct interviews and how to abstract and record data. The questionnaire was also pretested prior to use in the study. In addition, standard operating procedures (SOPs) a data collection manual was prepared and used to guide data collection. Each questionnaire was checked for completeness after data collection.

7.12 Study Efficacy Measurements

- Pain intensity scores using VAS at rest at 6, 12, 24 and 72 hours.
- Patient satisfaction with post-surgical pain control (using a 5-point Likert scale) at 72 hours (prior to hospital discharge)
- Date, amount and cost of all postsurgical analgesia taken during the 72 hours post-surgery.
- Open-ended staff questionnaires on ease of drug administration, availability of medications and their perception on pain relief to the patients.

7.13 Data Management and Analysis

The outcomes were adequacy of pain control using the visual analog scale, post-operative pain satisfaction using the Likert scale and cost of medication in the WHO recommended versus the routine care NCRH. The collected data was counter checked for completeness by the principal investigator and data manager daily before being uploaded to the excel software for analysis The primary outcomes were adequacy of pain control using the visual analog scale at immediately post-operatively, at 6,12,24 and 72 hours, patient satisfaction on pain control after 72 hours post-operation and cost of medications in each group. Descriptive statistics was used to evaluate the socio demographic data of participants. Adequacy of pain control from the visual analog scale was compared using independent T-test. Proportion of pain satisfaction 72 hours post-operatively was done using chi-square test. Statistical testing was conducted at 5% level of significance (p value<0.05). Cost analysis was done by multiplying the average cost of each medication with the total medications used by patients in

each group. This was presented as total cost of pain management in each group. Intention-To-Treat (ITT) analysis was used. Data was analyzed using STATA® analytical package version 13. This study was approved by Kenyatta National Hospital-University of Nairobi Ethics and research committee under protocol number P766/11/2018 and was submitted for trial registration at the Pan African Clinical Trial Registry.

7.14 Ethical Considerations

This study protocol and informed consent forms in appendix were submitted for review and approval by Kenyatta National Hospital/University of Nairobi Ethics Research Committee (KNH-UoN ERC). Approval was sought from the Nyeri County government as well.

For patients who in the unlikely event developed complications from the pain management, they would be managed by the obstetric team at the NCRH. Safety and progress reports will be submitted to the KNH-UoN ERC, after study completion or in the case of study termination or occurrences of any adverse events. The reports will include the number of study participants enrolled, participants who completed the study, changes to research activities, and all other problems that were not anticipated such as risks to human subjects. Finally, all open DSMB reports will be submitted to the KNH-UoN ERC.

The study participants in both arms underwent pain management using the available drugs at the Nyeri County Hospital. This being a referral hospital, it implements the National Insurance scheme through the 'Linda Mama initiative' where mothers are offered free maternity services at no cost to the patient. No incentives were therefore provided to the patients participating in the study. All medications in the study were easily available the NCRH pharmacy at no extra cost.

This study was approved by Kenyatta National Hospital-University of Nairobi Ethics and research committee and was submitted for trial registration at the Pan African Clinical Trial Registry currently awaiting confirmation.

7.15 Informed consent

We obtained a written informed consent from participants or from the parents/guardians of patients who were unable to provide consent. Adequate explanation and counseling was done before attaining consent. Participant's partners were informed about the study. Participant requests for the partner's presence or advice before consenting was granted if the partner was within the hospital at the time of the request. The partner appended their signature as a witness. However, the participant's approval was considered as tacit approval from the partner, unless otherwise specified. The informed consent form described the purpose of the study.

Literate participants appended their signatures at the provided space in the consent form. Non-literate participants documented their approval by marking the form using their thumbprint, in the presence of a third party who acted as a witness. Any other local ERC requirements for consenting non-literate persons were followed. Participants or their parents/ guardians received a copy of the informed consent form. Participants were free to withdraw at any time.

7.16 Study discontinuation

The study's goal was to achieve ≥ 95% participant retention. We made every reasonable effort to retain any enrolled study participant until completion of the study. Participants were at will to withdraw from the study if they were unwilling or unable to comply with the required study procedures.

7.17 Dissemination of Research Findings

All participants including supervisors in the research team were given a report of the findings and were encouraged to comment on them. This was done either via email or in scheduled meetings. As well as the above, dissemination of the results will take place by three methods:

- Production of a report that was sent to the department of obstetrics and gynecology.
- Publishing papers in specialist and general, national and international journals.
- Presentation of papers at both national and international conferences.

8.0 RESULTS

8.1 Characteristics of enrolled patients.

A total of 400 patients scheduled for both elective and emergency cesarean section at Nyeri County Referral Hospital were screened between June 2019 to September 2019. Total of 13 patients were excluded for not meeting the inclusion criteria. A final number of 387 patients were enrolled into the study and randomly assigned to either the control or intervention group as shown in figure 3.

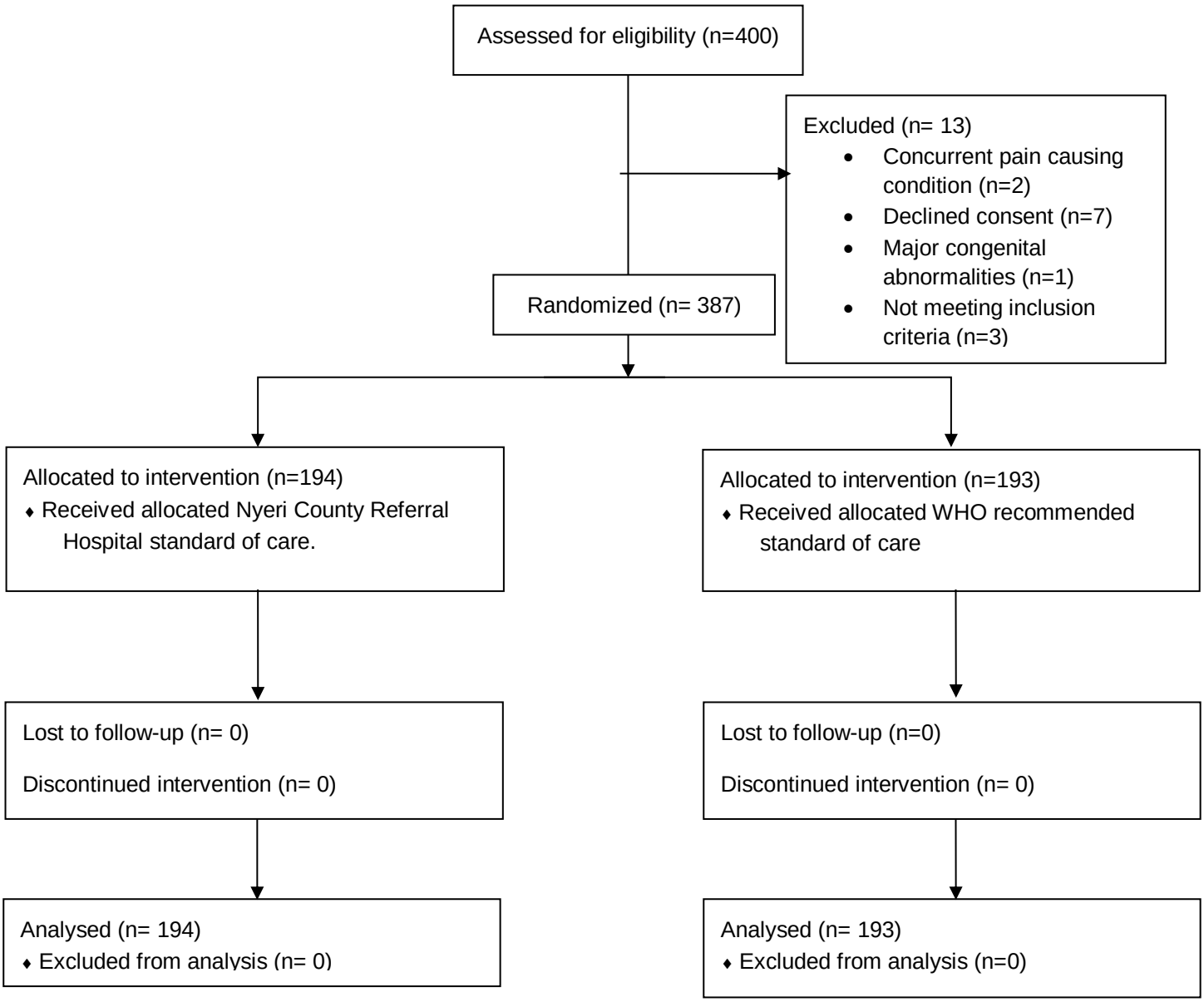

Figure 4: CONSORT flow diagram

Figure 3: Participants study flow diagram

8.1 Baseline Social Demographic Characteristics.

The baseline characteristics were similar between the groups as shown in table 2. The mean age was 26 years. About two thirds were married, three quarters had higher educational level while one third were unemployed.

Table 2: Baseline Social Demographic Characteristics.

	NCRH N=194	WHO N=193	Total	p-value
Age				
Mean ± SD	26.1 ± 5.9	26.0 ± 5.5		0.853
Marital status				
Single	57 (29.4)	46 (23.8)	103 (26.6)	0.217
Married	133 (68.6)	142 (73.6)	275 (71.1)	0.276
Divorced	0 (0)	2 (1.0)	2 (0.5)	0.155
Separated	4 (2.1)	3 (1.6)	7 (1.8)	1.000
Education				
Primary	45 (23.2)	38 (19.7)	83 (21.4)	0.401
Secondary	126 (64.9)	129 (66.8)	255 (65.9)	0.695
Tertiary	23 (11.9)	26 (13.5)	49 (12.7)	0.633
Employment status				
Self-employed	60 (30.9)	52 (26.9)	112 (28.9)	0.387
Salaried employed	50 (25.8)	62 (32.1)	112 (28.9)	0.168
Unemployed	84 (43.3)	79 (40.9)	163 (42.1)	0.637

8.2 Baseline Obstetrics Characteristics.

The mean gestational age at delivery was 39 weeks as shown in table 3. More than three quatres had haemoglobin levels above 11g/dl. About half the patients attended ANC at NCRH with more than 4 visits per patient.

Table 3: Baseline Obstetrics Characteristics

	NCRH N=194	WHO N=193	Total	P value
ANC facility attended				
NCRH	127 (65.5)	117 (60.6)	244 (63.0)	Ref
Other facility	67 (34.5)	76 (39.4)	143 (37.0)	0.324

Number of ANC visits				
<4	46 (23.7)	32 (16.6)	78 (20.2)	0.080
≥4	148(76.3)	161 (83.4)	309 (79.8)	
Hemoglobin				
<11g/dl	29(18.5)	21(10.9)	50(13.4)	0.216
≥11g/dl	157(80.9)	166(86)	323(86.6)	
Gestational age at delivery				
Mean ± SD	39.73(1.5)	39.72(1.2)		0.933
Gestational age determination				
Dates	127 (65.5)	126 (65.3)	253 (65.4)	1.000
Ultrasound	63 (32.5)	62 (32.1)	125 (32.3)	1.000
First clinic visit estimate	0 (0.0)	2 (1.0)	2 (0.5)	0.248
Quickening	2 (1.0)	1 (0.5)	3 (0.8)	0.565
Fundal height	2 (1.0)	2 (1.0)	4 (1.0)	1.000
History of chronic co-morbid				
Yes	40 (20.6)	34 (17.6)	74 (19.1)	0.453
No	154 (79.4)	159 (82.4)	313 (80.9)	
Co-morbid	**NCRH N=194**	**WHO N=193**		
HIV	5 (45.5)	6 (54.5)		
Diabetes	4 (57.1)	3 (42.9)		
HTN	1 (25)	3 (75.0)		
Anemia	17 (60.7)	11 (39.3)		
PROM	1 (25.0)	3 (75.0)		
Asthma	2 (66.7)	1 (33.3)		
PET	8 (61.5)	5 (38.5)		
DVT	0 (0.0)	1 (100.0)		
PPROM	1 (100.0)	0 (0.0)		
Epilepsy	1 (100.0)	0 (0.0)		
None	154 (49.0)	160 (51.0)		

8.3 Adequacy of Pain control using mean VAS score.

Adequacy of pain control was evaluated by comparing mean VAS pain scores at the following time points post-operatively: Immediately (1-60 minutes) post operation, at 6 hours, 12 hours, 24 hours and 72 hours between the two groups. As indicated in table 4, the mean VAS pain score for WHO was statistically significantly lower immediately post operation and at 6 hours but not at 12-72 hours compared to NCRH.

Table 4: Adequacy of Pain control using mean VAS score

	NCRH N=194 (%) Mean (SD)	WHO N=193(%) Mean (SD)	p-value
1-60 minutes (immediately postoperatively)	1.56(1.9)	0.93(1.3)	<0.001
6 hours post operatively	5.27(1.9)	4.71(2.1)	0.006
12 hours post operatively	4.15(1.7)	4.12(1.8)	0.887
24 hours post operatively	3.19(1.3)	3.01(1.5)	0.205
72 hours post operatively	2.11(1.1)	1.93(1.2)	0.144

We also categorized the pain scores as none/mild, moderate or severe using the visual analog scale for pain assessment and compared these between the two groups. The VAS categorizes pain on a scale of 1 to 10 as: no/mild pain 1-3, moderate pain 4-7 and severe pain 8-10. As shown in table 5, the proportion of participants with moderate/severe pain was significantly lower for the WHO group at immediately post-operative and at 6 hours post-operatively compared to NCRH. The severity of pain at other times was however similar between the two regimens.

Table 5: Severity of pain from immediate to 72 hours post-operatively following WHO and NCRH post cesarean pain management regimens.

	NCRH N=194 (%)	WHO N=193(%)	p-value
1-60 minutes (immediately postoperatively)			
No pain/Mild	177 (91.2)	188 (97.4)	Ref
Moderate/severe	17 (8.7)	5(2.6)	0.009
6 hours post operatively			
No pain/Mild	46 (23.7)	68 (35.2)	Ref
Moderate/severe	148(76.2)	125 (64.7)	0.013
12 hours post operatively			
No pain/Mild	87 (44.8)	96 (49.7)	Ref
Moderate/severe	107 (55.1)	97(50.3)	0.335
24 hours post operatively			
No pain/Mild	130 (67.0)	141 (73.1)	Ref
Moderate/severe	64 (33)	52 (26.9)	0.194
72 hours post operatively			
No pain/Mild	168 (86.6)	167 (86.5)	Ref

Moderate/severe	26 (13.4)	26 (13.5)	0.984

8.4 Pain control satisfaction 72 hours Post-operatively using the 5point Likert scale.

Participants status of pain control satisfaction was done 72 hours post-operatively using the Likert scale as shown in table 6. There was a statistical difference in participants who rated their pain satisfaction level as dissatisfied, however there was no statistical differences in the other levels.

Table 6: Pain control satisfaction 72 hours post-operatively using the 5 point Likert scale.

	NCRH N=194	**WHO N=193**	**Total**	**p-value**
Dissatisfied	0 (0.0)	6 (3.1)	6 (1.6)	0.030
Neither satisfied nor dissatisfied	33 (17.0)	26 (13.5)	59 (15.2)	0.220
Satisfied	141(73.1)	147 (75.8)	288(74.4)	0.799
Extremely satisfied	14 (7.2)	20 (10.4)	34 (8.8)	0.366

8.5 Cost of medications

The estimated costs of the different regimens are shown in table 7 and 8. The average cost of drugs assuming patients used all the prescribed medication for the WHO was 178,332 Ksh compared to 33,756ksh for NCRH. Thus, for each patient there was a net higher of 750ksh.

Table 7: Projected cost of NCRH routine medications

Drug: Day 1	**Cost (Kshs.)**	Sub-Total (Kshs)
IM Morphine 10mg 8 hourly	50.00 per Ampoule x 6	150.00
Total		150.00
Drug: Day 2 and 3	**Cost (Kshs)**	**Sub-Total**
PO Paracetamol 1g 8 hourly	1.00 per 1 tablet x 3	3.00
PO Diclofenac 50mg 8 hourly	3.00 per tablet x 3	9.00
Total		12.00
Total Cost for 2 days=12.00 x 2 days		24.00
Total cost per person		174.00
Total projected cost for 194 patients		174 x 194=33,756

Table 8: Projected cost of WHO recommended regimen

Drug: Day 1	**Cost (Kshs.)**	**Sob-Total**
IM Morphine 10mg 4 hourly	50.00 per Ampoule x 3	300.00
IV Paracetamol 1g 8 hourly	150.00 per bottle x 3	450.00
IM Diclofenac 75mg 8 hourly	30.00 per vial x 3	90.00
Total		840.00
Drug: Day 2	**Cost (Kshs.)**	**Sub-Total**
IV Tramadol 100mg 8 hourly	20.00 per Ampoule x 3	60.00
PO Paracetamol 1g	1.00 per tablet x 3	3.00
PO Diclofenac 50mg 8 hourly	3.00 per tablet x 3	9.00
Total		72.00
Drug: Day 3	**Cost (Kshs)**	**Sub-Total**
PO Diclofenac 50mg 8 hourly	3.00 per tablet x 3	9.00
PO Paracetamol 1g 8 hourly	1.00 per tablet x 3	3.00
Total per person		924.00
Total projected cost for 193 patients		**178,332**

We also analyzed the actual cost of medications between the two groups by tallying the total number of medications the participants received and multiplying with the cost of each drug as shown in tables 9 and 10.

Table 9: Actual cost of NCRH routine medications

Drug: Day 1	**Cost (Ksh)**	**Sub-Total (Ksh)**
I.M Morphine 10mg	50 ksh per Ampoule 582 ampoules used x 50	29,100
Drug: Day 2&3		
Paracetamol 1g	1 ksh per tablet 582 tablets used x 1	582
Diclofenac 50mg	3 ksh per tablet 500 tablets used x 3	1,500
	2,082 x 2 days	4,164
Total		**33,264**

Table 10: Actual cost of WHO recommended regimen

Drug: Day 1	**Cost (Ksh)**	**Sub-Total**
IM Morphine 10mg	50.00 per ampoule x 1000 used	50,000
IV Paracetamol 1g	150.00 per bottle x 579	86,850
IM Diclofenac 50 mg	30.00 per vial x 576	17,280
Total		**154,130**
Drug: Day 2	**Cost (Ksh)**	**Sub-Total**
IV Tramadol 100mg	20.00 per ampoule x 420 used	8,400
PO Paracetamol 1g	1.00 per tablet x 570 tablets	570
PO Diclofenac 50mg	3.00 per tablet x 400	1,200
Total		**10,170**
Drug: Day 3	**Cost (Ksh)**	**Sub-Total**
PO Diclofenac 50mg	3.00 per tablet x 579 tablets	1,737
PO Paracetamol 1g	1.00 per tablet x 502	502
Total		2,239
Total actual cost for 193 patients		**165,969**

Some patients were noted to have missed some medications in both the WHO and NCRH group. This is further elaborated in table 11 as total number of doses missed per day in each group.

Table 11: Total doses of missed medication in both the WHO and NCRH arms.

Day	**Drug missed**	**Total number of doses missed**
NCRH group		
Day 2	P.O Diclofenac	20 tablets
Day 3	P.O Diclofenac	7 tablets
WHO group		
Day 1	I.M Morphine	158 doses
	P.O Diclofenac	79 tablets
Day 2	I.V Tramadol	159 doses
	P.O Paracetamol	9 tablets
	P.O Diclofenac	79 tablets
Day 3	P.O Paracetamol	77 tablets

9.0 DISCUSSION

The aim of this study was to compare the adequacy and cost of World Health Organization recommended regimen versus the routine Nyeri County Referral Hospital regimen for post cesarean pain management. Mean pain scores were lower in the WHO group than the NCRH group immediately post-operatively. However, there was no difference at 12-72 hours post-operatively. Similarly, severe pain control was significantly lower at 24 hours post-operatively in the WHO group compared to NCRH group. Although similar comparisons have not been evaluated before, Heidar Darvish et al. in 2014 found that combination of diclofenac and paracetamol was more effective than meperidine alone(25). This finding is comparable to our study finding in that WHO recommended regimen which combined morphine, diclofenac and paracetamol had lower mean scores at 6 hours post operation compared to NCRH that had morphine alone. (26). Munishankar et al in 2008 also had similar findings concluding that use of paracetamol and diclofenac combination caused 38% reduction in morphine use compared to using paracetamol alone(27).

There was no statistical difference in pain control from 12-72 hours post operatively in both arms of this study which contrasted S.M Siddik et al 2014 who found out that combination of propacetamol, morphine and diclofenac had lower pain scores at 24 hours than morphine and diclofenac combination. We found that some patients missed tramadol and diclofenac scheduled doses in the WHO group which would probably explain the lack of statistical difference in pain control.

Despite our study not showing any statistical difference in pain control at 72 hours, other studies have shown reduced pain scores when combining diclofenac and paracetamol analgesics to control post cesarean pain. Romsing et al. 2010 showed the combination of acetaminophen and NSAID had better analgesia than acetaminophen alone(28). Ong et al. 2017 also showed using acetaminophen and NSAID combination compared to the separate use of each drug was more effective(29). Pain medications at 48 to72 hours post operatively were similar in the two study arms, diclofenac and paracetamol which would explain the almost similar pain scores.

This study showed pain satisfaction status after 72 hours post-operatively were generally better in the WHO group than the NCRH group which is similar to Enav et al.2017 study which compared use of long acting spinal morphine versus fixed time interval oral analgesia (Tramadol, paracetamol and diclofenac)(30).

Despite lack of similar studies evaluating cost of WHO recommended regimen for all the three days, Vercauteren et al. in 2002 compared cost-effectiveness of intrathecal morphine with epidural PCA. The research demonstrated that epidural PCA has better analgesic effect with less nausea and vomiting, but it is more costly. Contreras-Hernandez et al. in 2008 compared cost-effectiveness of NSAIDs to cyclooxygenase-2 selective inhibitors. It has been

concluded that cyclooxygenase-2 inhibitors such as celecoxib, is the most cost-effective in the treatment of joint pain. This study showed that the actual cost of WHO recommended regimen was 4.98 times higher than the NCRH routine medications for pain control. Assuming all patients had received the medications as prescribed, the cost of WHO recommended regimen would be 5.28 times higher than the NCRH routine medications.

10.0 CONCLUSION

Cesarean delivery rates are high all over the world, increasing the need for effective pain management during birth. Multiple modalities for post-operative cesarean delivery pain management exist. The current recommendations include multimodal therapy for improving quality of analgesia, reducing the need for opioids, reducing adverse effects, and increasing maternal and neonatal safety. Economic evaluation of analgesics is an important criterion in clinical practice and efficiency of the health system.

In this randomized controlled trial, we evaluated the efficacy and cost of WHO recommended regimen versus the current routine care at NCRH and we found that WHO regimen had reduced mean VAS scores immediately post-operatively and at six hours postpartum. The cost of WHO recommended regimen was 4.98 times higher than in the NCRH group.

11.0 RECOMMENDATIONS

- We recommend use of the WHO recommended regimen to control post-operative pain in the first six hours postpartum as per the findings from our study.
- The cost of WHO recommended pain control regimen should be re-evaluated and lowered to make them available to patients as they were 4.98 times higher than the NCRH group.

12.0 STUDY STRENGTHS

- This is the first study to evaluate adequacy and cost of World Health Organization post cesarean pain management in all the three applied ladder steps for pain control and will therefore form a platform for policy making.

- Findings will inform on post cesarean pain management in both Nyeri county referral hospital and other Nyeri county hospitals.

- This being a single blind randomized controlled trial it provides level one evidence.

- Findings will provide standardized recommendations for post cesarean pain management using the World Health Organization guidelines.

- This is the first study on costing of medications that are used in the WHO ladder step for pain control.

13.0 STUDY LIMITATIONS

- During the study we lacked control over execution of medication as prescribed by the primary doctor and therefore some patients missed some medications.

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APPENDICES
APPENDIX I: CONSENT FORM

Date (date/month/year): _____

Study Title: EFFICACY AND COST OF WHO POST CESAREAN PAIN MANAGEMENT VERSUS STANDARD OF CARE AT NYERI COUNTY REFERRAL HOSPITAL: A RANDOMIZED CONTROLLED TRIAL.

Principal Investigator:

Dr. Mugambi Jackline(MBChB)

Department of Obstetrics and Gynecology, University of Nairobi.

Telephone Number: 0723-032054

Investigator's Statement:

We are requesting you to kindly participate in this research study comparing the efficacy and cost of WHO post cesarean pain management versus standard of care at Nyeri County Referral Hospital. The purpose of this consent form is to provide you with the information you will need to help you decide whether to participate in the study. This process is called 'Informed Consent'. Please read this consent information carefully and ask any questions or seek clarification on any matter concerning the study with which you are uncertain. You are free to ask any questions about the study. The investigator will be available to answer any questions that arise during the study and afterwards.

Introduction:

Adequate postoperative pain control is an important postoperative care in most procedures and even greater importance after cesarean section because the patients are mothers and need

to take care of the newborns. Effective pain control is vital in aiding mobilization, thus reducing the risk of postoperative venous thromboembolism, it allows the mother to give her new baby optimal care (increased mother-child bonding time and breastfeeding) and can shorten hospital stay. In this study, we compare the efficacy and cost of WHO recommended versus the current standard of care for post cesarean pain management at NCRH.

Study procedure:

While in this study, you will be interviewed and questionnaires will be filled for the purpose of this study. If you agree to participate in the study, you will be randomly allocated into one of the groups described below. Randomization means that you are put into a group by chance. There is no way to predict which group you will be assigned to. You will have an equal chance of being placed in either/any group. Neither you nor your doctor can choose what group you will be in. You will be blinded in this study meaning, you will not know which group of the study you fall in.

There are two groups/arms in this study. One group is the World Health Organization (WHO) intervention group while the other group is the routine care at Nyeri County Referral Hospital (NCRH). In the WHO group, pain management will be instituted from day one post-operation to 3rd day post cesarean section by receiving the following medications either intra-muscular (I.M), intravenous (I.V) or orally (P.O):

Day 1: I.M Morphine 10mg 4hrly/PRN, I.V paracetamol 1 g 8hrly, I.M diclofenac 100mg 8hrly.

Day 2: I.V tramadol 100mg 8hr, P.O paracetamol 1 g 8hrly, P.O diclofenac 50mg 8hrly.

Day 3: P.O diclofenac 50mg 8hrly, P.O paracetamol 1g 8hrly

The NCRH group will receive the routine care at NCRH for post-operative pain management from day one to 3rd day post cesarean section. This means you will receive pain medication as follows; 10mg intramuscular morphine, every 8 hours on day one followed by 1-gram paracetamol and 50mg diclofenac oral on subsequent days.

You are expected to give an honest level of pain control using the Visual Analog Scale provided to you at rest, 6, 12, 24 and 72 hours.

.

Benefits:

As a participant you will benefit from the study by receiving close monitoring. You will

benefit by receiving health education and advice on postpartum and neonatal care. You will be able to access the principal investigator at any time during the study period. Your participation in the study may benefit others in future from the information we find in this study.

Voluntariness:

Taking part in this study is voluntary. There will be no financial rewards to you for participating in the study. One is free to participate or withdraw from the study at any point. Deciding not to take part or deciding to leave the study later will not result in any penalty or any loss of benefits to which you are entitled. Refusal to participate will not compromise you or your child's care in any way.

Confidentiality:

All the information obtained from you will be held in strict confidentiality. Any information that may identify you or your child will not be published or discussed with any unauthorized persons. No specific information regarding you, your child or your family will be released to any person without your written permission. Your research number will be used in place of your names.

Risks

Being part of this study may involve some risks or discomforts. Any medication or procedure may cause side effects. You will be monitored for side effects from the study drugs. It is important that you report any side effects to your doctor right away. While in the study, you are at risk of the following most common side effects. These side effects have been identified through past studies.

Morphine: Pruritus, vomiting, constipation, headache, urinary retention, rash, sweating, loss of appetite, insomnia.

Tramadol: Constipation, nausea, vomiting, anxiety, pruritus, rash, dry mouth, tremor, vertigo, agitation.

Diclofenac: Abdominal distention and flatulence, fluid retention, nausea, peptic ulcer, rash, pruritus, dyspepsia.

Paracetamol: Rash, dizziness, neutropenia, angioedema, thrombocytopenia, nephrotoxicity.
You will be monitored closely for any side effects and when possible, other drugs will be given to you to make side effects less serious and more tolerable. Most side effects go away when the drugs being used are stopped.

Access of health records

You may apply for access to your own records, or may authorize third parties such as lawyers, employers, or insurance companies to do so on your behalf. The Principal Investigator can be contacted if access to health records is required.

Sharing of results

Study staff will protect your personal information closely so no one will be able to connect your responses and any other information that identifies you. Federal or state laws may require us to show information to university or government officials (or sponsors), who are responsible for monitoring the safety of this study. Directly identifying information (e.g. names, addresses) will be safeguarded and maintained under controlled conditions. You will not be identified in any publication from this study.

Problems or Questions:

If you ever have any questions about the study or about the use of the results you can contact the principal investigator, Dr. Mugambi Jackline by calling 0723032054. If you have any questions on your rights as a research participant, you can contact the Kenyatta National Hospital Ethics and Research Committee (KNH- ESRC) by calling 2726300 Ext. 44355.

Consent Form: Participant's Statement:

I _____ having received adequate information regarding the study research, risks, benefits hereby AGREE / DISAGREE (Cross out as appropriate) to participate in the study. I understand that our participation is fully voluntary and that I am free to withdraw at any time. I have been given adequate opportunity

to ask questions and seek clarification on the study and these have been addressed satisfactorily.

Participant's name: _____ Signature/thumb print: _____

Date _____

Witness name: _____ Signature/thumb print: _____

Date: _____

I _____ declare that I have adequately explained to the above participant, the study procedure, risks and benefits and given her time to ask questions and seek clarification regarding the study. I have answered all the questions raised to the best of my ability.

Interviewer's name and Signature: _____ Date: _____

APPENDIX II: CONSENT FORM IN KISWAHILI

FOMU YA RIDHAA

Tarehe (siku/mwezi/mwaka): _____

Study Title: EFFICACY AND COST OF WHO POST CESAREAN PAIN MANAGEMENT VERSUS STANDARD OF CARE AT NYERI COUNTY REFERRAL HOSPITAL: A RANDOMIZED CONTROLLED TRIAL.

Mtafiti Mkuu:

Dkt. Mugambi Jackline (MBChB)

Idara ya Uzazin aAfy ya kina mama, Chuo kikuu cha Nairobi.

Nambari ya simu: 0723032054

Taarifa ya mtafiti:

Tunakuomba wewe kushiriki kwenyeutafiti huu. Lengo la fomu hii ya idhini ni kukupa habari utakayohitaji iliikusaidie kuamua ikiwa utashiriki kwenye utafiti. Utaratibu huu unaitwa 'Idhini ya kujulishwa'. Tafadhali soma ujumbe wa idhini hii kwa uangalifu na uulize maswali yoyote au ufafanuzikwa mambo yoyote yanayohusisha utafiti ambayo hauna uhakika nayo. Uko huru kuuliza maswali yoyote kuhusu utafiti. Mtafiti atakuwa kokujibu maswali ya takayotokea wakati wa utafiti na baadaye.

Faida:

Kama mshiriki utafaidika kutokana na utafiti kwa kupata malezi ya kufwatiliwa kwa karibu. Utafaidika kwa kupata masomo ya kiafya na ushauri wa malezi ya mtoto mchanga. Utaweza kumufikia mtafiti mkuu wakati wowote kwa wakati wa utafiti. Kushiriki kwako kwenye utafiti kwaweza wafaidi wengine wakati wa usoni kutokana na habari tutakoyopata kwenye utafiti huu.

Utaratibu wa kujifunza:

Wakati wa utafiti huu, utaulizwa na maswali yanajazwa kwa kusudi la utafiti huu. Ikiwa unakubali kushiriki katika utafiti huo, utakuwa umewahi nasibu katika mojawapo ya vikundi vilivyoelezwa hapo chini. Randomization ina maana kwamba wewe huwekwa katika kundi kwa bahati. Hakuna njia ya kutabiri kikundi gani utakachopewa. Utakuwa na nafasi sawa ya kuwekwa katika kikundi chochote. Si wewe na daktari wako anayeweza kuchagua kundi gani utakapoingia. Utafunguliwa kwenye maana hii ya utafiti, hutajua ni kundi gani la utafiti unaoingia. Kuna makundi mawili / silaha katika utafiti huu. Mkono mmoja ni kundi la kuingilia kati la Shirika la Afya la Ulimwenguni (WHO) wakati mkono mwingine ni utunzaji wa kawaida katika Hospitali ya Rufaa ya Nyeri County (NCRH). Katika mkono wa WHO, usimamizi wa maumivu utaanzishwa tangu siku moja baada ya utendaji hadi siku ya tatu ya siku baada ya kupokea sehemu ya dawa kwa kupokea dawa zifuatazo ama intra-muscular (I.M), intravenous (I.V) au mdomo (P.O): : Siku ya 1: I.M Morphine 10mg 4hrly / PRN, I.V paracetamol 1 g 8h, I.M diclofenac 100mg 8hrly. Siku ya 2: I.V tramadol 100mg 8hr, P.O paracetamol 1 g 8 hrs, P.O diclofenac 50mg 8hrly. Siku 3: P.O diclofenac 50mg 8hrly, P.O paracetamol 1g 8hrly Wakati wa kundi la udhibiti, wagonjwa katika mkono huu watapata huduma ya kawaida kwa NCRH kwa usimamizi wa maumivu baada ya kazi kutoka kipindi cha ushirika hadi siku ya tatu baada ya sehemu ya sehemu. Utunzaji wa kawaida kwa NCRH kwa maumivu baada ya maumivu hujumuisha 10mg morphine ya intramuscular, 8 saa moja, siku moja ikifuatiwa na paracetamol 1 gramu na mdomo na diclofenac kwa siku zifuatazo.

Tathmini ya maumivu itafanyika na wagonjwa wanaotumia kiwango cha analog ya visual katika mchana, 6, 12, 24 na 72 masaa.

Mafunzo ya Utafiti:

Katika kundi la kuingilia kati, wagonjwa wataonekana na msaidizi wa utafiti na WHO ilipendekeza usimamizi wa maumivu utaanzishwa tangu siku moja baada ya kazi hadi siku ya siku ya tatu baada ya misaada kama ifuatavyo

Hatari:

Kuwa sehemu ya utafiti huu inaweza kuhusisha baadhi ya hatari au kutokuwepo. Dawa yoyote au utaratibu unaweza kusababisha madhara. Utafuatiliwa kwa athari za madawa ya kujifunza. Ni muhimu kwamba ueleze madhara yoyote kwa daktari wako mara moja. Wakati katika utafiti huo, uko katika hatari ya madhara ya kawaida yafuatayo. Madhara haya yamejulikana kupitia masomo ya zamani.

Morphine: Kujikuna, kutapika, kuvimbiwa, maumivu ya kichwa, uhifadhi wa mkojo, upele, jasho.

Tramadol: kichefuchefu, kutapika, wasiwasi, pruritus, kupoteza, kinywa kavu, kutetemeka

Diclofenac: Msongamano wa tumbo na upofu, uhifadhi wa maji, kichefuchefu, kidonda cha peptic, upele, pruritus, dyspepsia.

Paracetamol: Rash, kizunguzungu, neutropenia, angioedema

Kujitolea:

Utafiti utakua wa kujitolea. Hakuta kuwa na malipo ya kifedha kwa kushiriki kwenye utafiti huu. Mtu ako huru kushiriki au kujiondoa kwe

Usiri:

Habari yoyote itakayotolewa kwako itawekwa kwa usiri wa hali ya juu. Habari yoyote ya kukutambulisha wewe haitachapishwa au kujadiliwa na watu wasiona kibali. Hakuna habari maalum kukuhusu, kuhusu mwanao au mtu wa familia yako itapeanwa kwa mtu mwingine bila ruhusa yako iliyoandikwa. Nambari yako ya utafiti itatumika badala ya jina lako.

Kupata rekodi za kimatibabu

Unaweza kuomba kuweza kufikia rekodi zako au kuruhusu watu wengine kama vile mawakili, waajiri au kampuni za fidia kufunya hivyo kwa niaba yako. Mtafiti mkuu anaweza fikiwa ikiwa rekodi zako zahitaji kufikiwa.

Kujulisha wengine matokeo

Wafanyakazi wa utafiti watalinda habari sana habari yako ya kibinafsi ilimtu yeyote asije akajua akaunganisha majibu yako na habari inayoweza kukutambulisha. Sheria za serikali zatuhitaji kuonyesha habari kwa wawakilikilishi wa serikali (wafadhili) au chuo kikuu ambao wana jukumu la kufuatilia usalama wa utafiti huu. Habari inayotambulisha moja kwa moja (majina, anwani) zitalindwa na kuwekwa katika hali salama. Hautatambulishwa na chapisho lolote kutoka na utafiti huu.

Shida au Maswali:

Ikiwa una maswali kuhusu utafiti au matumizi ya majibu waweza asiliana na mtafiti, Dkt. Mugambi Jackline kwa kupiga 0723032054. Ikiwa una maswali kuhusu haki yako kam mshiriki waweza wasiliana na kamati ya madili na tafiti ya hospitali kuu ya (KNH- ESRC) kwakupiga 2726300 Ext. 44355.

Fomu ya Idhini: Taarifaya Mshiriki:

Mimi_____Nimepewa habari ya kutosha kuhusiana na utafiti , hatari, faida, NINAKUBALI/SIKUBALI (weka alama inavyostahili). Kushiriki kwenye utafiti na mwanangu. Ninaelewa kwamba kushiriki kwangu ni kwa kujitolea na niko huru kujiondoa wakati wowote. Nimepewa nafasi ya kutosha ya kuuliza ma swali na kuuliza ufafanuzi wa utafiti na nimeelezewa haya nikatosheka.

Jina la mshiriki: _____ Sahihi/alamayakidole:

_____

Tarehe _____

Jina la mshahidi: _____ Sahihi/alamayakidole:

_____

Tarehe: _____

Mimi_____Natangaza yakwamba nimemwelezea mshiriki aliye hapo juu yakutosha, taratibu za utafiti, hatari na faida na nimempa wakati wakuuliza naswali nakuuliza ufafanuzi kuhusu utafiti. Nimejibu maswali yake yote kwa uwezo wangu wote.

Jina la anayeuliza ma swali na sahihi: _____Tarehe: _____

Shida au Maswali:

Ikiwa una maswali kuhusu utafiti au matumizi ya majibu waweza asiliana na mtafiti, Dkt. Mugambi Jackline kwa kupiga 0723032054. Ikiwa una maswali kuhusu haki yako kam mshiriki waweza wasiliana na kamati ya madili na tafiti ya hospitali kuu ya (KNH- ERC) kwakupiga2726300 Ext. 44355.

APPENDIX III: QUESTIONNAIRE

VAS (Visual Analogue Score) PAIN SCALE

• Assess pain intensity (VAS) at rest the subject should rest quietly in a supine or seated position that does not exacerbate her postsurgical pain for 3-5 minutes before entering the pain score

• Assess your pain at rest at 6, 12, 24 and 72 hours

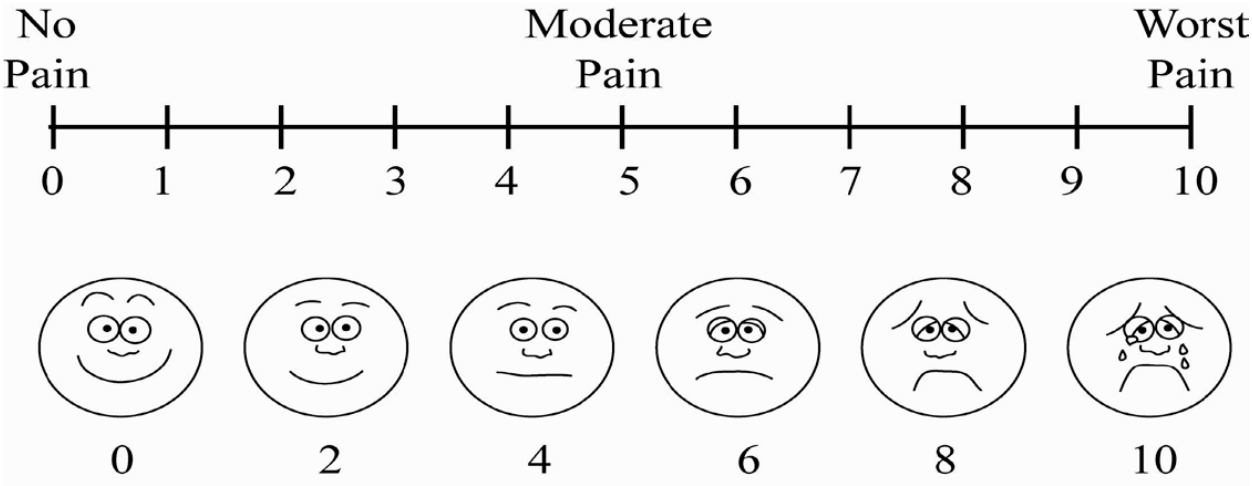

Figure 4: VAS

Questionnaire 2

Subject Satisfaction with Postsurgical Pain Control -Likert Scale

• Please circle the number below that best describes your overall satisfaction with your pain control, pain management and treatment after surgery. (Select one number only.)

• To be conducted at 72 hours after surgery (or at hospital discharge, whichever occurs first)

1. Extremely dissatisfied

2. Dissatisfied

3. Neither satisfied nor dissatisfied

4. Satisfied

5. Extremely satisfied

Questionnaire 3.-Health care providers questionnaire

Please write yes or no in the provided questionnaire

Yes

No

Q1 Giving narcotics on a regular schedule is preferred over as needed (PRN) schedule for continuous pain

Q2 A patient should experience discomfort prior to giving the next dose of pain meds

Q3 When a patient requests increasing amounts of analgesics to control pain, this usually indicates that the patient is psychologically dependent

Q4 The most accurate judge of the intensity of the patient's pain is the patient

Q5 Staff can always pick up cues from patients that indicate that they are in pain

Q6 Because narcotics can cause respiratory depression, they should not be used in patients

Yes

No

Q7 The most suitable dose of morphine for a patient in pain is a dose that best controls the symptoms; there is no maximum dose

Q8 It may often be useful to give a placebo to a patient in pain to assess if she is genuinely in pain

Q9 For effective treatment of post cesarean pain it is necessary to continuously assess the pain and the efficacy of the therapy

Q10 It is a patient's right to expect total pain relief as a consequence of treatment

Q11 Lack of pain expression does not mean lack of pain

Q12 Estimation of pain by a health care provider is as valid a measure of pain as a patient's self-report.

APPENDIX IV: DUMMY TABLES

Table 3: Maternal baseline characteristics

Characteristic	Category	n (%) / mean (SD deviation) NCRH	n (%)/ mean (SD deviation) WHO	P value
Socio demographics				
Age	18-25 26-35 36-50 >50			
Obstetric History				
Parity	0 1 2 3 4 5			
ANC attendance	Yes No			
Facility attended	NCRH Other facility			
Number of visits	1 2-4 >4			
Gestational age at first visit				
Hb(g/dl) at 1st visit				
Repeat Hb(If available)				
Blood group	A+ B+ AB+ O+ A- B- AB- O-			
VDRL	Positive Negative Unknown			
HIV	Positive Negative Unknown			
Medications	Magnesium-sulphate Steroids Antihypertensive Narcotics Antibiotics			

Table 4: VAS SCORE

VAS SCORE		n (%) / mean (SD deviation) NCRH	n (%)/ mean (SD deviation) WHO	P value
0				
1 2				
3				
4				
5				
6				
7				
8				
9				
10				

Table 5: COST

COST		n (%) / mean (SD deviation) NCRH	n (%)/ mean (SD deviation) WHO	P value
0-1000				
1000-2000				
2000-3000				

APPENDIX V: INCLUSION AND EXCLUSION SCREENING ENROLMENT FORM

Study Title: EFFICACY AND COST OF WHO POST CESAREAN PAIN MANAGEMENT VERSUS STANDARD OF CARE AT NYERI COUNTY REFERRAL HOSPITAL: A RANDOMIZED CONTROLLED TRIAL.

Date: (date/month/year): _____

Enrolment identification number: _____

Inclusion Criteria: Answers MUST be 'yes' for these questions.

1. Females 18 years of age and older at screening.
2. All patients who have undergone cesarean section.
3. Participants able to provide informed consent both verbal and written.

Exclusion criteria: *If any answer is 'Yes' exclude from enrolment*

1. Patients having concurrent pain-causing condition e.g. arthritis, neuropathy, multiple sclerosis
2. Allergy, hypersensitivity, intolerance or contraindication to any of the study medication.
3. Patient is in a vulnerable population such as prisoner, mentally unstable to provide direct consent etc.
4. History of suspected or known addiction to or abuse of illicit drugs, prescription medicines or alcohol in the past five years throw through history taking and collaboration with next of kin.
5. Unable to provide informed consent due to being clinically unstable

APPENDIX VI: DATA COLLECTION TOOL

Study Title: EFFICACY AND COST OF WHO POST CESAREAN PAIN MANAGEMENT VERSUS STANDARD OF CARE AT NYERI COUNTY REFERRAL HOSPITAL: A RANDOMIZED CONTROLLED TRIAL.

BASELINE QUESTIONNAIRE 1

Part I: Socio demographics

Indicate all times using the 24-hour clock, and dates in this format date/month/year.

DATE _____

Enrolment identification number: _____ Randomization group: _____

Date of Signed Informed Consent: ____/_____/_____

Copy given to patient: Yes / No ……..……..

1. Age of mother (years) …….
2. Marital Status

Single	□	Widowed	□
Married	□	Separated	□
Divorced	□		

3. Level of Education

Primary	□	Secondary	□	Tertiary	□

4. Employment status

Self-employed	□	Salaried employment	□	Unemployed	□

Part II: Obstetric History

5. Parity ……

6. Obstetric History

	Date (Year)	Place Home or	GA** at delivery	Mode of Deliver	Maternal Complications	Neonatal Outcome

		HF*		y		
1						
2						
3						

*HF-Health Facility GA** Gestational age

7. ANC attendance Yes □ No □
8. If yes, facility attended: NCRH □ Other facility □
9. Number of visits ……..
10. Date of first visit ……/……. /……..
11. Gestational age at first visit (in completed weeks) ……/40
12. Iron supplementation during pregnancy Yes □ No □
13. Duration of Iron supplementation……
14. ANC Profile:

    Haemoglobin (g/dl) ……

    Blood group: …….. Rh: ……

    VDRL:

    HIV:

Part Ill: Index Admission

15. Date of Admission ……/……. /…….
16. Time of admission…….
17. Referral status

    Referred from other facility □

    Self-referred □

    Booked for delivery at NCRH □
18. Gestational age at delivery (in completed weeks) ……../40
19. Gestational age calculated by Dates □ Quickening □

    Ultrasound □ Fundal Height □

First clinic visit estimate □

20. Maternal Haemoglobin levels at admission ……..
21. Maternal PCV at admission …….
22. History of chronic/ Co-morbid illness: Yes No
23. If 'yes' for question 22 please state which illness and drug history (type and frequency):
    …….

APPENDIX VII: DATA AND MONITORING SAFETY PLAN

Data and Safety Monitoring Plan

Study Title: **EFFICACY AND COST OF WHO POST CESAREAN PAIN MANAGEMENT VERSUS STANDARD OF CARE AT NYERI COUNTY REFERRAL HOSPITAL: A RANDOMIZED CONTROLLED TRIAL.**

Principal Investigator: Dr Mugambi Jackline

MEMBERS

1. Dr. Alex Bosire -Obstetrician and Gynecologist, MBchB, M.MED

2. Dr. Rosa Chemwey- Obstetrician and Gynecologist, MBchB, M.MED

3. Mr. Francis Njiiri- statistician, Program and Data Manager, MSc, Statistics

BRIEF STUDY OVERVIEW

Objective: To compare the efficacy and cost of WHO recommended versus the current standard of care for post cesarean pain management at NCRH.

Methodology: Randomized controlled trial in Nyeri county referral hospital. Once a patient is identified as being qualified for the study in accordance with the eligibility criteria, a random number will be assigned, a sealed envelope will be given by the study personnel who will give it to the un-blinded surgical team (anesthesiologist and operating surgeon). The envelope to be opened after delivery of the fetus.

DSMB OVERSIGHT RESPONSIBILITIES

Oversight of the trial is provided by the DSMB. Meetings will take place to monitor on safety of patients and signals of efficacy, futility or harm. The DSMB members will have a first meeting before study is commenced. A meeting will be constituted in case of any adverse event and a final meeting on conclusion of the study. In the case of unacceptable safety concerns/results occur, the board can recommend termination of the study. The safety of the participant is paramount.

MONITORING PROCEDURES

Dr. Mugambi Jackline will ensure that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the ERC-approved research plan.

Study data are accessible at all times for the PI to review. The PI will review study conduct every alternate day that is acquisition of consent, any dropouts, and completeness of questionnaire. The PI will review AEs individually real-time and in aggregate on a daily basis.

The PI will ensure all protocol deviations, AEs, and SAEs are reported to the ERC and KNH administration according to the applicable regulatory requirements.

COLLECTION AND REPORTING OF SAEs AND AEs

For this study, the following standard AE definitions are used:

Adverse event: Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

Serious Adverse Event: Any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

AEs are graded according to the following scale:

Mild: An experience that is transient, & requires no special treatment or intervention. This includes transient laboratory test alterations.

Moderate: An experience that is alleviated with simple therapeutic treatments. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:

Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

Related: The AE is clearly related to the study procedures.

DATA ANALYSIS PLANS

The statistician will not be blinded and data monitoring will be continuous, he will alert the principal investigator of any overt differences in the two groups. The study will be halted if there is evidence of significant statistical advantage in whichever group, to avoid denying the corresponding group an advantageous intervention.

In case of SAE, a report will be forwarded to ERC and study halted immediately pending clearance.

PLAN FOR DATA MANAGEMENT

Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process.

APPENDIX VIII: SEVERE ADVERSE EVENT NOTIFICATION PROTOCOL REPORTING FORM

Title of Proposal: **EFFICACY AND COST OF POST CESAREAN PAIN MANAGEMENT USING THE WORLD HEALTH ORGANISATION RECOMMENDATIONS VERSUS ROUTINE CARE AT NYERI COUNTY REFERRAL HOSPITAL: A RANDOMIZED CONTROLLED TRIAL**

Principal Investigator: Dr Mugambi Jackline Wanjiku

Co-Investigators: Dr. Weston Khisa MBchB, M.MED ,
Dr. Alfred Osoti MBchB, M.MED, MPH, Ph. D
Dr. Moses Obimbo MBchB, Dip FELASA C, MSci, M.MED(Obs/Gyn), Ph.D.

1. Study participant identification number:

2. Date of serious adverse event:

3. Study participant age and sex:

4. Study participant identification number:

5. Study participant enrollment date:

6. Provide a description explanation of the serious adverse event: Was the serious adverse event related to the study:
.

Date:

Prepared by:

Sign:

APPENDIX IX: CLINICAL REPORT FORM

CASE REPORT FORM TEMPLATE
Version: 6.0 (8 November 2012)

PROTOCOL: EFFICACY AND COST OF POST CESAREAN PAIN MANAGEMENT USING THE WORLD HEALTH ORGANISATION RECOMMENDATIONS VERSUS ROUTINE CARE AT NYERI COUNTY REFERRAL HOSPITAL: A RANDOMIZED CONTROLLED TRIAL

Participant Study Number:	| | | | | |
Study group:	| | |

BASELINE DATA

General Instructions for Completion of the Case Report Forms (CRF)

Completion of CRFs

- A CRF must be completed for each study participant who is successfully enrolled (received at least one dose of study drug)
- For reasons of confidentiality, the name and initials of the study participant should **not** appear on the CRF.

General

- Please print all entries in BLOCK CAPITAL LETTERS using a **black** ballpoint pen.
- All text and explanatory comments should be brief.
- Answer every question explicitly; do not use ditto marks.
- Do not leave any question unanswered. If the answer to a question is unknown, write "**NK**" (Not Known). If a requested test has not been done, write "**ND**" (Not Done). If a question is not applicable, write "**NA**" (Not Applicable).
- Where a choice is requested, **cross (X)** the appropriate response.

Dates and Times

- All date entries must appear in the format DD-MMM-YYYY e.g. 05-May-2009. The month abbreviations are as follows:

January	=	Jan	May	=	May	September	=	Sep
February	=	Feb	June	=	Jun	October	=	Oct
March	=	Mar	July	=	Jul	November	=	Nov
April	=	Apr	August	=	Aug	December	=	Dec

In the absence of a precise date for an event or therapy that precedes the participant's inclusion into the study, a partial date may be recorded by recording "NK" in the fields that are unknown e.g. where the day and month are not clear, the following may be entered into the CRF:

N	K	N	K		2	0	0	9			
DD		MMM			YYYY						

- All time entries must appear in **24-hour format** e.g. 13:00. Entries representing midnight should be recorded as 00:00 with the date of the new day that is starting at that time.

Correction of Errors

- **Do not** overwrite erroneous entries, or use correction fluid or erasers.
- Draw a straight line through the entire erroneous entry without obliterating it.
- Clearly enter the correct value next to the original (erroneous) entry.
- Date and initial the correction.

BASELINE DATA

Participant Number:					

BASELINE DATA

Participant Number:					

PARTICIPANT INFORMATION			
Participant Number			
Study Group	_____		
Study Site (Health Centre Name)	_____		
Inclusion/exclusion criteria *Patient must meet all criteria to eligible for the study	Met all ☐1.	Not met* ☐2.	
Date of Informed Consent	D D M M M Y Y Y Y		
Date of Birth	D D M M M Y Y Y Y	Or estimated age _____	
Gender	☐1 Male ☐2 Female		
Pregnant	☐1. Yes	☐2. No	☐9. Unknown
If pregnant, Estimated Gestational Age _____weeks			
Date of Enrolment	D D M M M Y Y Y Y		
Had malaria in the last 28 days	☐1. Yes	☐2. No	☐9. Unknown
Had antimalarial in the last 28 days	☐1. Yes	☐2. No	☐9. Unknown

BASELINE DATA

Participant Number:					

BASELINE SYMPTOMS			
Fever (in last 24 hours)	☐1. Yes	☐2. No	Duration: _____ days
Dizziness	☐1. Yes	☐2. No	Duration: _____ days
Headache	☐1. Yes	☐2. No	Duration: _____ days
Nausea	☐1. Yes	☐2. No	Duration: _____ days
Anorexia	☐1. Yes	☐2. No	Duration: _____ days
Vomiting	☐1. Yes	☐2. No	Duration: _____ days
Diarrhoea	☐1. Yes	☐2. No	Duration: _____ days
Abdominal pain	☐1. Yes	☐2. No	Duration: _____ days
Itching	☐1. Yes	☐2. No	Duration: _____ days
Skin rash	☐1. Yes	☐2. No	Duration: _____ days
Urticaria	☐1. Yes	☐2. No	Duration: _____ days
Joint pain	☐1. Yes	☐2. No	Duration: _____ days
Muscle pain	☐1. Yes	☐2. No	Duration: _____ days
Palpitations	☐1. Yes	☐2. No	Duration: _____ days
Dyspnoea	☐1. Yes	☐2. No	Duration: _____ days
Hearing problem	☐1. Yes	☐2. No	Duration: _____ days
Confusion	☐1. Yes	☐2. No	Duration: _____ days
Visual blurring	☐1. Yes	☐2. No	Duration: _____ days
Fatigue	☐1. Yes	☐2. No	Duration: _____ days
Other symptom:	_____		Duration: _____ days
Other symptom:	_____		Duration: _____ days
Other symptom:	_____		Duration: _____ days

CASE REPORT FORM TEMPLATE

BASELINE DATA

Participant Number: | | | | |

MEDICATION HISTORY (within the last 7 days)

- Make multiple copies of this page if required

Medication Name (write NK if unknown)	**Start Date**	**Stop Date**
______________	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
______________	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
______________	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
______________	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
______________	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
______________	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
______________	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
______________	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
______________	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
______________	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
______________	D D M M M Y Y Y Y	D D M M M Y Y Y Y

BASELINE DATA

Participant Number:					

___	*OR* ☐1 Unknown	*OR* ☐1 Ongoing
_____ ___	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
_____ ___	D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing

BASELINE DATA

Participant Number:					

SIGNIFICANT MEDICAL HISTORY (within the past 5 years)
- Make multiple copies of this page if required

Does the participant have a history of any background/concomitant conditions/symptoms according to the following schedule? ☐1 Yes ☐2 No

If **Yes**, detail in the table below and reference the ICD10 system code
http://apps.who.int/classifications/apps/icd/icd10online/

Code	Title	Code	Title
1	Certain infectious and parasitic diseases	12	Diseases of the skin and subcutaneous tissue
2	Neoplasms	13	Diseases of the musculoskeletal system and connective tissue
3	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	14	Diseases of the genitourinary system
4	Endocrine, nutritional and metabolic diseases	15	Pregnancy, childbirth and the puerperium
5	Mental and behavioural disorders	16	Certain conditions originating in the perinatal period
6	Diseases of the nervous system	17	Congenital malformations, deformations and chromosomal abnormalities
7	Diseases of the eye and adnexa	18	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
8	Diseases of the ear and mastoid process	19	Injury, poisoning and certain other consequences of external causes
9	Diseases of the circulatory system	20	External causes of morbidity and mortality
10	Diseases of the respiratory system	21	Factors influencing health status and contact with health services
11	Diseases of the digestive system	22	Codes for special purposes

SIGNIFICANT MEDICAL HISTORY (within the past 5 years)

Code	Condition/Symptom	Onset Date	Stop Date
		D D M M M Y Y Y Y	D D M M M Y Y Y Y

BASELINE DATA

Participant Number:					

		OR ☐1 Unknown	*OR* ☐1 Ongoing

BASELINE PHYSICAL EXAMINATION – PART 1

		D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
		D D M M M Y Y Y Y *OR* ☐1 Unknown	D D M M M Y Y Y Y *OR* ☐1 Ongoing
		D D M M M Y Y Y Y *OR* ☐1 Unknown	**D D M M M Y Y Y Y** *OR* ☐1 Ongoing
		D D M M M Y Y Y Y *OR* ☐1 Unknown	**D D M M M Y Y Y Y** *OR* ☐1 Ongoing

BASELINE DATA

Participant Number: | | | | | |

Weight	___.___ kg	Height	___.___ cm
Temperature	___.___ °C	Heart rate	___ bpm

Method of Recording

Axillary	Tympanic	Rectal	Oral
☐1	☐2	☐3	☐4

Respiratory rate	___ bpm	Blood pressure	___ / ___ mmHg
Hepatomegaly	☐1. Yes ☐2. No	If yes, size:	___ cm
Splenomegaly	☐1. Yes ☐2. No	If yes, size:	___ cm

	Normal	Abnormal	Specify if abnormal
Central Nervous System	☐1.	☐2.	_____
Cardiovascular System	☐1.	☐2.	_____
Respiratory System	☐1.	☐2.	_____
Gastrointestinal System	☐1.	☐2.	_____
Skin	☐1.	☐2.	_____
Joints	☐1.	☐2.	_____

BASELINE DATA

Participant Number:					

BASELINE PHYSICAL EXAMINATION – PART 2				
Danger signs or features of severe malaria? (If no symptoms tick box on the right. Otherwise complete list below)		**No symptoms** ☐2		
		Yes	**No**	**Not Known**
Clinical manifestations	Impaired consciousness	☐1	☐2	☐99
	Prostration	☐1	☐2	☐99
	Multiple convulsions	☐1	☐2	☐99
	Respiratory distress (metabolic acidotic)	☐1	☐2	☐99
	Circulatory collapse	☐1	☐2	☐99
	Jaundice	☐1	☐2	☐99
	Haemoglobinuria	☐1	☐2	☐99
	Abnormal bleeding	☐1	☐2	☐99
	Pulmonary oedema (radiological)	☐1	☐2	☐99
Laboratory findings	Hypoglycaemia (blood glucose <2.2 mmol/l or <40 mg/dl	☐1	☐2	☐99
	Acidosis (plasma bicarbonate <15 mmol/l)	☐1	☐2	☐99
	Severe anaemia (Hb < 5g/dl or haematocrit <15%)	☐1	☐2	☐99
	Hyperparasitaemia (>4% in non-immune patients)	☐1	☐2	☐99
	Hyperlactataemia (venous lactic acid >5 mmol/l)	☐1	☐2	☐99
	Renal impairment (serum creatinine above normal range for age)	☐1	☐2	☐99

HAEMATOLOGY

Participant Number						

CASE REPORT FORM TEMPLATE

BASELINE DATA

Participant Number: | | | | |

HAEMATOLOGY – *make multiple copies of this page if required*

Day0	Date	Time 24hr	Hb (g/dL)	Hct (%)	WBC (10^9/L)
	D D M M M Y Y Y Y	H H : M M	.	.	.
	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Platelets (10^9/L)
	.	.	.	.	.
Day_	Date	Time 24hr	Hb (g/dL)	Hct (%)	WBC (10^9/L)
	D D M M M Y Y Y Y	H H : M M	.	.	.
	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Platelets (10^9/L)
	.	.	.	.	.
Day_	Date	Time 24hr	Hb (g/dL)	Hct (%)	WBC (10^9/L)
	D D M M M Y Y Y Y	H H : M M	.	.	.
	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Platelets (10^9/L)
	.	.	.	.	.
Day_	Date	Time 24hr	Hb (g/dL)	Hct (%)	WBC (10^9/L)
	D D M M M Y Y Y Y	H H : M M	.	.	.
	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Platelets (10^9/L)
	.	.	.	.	.
Day_	Date	Time 24hr	Hb (g/dL)	Hct (%)	WBC (10^9/L)
	D D M M M Y Y Y Y	H H : M M	.	.	.
	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Platelets (10^9/L)
	.	.	.	.	.
Day_	Date	Time 24hr	Hb (g/dL)	Hct (%)	WBC (10^9/L)
	D D M M M Y Y Y Y	H H : M M	.	.	.
	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Platelets (10^9/L)

BASELINE DATA

Participant Number:					

	. -	.	.	.	.
Day_	Date	Time 24hr	Hb (g/dL)	Hct (%)	WBC (10^9/L)
	D D M M M Y Y Y Y	H H : M M	.	.	.
	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Platelets (10^9/L)
	. -	.	.	.	.

PHYSICAL EXAMINATION

Participant Number	

PHYSICAL EXAMINATION: DAY_ – *make multiple copies of this page if required*

Date	D D M M M Y Y Y Y		Time	H H : M M			
Weight	. kg		Height	. cm			
Temperature	. °C	Method of Recording				Heart rate	bpm
		Axillary	Tympanic	Rectal	Oral		
		☐1	☐2	☐3	☐4		
Respiratory rate	bpm		Blood pressure	/			mmHg
Hepatomegaly	☐1. Yes	☐2. No	If yes, size:	cm			
Splenomegaly	☐1. Yes	☐2. No	If yes, size:	cm			

Danger signs or features of severe malaria? (If no symptoms tick box on the right. Otherwise complete list below)		**No symptoms** ☐2		
		Yes	**No**	**Not Known**
Clinical manifestations	Impaired consciousness	☐1	☐2	☐99
	Prostration	☐1	☐2	☐99
	Multiple convulsions	☐1	☐2	☐99
	Respiratory distress (metabolic acidotic)	☐1	☐2	☐99
	Circulatory collapse	☐1	☐2	☐99
	Jaundice	☐1	☐2	☐99
	Haemoglobinuria	☐1	☐2	☐99
	Abnormal bleeding	☐1	☐2	☐99
	Pulmonary oedema (radiological)	☐1	☐2	☐99
Laborat	Hypoglycaemia (blood glucose <2.2 mmol/l or <40 mg/dl	☐1	☐2	☐99
	Acidosis (plasma bicarbonate <15 mmol/l)	☐1	☐2	☐99

BASELINE DATA

Participant Number:					

	Severe anaemia (Hb < 5g/dl or haematocrit <15%)	☐1	☐2	☐99
	Hyperparasitaemia (>4% in non-immune patients)	☐1	☐2	☐99
	Hyperlactataemia (venous lactic acid >5 mmol/l)	☐1	☐2	☐99
	Renal impairment (serum creatinine above normal range for age)	☐1	☐2	☐99
Are there **new symptoms** or is the patient showing a **worsening from baseline**?			☐1. Yes	☐2. No

SYMPTOM CHECK

Participant Number					

SYMPTOM CHECK – *make multiple copies of this page if required*

Day

Date	Fever	Dizziness	Headache	Nausea	Anorexia	Vomiting	Diarrhoea	Abdominal pain	Itching
D D M M M Y Y Y Y	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Time 24hr	Skin rash	Urticaria	Joint pain	Muscle pain	Palpitations	Dyspnoea	Hearing problem	Confusion	Visual blurring	Fatigue
H H : M M	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Day

Date	Fever	Dizziness	Headache	Nausea	Anorexia	Vomiting	Diarrhoea	Abdominal pain	Itching
D D M M M Y Y Y Y	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Time 24hr	Skin rash	Urticaria	Joint pain	Muscle pain	Palpitations	Dyspnoea	Hearing problem	Confusion	Visual blurring	Fatigue
H H : M M	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Day

Date	Fever	Dizziness	Headache	Nausea	Anorexia	Vomiting	Diarrhoea	Abdominal pain	Itching
D D M M M Y Y Y Y	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Time 24hr	Skin rash	Urticaria	Joint pain	Muscle pain	Palpitations	Dyspnoea	Hearing problem	Confusion	Visual blurring	Fatigue
H H : M M	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

BASELINE DATA

Participant Number:					

PARASITEMIA

Participant Number	

PARASITEMIA – *make multiple copies of this page if required*

Date smear taken	Time smear taken	Malaria species (Record counts for different species on separate rows)	Parasite count	Units (tick one)	Gametocytes	Gametocyte count	Units (tick one)	PCR/DNA sample collected?
Day_ D D M M M Y Y Y Y	H H : M M	PF ☐1 PV ☐2 PO ☐3 PM ☐4		☐ /1000RBC ☐ /200WBC ☐ /500WBC ☐ /µL	Yes ☐1 No ☐2		☐ /1000RBC ☐ /200WBC ☐ /500WBC ☐ /µL	Yes ☐1 N

Day_	Date smear taken	Time smear taken	Malaria species (Record counts for different species on separate rows)	Parasite count	Units (tick one)	Gametocytes	Gametocyte count	Units (tick one)	PCR/DNA sample collected?
	D D M M M Y Y Y Y	H H : M M	PF ☐1 PV ☐2 PO ☐3 PM ☐4		☐ /1000RBC ☐ /200WBC ☐ /500WBC ☐ /µL	Yes ☐1 No ☐2		☐ /1000RBC ☐ /200WBC ☐ /500WBC ☐ /µL	Yes ☐1 No ☐2

BASELINE DATA

Participant Number: ☐☐☐☐☐☐

Day_	**Date smear taken** D D M M M Y Y Y Y	**Time smear taken** H H : M M	**Malaria species** (Record counts for different species on separate rows) **PF** **PV** **PO** **PM** ☐1 ☐2 ☐3 ☐4	**Parasite count** ☐☐☐☐☐	**Units** (tick one) ☐ /1000RBC ☐ /200WBC ☐ /500WBC ☐ /µL	**Gametocytes** **Yes** **No** ☐1 ☐2	**Gametocyte count** ☐☐☐	**Units** (tick one) ☐ /1000RBC ☐ /200WBC ☐ /500WBC ☐ /µL	**PCR/DNA** sample collected? **Yes** **No** ☐1 ☐2
Day_	**Date smear taken** D D M M M Y Y Y Y	**Time smear taken** H H : M M	**Malaria species** (Record counts for different species on separate rows) **PF** **PV** **PO** **PM** ☐1 ☐2 ☐3 ☐4	**Parasite count** ☐☐☐☐☐	**Units** (tick one) ☐ /1000RBC ☐ /200WBC ☐ /500WBC ☐ /µL	**Gametocytes** **Yes** **No** ☐1 ☐2	**Gametocyte count** ☐☐☐	**Units** (tick one) ☐ /1000RBC ☐ /200WBC ☐ /500WBC ☐ /µL	**PCR/DNA** sample collected? **Yes** **No** ☐1 ☐2

MOLECULAR GENOTYPE

Participant Number					

PHARMACOKINETIC PROFILE		
Date	**Time**	**Sample number**
D D M M M Y Y Y Y	H H : M M	**B00**
D D M M M Y Y Y Y	H H : M M	**B01**
D D M M M Y Y Y Y	H H : M M	**B02**
D D M M M Y Y Y Y	H H : M M	**B03**
D D M M M Y Y Y Y	H H : M M	**B04**
D D M M M Y Y Y Y	H H : M M	**B05**
D D M M M Y Y Y Y	H H : M M	**B06**
D D M M M Y Y Y Y	H H : M M	**B07**
D D M M M Y Y Y Y	H H : M M	**B08**
D D M M M Y Y Y Y	H H : M M	**B09**
D D M M M Y Y Y Y	H H : M M	**B10**
D D M M M Y Y Y Y	H H : M M	**B11**
D D M M M Y Y Y Y	H H : M M	**B12**

BASELINE DATA

Participant Number: | | | | | |

STUDY DRUG ADMINISTRATION

Participant Number					

STUDY DRUG ADMINSTRATION – *make multiple copies of this page if required*

Study drug	Dose	Treatmet observed?	Date of dose	Time of dose	Vomited?	Time of vomit	Retreatment?	Retreatment dose	Time of retreatment
______	______	Yes ☐ No ☐	D D M M M Y Y Y Y	H H : M M	Yes ☐ No ☐	H H : M M	Yes ☐ No ☐	______	H H : M M
______	______	Yes ☐ No ☐	D D M M M Y Y Y Y	H H : M M	Yes ☐ No ☐	H H : M M	Yes ☐ No ☐	______	H H : M M
______	______	Yes ☐ No ☐	D D M M M Y Y Y Y	H H : M M	Yes ☐ No ☐	H H : M M	Yes ☐ No ☐	______	H H : M M
______	______	Yes ☐ No ☐	D D M M M Y Y Y Y	H H : M M	Yes ☐ No ☐	H H : M M	Yes ☐ No ☐	______	H H : M M
______	______	Yes ☐ No ☐	D D M M M Y Y Y Y	H H : M M	Yes ☐ No ☐	H H : M M	Yes ☐ No ☐	______	H H : M M

BASELINE DATA

Participant Number: | | | | | |

________	______	Yes ☐ No ☐	D D M M M Y Y Y Y	H H : M M	Yes ☐ No ☐	H H : M M	Yes ☐ No ☐	______	H H : M M
________	______	Yes ☐ No ☐	D D M M M Y Y Y Y	H H : M M	Yes ☐ No ☐	H H : M M	Yes ☐ No ☐	______	H H : M M
________	______	Yes ☐ No ☐	D D M M M Y Y Y Y	H H : M M	Yes ☐ No ☐	H H : M M	Yes ☐ No ☐	______	H H : M M
________	______	Yes ☐ No ☐	D D M M M Y Y Y Y	H H : M M	Yes ☐ No ☐	H H : M M	Yes ☐ No ☐	______	H H : M M
________	______	Yes ☐ No ☐	D D M M M Y Y Y Y	H H : M M	Yes ☐ No ☐	H H : M M	Yes ☐ No ☐	______	H H : M M
________	______	Yes ☐ No ☐	D D M M M Y Y Y Y	H H : M M	Yes ☐ No ☐	H H : M M	Yes ☐ No ☐	______	H H : M M

CONCOMITANT MEDICATIONS

Participant Number	☐☐☐☐☐

CONCOMITANT MEDICATIONS – *make multiple copies of this page if required*

Medication name	Formulation	Dose	Units	Frequency	Route	Date started	Date stopped	Ongoing?	Indication
____________	_______	_____	_____	_______	_______	D D M M M Y Y Y Y	D D M M M Y Y Y Y	Yes ☐ No ☐	____________
____________	_______	_____	_____	_______	_______	D D M M M Y Y Y Y	D D M M M Y Y Y Y	Yes ☐ No ☐	____________
____________	_______	_____	_____	_______	_______	D D M M M Y Y Y Y	D D M M M Y Y Y Y	Yes ☐ No ☐	____________
____________	_______	_____	_____	_______	_______	D D M M M Y Y Y Y	D D M M M Y Y Y Y	Yes ☐ No ☐	____________
____________	_______	_____	_____	_______	_______	D D M M M Y Y Y Y	D D M M M Y Y Y Y	Yes ☐ No ☐	____________

CASE REPORT FORM TEMPLATE

BASELINE DATA

Participant Number: | | | | | |

____	____	____	____	____	____	D D M M M Y Y Y Y	D D M M M Y Y Y Y	Yes ☐ No ☐	____
____	____	____	____	____	____	D D M M M Y Y Y Y	D D M M M Y Y Y Y	Yes ☐ No ☐	____
____	____	____	____	____	____	D D M M M Y Y Y Y	D D M M M Y Y Y Y	Yes ☐ No ☐	____
____	____	____	____	____	____	D D M M M Y Y Y Y	D D M M M Y Y Y Y	Yes ☐ No ☐	____
____	____	____	____	____	____	D D M M M Y Y Y Y	D D M M M Y Y Y Y	Yes ☐ No ☐	____
____	____	____	____	____	____	D D M M M Y Y Y Y	D D M M M Y Y Y Y	Yes ☐ No ☐	____

ADVERSE EVENTS

Participant Number	

ADVERSE EVENTS – *make multiple copies of this page if required*			
Adverse event name			
Intensity	☐1 Mild	☐2 Moderate	☐3 Severe
If SAE specify:	☐1 Death ☐2 Life-threatening ☐3 Persistent or symptomatic disability or incapacity ☐4 Hospitalisation or prolongation of hospitalisation ☐5 Congenital anomaly or birth defect ☐6 Other important medical event		
Onset Date	D D M M M Y Y Y Y		
End Date	D D M M M Y Y Y Y	**OR** ☐ Ongoing at the end of study	
Therapy	☐1 None ☐3 Other	☐2 Drug ☐4 Drug and other	
Action Taken with Study Drug	☐1 Dose unchanged ☐4 Drug withdrawn ☐99 Not Known	☐2 Dose reduced ☐5 Dose increased	☐3 Drug temporarily interrupted
Outcome	☐1 Recovered ☐3 Recovering with sequelae ☐5 Fatal	☐2 Recovering ☐4 Continuing ☐99 Not Known	
Relationship to Study drug	☐1 Certain ☐4 Unlikely	☐2 Probable ☐5 Not related	☐3 Possible ☐6 Unclassified

FINAL STUDY OUTCOME

Subject has completed the study? ☐1	**Completion date :**	D D M M M Y Y Y Y
If NOT completed specify last follow up date:		D D M M M Y Y Y Y

Reason not completed: (Tick only **one** box)	☐1 Significant non-compliance ☐2 Drug-related AE ☐3 Treatment failure ☐4 Consent withdrawn ☐5 Lost to follow-up ☐6 Other (specify) _____
Remarks:	

Investigator's Statement: I have reviewed the data recorded in this CRF and confirm that the data are complete and accurate

Investigator (Full name): _____

Investigator Signed? ☐1

Signature Date: D D M M M Y Y Y Y