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REPORTING OF ADVERSE EVENTS OF ARTEMISININ BASED COMBINATION THERAPIES AMONG PATIENTS ATTENDING WAR MEMORIAL HOSPITAL OF THE KASSENA NANKANA MUNICIPALITY

BY

BEERI PAULA

(10551022)

THIS DISSERTATION IS SUBMITTED TO THE SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF GHANA, LEGON IN PARTIAL FULFILLMENT FOR THE REQUIREMENT OF THE AWARD OF MASTER OF SCIENCE (CLINICAL TRIALS) DEGREE

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DECLARATION

I, Beeri Paula, declare that except for other people's investigations which have been duly acknowledged, this work is the result of my own original research and this dissertation either in part or in whole has not been presented elsewhere for another degree.

BEERI PAULA SIGNATURE …….. DATE: …….

STUDENT

DR. ANTO FRANCIS SIGNATURE: …… DATE: ……..…..

ACADEMIC SUPERVISOR

DEDICATION

This dissertation is dedicated to my family for supporting me through the Master of Science (Clinical Trials) programme.

ACKNOWLEDGEMENT

I would like to give thanks to the Almighty God for taking me through the Master of Science, Clinical Trials Programme. It would not have been possible to write this dissertation without the help and support of the kind people around me, of which only few can be mention here. I would like to sincerely thank my supervisor Dr. Francis Anto for his hard work and mentorship during this research. Special thanks also go to Mr. Mensah Nathan and staff of the Navrongo Health Research Center for their support. Finally, special thanks to all my study participants for willingly participating in this study.

ABSTRACT

The growing need to capture data on health events using faster and efficient means makes active surveillance an alternative means to capture anti-malarial drug safety data. A prospective cohort study was conducted at the Navrongo War Memorial hospital to determine the level of adverse events reporting following the intake of artimisinin based combination therapies (ACTs) by patients with uncomplicated malaria.

The study employed active follow-up by telephone or home visit to document adverse events (AEs) associated with anti-malarial drugs. Exit interviews were conducted using questionnaires. Epidata version 3.1 was used to design the data base and STATA version 13 was used for analysis.

Of 417 patients who participated in the study, 413 (99.0%) were successfully followed. Of these 228/413 (55.2 %) were female, 151/413(36.6%) had basic education and 175/413 (42.4%) were aged 18-64yrs. The ACTs taken were artesunate-amodiaquine 268/413 (64.9%), artemether-lumefantrine 138/413(33.4%) and diahydroartemisin-piparaquine. Overall, follow up by phone (312/413—75.5 %) was more than four times the number done by home visits (76/413—18.4 %). Forty six per cent (191/413) of patients reported AEs. In total, 15 AE were reported, 143/193(74.1%) by telephone and 32/193 (16.6 %) by home visits and the rest by health facility visit. Events such as general malaise, restlessness, nausea, dizziness, insomnia and vomiting were commonly reported. Majority of the AEs were mild. Chi square test showed a significant relation between age, severity of AE, means of reporting, type of ACT, and reporting of adverse events. A p-value ≤ 0.05 was considered statistically significant.

In conclusion, majority of the AEs experienced by participants in this study were mild. Seven AEs were commonly reported by phone call and home visit. Phone call was the most used means of reporting. To improve upon reporting of AEs, patients should be actively encouraged to report AEs after intake of drugs any day they visit the health facility. With the high AE reporting rate by mobile phone, its use is recommended for reporting of AEs and studies to determine relatedness of adverse events to ACTs in real life settings are recommended.

TABLE OF CONTENT

Content **Page**

DECLARATION i

DEDICATION ii

ACKNOWLEDGEMENT iii

ABSTRACT iv

TABLE OF CONTENT v

LIST OF TABLES viii

LIST OF FIGURES ix

LIST OF ABBREVIATIONS x

CHAPTER ONE 1

INTRODUCTION 1

1.1 Background 1

1.1.1 Safety profile of ACTs 2

1.2 Problem statement 5

1.3 Factors Affecting Reporting of Adverse Events 6

1.4 Justification 7

1.5 Objectives 8

1.5.1 General Objective 8

1.5.2 Specific objectives 8

CHAPTER TWO 9

LITERATURE REVIEW 9

2.1 Introduction of Artemisinin Based Combination Therapies 9

2.2 History of adverse event reporting 10

2.3 Identification and Grading of Adverse events 11

2.4 Monitoring of adverse events 13
2.4.1 Passive Surveillance (Spontaneous reporting of ADR) 14
2.4.2 Active Surveillance (Cohort Event Monitory CEM) 16
2.5 Burden of Adverse Events 17
2.6 Adverse events of ACTs 18
2.7 Reporting of AEs of ACTs 19
2.8 Reporting of AEs by patients 20

CHAPTER THREE 21
METHODOLOGY 21
3.1 Study Design and Location 21
3.2 Study Area 21
3.3 Health Service Organization in Kassena-Nankana Municipality 22
3.4 Study Variables 23
3.4.1 Dependent Variable 23
3.5 Sample size determination 24
3.6 Sampling Procedure 25
3.6.1 Inclusion and Exclusion Criteria 25
3.9 Quality Control 27
3.10 Data processing and Data Analysis 28
3.11 Ethical Considerations 29

CHAPTER FOUR 30
RESULTS 30
4.1 Background of study participants 30
4.1.1 Number and types of ACTs prescribed 31
4.2 Outcome of clinical condition after ACT intake 32

4.2.1 Adverse events (AEs) reported 32

4.2.2 Severity of AEs 34

4.2.3 Proportion of Adverse by means of reporting 37

CHAPTER FIVE 38

DISCUSSION 38

5.1 Limitations 42

CHAPTER SIX 43

CONCLUSION AND RECOMMENDATIONS 43

6.1 Conclusion 43

6.2 Recommendation 43

REFERENCES 45

APPENDICES 48

Appendix 1: Pretreatment questionnaire 48

Appendix 2: Post treatment questionnaire: 57

Appendix 3: Informed Consent form 62

Appendix 4: introductory Letter from University of Ghana School of Public Health ... 66

Appendix 5: Ethical Approval letter from Ghana Health Service 67

LIST OF TABLES

Table 1: Independent variables and their indicators 24

Table 2: Demographic and background characteristics of patients enrolled 31

Table 3: Distribution of new or worsening clinical conditions reported after ACT intake and means of reporting.....34

Table 4: Distribution of type of adverse event by sex 35

Table 5: Severity of AEs by type of ACT.....36

Table 6: Distribution of adverse events by age group 36

Table 7: Severity of event and means of reporting 37

LIST OF FIGURES

Figure 1: Factors affecting reporting of adverse events.....6

Figure 2: Map of Kassena/Nankana Municipality and Health Facilities 23

Figure 3: Percentage distribution of AEs reported after taking ACTs.....33

LIST OF ABBREVIATIONS

A/A	Artesunate Amodiaquine
ACTS	Artimisinine- Based Combination Therapies
ADR	Adverse Drug Reaction
AE	Adverse Events
CEM	Cohort Event Monitor
DHP	Dihydroartemisinin-piperaquine
FDA	Food and Drugs Authority
GHS	Ghana Health Services
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Reports
WHO	World Health Organisation

DEFINITION OF TERMS

Active Surveillance	A treatment plan that involves closely watching a patient's condition but not giving any treatment unless there are indicators that show the condition is getting worse.(LSHTM,2009)
Adverse event	Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with the treatment. Includes worsening of clinical condition.(ICH,2001)
Passive surveillance	Gathers disease data from all potential reporting health care workers. Health authorities do not stimulate reporting by reminding health care workers to report disease nor providing feedback to individual health workers.(LSHTM,2009)
Pharmacovigilance	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem(ICH, 2002)

CHAPTER ONE

INTRODUCTION

1.1 Background

Malaria remains a major public health problem worldwide. One hundred and ninety-eight million cases of malaria occurred globally in 2013 with 584 000 deaths (WHO, 2014). The epidemic of malaria has been fuelled by widespread resistance to cheap antimalarial drugs like chloroquine. Thus, there was an urgent need to shift from monotherapy to combination therapy in order to prevent further development of resistance.

Artemisinin derivatives have been shown to produce faster relief of clinical symptoms and faster clearance of parasites from the blood than other antimalarial drugs (Broek et al., 2005). ACTs are not only good in treating malaria but also serve as tools for prevention and control of malaria due to their ability to reduce the infectivity of mosquitoes especially in areas of low or moderate malaria transmission (Broek et al., 2005).

Fast acting artemisinin-based compounds are combined with a drug from a different class to form artimisinin-based combination therapy (ACT). Artemisinin derivatives include dihydroartemisinin, artesunate and artemether. The other drugs include lumefantrine, mefloquine, amodiaquine, sulfadoxine/pyrimethamine, piperaquine and chlorproguanil/dapsone.

Types of ACTs include artemether-lumefantrine (AL), artesunate-amodiaquine (A/A), artesunate-mefloquine (AS/MQ), artesunate-chlorproguanil-dapsone(AS/CD), artesunate-sulphadoxine-pyrimethamine (AS/SP), dihydroartemisinin-piperaquine (DHP), artesunatepiperazine(AS/PZ), and artesunate-atovaquone-proguanil(A/AP) [(Njau et al., 2013].

In 2001, the World Health Organization (WHO) recommended artemisinin-based combination therapy (ACT) as the first line therapy for uncomplicated malaria. Due to the urgency of the policy change, many health systems including Ghana embraced the new policy without conducting effectiveness studies to understand the appropriateness of the different formulations of ACTs for their populations. The choice of an ACT was based primarily on available literature with limited trials in their countries to determine their safety, efficacy, cost effectiveness and the capacity of local industry to produce the drugs (Chatio et al., 2016).

Ghana changed her first-line anti-malarial drug policy in 2004, from chloroquine to the use of Artesunate amodiaquine as the first-line drug for the treatment of uncomplicated malaria. Based on evidence of efficacy, compliance, side effects, cost effectiveness, impact on local industry and key demographic variables such as the appropriateness for treating malaria in children under five years and in pregnancy, Artesunate-Amodiaquine was selected as the first line drug for the treatment of uncomplicated malaria. However, the implementation process was faced with challenges such as adverse drug reactions, lack of other treatment options and safety concerns. It was therefore necessary to review the drug policy and address all identified concerns. Two additional ACTs namely; Artemether- Lumefantrine and Dihydroartemisinin/Piperaquine were selected (GHS, 2010). Several countries in Africa have now adopted ACTs as the first line agents for uncomplicated malaria (WHO, 2014).

1.1.1 Safety profile of ACTs

Studies of artemisinin derivatives in animals have reported significant neurotoxicity (brain damage), but this has not been seen in human studies (Price et al., 1999). Animal studies have also shown adverse effects on the early development of the fetus, but the artemisinin

derivatives have not been fully evaluated during early pregnancy in humans. Other reported adverse events include headache, body weakness, dizziness and vomiting, dizziness, tinnitus (ringing in the ears), neutropenia (low levels of white blood cells), elevated liver enzymes (a marker for liver damage), and electrocardiographic (ECG) abnormalities (Nosten, 2007). Patients who experienced side effects were required to report to the nearest health facility, but compliance was low due to poor adverse events reporting systems. Patients with mild side effects were able to contain them at home and severe cases reported to health facilities. Although most of the causes of the side effects were drug-related, some were due to the introduction of generics that were poorly formulated and poor compliance to drug regimens (Chatio et al., 2016).

Adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product (ICH, 2003). According to the ICH guidelines, new clinical conditions or worsening of existing clinical conditions are adverse events. Adverse drug events can be preventable or non-preventable. Preventable adverse drug events arise from medication errors that may occur in the process of ordering, transcribing, dispensing, or administering a drug. Potential adverse drug events are errors that have the capacity to cause injury, but fail to do so either by chance or because they are intercepted (GHS, 2010).

Introducing newer medicines with limited real-world safety data, such as ACT, into poorly funded health care systems combined with large scale-up access programmes make it important imperative to monitor their use and safety (Stergachis et al., 2010).

Pharmacovigilance is the science and activities relating to the detection, evaluation, understanding and prevention of adverse reactions to medicines or any other medicine-related problems and is critical for evaluating and characterizing a drug's risk benefit profile after being released onto the market. Pharmacovigilance is important in resource-constrained settings because patients may present different susceptibility profiles for adverse events due to genetic, nutritional, co-morbidity, and other differences and many resource-limited countries lack some or all of the World Health Organization's (WHO) basic elements of a pharmacovigilance system (Stergachis et al., 2010).

Since the greatest burden of malaria is in low and middle-income countries with inadequate pharmacovigilance systems in place, it is important that programmes to support malaria case management also include provisions for pharmacovigilance surveillance.

In general, safety information can be collected through two main pharmacovigilance channels: (a) spontaneous reporting system (Passive surveillance). The spontaneous adverse drug reaction monitoring rely in part on the patient spontaneously reporting symptoms to health care professionals after ingesting a drug but this is difficult to accomplish in hard to reach and resource poor communities of Africa (Adedeji et al., 2014). (b) Active surveillance Systems using pharmacoepidemiological methods through phase IV clinical trials or cohorts studies. While spontaneous reporting is essential for signal detection of rare events, the pharmacoepidemiological methods provide additional information on both, the utilization and the extent of consumption that will permit the determination of frequency of ADRs in the studied population or the safety comparison between two or more products (Adedeji et al., 2014). Ghana joined World Health Organization Programme for International Drug Monitoring in June 2001 and was the first country in West Africa to become a full member of the WHO Programme for international drug monitoring. The system is however affected by low reporting (Sabblah, 2014). If

efforts are not put in place to ensure that accurate and timely safety information is generated and used, low quality products could cause harm to consumers, significant resources could be wasted and suboptimal use of medicines could adversely affect patient outcomes and the goal of improved access to quality, efficacious medicines at affordable cost would not be achieved.

1.2 Problem statement

Unknown and rare adverse events of medicines after they have been approved and in use by the general public may lead to negative consequences such as death and disability. Spontaneous reporting of suspected adverse drug reactions is the means by which such reactions can be brought to the attention of regulatory authorities for the necessary attention. Unfortunately, the level of adverse drug reaction (ADR) reporting is low in many health systems all over the world **(**Hazel et al., 2006).

The National Pharmacovigilance Centre (Ghana) receives on average 12 adverse drug reaction reports per 1,000,000 Ghanaians per year **(**WHO 2015**)** which is less than the WHO recommendation that a fully functional pharmacovigillance system should receive 200-250 reports per 1,000,000. Based on this recommendation and the 2013 estimated population of 25,900,000, it is expected that 5,180 -6475 reports should be received by the National Centre per year. However, Ghana reports only 311 ADR annually per 25,900,000 (WHO, 2015).

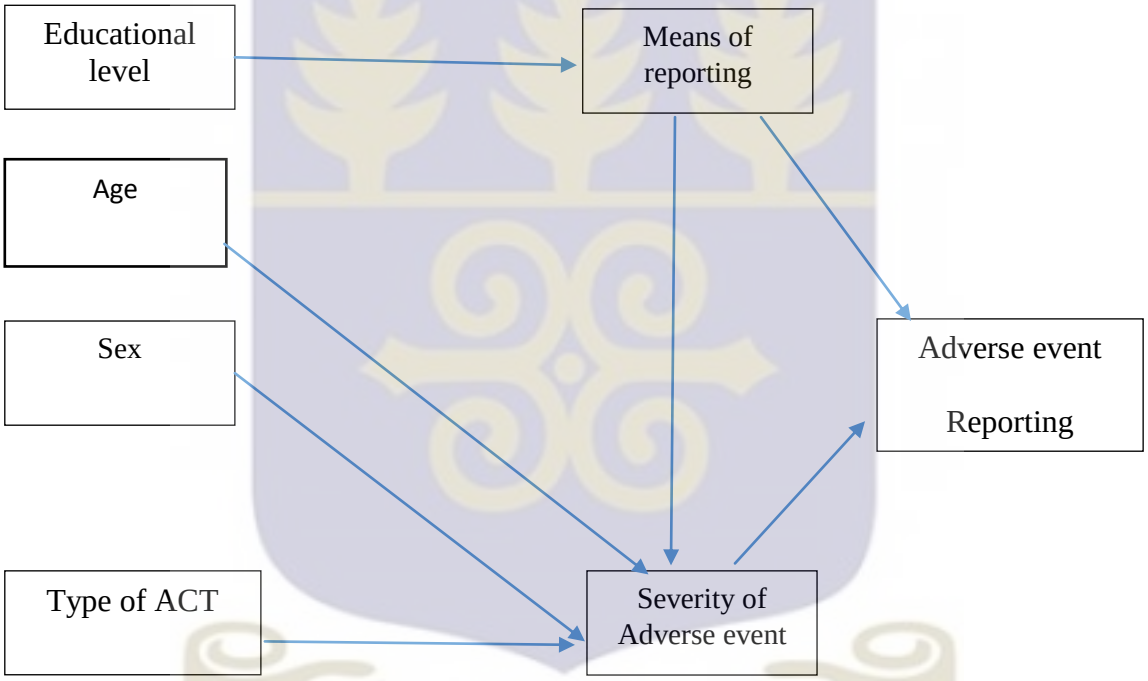
A study in Uganda using mobile phones for active surveillance reported that the approach is efficient in determining adverse events with as high as 89.5% response rate with 47% of the 183 patients enrolled reporting adverse events (Adedeji et al, 2014). The purpose of the current study therefore was to investigate the possibility of using mobile phones to capture adverse events after intake of artemisinin-based combination therapy among

patients treated for uncomplicated malaria in the Kassena-Nankana Municipality of Northern Ghana.

1.3 Factors Affecting Reporting of Adverse Events

The main construct for the conceptual framework is reporting of adverse events by patients.

Figure 1: Factors affecting reporting of adverse events



Variables such us age and sex may directly affect the metabolism of ACTs and may result in adverse events that warrant reporting. Likewise, the severity of adverse events can also restrict people from reporting them. Patients might report only severe or serious adverse events and not report mild adverse events since they do not interfere with their daily lives. Factors such us educational level and well-informed means of adverse events reporting system in place can also encourage people to report adverse events.

1.4 Justification

In 2004, Ghana changed her anti-malarial drug policy selecting artesunate-amodiaquine combination as the first line drug for the treatment of uncomplicated malaria and later added artemeter-lumefantrine and dihydroartemisinin-piperaquine based on efficacy and safety of ACTs. Efficacy and safety trials deliver new interventions under relatively ideal and controlled conditions, usually in a carefully selected group of individual participants not necessarily representative of a real world setting.

To date the reporting of adverse events after intake of ACTs in Ghana and beyond has not been comprehensively studied. Adverse drug reaction reporting is an essential mechanism for determining the clinical usefulness of a medication; contributes to decisions in keeping medicines in circulation and also preventing unnecessary death or disability from medicines. Spontaneous adverse drug reaction reporting system (SADRS) is a method used in Ghana for detecting adverse effects of medicines. Health professionals (doctors, nurses, medical assistants, nurses and pharmacists) and patients are important in ensuring that this system functions well.

Cohort event monitoring (CEM) should be integrated with existing patient management and pharmacovigilance systems in other to strength the system. The increasing need to capture data on health and health events using faster and efficient means to enable prompt evidence-based decision-making is making the use of mobile phones for health an alternative means to capture safety data on anti -malaria drugs. This study therefore used CEM to determine reporting of adverse events among patients who took ACTs using mobile phone and home visit as means of reporting.

1.5 Objectives

1.5.1 General Objective

To determine adverse events reporting by patients after intake of artimisinin based combination therapy (ACT)

1.5.2 Specific objectives

1. To assess the adverse events experienced by patients after taking artimisinin based combination therapy
2. To determine the proportion of patients treated with artimisinin based combination therapy who experience adverse event
3. To compare the proportion of adverse events reported through mobile phone and home visit.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction of Artemisinin Based Combination Therapies

Malaria transmission occurs in all six WHO regions. Globally, an estimated 3.2 billion people are at risk of being infected with malaria. The burden is heaviest in the WHO African Region, where an estimated 90% of all malaria deaths occur, and in children aged under 5 years, who account for 78% of all deaths (WHO, 2014).

The introduction of artemisinin-based combination therapies (ACTs) in early 2000 for the treatment of uncomplicated malaria in endemic countries highlighted a need for studies that would yield more complete safety data in the post-licensure period, especially under large-scale use. (Kunak et al., 2015). The number of ACT treatment courses procured from manufacturers by both public and private sectors has increased greatly, rising from 11 million in 2005 to 392 million in 2013. Artemether-lumefantrine (AL) accounts for the largest volume of ACTs procured (73% in 2013), followed by artesunate - amodiaquine (26%) (WHO, 2014).

The current wide-scale deployment of new antimalarials, including artemisinin-based combination therapies (ACTs), provides an important opportunity to strengthen the pharmacovilance system. Although ACTs are generally considered safe, there is no much information about their use in real-life settings and the published data are mainly from clinical trials. (Kuemmerle et al., 2011). With the wide use of ACTs in endemic areas, safety monitoring of anti-malarial drugs is critical.

2.2 History of adverse event reporting

The Elixir Sulfanilamide disaster which occurred in 1937 was one of the most consequential mass poisonings of the 20th century. This tragedy occurred shortly after the introduction of sulfanilamide, the first sulfa antimicrobial drug, when diethylene glycol was used as the diluent in the formulation of a liquid preparation of sulfanilamide known as Elixir Sulfanilamide. One hundred and five patients mostly children died from its therapeutic use. In reaction to this disaster, the U.S. Congress passed the 1938 Federal Food, Drug and Cosmetic Act, which required proof of safety before the release of a new drug. The 1938 law changed the drug focus of the Food and Drug Administration from that of a policing agency primarily concerned with the confiscation of adulterated drugs to a regulatory agency increasingly involved with overseeing the evaluation of new drugs (Wax, 1995).

Another important drug in the history of drug safety is Thalidomide (alpha-phthalimido-glutarimide) an anticonvulsant drug which caused massive serious adverse events in thousands of people. It had sedative properties and overdoses simply caused prolonged sleep not death. The drug was first marketed in Germany in 1957 and in the UK in April 1958. It was marketed in many countries including African countries. Later, compound preparations which combined thalidomide with other drugs were marketed for a wide variety of indications such as hypertension, asthma, migraines and many more. It caused birth defects including congenital heart disease, microphthalmos and coloboma, intestinal atresia, renal malformations, abnormal pinnae and facial naevu in thousands of babies from all parts of the British Isles, Germany, Japan, Kenya, Belgium, Sweden, Peru, Switzerland, Canada Lebanon, Israel, Netherland, Brazil and the USA. Mortality rate in these babies was about 40%. It was later withdrawn from the market (Newman et al., 1992) .

A case control study conducted in Bangladesh in 1990 among 339 children to determine the cause of a large increase in the number of children with unexplained renal failure found that among children with an identified cause for their renal failure, children with initially unexplained renal failure were more likely to have hepatomegaly, hypertension, oedema, lower serum bicarbonate concentration and high creatinine concentration.. A year after a government ban on the sale of paracetamol elixir, new cases of renal failure decreased by 54% and cases of unexplained renal failure decreased by 84%.Paracetamol elixirs with diethylene glycol as a diluent were responsible for a large outbreak of fatal renal failure in Bangladesh (Hanif et al., 1995).

2.3 Identification and Grading of Adverse events

All AE reporting begins with a suspicion by the physician (or responsible person who obtains or receives information) that a patient exposed to a medicinal product has experienced some AE and that the event has a reasonable possibility of being causally related to the product being used. Some registries also collect and record AEs reported directly by the patients or their caregivers. It is important to develop a plan for detecting, processing, and reporting AEs for any registry that has direct patient contact(National Institute of Health, 2010)

AE reporting is based on categorization of the AE according to the seriousness of the event, its expectedness based on product labeling, and presumed causality or possible association with use of the product, as follows: Mild (AE consist of AE which can be tolerated by the individual. It does not interfere with the day to day activities of the person and usually does not require intervention). Moderate (These events usually interfere with the normal daily activities of the person and require some level of intervention). Severe (AEs interferes with the day to day activities of the individual and require major

intervention such as a visit to the health facility but does not result in hospitalization) and Seriousness (SAEs) include events that result in death, are life threatening, require hospitalization or prolong inpatient hospitalization, result in persistent or significant disability or incapacity, or result in a congenital anomaly. Important medical events may also be considered serious when, based on medical judgment, they may jeopardize the person exposed and may require medical or surgical intervention to prevent one of the outcomes listed above (ICH, 2001).

All AEs that are previously unobserved or undocumented are referred to as "unexpected," in that their nature and severity are not consistent with information provided in the relevant product information (e.g., approved professional package insert or product label). A determination is then made to know the possibility of being related to the exposed product. This assessment of causality may be based on factors such as biological plausibility, prior experience with the product, and temporal relationship between product exposure and onset of the event, as well as discontinuation of the product to determine if the AE resolve and reintroduction of the product to determine if the AE recurs (ICH, 2001)

Many terms and scales are used to describe the degree of causality, including terms such as certainly, definitely, probably, possibly, or likely related or not related, but there is no standard nomenclature. All spontaneous reports have an implied causal relationship as per regulatory guidance, regardless of the reporter's assessment (ICH, 2003).

The registry may use forms such as a structured questionnaire or an AE case report form to collect the information from providers or patients. When solicitation of AEs is not pre specified in the registry's operating plans, the registry may permit AE detection by asking general questions to solicit events, such as "Have you had any problems since your last

visit or since we last spoke?" and then following up any such reports with probes as to what happened, diagnoses, and other documentation (National Institute of Health, 2010).

2.4 Monitoring of adverse events

Pharmacovigilance programs (Passive and Active surveillance) can monitor and help ensure the safe use of medicines that are critical to the success of global public health programs. Adverse reactions associated to drugs are known to be responsible for significant levels of mortality and morbidity with a massive negative impact on both health and healthcare costs across the world (Bukirwa et al., 2008). ADRs have the potential to cause significant harm in patients. There is increasing awareness of the significant global and local impact of ADRs on patient care and public health. Though most cases go undetected particularly in developing countries, data from the US estimates that adverse drug events (ADEs) are the fourth to sixth leading cause of death. ADEs constitute a huge cost to the health system, estimated in the US at $177 billion in 2000. Economic consequences of adverse events that are not frequently reported include the impact of adverse events on patient adherence to treatment, drug resistance, and treatment outcomes. Besides the economic consequences, cases of adverse events affect the credibility of the health system leading to loss of confidence (Alexander et al., 2014)

Existing pharmacovigilance systems and activities have proven to be useful in identifying patient safety issues, although there is scope for optimizing and improving their use. Allowing patients to report adverse drug reactions (ADRs) directly to the competent authorities is seen by the European Commission as a way to improve pharmacovigilance. The introduction of patient reporting in pharmacovigilance indicates a change in attitude in which the patient's experience is valued (Pal et al., 2012). Pharmacovigilance activities

in Ghana are the mandate of the National Pharmacovigilance Centre, the Food and Drugs Authority.

2.4.1 Passive Surveillance (Spontaneous reporting of ADR)

Most pharmacovigilance systems rely on passive surveillance in which adverse events are voluntarily reported by patients to health workers and health workers also completing and voluntarily submit the AE form to FDA. Although passive reporting provides fairly weak epidemiological evidence, its advantages include low cost, the ability to detect rare events, and continuous monitoring of safety of drugs. Voluntary reporting depends on patients' ability to recognize adverse events, and their willingness to report them. Perceptions of disease, expectations of treatment, and motivations for reporting by patients and health workers influence the success of passive surveillance, and may vary by culture and country (Bukirwa et al., 2008).

In Ghana, health professionals are expected to voluntarily report suspected ADRs to the National Pharmacovigilance Centre. From January 2013-September 2013, The National Pharmacovigilance Centre received two hundred and sixty (260) reports of suspected ADRs (Mogtari, 2014). These reports were received from 78 different health facilities from nine of the ten regions. No spontaneous report was received from the Northern Region. Bolgatanga Regional Hospital submitted majority of the reports 44/260(17.0%). Of the reports received, 179 (68.9%) were experienced by females whereas the rest (31.1%) were by males.

The 15 drugs with most commonly reported Adverse Drug Reaction were Nifedipine, Lisinopril, Artemether /Lumefantrine, Artesunate/Amodiaquine, Sufadoxine-/Pyrimethamine, Ciprofloxacin, Nevirapine, Albendazole/Ivermectin, Quinine,

Cotrimoxazole, Amlodipine besilate tablet, Amoxicillin/Clavunalic acid, Albendazole/Praziquantel, Clindamycin and Diclofenac sodium.

Artemether/Lumefantrine was third and Artesunate/Amodiaquine was the fourth drug with the most reported forms received.

These reports were submitted by various health professionals. Pharmacist reported 56%, doctors 16.8%, nurses contributed 8.8% , physician assistants contributed 8.1% and the rest were from pharmacy technicians, disease control officers and other health professionals (FDA, 2014).

A multi-center study conducted in Ghana and Tanzania from 2009 to 2011 to assess safety of ACTs based on passive surveillance recorded 256 AEs and 53 serious adverse events. Some of the reported events were abdominal crumps, nausea, blisters, rashes on male organ, bleeding, oedema, blurred vision, body pains, palpitations, body itching, severe pain during menstruation, cardiac arrest, rashes/blisters, cold/chills, body swelling, convulsion, body tightening, sores, diarrhea, sleeplessness, body weakness, difficulty in hearing, vomiting, dizziness, Steven Johnson syndrome, among others (Binka, 2012).

The spontaneous reporting system however, is affected by underreporting of adverse drug reactions. Some of these factors include: reporting forms not available, inability to diagnosis ADR, workload and lack of time and potential conflicts of interest (Sabblah et al, 2014). Many patients are also unaware of the reporting system.

Some solutions suggested for improving spontaneous reporting were to define the kind of ADRs which should be reported to FDA, training of health workers on how to complete the ADR forms and actively encourage patients to report ADR.

2.4.2 Active Surveillance (Cohort Event Monitory CEM)

Cohort event monitoring (CEM) is an intensive method of post-marketing surveillance for medicines safety. The method is based on prescription event monitoring, which began in the 1970s, and has since been adapted by WHO for monitoring the safety of medicines used in Public Health Programmes. CEM aims to capture all adverse events that occur in a defined group of patients after starting treatment with a specific medicine during the course of routine clinical practice (Kunak et al., 2015). By capturing all clinical events, regardless of suspicion of causality, CEM has the potential to identify previously unrecognized and unsuspected adverse drug reactions. The CEM method has been used to monitor the safety of antimalarial medicines in Ghana, Kenya, Nigeria, Tanzania and Zimbabwe (Kunak et al., 2015).

A cohort event monitory study conducted in Uganda by use of mobile phone recorded four hundred and four (404) incidences of different reactions to drugs out of 420 drugs purchased. Gastrointestinal (GIT) disturbances were the most frequently reported reactions to drugs accounting for 44.1 %, followed by central nervous system (CNS) effects with 31.2%. Among the GIT reactions reported, abdominal pain had the highest frequencies with 44.4%, followed by nausea (34.7%) and diarrhea (10.2%). The most frequently reported CNS effects were headache (42%), followed by drowsiness (40.3%) and sedation (17.6%). Other reactions that were reported by the participants included body weakness (11.7%), followed by dry mouth (2.2%) and metallic taste (2.2%) [Adedeji et al., 2014].

Another study of 3,708 patients treated with ACTs in Senegal, found 73% mild AE and 27% severe AE (Brasseur et al., 2012). A CEM study also conducted in Ghana found out that out of 11,379 patients treated with ACTs, 1,970 of them reported adverse events which were similar to the ADRs reported in the Uganda study (Binka, 2012).

Factors that accounted for high reporting rates were training of health workers on AE reporting, availability of forms, use of mobile phones and home visits. Cohort event monitoring (CEM) provides an opportunity to raise awareness of pharmacovigilance among healthcare providers and patients and to encourage a perception that pharmacovigilance falls within the scope of clinical practice (Binka, 2012). Actively encouraging patients to immediately report any adverse effects or intolerance to the medication ensures that adverse effects that may be affecting adherence or causing harm are identified as soon as possible and managed efficiently.

2.5 Burden of Adverse Events

A meta-analysis of 69 prospective and retrospective studies conducted in various regions of the world involving 419,000 patients found that approximately 6.7% of all hospitalizations were as a result of ADRs (Mehta, 2011). In the US, in 2000, there were 46,249 reports submitted by consumers, increasing to 272,989 in 2009. Since 2006, the FDA has received more reports from consumers than physicians and pharmacists. In the UK, to the end of 2009, 10 284 ADR reports were submitted and only 18% of ADR reports were submitted by patients (Florence van Hunsel, Linda Ha¨rmark, Shanthi Pal, 2012)

An observational study conducted in the medical wards of a secondary hospital in the Western Cape (South Africa) estimated that 6.3% of hospitalized patients were admitted as a direct result of an ADR, while a further 6.3% of patients developed a significant ADR while in hospital. More than half of the ADRs that occurred in patients in the community were considered to be preventable with improved prescribing, administration, monitoring and adherence. Patients with HIV/AIDS were found to have an increased risk of ADRs. This is probably due to the effect of the disease on the immune system (which is

responsible for many idiosyncratic drug reactions) as well as the safety profile of the complex drug regimens that patients with HIV/AIDS are often receiving (Mehta, 2011).

2.6 Adverse events of ACTs

A study conducted in twelve sites in seven sub-Saharan African countries among 4,108 patients, thirty seven (37) patients experienced SAEs, their occurrence being relatively more frequent in patients treated with Artesunate/Amodiaquine than among those treated with Artemether/Lumefantrine (Walter, 2011).

Another study conducted in rural Tanzania over a two year period recorded 95 AEs of antimalarial drugs. About 78% of patients or caretakers interviewed reported experiencing multiple ADR symptoms within 36 hours of SP and/or AS intake. The dominant illness conditions reported by the 67 patients included a combination of one or multiple illness diagnostic conditions such as; body blisters and skin detachment, body swelling, itching, rashes, multiple lesions on mucous membranes around the mouths, nose or conjunctivae, and facial oedema, and other side effects like light-headedness, headache, shortness of breath, stomach ache, diarrhoea, vomiting, and also severe kidney pain. Four patients died as a result of drug reactions associated with SP use (Njau et al, 2013).

Another study conducted in Senegal to monitor safety of ACTs in patients aged six months to 93 years between 2007 and 2009, a total of 123 patients with AEs related to ACT were reported. Sixty seven percent of the notifications were gathered from public health posts while district hospitals reported 30.1% of the AEs. Only 2.4% of AEs were collected from private health facilities. Nurses represented 86% of reporters while physicians and midwives represented 13% and 1% respectively (Thiam et al., 2013). Mild AEs were in 69.1% of cases and 7.3% severe, while 23.6% of AEs were serious. The percentage of serious effects was about two times higher with the AS-AQ co-blister than

the fixed dose (25.7% vs. 11.7%) and one death was recorded and it was caused by taking all the tablets in one day (Thiam et al., 2013).

In another study which was conducted in Nigeria to evaluate safety of ACTs, out of 210 patients that took ACTs (namely artesunate plus amodiaquine, arthemether-lumefantrine, artesunate plus sulphadoxine/pyrimethamine, and artesunate plus mefloquine), 69 (32.9%) experienced AEs (Adisa et al, 2008).

From the Cochrane database, there is evidence that DHA-P is better tolerated than artesunate-mefloquine (AS+MQ). Central nervous system (CNS) related adverse events (at least one of sleep disturbance, dizziness, or anxiety) were reported as more common with AS+MQ in five out of the nine trials. Five trials also reported significantly more nausea and vomiting with AS+MQ and two trials reported more palpitations and dyspnoea. Abdominal pain and diarrhoea were reported as significantly more common with DHA-P in one trial each. Seven trials reported some measure of early vomiting (Sinclair et al., 2009).

2.7 Reporting of AEs of ACTs

Studies have been conducted to assess global reporting of adverse drug reactions of anti-malarials, including ACTs to the WHO programme for International Drug Monitoring. A study reported that 64 countries transmitted 21,312 individual case safety reports (ICSR) to the Uppsala Monitoring Centre (UMC) from 1968 to 2008. Two thousand seven hundred and eighty one (2,781) ICSRs reported more than one anti-malarial evaluated by the national centre as suspected or interacting in causing the ADR (Kuemmerle et al., 2011).

The findings indicate that 89% of reports were submitted by 10 countries, and 97% of reports were submitted by 20 countries. There were only three countries in the malaria control phase (Ghana, South Africa and Thailand rank in the top 20 countries submitting ICSRs to the UMC (Kuemmerle et al., 2011).

2.8 Reporting of AEs by patients

Patients are important stakeholders in pharmacovigilance however; little formal evaluation has been undertaken of existing patient reporting schemes. If patient reporting is to be recognized as beneficial for pharmacovigilance and further optimized, methodology and best practice must be internationally shared and promoted. In the US, Canada, Australia and New Zealand, patients have been allowed to report ADRs directly since the start of their pharmacovigilance schemes. Methods that have been used to encourage patient reporting are telephone calls and email (Pal et al., 2012).

In Africa, patients have little knowledge about reporting of ADRs. A study conducted in Uganda on pharmacovigilance of antimalarial drugs found that patients reported adverse events in the context of seeking additional medical care, either for persisting illness or severe events, or upon subsequent visits to health care providers for new problems (Bukirwa et al., 2008).

Another study conducted in Nigeria found that out of 210 patients treated with ACTs, 69 experienced AE but majority, 52 (75.4%), of those that experienced adverse reactions with ACTs did not report the reactions to any health care professional. Reasons for not reporting AEs were that the study participants did not know how and where to report such reactions and also they felt that most of the reactions were tolerable. About twenty four percent (24.6%) of those that experienced adverse reactions however claimed to have reported these reactions to a healthcare provider (Adisa et al., 2008).

CHAPTER THREE

METHODOLOGY

3.1 Study Design and Location

The study was a prospective cohort study. Enrolment of participants into the study was done at the war memorial hospital of the Kasena/Nankana municipality. Exit interviews were conducted at the dispensary. Patients with uncomplicated malaria who were prescribed an ACT were enrolled. At recruitment, demographic information of patients were collected in addition to information on all medicines prescribed at the counter. Presenting signs, symptoms and co-diagnoses were recorded before the patient left the hospital for home. Participants were instructed to call a dedicated mobile phone number on any day upon starting to take the drugs to report any adverse reactions experienced. For those who did not call by the fourth day, the researcher followed up by phone on the fifth and sixth day. Any person who could not be reached by phone was followed up by home visits on the seventh day for safety assessments. All adverse events were recorded regardless of severity and seriousness. Absence of adverse events were also documented. Participants were also given the opportunity to report all adverse events up to seven days post drug administration. Toll charges for those who made the phone calls were refunded. Duration of participation in the study for each person was seven days after enrolment.

3.2 Study Area

The study was conducted in the Kassena-Nankana Municipality of the Upper East Region of Ghana with a population of 151,000; 140,000 of whom are under continuous demographic surveillance by the Navrongo Demographic Surveillance System. The population is

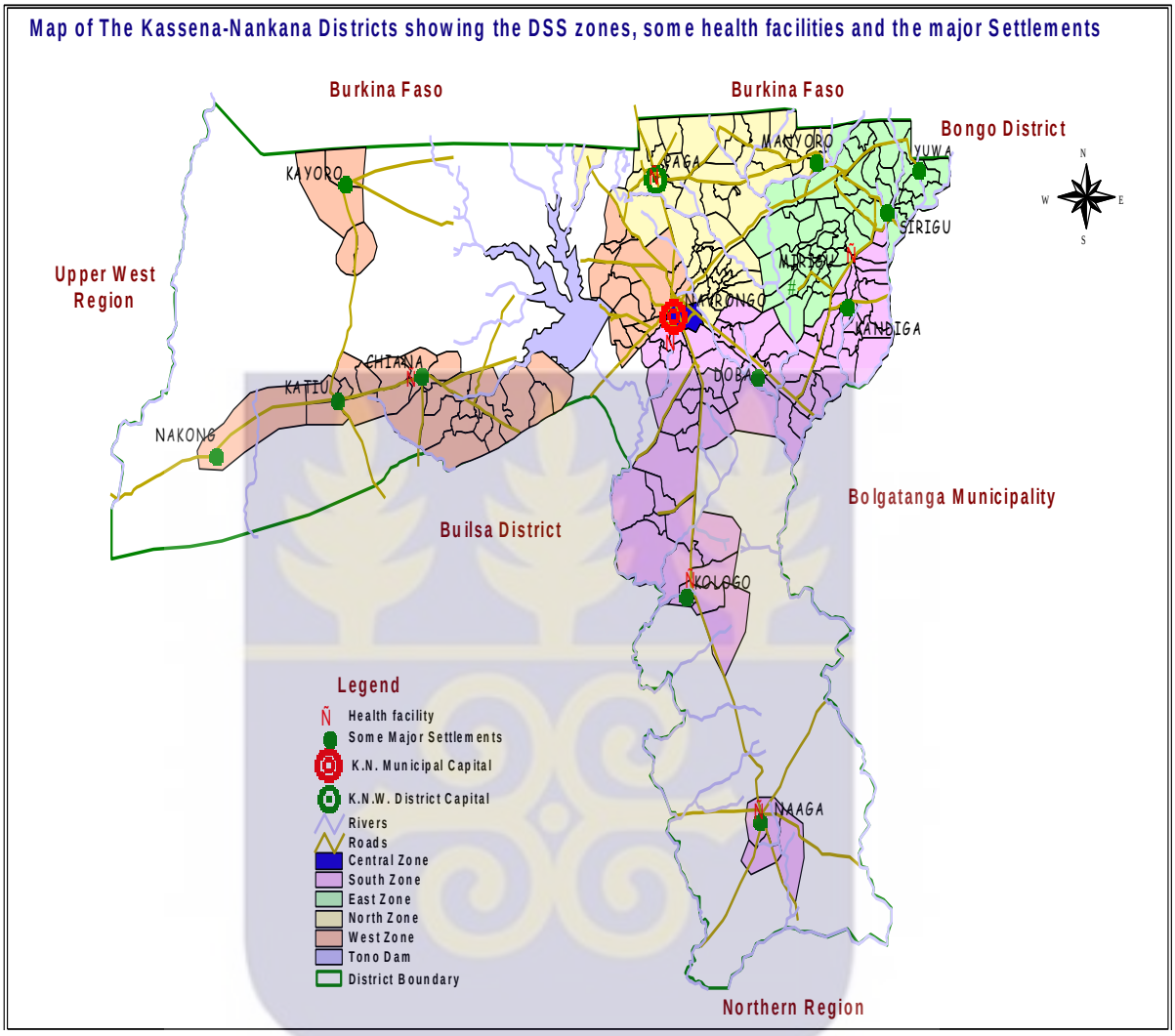
predominantly rural with subsistence farming as the mainstay of its economy. People live in multi-family compounds which form the basis of an address system used in the Navrongo Health Demographic Surveillance System (NHDSS). There are five zones (North, South, East West and Central) in the NHDSS used for address system. Annual rainfall averages 850 mm, almost all of which occurs in the wet months of May - September with the rest of the year being relatively dry.

3.3 Health Service Organization in Kassena-Nankana Municipality

There is one hospital and eight health centers, which provide curative and preventive health care. There are 28 CHPS compounds located in various communities and providing treatment for minor ailments and mostly childhood immunizations and antenatal services. Patients who need referral from the CHPS compounds are first referred to the health centers. Cases beyond the management of the health center are subsequently referred to the hospital. This is all done by completing a referral form for patient to take along to the next level of care. Figure 2 below is the map of the Municipality and some health facilities.

Malaria Transmission in the Kassena-Nankana Municipality: Malaria transmission in the Kassena-Nankana municipality of northern Ghana is holoendemic but with marked seasonal variation. Malaria transmission occurs during most months of the year but there is a distinct seasonal pattern with the peak of transmission coinciding with the period of the major rains and the dry season seeing very low rates of malaria infection. Transmission has been estimated to be 418 infective bites person per year (Appawu et al, 2004).

Figure 2: Map of Kassena/Nankana Municipality and Health Facilities



3.4 Study Variables

3.4.1 Dependent Variable

The main outcome variable is adverse events reporting. The independent variables such age, sex, educational level, type of ACT, means of reporting and severity of adverse events are used in the study to establish the determinants of adverse events reporting (Table 1).

Table 1: Independent variables and their indicators

Independent Variable	Indicator
Age	Years
Sex	Male or Female
Means of reporting	Home visit or Phone call
Type of ACT	A/A or A/L or DHP
Educational level	No formal education, Basic Education or Tertiary Education
Severity of adverse event	Mild or Moderate or Severe or Serious

3.5 Sample size determination

The sample size determination was based on the formula;

$$n=\frac{Z^2\ P(1-P)}{d2}$$

Z = Z statistic for a level of confidence at 95% Confidence Interval

P = expected prevalence of reporting of adverse events and d = precision [this is fixed at 5% (i.e. 0.05)].

There was no information about the prevalence of reporting or an estimate of reported adverse events in the Kassena/Nankana municipality, assuming 50% (i.e. 0.5) of reporting in the region as suggested by Macfarlane (1997) and with a precision of 0.05 at 95% confidence interval, the minimum sample size obtained using the formula was 384. To account for non-responses and incomplete questionnaires 10% of estimated sample (38)

was added to arrive at a total sample size of 422. The number of patients enrolled into the study was 417 but 4 were lost to follow up hence 413 was used for the analysis.

3.6 Sampling Procedure

The study was conducted at the War memorial hospital. The average daily attendance for the hospital is 150 patients per day with 40% being malaria cases. The daily expected malaria cases was therefore 60. The planned maximum number to be enrolled per day was 20 to allow for effective follow-up. With a sampling interval of 3, each third person with malaria was contacted and consent sought. If consent was denied, the next malaria patient was contacted until about 20 participants were enrolled for the day. This was repeated daily until the predetermined sample size was reached.

3.6.1 Inclusion and Exclusion Criteria

Inclusion criteria:

1. Patients with a clinical diagnosis of uncomplicated malaria and received ACT
2. Patients enrolled in the NHDSS at the time of the study
3. Patients who consented to participate in the study

Exclusion criteria:

1. Patients with chronic disease such as asthmas, hypertension, TB, HIV, etc

3.7 Data Collection tools and Techniques

The data collection tools were structured questionnaires and mobile phones. The questionnaires were used to record the information received from the study participants. The questionnaires were in two forms:

I. A pretreatment questionnaire which was used to record demographic information, presenting signs, symptoms, co-diagnoses and all medicines prescribed at the counter before the patient left the hospital for home.

II. A post treatment questionnaire which was used to record new clinical conditions or worsening of the existing condition after the intake of ACTs, concomitant medication, adherence to treatment, means of follow up and severity of adverse event.

Mobile phones were also used to follow up study participants in order to determine presence or absence of adverse events to enable completion of the post treatment form. Exit interviews were conducted at the dispensary.

3.8 Data collection procedure

On each day of enrollment, the study team upon arrival at the dispensary informs the pharmacists and all the hospital staff at the dispensary about their presence. The study team arrived before the start of patient consultations each day. Every third patient with uncomplicated malaria who was prescribed an ACT was directed to the study team. Every patient was greeted and the purpose of the study explained to them. Those who agreed and participated in the study completed and signed two informed consent forms. Those who could not sign the informed consent form thumb printed. A copy of the consent form was given to every study participant and the other one was retained with the study team and under lock and key.

At recruitment, demographic information of patients was collected into the pre-treatment questionnaire in addition to information on all medicines prescribed at the counter. Presenting signs, symptoms and co-diagnoses were recorded before the patient left the hospital. All participants were asked to provide a functional phone number for follow up.

The demographic information of those who could not provide phone numbers were used to conduct home visit to determine adverse event. All study participants were informed to call a dedicated mobile phone number on any day upon taken the ACT to report any adverse events experienced. For those who did not call by the fourth day, a followed up by phone on the fifth and sixth day was made. Any person who could not be reached by phone was followed up by home visits on the seventh day for safety assessments. All adverse events were recorded regardless of severity and seriousness into the questionnaire and later entered into the database. Absence of adverse events was also documented. Toll charges for those who made the phone calls were refunded.

3.9 Quality Control

The study questionnaire was pretested to determine its appropriateness and suitability for the study. The pretesting resulted in correction, rearrangement and rephrasing of sentences and sections in the questionnaire. The screens developed for data entry were also pre-tested to ensure it could be usable and able to store data. The screens were then merged by unique identifiers such as patient ID to enable credible analysis to be performed.

In order to ensure uniformity of the process, the two data collectors involved in the study were trained on how to explain the study objectives and overview of the questionnaire to the participants. To increase daily enrolment all health staff of the hospital who work in the dispensary were informed about the purpose of the study and the sampling procedure and as patients came to the counter to receive their medicine those who received ACTs were directed to the study team.

3.10 Data processing and Data Analysis

The data collected were crosschecked for inconsistencies and logic. Inconsistencies were resolved by contacting the data collector or the respondent where necessary. Two screens were developed using Epidata version 3.1 for data entry. The screens were exactly the same as the pre-treatment questionnaire and the post treatment questionnaire to enable smooth data entry and minimize human errors during entry. Data from the two questionnaires were double entered by two data entry clerks into the Epidata database. The entered data was validated and cleaned until all inconsistencies and logic were resolved. The cleaned data was then exported to STATA Version 13 and analysis was performed.

Descriptive statistics (frequency tables) was used to describe the background characteristics of the study participants. The age of study participants was regrouped into four categories (<2years, 2-11, 12-17, 18-64, 65+) in accordance with ICH guidelines for assessing individual case safety report. The educational level of study participants was also regrouped into four categories (No formal education, Basic education, Secondary education and Tertiary education). A frequency table was used to display the outcome of clinical conditions of study participants after taking ACT.

The adverse events experienced by participants after taking the ACT and the means of reporting were presented using frequency tables. A bar graph was used to display the percentage distribution of adverse events after taking ACT as reported by the study participants.

The distribution of adverse events according to the study variables: Ages, sex, type of ACT, severity of adverse event, means of reporting and educational level were represented using frequency tables.

Chi squared test was used to determine the association between the dependent variable (adverse events reporting) and the independent variables (age, sex, educational level, type of ACT, means of reporting and severity of adverse event). The results were then expressed as chi-squared, degree of freedom and p-values. A p-value ≤ 0.05 was considered statistically significant.

3.11 Ethical Considerations

Ethical approval was obtained from the Ghana Health Service ethics review committee (approval number GHS-ERC 84/02/16) before commencement of the study. Written permission was also sought from the Regional Director of Health Services, Ghana Health Service, Upper East Region and the medical Superintendent of the War Memorial Hospital, Navrongo. Written informed consent was obtained from each participant before the interviews. The aims, methods, anticipated benefits, potential risks, voluntariness, right to withdrawal from the study and confidentiality of participant information were explained to the participants or their legally acceptable representative. It was also explained to the patients that they had the right to refuse to take part in the study without suffering any consequences. Participants were not paid for participating in this study. Call charges of participants who made the phone calls to the study team were however reimbursed to them. This research was for academic purpose only and there is no conflict of interest.

CHAPTER FOUR

RESULTS

4.1 Background of study participants

A total of 417 patients prescribed artemisinin-based combination therapies (ACTs) from the War memorial hospital of the Kassena/Nankana Municipality were enrolled, out of these 4 (1.0%) could not be interviewed for post treatment follow-up to assess adverse events. The reasons were inability to locate the residence of participants or not meeting them upon home visit. Analysis was therefore performed on 413 patients who successfully completed the post treatment follow up.

Out of the 413 patients 228 (55.2%) were females. The mean age of participants was 23.0 (SD: ±20, range 1-84 years). Over forty percent of the participants 175/413(42.4%) were between 18-65 years and 118/413(28.6%) were between 2-11 years. Of the 413 participants enrolled, 151/413(36.6%) had basic education, 87/413(21.0%) had secondary education and a third 125/417(30.0%) had no education. The age distribution of the participants and other background characteristics are shown in Table 2.

Table 2: Demographic and background characteristics of patients enrolled

Characteristics		Frequency (N)	Percent (%)
Sex	Male	185	44.8
	Female	228	55.2
Age (years)			
	<2	51	12.4
	2-11	118	28.6
	12-17	48	11.6
	18-64	175	42.4
	65+	21	5.0
Educational level			
	No education	125	30.3
	Basic	151	36.6
	Secondary	87	21.0
	Tertiary	50	12.1
Village			
	North	30	7.3
	South	108	26.1
	East	28	6.8
	West	32	7.7
	Central	215	52.1

4.1.1 Number and types of ACTs prescribed

Three different types of ACTs were in stock and were prescribed at the time of the study. They were Artesunate/Amodiaquine (A/A), Artemether/lumefantrine (A/L) and

Dihydroartemisinin-piperaquine (DHP). The most prescribed ACT among the three was A/A, constituting 268/413 (64.9%) and the least prescribed ACT was DHP, 5/413 (1.2%).

4.2 Outcome of clinical condition after ACT intake

Post assessment results during the follow-up showed that slightly less than half 190/213(46.0%) of the participants reported new clinical events. While the clinical condition of majority 400/413 (96.9%) of the participants improved after they took the prescribed ACT, that of four (1.0 %) participants deteriorated. The condition of nine patients (2.1%) however remained unchanged after taking the prescribed ACT. Of all patients enrolled into the study 384/413(92.1%) were not informed by health workers in the hospital to report AEs. Adherence to ACTs was 361/413(87.4%). Adverse events, forgetfulness and caregiver not at home were some of the reasons for incomplete adherence.

4.2.1 Adverse events (AEs) reported

Overall, out of 413 participants who completed the study, slightly less than half 191/413(46.2 %) reported at least one AE and less than 8% reported moderate to severe adverse event. There were no serious AEs reported at the time of the study. This is shown in figure 3 below.A total of 15 AEs were reported. These comprised new or worsening reported AEs. Overall, about a third 53/193(27.5%) of the participants experienced general malaise. Dizziness 30/193(15.5%) and restlessness 30/193(15.5%) were the second most reported AEs. Other reported AEs such as nausea, insomnia, loss of appetite, abdominal pain, irritability, cough, sore mouth, headache and puffy face were less frequently reported. The frequency of the 15 AEs and the means of reporting are shown in table 3.

Figure 3: Percentage distribution of AEs reported after taking ACTs

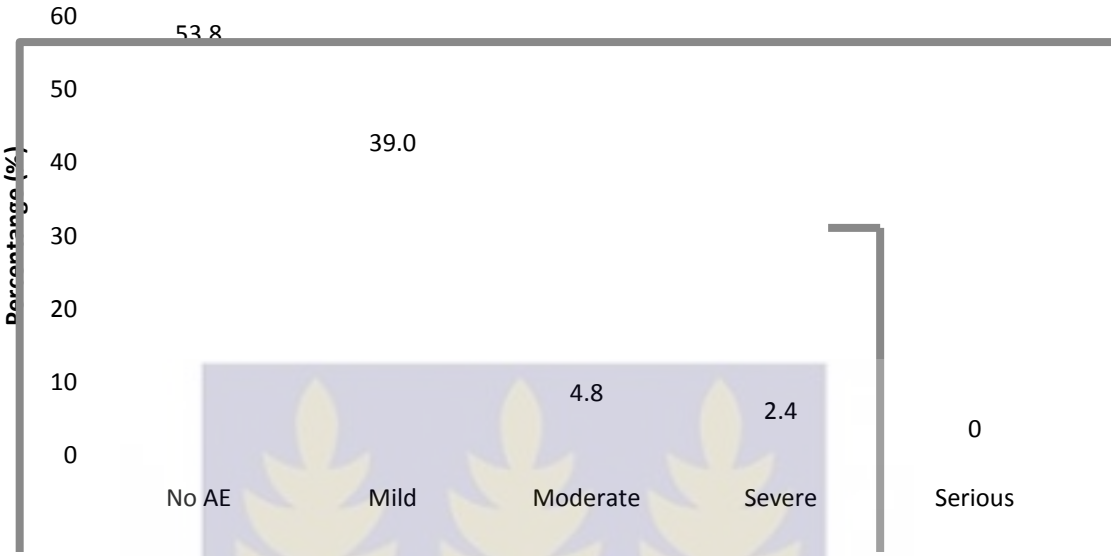


Table 3: Distribution of new or worsening clinical conditions reported after ACT intake and means of reporting.

New/worsening Event	Health Facility (%)	Home (%)	Phone Call (%)	Frequency(N)	Percent (%)
General malaise	2(1.0)	8(4.2)	43(22.3)	53	27.5
Dizziness	3(1.6)	2(1.0)	25(13.0)	30	15.6
Restlessness	3(1.5)	8(4.2)	19(9.8)	30	15.5
Nausea	2(1.0)	2(1.0)	14(7.3)	18	9.3
Insomnia	2(1.0)	4(2.1)	10(5.2)	16	8.3
Loss of appetite	0(0.0)	1(0.5)	15(7.8)	16	8.3
Vomiting	1(0.5)	3(1.5)	5(2.6)	9	4.6
Difficulty in breathing	0(0.0)	1(0.5)	4(2.1)	5	2.6
Abdominal pain	0(0.0)	1(0.5)	2(1.0)	3	1.5
Cough	1(0.5)	0(0.0)	2(1.0)	3	1.6
Irritability	0(0.0)	0(0.0)	3(1.6)	3	1.6
Sore mouth	3(1.6)	0(0.0)	0(0.0)	3	1.6
Diarrhoea	0(0.0)	2(1.0)	0(0.0)	2	1.0
Headache	0(0.0)	0(0.0)	1(0.5)	1	0.5
Puffy face	1(0.5)	0(0.0)	0(0.0)	1	0.5
Total	18(9.3)	32(16.6)	143(74.1)	193	100

4.2.2 Severity of AEs

The severity of AEs reported were mild 161/191(84.3 %), moderate 20/191(10.5%) and severe 10/191(5.2%). Out of all reported AEs, females 82/191(42.9%) reported mild AEs, 9/191(4.7%) females reported moderate AEs and 3/191(1.6%) females reported severe AEs. There was no association between sex and severity of AE (Chi (2) = 1.81, p = 0.41) as shown in Table 4. Among those who experienced mild AEs 30.5% had no education.

There was also no association between educational level and severity of adverse event (Pearson chi2 (6) = 3.1924 Pr = 0.784).

Table 4: Distribution of type of adverse event by sex

Type of AE	Male (%)	Female (%)	Total (%)
Mild	79 (41.4)	82(42.9)	161 (84.3)
Moderate	11(5.8)	9(4.7)	20 (10.5)
Severe	7 (3.7)	3(1.6)	10 (5.2)
Serious	0 (0.0)	0 (0.0)	0 (0.0)
Total	97 (50.8)	94 (49.2)	191 (100)

For the severity of adverse event reported by type of ACT prescribed, sixty six percent of all AEs reported were from those who took A/A. Slightly more than half of all participants who took A/A experienced mild AEs 102/191(53.4%), 16/191(8.4%) participants who reported moderate AEs took A/A and 8/191(4.2%) that reported severe AEs took A/A. Among those who took DHP, there was no moderate or severe AE reported, only 1.1% reported mild AEs. A chi square test was performed to determine the association between severity of adverse event and the type of ACT but the results showed there was no relationship. (Chi (6) = 3.32, p = 0.77) .Table 5 below shows the severity of AE by type of ACT.

Table 5: Severity of AEs by type of ACT

Type of AE	A/A (%)	A/L (%)	DHP (%)	Other (%)	Total (%)
Mild	102(53.4)	56(29.3)	2(1.1)	1(0.5)	161(84.3)
Moderate	16(8.4)	4(2.1)	0(0.0)	(0.0)	20(10.5)
Severe	8(4.2)	2(1.0)	0(0.0)	0(0.0)	10(5.2)
Serious	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Total	126(66.0)	62(32.5)	2(1.0)	1(0.5)	191(100)

When comparing the reported AEs by age groups, of the less than 2 years old only 10.0% experienced mild AEs. Among the age groups (2-11) and those aged (18-64) that experienced a type of AE, a third each reported mild AE, (31.4%) and (32.5%) respectively. In the moderate, severe and serious categories, between zero and 4.0% of all age groups reported an AE as seen in table 6. A chi square test done to determine any relationship between severity of AE and the various age categories indicated that these differences were significant. (Chi (8) = 15.87, p = 0.04)

Table 6: Distribution of adverse events by age group

Adverse event	<2(%)	2-11(%)	12-17(%)	18-64(%)	65+ (%)	Total (%)
Mild	19(10.0)	60(31.4)	16(8.4)	62(32.5)	4(2.1)	161(84.3)
Moderate	6(3.1)	1(0.5)	3(1.6)	8(4.2)	2(1.1)	20(10.5)
Severe	2(1.1)	2(1.1)	2(1.1)	3(1.6)	1(0.5)	10(5.2)
Serious	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Total	27(14.1)	63(33.0)	21(11.0)	73 (38.2)	7(3.7)	191(100.0)

4.2.3 Proportion of Adverse by means of reporting

The means used to follow up participants enrolled into the study was by home visit or phone call. However, some few participants were met at the health facility Of those successfully followed up, 312/413(75.5%) were interviewed by telephone and 76/413(18.4%) were interviewed at home. The reporting rates were higher among telephone contacts than by home visit and health facility visit. Of the 161 mild AEs reported 126 was by phone call representing 66.0% and 17/20 (8.9%) moderate AEs were also reported by phone call. This is shown in table 7 below. Common events such as general malaise, nausea, dizziness, insomnia, restlessness and vomiting were reported by health facility visit, home visit and telephone call. The chi square results proved an association between severity of event and means of reporting (Pearson chi2(4) = 41.5856 Pr = 0.000).

Table 7: Severity of event and means of reporting

	Type of follow up			
Type of AE	HF (%)	Home (%)	Phone (%)	Total (%)
Mild	8(4.2)	27(14.1)	126(66.0)	161(84.3)
Moderate	1(0.5)	2(1.1)	17(8.9)	20(10.5)
Severe	6(3.1)	2(1.1)	2(1.1)	10(5.2)
Serious	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Total	15(7.9)	31(16.2)	145(75.9)	191(100)

CHAPTER FIVE

DISCUSSION

The current study was carried out in the Kassena/Nankana Municipality of northern Ghana to document adverse events experienced by patients, after taking ACTs for the treatment of uncomplicated malaria and to compare the outcomes recorded during home visits and those captured through mobile phone calls. Overall, a total of 15 AEs were reported with 46% of the study participants reporting at least one AE.

Among the three ACTs received by patients in this study, Artesunate-amodiaquine was the most prescribed ACT because it was the most stocked and Dihydroartimisin-piparaquine was the least prescribed because it ran out of stock at the time of the study. The incidence of adverse events reported by intake of the ACTs (Artesunate-amodiquine, Artemether-lumefantrine and Dihydroartemisinin-piparaquine) used for malaria treatment in this study was found to be generally mild and tolerable. Only a few participants did not adhere to treatment due to adverse events experienced. The type of ACT did not appear to have any significant effect on the severity of adverse event. However there was a significant relationship between age and severity of adverse events. This study results did not reveal any serious adverse events among those who took the prescribed ACT. This is contrary to the findings by Binka, et al., 2012 who reported 53 serious adverse events which included cardiac arrest and Steven Johnson syndrome in a multi-center study conducted in Ghana and Tanzania. Another cohort study conducted in Uganda to determine reporting of adverse events using mobile phone as a means of reporting also reported serious adverse events which included one death which was due to drug over dose (Adedeji et al, 2014).

Majority of participants who took the ACTs did not experience adverse events (53.8%). Similar findings were reported by a study in Uganda with 53% of participants who experienced no adverse event (Adedeji et al, 2014). This was also reported by Kukula et al

(2015) in a study conducted to determine the feasibility of using mobile phone to capture drug safety information in peri-urban Ghana. In that study 72.7% of participants who took ACTs did not experience adverse events.

Another study conducted in India to determine adverse drug reactions (ADR) among 500 patients treated with antimalarial drugs found that 49.8% of patients did not experience an ADR. Out of 318 male patients (46.8%) did not experience any ADRs and out of 182 female patients (54.9%) complained of ADRs (Belhakar et al, 2012)

This study revealed that 46.2% (191/413) of the 413 study participants experienced adverse events. This proportion is similar with that of Adedeji, 2014 who reported 47% (86/183) adverse events experienced after drug intake. Though Kukula, 2014 reported similar adverse events, the proportion of participants who reported adverse events was 32% (1128/4124). Another study conducted in India among 500 patients, 251 (50.2%) patients reported ADRs to antimalarial treatment. A total of 442 ADRs were reported, since many patients complained of more than one ADR. Out of 318 male patients 169 (53.15%) complained of ADRs and out of 182 female patients 82 (45.1%) complained of ADRs.

According to that study, assessment of all the ADRs was done according to WHO causality assessment scale and almost all the adverse drug reactions were possibly due to the treatment with antimalrials. However in this study conducted in the Kassena Nankana Municipality, causality assessment to determine the relatedness of adverse events reported to the ACTs prescribed was not done. Further studies are therefore needed to investigated the relatedness of the adverse events reported in this study to the ACTs (Artesunate-amodiquine, Artemether-lumefantrine and Dihydroartemisinin-piparaquine) studied.

The clinical condition of majority of study participants in this study improved, this indicates that the ACTs are effective in treating malaria. Studies on efficacy of ACTs reported that ACTs clear parasites from the peripheral blood quicker than chloroquine monotherapy (parasitaemia after 24 hours of treatment: RR 0.42, 95% CI 0.36 to 0.50, 1652 participants). Recurrent parasitaemias before day 28 were very low (2%) following treatment with ACTs but comparatively high (9%) following treatment with chloroquine was reported (Binka et al, 2012).

The most reported adverse events were not different from those reported in the literature. A study conducted in Uganda on use of mobile phones for reporting adverse drug reactions reported similar adverse events (Adedeji et al 2014). Binka, et al (2012) reported similar adverse events in addition to over 200 other adverse events reported in that study.

This study showed a significant relationship between severity of adverse events reported and the various age categories but there was no significant relationship between severity of adverse events reported and the type of ACT. Sex had no relationship with severity of adverse events. However the relationship between the severity of adverse event and the means of reporting was highly significant. This results are similar to study conducted by Belhekar et al (2012) in a prospective study of adverse drug reactions to artemisinin-based combination therapy in a tertiary care hospital in India among 500 patients (318males, 182 females). One hundred and sixty nine male patients complained of 305 ADRs and that 82 female patients complained of 137 ADRs as more than one ADR was observed in most patients. The most common ADR reported was nausea (208 (41.6%), followed by anorexia (104(20.8%) patients, vomiting (75(15%), bitterness in mouth (in 34 i.e., 6.8% patients) and other ADR events like giddiness and dizziness in (21 (4.2%). The difference in the occurrence of adverse drug events between male and female patients was not statistically

significant, hence gender did not seem be associated with the reporting or occurrence of ADR.

The means of reporting of adverse events in this study was by home visit or phone call and they proved effective in capturing adverse events. Majority of participants provided a mobile phone number which was used to make the call to them, those who did not own a phone and could not remember the telephone number of a relative they live with provided a home address and majority of them were located and interviewed. Adverse events were also reported from those visited at home.

There were however other study participants who visited the health facility were the study was on going to report adverse events. Most of the adverse events reported by health facility visit was among participants whose clinical condition worsen or was remained unchanged after having been enrolled into the study. They therefore visited the health facility under the context of seeking additional health care. One of such participants had a puffy face after taking Artesunte-Amodiaquine and was diagnosed of reacting to artesunate. For all the 10 study participants that returned to the health facility for further treatment including the participant who was diagnosed of a drug reaction, no adverse event forms where completed by health workers to be submitted to the national pharmacovigilance center. This goes to confirm the under reporting associated with the spontaneous system as stated in the literature. However in this cohort study, adverse events forms were completed for all the 191 study participants who reported adverse events. These reports are more than half of the annual adverse events forms submitted by the national pharmacovilance center (Ghana) to WHO.

The methods used to report adverse events are not unique to this study. Several studies have used these methods as means of capturing drug safety information in various health

systems all over the world. Considering that the setting of the study is predominantly rural and there is a high rate of reporting of adverse events through mobile phone (75.5%), this shows in order to improve upon reporting of AEs mobile phone could be an efficient means of reporting. This finding is similar to a study conducted in peri-urban Ghana among 4, 1240 patients to determine feasibility and cost of using mobile phones to capture drug safety information. The study reported 64.8% success rate of using mobile phones to report adverse events of ACTs (Kukula et al, 2015). Another study conducted in Uganda using mobile phones for active surveillance reported that the approach is efficient in determining adverse events with as high as 89.5% response rate with 47% of the 183 patients enrolled reporting adverse events (Adedeji et al, 2014). They also reported that few study participants returned to the health facility under the context of seeking additional health care.

5.1 Limitations

There are few limitations to this study that merit mentioning. Factors associated with self-reporting studies such as accuracy of recall and personal bias may affect the study. The type of ACTs available in stock at the facility was what was prescribed. This may have affected the study in determining the proportion of patients prescribed ACTs who experienced adverse event. The determination of the severity of the adverse events was based on the judgment of the interviewer and therefore could have introduced some bias. Effort was made to minimize this bias by providing adequate training on ICH guidelines on grading of severity of adverse event to the interviewers. Children less than 12 years who could not speak for themselves were not directly interviewed. The determination of an adverse event was based on the judgment of their respondents.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Less than half of the study population experienced adverse events. The artimisinin-based combination therapies observed in this study conducted under real life settings are generally safe as most adverse events were mild. Cohort event monitory was an efficient method in the reporting of adverse events after intake of artimisini-based combination therapy. Capturing of clinical events, regardless of causality, provides an opportunity to raise awareness of pharmacovigilance among patients and encourages reporting of adverse events.

Majority of patients were successfully followed up by telephone and most AEs were reported on phone. Mobile phones proved to be an effective means of monitoring drug safety in resource-limited settings as demonstrated by this study in the Kassena/Nankana Municipality whose population is predominantly rural.

6.2 Recommendation

In other to improve upon reporting of adverse events and meet the WHO criteria of a fully functional pharmacovigilance system:

1. Patients should be actively encouraged to report AEs after intake of drugs any day they visit the health facility. This could be done by all health staff especially the dispensing pharmacist and prescribing clinician.
2. With the high adverse event reporting rate by mobile phone, its use is recommended for reporting of AEs. Currently, mobile phones are available in almost every home and the cost of using the phone to report an adverse

even in most cases may be lower than traveling back to the health facility except if one needed further health care.

3. Studies on the cost of using mobile phone to report adverse events are recommended to enable budgeting for pharmacovigilance activities within the health care system.
4. There should be a dedicated phone number in all health facilities for reporting of adverse events. This facility could be conveniently located at the pharmacy for receiving all reports.
5. Studies to determine relatedness of adverse events to artimisinin based combination therapies in real life settings are recommended.

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APPENDICES

Appendix 1: Pretreatment questionnaire

PRE-TREATMENT QUESTIONNAIRE

(*To be completed on day of enrollment*)

PATIENT ID | | | | |

Health facility visit date…… | | | | | 2 | 0 | 1 | | **VDATE**

SECTION 1: IDENTIFICATION AND DEMOGRAPHIC DATA

1.1 Name of Patient:

NAM

1.3 Name of Village_____ **VILLAGE**

1.4 Section of Village_____**SECTION**

1.5 Compound ID…… | | | | | | | **COMPID**

1.6 Compound Name_____**COMPNAM**

1.7 Number of Households in Compound

1.7 Date of Birth…… | | | | | | | | | **DOB**

1.8 Age (**in years**)…… | | | | **AGEYR**

1.9 Age (**in months if child less than 1 year**) …….... | | **AGEMT**

1.10 weight…… | |

1.11 Tempreture ……

1.12 Gender……..... | 1. Male | 2. Female | **SEX**

EDUCATIONALLEVEL……	**NO EDUC**	**BASICEDUC**	**SECONDARY EDU**	**TERTIARY EDU**

1.13 Pregnant ……	1. Yes	2. No	3. Uncertain	8. NA	**PREG**

Circle NA for ALL males and females aged below 12yrs

1.1 Trimester ……	1. 1st	2. 2nd	3. 3rd	8. NA	**TRIME**

/

1.15 Name of Respondent:

RNAM

1.16 Do you own a bednet**……..**

YES	**NO**

1.17 How many households own a bednet**……**

1.18 How many bednets are in your compound**……..**

1.9 Did you sleep under a bednet last night**……**

YES	**NO**

1.20 If no when was the last time you slept under a bednet **……**

1.21 Has your compound ever been sprayed against mosquitoes (IRS)

YES	**NO**

1.22 When was the last time it was sprayed**……**

										PHONE1
										PHONE2

1.12 Patient/Respondent Phone Numbers ……

SECTION 2: ILLNESS AND MEDICAL INFORMATION

2.1 What are the events (signs and symptoms) at presentation within the last five days?)

Events	Response (Please circle)				If yes, record start date								
					D	D	M	M	Y	Y	Y	Y	
General malaise	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP1**
Fever (hot body)	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP2**
Chills	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP3**
Irritability	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP4**
Excessive sweating	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP5**
Fatigue	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP6**
Joint pain	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP7**
Myalgia (muscle pain)	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP8**
Convulsions	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP9**
Headache	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP10**
Dizziness	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP11**
Drowsiness	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP12**
Ear problem, (specify ……)	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP13**

Nasal/sinus congestion	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP14**
Eye problem (specify ……)	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP15**

Cough	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP16**
Chest pains	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP17**
Difficult breathing	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP18**
Palpitations	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP19**
Nausea	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP20**
Vomiting	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP21**
Loss of appetite	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP22**

Stomach ache	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP23**
Diarrhoea	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP24**
Difficult/painful urinating	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP25**
Penile/ Vaginal discharge	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP26**
Lower abdominal pain	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP27**
Skin rash	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP28**
Trauma/bite/other injury	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP29**

Other, (specify ……)	1. Yes Spontaneous	2. Yes Prompted	3. No	9. DK					2	0	1		**SYMP30**

2.2 Did you do any malaria diagnostic test? …… | 1. Yes | 2. No | **MDTT**

If yes, please record malaria diagnostic test

Test	**Date**								**Result (Please circle)**			
	D	**D**	**M**	**M**	**Y**	**Y**	**Y**	**Y**				
Rapid Diagnostic Test					2	0	1		1. Positive	2. Negative	3. Not Done	**MRDT**
Microscopy					2	0	1		1. Positive	2. Negative	3. Not Done	**MICR**
Heamoglobin (Hb) (g/dl)					2	0	1		.		3. Not Done	**HAEM**
Other, specify ……..					2	0	1					**OTST**

2.3 What medicines have you taken in the last 2 weeks? *(Medicines indicated in patient folder as taken within*

the last 2 weeks should be copied as well)

#	**Drug Code**	**Name of Medicine**	**Dose and Frequency**	**D**	**D**	**M**	**M**	**Y**	**Y**	**Y**	**Y**	
1								2	0	1		**MEDT1**
								2	0	1		
2								2	0	1		**MEDT2**
								2	0	1		
3								2	0	1		**MEDT3**
								2	0	1		
4								2	0	1		**MEDT4**
								2	0	1		
5								2	0	1		**MEDT5**
								2	0	1		
6								2	0	1		**MEDT6**
								2	0	1		

2.4 Have you taken any traditional or herbal medicines during the last 2 weeks?

1. Yes	2. No	9. DK

HERB

2.4.1 If Yes: please specify/describe_____**HERBN**

2.5 What are the past or present medical conditions?

#	**Medical Condition**				
1	Hypertension	1. Yes Past	2. Yes Present	3. Never had	**MCOD1**
2	Other heart disease (Specify) ……	1. Yes Past	2. Yes Present	3. Never had	**MCOD2**
3	Diabetes	1. Yes Past	2. Yes Present	3. Never had	**MCOD3**
4	Malaria	1. Yes Past	2. Yes Present	3. Never had	**MCOD4**
5	Typhoid fever	1. Yes Past	2. Yes Present	3. Never had	**MCOD5**
6	Bacteraemia	1. Yes Past	2. Yes Present	3. Never had	**MCOD6**
7	Diarrhea/dysentery	1. Yes Past	2. Yes Present	3. Never had	**MCOD7**
8	Sickle Cell	1. Yes Past	2. Yes Present	3. Never had	**MCOD8**
9	Asthma	1. Yes Past	2. Yes Present	3. Never had	**MCOD9**
10	TB	1. Yes Past	2. Yes Present	3. Never had	**MCOD10**
11	Kidney disease	1. Yes Past	2. Yes Present	3. Never had	**MCOD11**
12	Liver disease	1. Yes Past	2. Yes Present	3. Never had	**MCOD12**
13	Epilepsy	1. Yes Past	2. Yes Present	3. Never had	**MCOD13**

14	Pneumonia/acute respiratory infection	1. Yes Past	2. Yes Present	3. Never had	**MCOD14**
15	Rheumatism	1. Yes Past	2. Yes Present	3. Never had	**MCOD15**
16	Leprosy	1. Yes Past	2. Yes Present	3. Never had	**MCOD16**
17	Meningitis	1. Yes Past	2. Yes Present	3. Never had	**MCOD17**
18	Cancer	1. Yes Past	2. Yes Present	3. Never had	**MCOD18**
19	Other 1 (Specify) ……	1. Yes Past	2. Yes Present	**MCOD19**	
20	Other 2 (Specify) ……	1. Yes, Past	2. Yes, Present	**MCOD20**	

2.6 What type of ACT was prescribed at this visit?	1. A/A	2. A/L	3. DHP	**AATYPE**

2.6.1 Please specify brand name_____

BRAND

2.7 Please record medicines prescribed at this visit?

#	DrugCode	Name of Medicine	Formulation*	Dose and Frequency	D	D	M	M	Y	Y	Y	Y	
1									2	0	1		**MPRES1**
									2	0	1		
2									2	0	1		**MPRES2**
									2	0	1		
3									2	0	1		**MPRES3**
									2	0	1		
4									2	0	1		**MPRES4**
									2	0	1		
5									2	0	1		**MPRES5**
									2	0	1		
6									2	0	1		**MPRES6**
									2	0	1		
7									2	0	1		**MPRES7**
									2	0	1		
8									2	0	1		**MPRES8**
									2	0	1		
9									2	0	1		**MPRES9**
									2	0	1		
10									2	0	1		**MPRES10**
									2	0	1		
11									2	0	1		**MPRES11**
									2	0	1		

*** Formulation: Tablet=1, Capsule=2, Powder=3, Syrup=4, Suspension=5, Suppository=6, Cream=7, Injectable=8**

SECTION 3: FOLLOW UP DETAILS

3.1 Name of nearest contact person for patient follow-up_____**NCONTACT**

3.2 Nearest Contact Person Phone Number(s)…….

										NPHONE1
										NPHONE2

3.3 Date of planned follow-up visit: ……

				2	0	1		**DFOLLOW**

SECTION 4: REPORTER IDENTIFICATION

4.1 Name of interviewer: _____

Signature:…… Date: …../……/..…..

Please note: *Completion of this form is not an admission of causation by, or contribution to, the suspected adverse event by the suspected medicine(s) or by the reporting professionals. This information will be analysed and will contribute to promoting the safe use of antimalarials.*

PLEASE ADVICE PATIENTS/RESPONDENTS TO KEEP PACKAGES OF ALL DRUGS TAKEN

Appendix 2: Post treatment questionnaire:

POST TREATMENT QUESTIONNAIRE

(*To be completed within 7 days after enrollment*)

Patient ID			

SECTION 2: FOLLOW UP DETAILS

2.1 Was the patient present at follow up visit? ……

1. Yes	2. No	**PRESENT**

2.1.1 ***If No, give reason for patient not present***_____ **REASON**

2.2 Date of follow-up Visit: ……

				2	0	1		**FODATE**

2.3 Type of follow-up……

1. HF attendance	2. Visit at home	3. By phone	**FOTYPE**

2.4 What is the status of the interview……1. Complete 2. Incomplete 3. Refused

2.4.1 If incomplete or refused, please record reasons

1. Patient/Care giver is traveling	2. Consent withdrawn	**INCOMP**
4. Other (Specify)_____	5. NA	

NB: If incomplete or refused, please end interview.

SECTION 2: MEDICATION AND POST CLINICAL INFORMATION

3.1 What type of ACT did you take?

1. A/A	2. AL	3. DHP	4. Other

AATYPE

3.1.1 Please specify name of brand taken _____**BRAND**

3.1.2 Please record all other medicines taken at any time during ACT treatment (Days 0-3)

#	Name of Medicine	
1		**ACTT1**
2		**ACTT2**
3		**ACTT3**
4		**ACTT4**
5		**ACTT5**
6		**ACTT6**
7		**ACTT7**
8		**ACTT8**
9		**ACTT9**
10		**ACTT10**

*

3.2 Please record outcome noted at post-treatment visit

	Outcome	**Please circle**			
1.	Clinical condition	1. Improved	2. Not changed	3. Deteriorated	**CLCON**
2.	New clinical event	1. Yes	2. No	3. Don't know	**NWCON**

3.3 Did patient adhere to complete ACT treatment? ..... 1. Yes | 2. No **ADHERE**

3.3.1 If no, please circle reasons (*Do not prompt*)

1. Patient/Care giver not at home	2. Forgot to take medicine	**REASON**
3. Did not understand dosing instructions	4. Medicine has bad taste	
5. Took/preferred other antimalarial	6. Experienced side effects	
7. Felt well	8. No reason given /don't know	
9. Other, specify		

3.4 Please describe new events or worsening problems after starting ACT treatment.

No	**New or worsening event**	
a.		**EVNT1**
b.		**EVNT2**
c.		**EVNT3**

d.		**EVNT4**
e.		**EVNT5**
f.		**EVNT6**

3.5 Severity of adverse event……..1. No adverse event 2. Mild 3. Moderate 4. Severe 5. Serious

SECTION 4: REPORTER IDENTIFICATION

4.1 Name of Interviewer: _____

Signature……. Date……

This report should be sent IMMEDIATELY to supervisor if outcome of the adverse event is death, life-threatening, resulted in persistent incapacity or disability or caused/ prolonged hospitalization.

Please note: *Completion of this form is not an admission of causation by, or contribution to, the suspected adverse event by the suspected medicine(s) or by the reporting professionals. This information will be analysed and will contribute to promoting the safe use of antimalarials.*

Appendix 3: Informed Consent form

Informed Consent form for Study Participants

Study title: Reporting of Adverse events of Artimisini-Based Combination Therapies (ACTs) among patients attending War memorial hospital of the Kassena Nankana Municipality.

INTRODUCTION

My name is ..... We are conducting a student master's study on drugs used to treat malaria. I would like to invite you to participate in the study because you have been given an ACT drug.

Malaria remains a major public health problem causing close to a million deaths annually. Artemisinin-based combination therapies (ACTs) are being used to treat malaria in endemic countries raising safety concerns as little is known about the safety of ACTs in several of the settings (including Ghana) where they are deployed. This study seeks to investigate the reporting of Adverse Drug Events (ADEs) after ACT use in real life setting. This will contribute to strengthen safety monitoring of drugs in Ghana.

STUDY PROCEDURE

You (or your child) are/is being invited to take part in this study because you (or he/she) is given an ACT for this illness episode. We will ask you a few questions about how you have been feeling since you (or he/she) took the antimalarial drug (ACT). We will also ask you about any other medications that you (or your child/ward) took, whether prescribed or obtained from another source. We will take your telephone number and also give you a telephone number to call and report any unusual signs and symptoms you experience after taking the ACT. If you are unable to call we will visit you at home. This will be done within seven days after this visit to the health facility. You will be reimbursed for the

phone call that you will make. Your (or his/her) participation in this study ends after the interview.

Voluntariness

Taking part in this study is completely voluntary. You have every right to refuse to participate or let your child/ward participate. If you should refuse, you (or your child/ward) will not suffer any consequences.

WITHDRAWAL

If you choose to participate (or let your child/ward) participate in this study, you have the right to withdraw from it at any point in time without any consequences to you (or your child/ward). You can also refuse any study procedure that you are not comfortable with.

RISKS AND BENEFITS OF THE STUDY

There are no direct benefits or risks to you (or your child/ward) for your (or his/her) participation in this study. However, we are hopeful that by your (or his/her) participation, you (or he/she) will be helping us provide national, regional and international health decision-makers with evidence on safety and reporting of adverse drug reactions in Ghana.

COMPENSATION

You (or your child/ward) will not be paid for your (or his/her) participation in this study.

CONFIDENTIALITY

All the information that will be collected in this study will be treated in strict confidence and will be used for the intended purposes only. You (or your child/ward) will not be identified by name in any dissemination or publication resulting from this study.

QUESTIONS

If you have any questions concerning the study you can contact Paula Beeri a student of the University of Ghana on 0243889936.

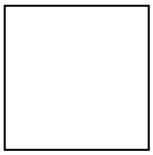
CONSENT FORM

I have been adequately informed of (or I have read and understood) the purpose, procedures, potential risks and benefits of this study. I have had the opportunity to ask questions about it. Any questions that I have asked have been answered to my satisfaction. I know that I can refuse to participate (or have my child/ward participate) in this study without any loss of benefit to which I (or my child/ward would have otherwise been entitled. I understand that if I agree to participate or have my child/ward participate), I can withdraw my consent at any time without losing any benefits or services to which I (or my child/ward) am/is entitled. I understand that any information collected will be treated confidentially. I freely agree to participate (or have my child/ward participate) in the study. After signing below, I will receive a copy each of the information sheet and this consent form.

Name of participant:

……

Signature or Right Thumb Print (participant/parent/guardian): ……



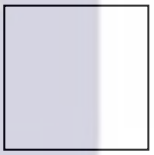
Date: -----/-----/-----

Name of parent/guardian (if applicable): …….

Name of witness:

……..

Signature or Right Thumb Print: ……..



Date: -----/-----/-----

I have adequately informed the participant of the purpose, procedures, potential risks and benefits of this study. I have answered all questions to the best of my ability.

Name of study personnel: ……..

Signature: ……

Date: -------/------/------

Appendix 4: introductory Letter from University of Ghana School of Public Health

UNIVERSITY OF GHANA
DEPARTMENT OF EPIDEMIOLOGY AND DISEASE CONTROL
SCHOOL OF PUBLIC HEALTH

Ref. No.:.....

9th May, 2016

The Regional Director of Health Services
Ghana Health Service
Bolgatanga
Upper East Region.

Dear Sir/Madam,

LETTER OF INTRODUCTION – PAULA BEERI

We wish to introduce to you, ***Paula Beeri***, a Master of Public Health student in the Department of Epidemiology and Disease Control of the School of Public Health, College of Health Sciences, University of Ghana, Legon.

Ms. Beeri is conducting a research on the topic ***"Reporting of Adverse Drug Events of Artemisinin based Combination Therapies among Patients in the WarMemorial Hospital of Kassena Nankana Municipality".***

It will be appreciated if you could provide her with the necessary support to undertake her research work in your institution.

We thank you for your cooperation.

Yours faithfully,

Dr. Patricia Akweongo
Head

cc: School Administrator
WarMemorial Hospital, Navrongo-UW

COLLEGE OF HEALTH SCIENCES
P. O. Box LG 13, Legon, Accra, Ghana.
• Telephone: +233 (0) 289 109 008 • Email: sph-epdc@ug.edu.gh • Website: www.publichealth.ug.edu.gh

Appendix 5: Ethical approval letter from the Ghana Health Service

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

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

Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra
Tel: +233-302-681109
Fax + 233-302-685424
Email: Hannah. Frimpong@ghsmail.org

My Ref. GHS/RDD/ERC/Admin/App/16/88
Your Ref. No.

Paula Beeri
University of Ghana
School of Public Health
Legon, Accra

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

GHS-ERC Number	**GHS-ERC 84/02/16**
Project Title	"Reporting of Adverse Drug Events of Artemisinin based Combination Therapies among Patients in the War Memorial Hospital of the Kassena Nankana Municipality"
Approval Date	12th April, 2016
Expiry Date	11th April, 2017
GHS-ERC Decision	**Approved**

This approval requires the following from the Principal Investigator

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

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

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

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

SIGNED.....
DR. CYNTHIA BANNERMAN
(GHS-ERC CHAIRPERSON)

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