UNIVERSITY OF NAIROBI

"THE EPIDEMIOLOGY AND ECONOMIC BURDEN OF STRUCTURAL BIRTH DEFECTS IN KENYA: A CASE OF KIAMBU COUNTY"

BY

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ACCRONYMS AND ABBREVIATIONS

AIC	Africa Inland Church
ANC	Antenatal Care
SBDs	Structural Birth Defects
BOD	Burden of Disease
DALYs	Disability-Adjusted Life Years
DW	Disability Weights
EUROCAT	European Surveillance of Congenital Anomalies
GBD	Global Burden of Disease
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICD-10	International Classification of Diseases 10th Edition
IFAS	Iron-Folic Acid Supplementation
KDHS	Kenya Demographic and Health Survey
KNBS	Kenya National Bureau of Statistics
NBDPN	National Birth Defects Prevention Network
NTD	Neural Tube Defects
PM	Particulate Matter
SEA	South-East Asia
SDCA	Step-Down Cost Accounting
WHO	World Health Organization
YLD	Years Lived with Disability
YLL	Years of Life Lost due to premature mortality

OPERATIONAL DEFINITIONS

Admission rate bias/ berkson bias The concept underlying this bias is that patients with more than one disease or condition are more likely to be hospitalized than patients with only one disease or condition; if a case-control study is exploring the relationship between diseases, this bias can cause an overestimation of exposed cases in the hospital population (Sutton-Tyrrell, 1991).

Ascertainment bias Ascertainment bias occurs when there is inaccurate ascertainment of either the disease or exposure; case-control studies relying on chart review for study data are particularly susceptible to ascertainment bias because the investigator has no control how the disease and exposure variables are ascertained and recorded in the patient chart (Sutton-Tyrrell, 1991).

Birth defects Birth defects also referred to as congenital abnormalities, congenital deformities or congenital anomalies are defined as abnormalities of body structures or functions, of prenatal origin present at birth detectable during pregnancy, at birth or soon after birth (World Health Organization, 2014; Brown-Viner, 2012; Sever, 2004). For this study, specific external structural birth defects of interest will include but not limited to neural tube defects, orofacial clefts, limb reduction defects, omphalocele and gastroschisis.

Case definition Case definition is a uniform set of criteria used to decide whether a child has a birth defect that will be included in the study; it is intended to increase the likelihood that included cases have the defect of interest (Tinker et al, 2015). In birth defects surveillance, a case refers to an individual with characteristics fitting into the defined parameters, that includes diagnosis,

pregnancy outcome information (live births, stillbirths, terminated pregnancies) and demographics (Sever, 2004).

Confounders This is a variable associated with the exposure in the population, associated with the outcome conditional on the exposure, e.g. among the unexposed, and not in the causal pathway between the exposure and outcome (Hernán, et al, 2002). Approaches for identifying confounders are automatic stepwise variable selection procedures, comparing adjusted and unadjusted effect estimates, (greater than 10 percent) and checking whether some necessary criteria for confounding are met (Hernán et al, 2002).

Costs Costs are monetary values of resources used in providing health care services; sometimes categorised as direct or indirect costs, variable or fixed costs, recurrent or capital costs (Kirigia, 2009).

Cost analysis Cost analysis is a form of partial economic evaluation entailing identification, measurement, valuation and comparison of costs of two or more alternatives but not their effectiveness and it's enough when the relative effectiveness of alternative(s) being considered is (are) not contentious (Kirigia, 2009; Drummond et al, 2005).

Direct costs Refer to all recurrent costs directly attributed to one intervention or program such as drugs, medical supplies, the time health worker spends with clients, out of pocket expenses borne by beneficiaries and their families (Kirigia, 2009). Direct costs include all resources used or "invested" to treat illness and disability such as medical care and developmental services (Waitzman et al, 1994).

Discounting	Discounting is the method used to account for individuals' time preference. Most individuals have a positive rate of time preference whereby benefits are preferred sooner rather than later and costs incurred later rather than sooner (McIntosh et al, 2006).
Hospital-control bias	For hospitalized patients to be an adequate control group, the disease that resulted in hospitalization cannot be related to the exposure of interest. If the exposure of interest is higher in the control group than in the general population, then a true relationship between the exposure and disease of interest could be masked. Likewise, if the exposure is protective against the disease causing hospitalization of the control group, then the relationship could be spuriously increased (Sutton-Tyrrell, 1991).
Indirect costs	Indirect costs refer to the value of productive time lost due to participation in health program or intervention (Kirigia, 2009), for example all resources lost to society from reduced productivity due to premature mortality and heightened morbidity (Waitzman et al, 1994).
Fixed costs	Fixed costs refer to costs that do not vary with the quantity of output in the short-term, also referred to as capital costs for example equipment, vehicles, buildings and others (Kirigia, 2009).
Live birth	Spontaneous delivery of an infant showing signs of life, including heartbeat, spontaneous breathing or movement of voluntary muscles (Sever, 2004).
Major anomaly	Major anomaly refers to birth defects requiring medical or surgical treatment, has serious adverse effect on health and development, or significant cosmetic effects (Sever, 2004).

Minor anomaly	Minor anomaly refers to birth defects not requiring medical or surgical treatment, does not seriously affect health and development, and does not have significant cosmetic effects (Sever, 2004).
Opportunity cost	Opportunity cost refers to the value of resources in its most valuable alternative use, that is, the value of resource in the best alternative use, also referred to as economic costs (Cunningham, 2000). It is investing resources in a health care intervention in its best alternative use (McIntosh et al, 2006).
Overhead costs	Overhead costs refer to the value of an input that are used for more than one program, for example staff, buildings, vehicles (Kirigia, 2009).
Particulate matter	This refers to a collection of particles less, greater and within a specified aerodynamic size-range selected to have special relevance to inhalation and deposition, source or toxicity (Pope et al, 2006).
Particulate matter air pollution	This is a mixture of solid and liquid particles varying in number, size, shape, surface area, chemical composition, solubility and origin suspended in air (Pope et al, 2006).
Referral bias	Referral bias occurs when the referral patterns specific to a community cause an overrepresentation or underrepresentation of exposed cases in the hospital population as compared to the general population. For referral bias to occur, referral patterns must be related to the exposure of interest (Sutton-Tyrrell, 1991).
Social welfare	This is a function of individual preferences where individuals are expected to maximize utility (Weinstein et al, 1997).

Sensitivity analysis	This is a means of representing uncertainty in the results of economic evaluations. The four main types of sensitivity analysis are:- one-way simple sensitivity analysis, multi-ways simple sensitivity analysis, threshold sensitivity analysis and probabilistic sensitivity analysis (McIntosh et al, 2006).
Structural birth defects	These are major birth malformations with significant impact on the health and development of a child (Parker et al., 2010).
Unit cost	These are the costs of providing one good or service and sometimes referred to as average cost (Conteh & Walker, 2004).
Utility	Utility refers to the value or worth of given health state or an improvement in that health state valued between zero and one, where zero is equivalent to death and one is equivalent to perfect health (Cunningham, 2000).
Variable costs	Variable costs refer to costs incurred every year often varying with the quantity of output for example personnel time, drugs, supplies, nurse or doctor time among others, also referred to as recurrent costs (Kirigia, 2009).

ABSTRACT

Background: Birth defects remain a worldwide public health problem causing prenatal, infant and, childhood morbidity, mortality, postnatal physical lifelong disabilities and reduced quality of life, life expectancy and economic productivity. Substantial economic resources are usually dedicated to treatment of SBDs among children in Kenya. **Study objectives:** This study seeks to determine epidemiology and economic burden of SBDs in Kiambu county from 1st January 2014 to 31st December 2018 through the following objectives: - To estimate the prevalence of SBDs, to identify the risk factors for major SBDs and to empirically determine the "shadow prices" of corrective health service for SBDs. **Methodology:** This study targets all children born in Kiambu county during the study period from 1st January 2014 to 31st December 2018 and cases defined as live-births of at least 28 weeks gestation, with at least a clinically obvious external SBDs of any body organ and/or system, and/or ascertained by a medical specialist(s) born to a resident mother of Kiambu county during the study period, born at home and/or any of the participating hospitals and/or received/receiving care at the hospitals participating in the study. Following sample sizes statistically determined, and probability proportional to size self-weighted samples, descriptive cross-sectional and case-control study designs will be conducted. **Objective 1:-**To estimate the prevalence of SBDs, a descriptive cross-sectional study will be carried out at the 14 hospitals, where numerator data consisting of live-births with SBDs will be abstracted retrospectively by research assistants lead by the principal investigator from MOH 333, NBU and pediatric records, whereas, the denominator will consist of the number of live births reported or projected by KNBS by years from 1st January 2014 to 31st December 2018. Retrospective data will include maternal education, age, sub-county, occupation, parity, gestation age, nature of gestation, alcohol consumption, trimester prenatal care began and antenatal care visits, sex of child. Categorical variables will be analyzed as descriptive statistics and summarized in proportions/percentages and results presented in graphs, tables and narratives summaries. Prevalence of specific SBDs will be calculated by dividing the numerator (number of cases of specific structural birth defects in the county each year) by the denominator (number of live births in the county reported/projected by the KNBS) yearly during the study period. **Objective 2:-** To identify the risk factors for major external SBDs, a hospital-based case-control study will be conducted at 2 specialized hospitals, where, primary data will be collected through structured interviewer-administered questionnaires. The occurrence of these defects will be hypothesised to depend on maternal education, age, residence, occupation, parity, gestation, alcohol consumption, indoor pollution, iron-folic acid supplementation, trimester prenatal care began and antenatal care visits, and a logistic regression model will be used to calculate odds ratios at 95% CI controlling for potential confounders. **Objective 3:-**To determine the "shadow prices" of corrective health service for SBDs, a descriptive cross-sectional study will be carried out at 2 specialized hospitals with primary data collected using healthcare provider/managers semi-structure interview guides, and secondary data through retrospective review of medical/hospital records. Continuous variables, i.e. total economic costs, unit economic costs and DALYs will be analyzed by descriptive statistics and summarized in mean at 95% CI, median, inter-quartile range (IQR), histograms and boxplots, linear regression analysis will estimate marginal effects of the predictors on shadow prices of health among children with SBDs, Lastly, the "shadow prices" of corrective health services, demand for health and health care will be econometrically estimated using two-stage least squares (2SLS) and ordinary least squares (OLS) models. The results will be presented in tables, graphs and narratives summaries. **Study utility:** Overall, the study results will be used to inform policy decisions on resource allocation for the defects, improve understanding of public and economic burden of SBDs, provide a reference point for establishment of national surveillance system, registry and formulation of public health policy framework for prevention and control of SBDs among women of reproductive age. The knowledge of the risk factors may be tailored to formulate specific interventions and inform risk-based surveillance of specific SBDs among women of reproductive age. Lastly, we envisage to contribute to the realm of epidemiol-economics or epi-economics which involves the application of epidemiology and economic theories in biomedical, public health and epidemiology studies.

Keywords: Birth defects. Demand. Determinants. Elasticity. Health. Health Care. Unit costs

CHAPTER ONE: INTRODUCTION

1.1 Background of the study

Structural birth defects (SBDs) are abnormalities of prenatal origin affecting development of body structures and evident before birth, at birth and after birth (World Health Organization, 2014; Bhandari et al., 2015; Penchaszadeh, 2002; Parker et al., 2010; Christianson et al., 2006; Ghazaryan, 2003). Intrauterine development of SBDs is attributed to single-gene defects, chromosomal disorders, multifactorial inheritance, environmental teratogens and micronutrient deficiencies (World Health Organization, 2014; WHO, 2010; Christianson et al., 2006). Micronutrient deficiencies include iodine, folic acid and multivitamin deficiencies, whereas, environmental teratogens include alcohol, cigarettes, syphilis and overweight. Maternal exposure to these teratogens before and after conception increases the risks for these defects, especially in the developing countries (WHO., 2010). Approximately half of pregnancies are unplanned and many pregnancies are not recognized until the end of the first trimester (14 weeks of gestation) in USA, thus compromising pre-conceptional and early pregnancy preventive strategies (Tinker et al, 2015).

These defects are detectable prenatally through genetic screening and medical imaging, whereas, at birth or soon after birth, they are clinically obvious and can be detected through physical examination, e.g. spina bifida (Tinker et al., 2015; Kishimba et al, 2015; Bhandari et al, 2015; Anyanwu et al, 2015; World Health Organization, 2014; Christianson et al, 2006). Major external SBDs, e.g. neural tube defects (NTD), orofacial clefts (OFC) and limb reduction defects (LRD) are common, salient, typical, easily recognizable at birth and have significant medical or surgical consequences (World Health Organization, 2014; Kishimba et al., 2015; Parker et al., 2010; Sever, 2004; Ghazaryan, 2003). Terms synonymous with “birth defect” and widely used interchangeably

are “congenital anomalies”, “congenital abnormalities” and “congenital malformations” (World Health Organization, 2014).

Worldwide, an estimated 134 million births are reported to occur each year of which 3 – 7% have some type of defect, however, these estimates have been highly variable between regions due to underreporting (Feldkamp et al, 2017; Lamichhane et al, 2016; Bhandari et al, 2015; Kishimba et al, 2015; Anyanwu et al., 2015; Salih et al, 2014; Wellesley et al, 2005; Christianson et al, 2006). The numerator for accurate estimation of structural birth defects prevalence consists of the number of terminated pregnancies due to the defects, stillbirths due to the defects and live births with defects, whereas, the number of live births becomes the denominator, however, only live births are usually considered in many developing countries. In Nepal and South Korea, the prevalence of congenital anomalies was estimated at 5.2 per 1000 and 54.33 per 1000 live births respectively (Bhandari et al., 2015; Lamichhane et al., 2016). Between 2010 and 2014, in Ethiopia, a linearly increasing trend of birth-defect specific proportions of neural tube defects, omphalocele, gastroschisis and orofacial clefts ranged from 1.14% to 2.83% (Taye et al, 2016). The prevalence of birth defects was estimated at 60.5 per 1000 live births in Tanzania (Kishimba et al., 2015), whereas, the prevalence of major birth defects was estimated at 15.0 per 1000 total births in Kenya (Muga et al, 2009).

Birth defects exert enormous financial burden on global health services (Feldkamp et al, 2017; Waitzman et al, 2013; Waitzman et al, 1994). In United States, direct costs of care of major birth defects were estimated at $ 2.6 billion in 2004 (Mburia-Mwalili et al, 2014; Feldkamp et al, 2017;Tinker et al., 2015). In the same country, the cost of lifetime care of an infant born in a single year with at least one major birth defect was estimated to cost approximately more than $ 6.0

billion (Week, 2006). In Germany, the average annual health expenditure of persons with spina bifida was estimated at € 4532, with inpatient health services contributing €1358 (30.0%), outpatient health services €644 (14.2%), rehabilitation health services €29 (0.6%), drug therapy €562 (12.4%), and other remedies €1939 (42.8%) (Bowles et al, 2014).

Childhood morbidity, mortality, reduced life expectancy, lifelong disabilities and substantial economic costs have been attributed to major structural birth defects (World Health Organization, 2014; Brown-Viner, 2012; Parker et al., 2010; Christianson et al., 2006; Sever, 2004). Worldwide, birth defects are the 10th leading cause of disability-adjusted life years (DALYs) accounting for 25 million disability-adjusted life years, and 2.9% of all years of life lived with disabilities (YLD), with the highest burden experienced in the developing countries (Hernandez-Diaz & Oberg, 2015; World Health Organization, 2014; Wu et al, 2013). Globally, at least 3.3 million children under five years of age die from birth defects yearly and 3.2 million of those who survive are likely to be disabled for life (Bhandari et al., 2015; Christianson et al., 2006). It is estimated that, one in three infants that die has a congenital anomaly, while, 2 – 4% of live born infants and 15 - 20% of still births have a significant birth defect (Sahib, 2016; Anyanwu et al., 2015). These defects can be prevented and controlled by increasing awareness and knowledge about their risk factors, optimizing preconception health, antenatal care services, healthcare services and manipulating lifestyle of those at risk (Yi et al, 2011).

1.2 Statement of the problem and significance of the study

Birth defects remain a worldwide public health problem causing prenatal deaths, infant deaths, childhood morbidity, mortality, postnatal physical lifelong disabilities and reduced quality of life, life expectancy and economic productivity (Feldkamp et al, 2017; Sahib, 2016; World Health Organization, 2014). Major external SBDs in developing countries are “silent epidemics”, because

of grossly underestimated incidence and prevalence mainly due to underreporting, leading to highly variable regional estimates. Lack of a national surveillance system, inadequate case definitions, ascertainment criteria, deficiencies in diagnostic capacities, and data sparsity, coupled with unreliability of medical records and health statistics of structural birth defects, are some of the factors explaining underreporting particularly in developing countries (WHO, 2013; Muga et al., 2009; Christianson et al., 2006; Penchaszadeh, 2002). Structural birth defects are however, observed to occur in comparable proportions, worldwide (WHO, 2013; Christianson et al., 2006; Penchaszadeh, 2002). Some of the prevalence estimates registered include 5% in Africa, 7% in South-East Asia (SEA) and 19% in Europe (WHO, 2013).

Many studies have investigated several factors known to be correlated to structural birth defects, e.g. maternal age, ethnicity, race, smoking, diet, alcohol consumption and environment contaminants among others, (Feldkamp et al., 2017; Anyanwu et al., 2015; Agbenorku, 2013; Bello et al, 2013; Hage et al, 2012; Ochako et al, 2011; Hackshaw et al, 2011; Edison et al, 2004; Moore et al, 2003a; Penchaszadeh, 2002. However, to the best of our knowledge, indoor smoke and pesticide exposure, diet, preconception iron-folic acid supplementation, trimester prenatal care began, and number of antenatal visits have not been investigated in Kenya. The fetus develops rapidly in the first eight weeks of pregnancy, when most pregnant women are unaware of their pregnancy, not attending antenatal clinics and/or not using iron-folic acid supplementation or multivitamins (World Health Organization, 2014). First antenatal visits are recorded mostly at the beginning of second trimester (KDHS, 2014; Honein et al, 2009), when foetal organ development (organogenesis) is almost complete, increasing exposure to teratogenic agents unknowingly. Therefore, determining the relationship between structural birth defects with indoor smoke and pesticide exposure, diet, preconception iron-folic acid supplementation, trimester prenatal care

began, and number of antenatal visits in addition to sociodemographic characteristics will elucidate the reasons underlying continued occurrence of these defects in Kenya. WHO recommendations for pregnant women include a minimum of eight antenatal care visits at 12, 20, 26, 30, 34, 36, 38- and 40-weeks' gestation to improve women's experience of pregnancy, however, even if all pregnant women were to honor these dates, many fetal organs have developed. Daily oral iron and folic acid supplementation with 30mg to 60mg of elemental iron and 0.4mg folic acid for pregnant women are also recommended to prevent maternal anemia, puerperal sepsis, low birthweight and preterm births and not necessarily development of birth defects. Additionally, at least an ultrasound scan before 24 weeks' gestation (early ultrasound) is advisable for pregnant women to estimate gestational age, improve detection of fetal anomalies (too late) and multiple pregnancies, reduce induction of labor for post-term pregnancy and improve a woman's pregnancy experience (WHO, 2018). Similarly, it is advisable that health care workers ask all pregnant women about their past and present alcohol and other substance use early in the pregnancy and at each antenatal care visit (WHO, 2018). These recommendations aim at reducing perinatal mortality and improving women's experience of care and not necessarily reducing the occurrence of birth defects.

Substantial direct and indirect resources are allocated to health services and support for people with structural congenital anomalies. However, due to paucity of disease data, their economic costs have not been accurately profiled and estimated in developing countries (Conteh et al, 2004; CDC, 1995). Similarly, to the best of our knowledge, actual dimensions of cost drivers at direct, indirect and intermediate costs centers for structural birth defect health services are not well understood because of few costing studies conducted in Kenya. Given the scarcity of healthcare resources against unlimited health needs in Kenya, it will be necessary to understand major costs drivers for providing health services to the children.

The burden associated with structural birth defects remain substantial despite improvements in medical and surgical treatments. These defects may lead to enormous financial burden and lifelong disabilities; however, they have been ignored, underestimated or vastly unappreciated as a public health and economic problem (Christianson et al., 2006). The burden of diseases associated with major external structural birth defects stem from disability-adjusted life years, years of life lost to premature mortality and years of life lost to disability, which to the best of our knowledge have not been estimated in Kenya. Children who survive to adulthood and their caregivers, do suffer lifelong disabilities and reduced or loss of economic productivity. Therefore, timely and responsive specialised medical and surgical health care would be lifesaving and reduce severity of disabilities associated with structural birth defects (Christianson et al, 2006). However, to the best of our knowledge, elasticity of healthcare costs and production costs associated with these defects are also not well understood in Kenya.

Lastly, the study of health problems is largely considered to be the concern of medical scientists and the realm of economics is seldomly included (Sengupta, 2016). However, no work in health sector is complete in the modern times without the application of economics because of uniqueness of health care market, coupled with growing population and increasing health care spending worldwide (Sengupta, 2016). Increasing modifiable risk factors, frequency and patterns of major structural birth defects characterize forever rising pressure of demand and costs for corrective health services, inadequate supply of health services and health infrastructure against scarce resources for health. This phenomenon perpetuates economic burden among individuals and national health care systems in any part of the world. Economic techniques leveraging on epidemiologic studies are important to adequately understand the actual socio-economic burden of these defects.

Overall significance for this study will be to inform policy decisions on resource allocation, improve understanding of public and economic burden of these defects, provide a reference point for establishment of national surveillance system, registry for birth defects and formulation of public health policy framework for structural birth defects. Ultimately, we envisage to contribute to the realm of epidemiol-economics or epi-economics which involves the application of epidemiology and economic theories in biomedical, public health and epidemiology studies.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This chapter presents a review and synthesis of empirical literature on description, classification, determinants, public health surveillance, prevalence and economic costs of major external structural birth defects, and associated disability-adjusted life years among others.

2.2 Description, classifications and determinantsof birth defects

Birth defects are described as structural and functional anomalies originating during intrauterine life and can lead to physical and developmental disabilities respectively (Christianson et al., 2006). Structural birth defects can affect an organ system or body part and detectable prenatally, at birth or soon after birth, whereas, functional birth defects can affect system(s) that help the body to operate, are latent and detectable much later in life after months or years of manifestation of clinical symptoms (Bhandari et al., 2015; World Health Organization, 2014; Penchaszadeh, 2002; Parker et al., 2010; Christianson et al., 2006; Ghazaryan, 2003). These defects can be described further as minor, when, inconspicuous, do not require specialized medical or surgical interventions and do not impair normal body functions significantly or reduce life expectancy (Penchaszadeh, 2002; Sever, 2004; Ghazaryan, 2003). Alternatively, they can be described as major, when, they cause serious adverse health, development or cosmetic effects (Kishimba et al., 2015; Parker et al., 2010; Sever, 2004; Ghazaryan, 2003).

More than two-thirds (60-80%) of factors associated with the occurrence of these defects are unknown, with genetic and environmental (non-genetic, i.e. modifiable) factors accounting for one-thirds of the birth defects (Feldkamp et al., 2017; Christianson et al., 2006; Penchaszadeh, 2002). Chromosomal abnormalities and single-gene defects account for defects of genetic-origin

and occur before fertilization (preconception origin) (Christianson et al., 2006). About 10-20% of these defects are known to arise from genetic causes (Penchaszadeh, 2002). On the other hand, environmental factors and multifactorial effects account for about 10-20% of the defects of non-genetic origin and occur after fertilization (post-conception origin) (Christianson et al., 2006). Sociodemographic factors, e.g. ethnicity, parity and level of education are known to mediate genetic, partial genetic and non-genetic birth defects (Kabubo-Mariara et al, 2012; Ochako et al, 2011; Wilkinson et al, 2003; Spencer, 2003).

Embryogenesis (intrauterine fetal development) occurs in the first 8 weeks of gestation and most birth defects form in the first trimester (14 weeks of gestation) (Tinker et al, 2015). Control and prevention measures are likely to be effective when implemented during preconception and early pregnancy, e.g. weight control, eating balanced diets supplemented with multivitamins and folic acid, managing chronic illnesses, having regular medical examinations and avoiding alcohol, tobacco and illicit drugs (Agbenorku, 2013; Week, 2006; Watkins et al., 2003). Exposure to environmental contaminants otherwise referred to as ambient air pollution, i.e. carbon-monoxide, low levels of nitrogen-dioxide, oxidized-nitrogen, ozone and components of particulates, e.g. metals or organic compounds increases the risks of birth defects (Sarigiannis et al., 2017; Ritz et al., 2002). The trimodal size distribution of total suspended particles (TSPs) in the ambient air are rough, fine and very-fine particles, with rough particles derived mainly from suspension or resuspension of dust, soil or other thick materials from roads, farming, volcanos, sea salts, pollen mould, spores and other plant parts (Pope et al, 2006). Fine particles on the other hand are derived largely from direct emissions from combustion processes, e.g. vehicles use of gasoline and diesel, wood burning, coal burning (power generation), smelting, cement plants, paper mills and steel mills (Sarigiannis et al., 2017; Pope et al, 2006). Additionally, low Knowledge on potential risk

factors compounds the occurrence of these defects (Bello et al, 2013), e.g. unknown exposure to pesticides. Some of the major structural birth defects include neural tube defects, omphalocele and gastroschisis. These defects are potentially fatal, and for children surviving beyond infancy, substantial economic resources are required to deal with associated childhood morbidities, lifelong disabilities, reduced quality of life and reduced life expectancy (World Health Organization, 2014; Brown-Viner, 2012; Parker et al., 2010; Christianson et al., 2006; Sever, 2004).

2.2.1 Neural tube defects

Major external structural birth defects affecting the brain and spine due to failure of neural tube to form or close correctly or completely within 28 days of fetal development are referred to as neural tube defects, e.g. spina bifida, anencephaly, encephalocele among other forms of neural tube defects (Penchaszadeh, 2002; World Health Organization, 2014; Hage et al, 2012). Neural tube defects occur along the spinal cord (cervical, thoracic and lumbar) associated with genetic and environmental factors such as maternal use of teratogenic medicines during pregnancy, preconception severe obesity and overweight (Anyanwu et al, 2015; Bowles et al, 2014; Rofail et al, 2013; Hage et al, 2012; Edison et al, 2004; Watkins et al, 2003). Maternal use of lovastatin 20mg/day (serum lipid-lowering agent) during first trimester with no concomitant medications or illness have been attributed to cervicothoracic-to-lumbar neural tube defect (Edison et al, 2004). Taking folic acid and folate supplements before and during early pregnancy has been shown to prevent up to 72% of environment-related major birth defects of the spine and brain among women of child bearing age (Week, 2006; Bowles et al., 2014; Hage et al, 2012). A spine-defect due to failure of back elements of the vertebrae to close, often located in the lumbar or sacral portion of the spine is referred to as spina bifida (World Health Organization, 2014), attributed to maternal diabetes type-1, unknown dose of atorvastatin (lipid-lowering agent) and preconception severe

obesity (Body Mass Index greater than 30kg/m^2) (Edison et al, 2004; Moore et al, 2003). Rare types of neural tube defect described as a sac-like protrusion or projection of the brain and the membranes through a defect in the skull, and those characterized by shortening of spinal column rotation and retroflexion of the head in addition to absence of the neck due to defective closure of the vertebral arches and bodies are referred to as encephalocele and iniencephaly respectively (World Health Organization, 2014; Tanriverdi et al, 2015). These defects have been attributed to poor socioeconomic status, low parity, folic acid deficiency obesity and drugs (sulfonamides, tetracycline, antihistamine and antitumor agents) (Tanriverdi et al, 2015). In iniencephaly, the cranium is always closed distinguishing it from cases of anencephaly with spine retroflexion (World Health Organization, 2014). Partial or complete absence of the brain characterizes anencephaly (World Health Organization, 2014). A continuous spine-defect without skin and meninges covering the neural tissue with anencephaly on the other hand is referred to as craniorachischisis (World Health Organization, 2014). These defects are fatal and children born with them mostly do not survive beyond infancy (Prashar et al, 2016).

2.2.2 Orofacial clefts (OFC)

The lip, the roof of the mouth (hard palate), or the soft tissue in the back of the mouth (soft palate) and the structures around the oral cavity, which, may extend into the facial structures resulting in oral, facial and craniofacial deformities, i.e. orofacial clefts (Pala et al, 2016; Agbenorku, 2013). Types of orofacial clefts are clefts of the lip and/or palate (CL/P) are the types of orofacial clefts whose etiology are both syndromic and non-syndromic due to multiple factors associated with chromosomal abnormalities, gene defects and environment factors (Wang et al, 2017; Stanier, 2004; Pala et al, 2016; Conway et al., 2015; Agbenorku, 2013). Other factors associated with the occurrence of orofacial clefts include; severe maternal obesity, maternal overweight, infections,

alcohol consumption, cigarette smoking, retinoic acid, anticonvulsants and prenatal nutritional deficiency of vitamin B6, and folate (Conway et al., 2015; Hackshaw et al, 2011; Moore et al., 2003). Zinc deficiency has been associated with occurrence of isolated cleft palate, while, riboflavin and vitamin A has been noted to be essential in foetal development (Agbenorku, 2013). These defects are preventable by manipulating lifestyle, improving diet, pre-conceptional folic acid supplementation, mineral supplementation, avoiding certain drugs and medicines, general awareness of social, occupational and residential risk factors among women of reproductive age (Pala et al, 2016; Agbenorku, 2013).

2.2.3 Limb reduction defects (LRD)

Deformities of the upper and lower limbs are referred to as limb reduction defects, where upper limb reduction refers to complete or partial absence of the upper arm (humerus), lower arm (radius and/or ulna, wrist (carpals), hand (metacarpals), or fingers (phalanges) (Sever, 2004). On the other hand, lower limb defect is the complete or partial absence of the upper leg (femur), lower leg (tibia and/or fibula), ankle (tarsals), foot (metatarsals), or toes (phalanges) (Sever, 2004). Right fibula and tibia 9% shorter than left side, lack of one ankle bone and right foot 16% shorter than left have been observed in children at 4 years of age (Edison et al, 2004). These defects have been attributed to maternal use of simvastatin (statins) 20mg/day between 0-6 weeks after lost menstrual period and concomitant use of aspirin, codeine, acetaminophen, propoxyphene during first month of gestation (Edison et al, 2004). Maternal use of simvastatin 10mg/day between 0-13 weeks after lost menstrual period and concomitant use of progesterone (10 days/month), duration 0-13 weeks have been associated with left femur being 16% shorter than right side and left foot failure to form and toes three, two and five (Edison et al, 2004).

2.2.4 Gastroschisis

Gastroschisis is a major anterior abdominal wall structural birth defect with an a congenital opening anteriorly to the umbilical cord, accompanied by protrusion of the small intestine, part of the large intestine and sometimes organs of the abdomen, e.g. liver and spleen (World Health Organization, 2014; Sever, 2004). Prolonged hospitalization and substantial financial implications associated with this defect arise from intestinal dysfunction and feeding intolerance (Hook-Dufresne et al, 2015). In the United States between 2007 and 2011, gastroschisis patients length of hospital stay was estimated to range between 37.6 – 39.4 days (Hook-Dufresne et al, 2015).

2.2.5 Omphalocele

Omphalocele refers to a birth defect of the anterior abdominal wall where umbilical cord is widened, allowing protrusion of abdominal organs, small intestines, part of large intestine and occasionally the liver and spleen into the umbilical cord (World Health Organization, 2014; Sever, 2004). The abdominal contents are protruded through an enlarged umbilical ring and umbilical cord inserted in the distal part of the membrane covering the defect (World Health Organization, 2014). It's attributed to preconception severe obesity and overweight (Moore et al, 2003).

2.3 Public health surveillance of major structural birth defects

World Health Organization proposed a three-staged strategy requiring surveillance to reduce public health impact of birth defects included interventions to prevent the defects to nearly 50 percent of what is possible, improvement of locally available care and treatment of infants with treatable genetic diseases (Luquetti et al, 2011). No single surveillance model is applicable universally because their establishments are within different political, social and geographic, economic and historical contexts reflecting individual interests, training and philosophy of their creators (Luquetti et al, 2011).

Public health surveillance is the ongoing systematic and continuous collection, management, analysis, interpretation and dissemination of data regarding a health-related event in a timely manner for use in public health action to reduce morbidity and mortality and to improve health (World Health Organization, 2014; Mburia-Mwalili et al, 2014; MacDonald, 2012; WHO-SEARO, 2016). Population-based and facility-based public health surveillance systems use active or passive or hybrid case ascertainment (pass and active) strategies to collect data on public health problems (World Health Organization, 2014). Passive case ascertainment refers to sharing of health data between healthcare-related individuals, either, immediately, weekly or monthly depending on the health condition, whereas, active case ascertainment refers to involvement of public health agencies in collecting health data on relevant health conditions, and hybrid (enhanced-passive) referring a combined passive and active surveillance systems (World Health Organization, 2014; MacDonald, 2012).

Surveillance allows tracking trends of health events over time, identifying potential individuals and clusters e.g. ethnic, residence, sex at increased risks in addition to providing clues for further research (World Health Organization, 2014). Frequency, severity, cost, preventability, communicability and public health interest are some of the criteria for identifying high-priority health events for surveillance (Lee et al, 2010). Frequency of health events are incidence, prevalence and mortality; severity of health events are case-fatality ratio, hospitalization rate, disability rate, years of potential life lost and quality-adjusted life years lost, while, costs of health events are direct and indirect costs (Lee et al, 2010). Birth defects surveillance interest was triggered by the thalidomide tragedy of the 1960s when increased number of children with limb deformities were born in Germany and other parts of the world where thalidomide was used for treating nausea and morning sickness among pregnant women (Mburia-Mwalili et al, 2014). This

led to creation of first birth defect registries for surveillance primarily to avoid occurrence of a similar tragedy (Luquetti et al, 2011).

The importance of public health surveillance include, establishment of a health condition baseline, understanding disease trends and patterns, outbreak detection, estimation of public health of a health problem, identification of resources required during and after a public health emergencies, public health programs and control measures evaluation, natural history of disease determination, monitoring changes in infectious agents and health practices, setting priorities and testing hypothesis, among others (World Health Organization, 2014; Luquetti et al, 2011; MacDonald, 2012). Additionally, surveillance data on birth defects can be used in societal impact studies of birth defects, census of people with disability for social welfare and medical services planning, assists in developing clinical genetic services for care and prevention and evaluation of effectiveness of preventive measures (Luquetti et al, 2011).

2.3.1 Facility-based surveillance

Facility-based birth defects surveillance programs capture birth outcomes with defects that occur in selected facilities within specific geographical areas, e.g. county (World Health Organization, 2014). Categories of facility-based surveillance systems are laboratory-based surveillance and sentinel-based surveillance (MacDonald, 2012). Sentinel birth defects surveillance programs are usually formed one or some facilities to capture quick estimates of an adverse birth outcome (World Health Organization, 2014). Facility-based surveillance often targets health conditions requiring the level of care and treatment provided by the facility (MacDonald, 2012). The denominator used for estimating prevalence in such a study consists of births occurring in the facility, whereas, the numerator (cases) consists of affected live births and stillbirths occurring in

the facility. Neonates with birth defects who are delivered at home are not included even if they are identified and captured in participating facilities (World Health Organization, 2014).

In Kenya, Muga et al, (2009), conducted a cross-sectional study in newborn unit of Kenyatta National Hospital for twelve months adopting quasi-experimental approach prospectively to determine patterns and incidence of birth anomalies, in addition to their risk factors. Our study design will be both descriptive and analytical to estimate the prevalence, determine risk factors and estimate economic costs of structural birth defects. Earlier than 1999, national birth defects prevalence estimates in the United States were based on hospital-based surveillance data from Birth Defects Monitoring Program (BDMP) which used hospital discharge data to ascertain defects diagnosed at birth and estimated prevalence at 3% (Week, 2006). Nonetheless, these were underestimates and informed establishment of National Birth Defects Prevention Network (NBDPN) tasked to describe and estimate national birth-specific defects prevalence using population-based surveillance data from 1999–2001 annually in 34 participating States in 34 States participating in NBDPN (World Health Organization, 2014; Week, 2006; Canfield, 2006). In China, surveillance system for monitoring twenty-three types of birth defects according ICD-10 began in 1986 and between 2001 and 2008 (Liu et al., 2015; Zhang et al, 2011). One of the studies used 52 hospitals surveillance data and analyzed prevalence and characteristics of birth defects in perinatal infants (livebirths, stillbirths and terminations of pregnancy for fetal anomaly; accessing within 7 days after delivery) in Hubei province (Zhang et al, 2011). In 2000 birth certificate was revised to include a field for registering birth defects in Brazil as a hospital-based surveillance system (Luquetti et al, 2011).

2.3.2 Population-based surveillance

Population-based birth defects surveillance programs obtain birth outcomes with defects occurring among resident population in a specific geographical area within a defined time (World Health Organization, 2014). Categories of population-based surveillance system include community-based surveillance and school-based surveillance systems (MacDonald, 2012). Population-based surveillance entails collection of health data that are representative of target populations, for example children born with structural birth defects, where probability sampling is used to select households so that findings can be generalized to the whole population (MacDonald, 2012). Best prevalence estimates and pattern of disease in a population is provided by population-based surveillance systems because of providing information on the entire target population, however, they are relatively expensive to conduct and may not capture all ill individuals including, e.g. those who don't seek medical care (MacDonald, 2012).The denominator for population-based prevalence is the number of births to resident mothers, whereas, numerator is the number of neonates with birth defects born to resident mothers, i.e. all hospital, maternity and home births in a population (World Health Organization, 2014).

In Kenya, Wu et al, (2013) conducted a population-based cross-sectional study to estimate prevalence and economic burden of birth anomalies requiring surgical interventions, which are of great importance in developing countries, however, risk factors for these defects should also be identified for purposes of prevention and control. This, therefore, underscores our analytical study intending to include identification of risk factors and estimation of economic costs of anomalies requiring surgical interventions and those that do not require surgical interventions in Kiambu County for purposes informing policy on the burden and magnitude of these defects. In the United States, the guidelines for conducting birth defects surveillance was established by National Birth

Defects Prevention and Network (NBDPN) in 1999 (Week, 2006). Objectives were to promote the quality of state birth defects surveillance data, including accuracy, comparability, completeness and timeliness, to enhance the utility of state birth defects surveillance data for research on the distribution and etiology of birth defects and to encourage and to promote the use of birth defects surveillance data for the purposes of linking affected children with services and evaluation of those services (Sever, 2004).

In community-based surveillance, community members, usually trained volunteers detect and report illnesses that may have not been reported to health facilities (MacDonald, 2012). Community-based surveillance is commonly used in developing countries and is useful for identifying people not seeking medical care, establishing health care network in the community and strengthening relations between the communities and local public healthcare systems, however, it may report high rate of false positives (MacDonald, 2012).

2.4 Prevalence of major external structural birth defects

Major congenital anomalies have been described as conditions present at birth arising from body part(s) malformation, deformation, or disruption and have serious adverse effects on health, development of functionality (Week, 2006). World Health Organization estimated total prevalence of birth defects in developed, middle and low-income countries at 47.2, 55.7 and 66.2 per 1000 live births respectively (Xie et al, 2016). However, worldwide incidence and prevalence of the defects ranging from 4 to 12 per 1000 births were likely underestimates (Sitkin et al., 2015). Congenital anomalies continued to occur globally and differences were being observed in different types, severity and regions (Sitkin et al, 2015). More than one million infants are born with major congenital anomalies annually with central nervous system being the most affected system (Feldkamp et al., 2017; Sahib, 2016; Anyanwu et al., 2015).

European Surveillance of Congenital Anomalies (EUROCAT), estimated overall rate of birth defects at 24.86 per 1000 births in Europe during 2010-2014 and 2.76% of new-borns in United States (Zahed et al, 2017). WHO in its 2013 report estimated the rates of structural and functional births defects at 69 per 1000 live births in Eastern Mediterranean and 51 per 1000 live births in South-East Asia (Zahed et al., 2017). In South Korea, the prevalence of birth defects was estimated at 54.33 per 1000 live births, 30.68 among boys and 24.15 among girls (Lamichhane et al., 2016). The incidence of birth defects in developing countries was estimated to be between 3.9 per 1000 and 11.8 per 1000 live births and 6.3 per 1000 live births in Kenya (Wu et al, 2013). In Kano metropolis, Nigeria, prevalence of overt congenital abnormalities was estimated at 28.5 per 1000 live births (Anyanwu et al, 2015). In Kenya, birth defects of the musculoskeletal system were the most frequently occurring accounting for 33.9% of all major anomalies, followed by malformations of the central nervous system (Muga et al, 2009).

Worldwide, the prevalence of neural birth defects varies by region, race and ethnicity and affect over 300,000 pregnancies, with spina bifida and anencephaly accounting for 90% of all cases (Bowles et al., 2014; Hage et al., 2012). Neural tube defects are among the most common birth defects and the second most common to cardiac defects among major birth defects (Bowles et al, 2014; Rofail et al, 2013; Hage et al, 2012). Anencephaly, encephalocele and spina bifida are the most prevalent types of neural tube defects (World Health Organization, 2014). In Iran, the estimated prevalence of neural tube defects was estimated at 32 per 1000 births (Zahedet al, 2017), while, in India, neural tube defects, estimated prevalence was 4 per 1000 total births (Allagh et al, 2015). In Kenya, overall prevalence of neural tube defects was estimated at 4.9 per 1000 births (Muga et al., 2009).

Worldwide, between 2005 and 2010, the prevalence of spina bifida was estimated prevalence at 0.471 per 1000 births excluding chromosomal associated spina bifida (Bowles et al., 2014). In America, spina bifida occurred in approximately 20 per 100,000 births (Young et al, 2013), while, between 2005 and 2010 in Kenya, the prevalence of spina bifida and encephalocele was estimated at 3.3 per 10,000 live-births, with highest prevalence being reported in 2007 at 4.4 per 10,000 live-births (Githuku et al, 2014). Between 2005 and 2010 the prevalence of encephalocele was estimated at 1.12 per10,000 births, excluding chromosomal associated encephalocele worldwide (Bowles et al., 2014). Incidence rate for Iniencephaly ranges from 0.1 to 10 in 10,000 pregnancies, and is reported more frequently in girls and most fetuses die before birth or soon after birth (Tanriverdi et al, 2015).

Worldwide, estimated occurrence of CL/P ranged from 1.0 per 300 to 1.0 per 2500 births, and 1.0 per 1500 births for cleft palate alone (CL) (Stanier, 2004). Generally, male were affected more than the females with a ratio of about 3:2, and males were more likely to have CL/CP, while females were at greater risk for CL alone (Pala et al, 2016; Agbenorku, 2013; Stanier, 2004). Geographical, racial and ethnic variations were reported in prevalence of orofacial clefts ranged from 1 per 500 to 1 per 2500 births (Pala et al, 2016; Agbenorku, 2013). Orofacial clefts occurred more commonly in children of Asian, Latino, or Native American descent, Asians had the greatest risk of OFC (14: 10,000 births) followed by Whites (10: 10,000 births) and African Americans (4: 10,000 births), whereas, CL/CP was reported as the fourth most common congenital anomaly in USA affecting 1:700 babies annually (Agbenorku, 2013). In Iran, estimated prevalence of OFC was 1.4 per 1000 births (Zahedet al, 2017). In India, the overall prevalence of orofacial clefts was estimated at 1.3 per 1000 total births (Allagh et al, 2015). Prevalence estimation of orofacial clefts in Africa varies and estimates in Nigeria were 0.3 per 1000 live births, Malawi 0.7 per 1000 live

births, Sudan 0.9 per 1000 live births, Kenya 1.65 per 1000 live births and Gambia 5.0 per 1000 live births (Agbenorku, 2013). In Kenya, cleft lip and palate was the most common cleft defect, followed by isolated cleft lip and isolated cleft palate (Onyango et al., 2005). Most orofacial clefts were observed to be on the left and males the most likely to be born with orofacial clefts than females in Kenya (Onyango et al, 2005).

2.5 Economic costs of major external structural birth defects

Economic costs are estimated through cost analysis studies which is a partial method of economic evaluation for health care programs or services (Kirigia, 2009; Drummond et al, 2005). Cost-effectiveness, cost-utility and cost-benefit analyses are some the methods of full economic based on marginal analysis (Drummond et al, 2005; Mogyorosy et al, 2005). Cost analysis involves economic costs estimation of health-related resources used in providing health care services based on average unit cost assessments. Theories of welfare economics underpins cost analysis and is concerned with understanding the impacts of health interventions to the total welfare of the society for purposes making informed decisions on allocation of scarce resources (Mogyorosy et al, 2005). The following questions must be answered while undertaking a costing study: - (a) Which costs should be considered in a costing study? (b) How should costs be estimated? (c) Overall, how accurate does costing must be? (Drummond et al, 2005). The answers to these questions, the range of cost elements, context and extent to which economic evaluation of health care programs are based on provider, individual and societal perspectives of economic evaluation. These perspectives are informed by the objective of cost analysis and decision problem of the policy maker, referred to as costing study question (Smith et al, 2003; Kirigia, 2009; Hendriks et al, 2014; Drummond et al, 2005).

The main costing techniques for identification, measurement and valuation of resources are gross costing (top-down/ingredient approach) which uses historical resource outlay and micro-costing (bottom-up)which uses ingredient approach, in addition to step-down full costing, activity based costing, time and motion, surveys and manager interviews (Mogyorosy et al, 2005). Step-wise health economic guidelines for collecting and analysing economic costs data include the choice of study perspectives, unit of analysis, identification of cost items, measurement of cost items, valuing of cost items and dealing with uncertainties explained below (Kirigia, 2009; Hendriks et al, 2014; Drummond et al, 2005). Valuation of resources into monetary units are done through market prices and opportunity costs. However, use of market prices have been controversial because of market distortions (monopoly, oligopoly), while the use of opportunity costs has been controversial because of productivity loss estimation due to illness (Conteh et al, 2004; Mogyorosy et al, 2005). Similarly, sharing of overhead costs have been controversial, however, step-down cost accounting, the number of workers, floor space among others have been use as ways of sharing joint costs (Mogyorosy et al, 2005). Because on uncertainties arising from sample size determination and data collection among other factors, statistical and sensitivity analysis must be carried out to ascertain robustness of economic evaluation results, while, capital costs must be discounted for differential timing (Drummond et al, 2005).

The hospital charges for new-borns with some congenital anomalies would be four to eight times higher than those with uncomplicated births (Simeone et al, 2015). The extent to which families and persons are affected by these defects, is further increased by added medical costs, costs related to earnings lost and matters pertaining to quality of life (Preedy, 2010; Simeone et al, 2015). In the United States, human capital method was used to compute direct and indirect cost of illnesses for most clinically important structural congenital anomalies in 1992, where direct cost included

medical, developmental and special educational cost (CDC, 1995). Similarly, indirect cost included costs of lost work and hospital productivity attributable to premature deaths and illness (CDC, 1995). Birth defect-specific costs ranged between $ 75,000 and $ 503,000, with cerebral palsy costing $ 503,000, Down syndrome costing $ 451,000, spins bifida costing $ 294,000, in addition to the highest total lifetime cost 2.4 billion, $ 1.8 billion and $489 million respectively and the combined estimated cost of 18 birth structural birth defects was $ 8 billion (CDC, 1995). In Germany, a retrospective analysis of health insurance data was carried out to determine the economic burden of illnesses associated with neural tube defects where International Classification of Diseases, 10th Edition (ICD-10) codes was used to identify the cases (Bowles et al., 2014). Age group-specific stratified analysis of outpatient and inpatient care, remedies and aids, pharmacotherapy use, long-term care and information on sick leave, revealed substantial economic costs of spina bifida throughout life (Bowles et al., 2014).

Orofacial clefts are among the most common birth defects with significant clinical impact requiring medical-surgical and psychological treatments among other interventions throughout life (Stanier, 2004). Differences have been observed in costs among children with orofacial defects, e.g. the annual difference in annual mean incremental costs between children aged 0 through 10 years and those without cleft was estimated at $13,405 (Boulet et al, 2009). The mean and median costs for children under 10 years of age were eight times higher than those of the same age without an orofacial cleft (Boulet et al, 2009). The mean costs for infants with a cleft and another major, unrelated defect were 25 times higher than those for an infant without a cleft, and five times higher than for infants with an isolated cleft (Boulet et al, 2009). Surgical repairs increase likelihood of children's survival to adulthood, however, lifelong medical management and enormous financial burden are still associated with comorbidities and disabilities (Bowles et al., 2014; Waitzman et

al, 2013; Waitzman et al, 1994). Significant direct and indirect costs are observed among children born with neural tube defects during first year of life, higher healthcare expenditures during childhood, adolescents and adulthood than those without NTDs, for example, inpatient expenditure for spina bifida was estimated at €1358 accounting for 30.0% of the total direct costs in Germany (Bowles et al., 2014). In addition, individuals and their caregivers experience negative impact on labor participation (Bowles et al., 2014). Financial implications associated with spina bifida remain substantial and economic burden is continuous throughout one's life, with, high monetary impact and health care expenditures being experienced during early years of life (Bowles et al., 2014). Worldwide, estimated average lifetime direct medical costs of spina bifida per person ranged from $ 285,959 to 378,000 in 2010 (Rofail et al, 2013). In the United States, children aged between 1-17 years with spina bifida were estimated to spend 13 times greater on medical expenditures than children without spina bifida (Ouyang et al, 2007). In Germany, the average annual health expenditure of persons with spina bifida was estimated at € 4532 (Bowles et al., 2014).

2.6 Disability-adjusted life years associated with major external structural birth defects

Disability-adjusted life years is a metric measure of disease burden in morbidity and mortality, where, 1 DALY equivalent to 1 healthy year (Sarigiannis et al., 2017; Wu et al, 2013; Sitkin et al, 2015; Preedy et al, 2010). Human productivity loses arising from YLD and YLL due to premature mortality because of preventable structural birth defects slows down national economic growth and development. Birth defects contribute significantly to the global disease burden among children accounting for 25 million disability-adjusted life years (Wu et al, 2013). Worldwide, DALYs attributed to birth defects accounted for a staggering 25.3 to 38.8 million, however, major birth defects may account for up to 120 DALYs per 1000 children and 361 DALYs per 1000 population (Sitkin et al, 2015; Penchaszadeh, 2002). Birth defects were reported as the world's

17th cause of burden of disease (GBD), however, heart defects represented the highest overall disease burden (Sitkin et al, 2015). NTDs and CL/CP accounted for 21 million DALYs, of which 575 DALYs (12 million) were estimated as surgically preventable if conditions of healthcare were to improve in the developing countries (Sitkin et al, 2015). In U.S.A, congenital abnormalities are the 5th leading cause of years of life lost to premature deaths (CDC, 1995). Worldwide, an estimated 9% of birth defects accounted for surgical disease burden leading to disability among 150 million children including Sub-Saharan Africa countries (Wu et al., 2013). In Gambia, birth defects was the 2nd highest proportion of surgical burden of disease attributed to birth defects followed by injuries among children presenting for surgical care (Wu et al, 2013). An estimated 40% of surgical procedures performed at a northern Nigerian leading hospital was related to birth defects and closer to 1 in 4 children in major hospital in Sub-Saharan Africa had birth defects resulting in morbidity and mortality (Wu et al, 2013). Spina bifida had the greatest burden of disease in Kenya, with a birth defect prevalence estimated at 6.3 per 1000 children accounting for 54-120 DALYs per 1000 children (Wu et al, 2013).

Globally, WHO attributed 276,000 neonatal deaths to birth defects in 2015 and 303,000 in 2016 (Zahed et al, 2017). In 2004, WHO estimated that about 260,000 deaths worldwide (7% of all neonatal mortality) were due to congenital anomalies. In 2006, 1:33 (3%) births had a birth defect translating into 7.9 million births with birth defects, globally (Feldkamp et al., 2017; Hernandez-Diaz & Oberg, 2015). It was also estimated that in 3 deaths of infants, one (33%) infant die as result of some type of birth defect globally (Anyanwu et al., 2015). Congenital abnormalities remain the leading cause of infant deaths in USA, accounting for 20% (1:5) in 2013 translating to 4778 infant deaths (Feldkamp et al., 2017; Lamichhane et al., 2016), and 20% (5,500) in the United States and Rhode Island in 2005 (Brown-Viner, 2012; Parker et al., 2010). In Europe, birth defects

accounted for 2.55% of infant mortality, 2.8% in Korea, however, in the South-East Asia regions the burden remains unknown due to lack of national level surveillance system (Lamichhane et al., 2016). Worldwide, at least 90% of child births and 98% of neonatal deaths were estimated to occur in Africa (WHO., 2010). Additionally, an estimated 94% of all birth defects and 95% of deaths due to birth defects occurred in developing countries, many of which were preventable (Kishimba et al., 2015). An estimated, half of children (4.7 million) born in Africa died before their fifth birth day due to birth defects accounting for 7% of under-five deaths (WHO., 2010; Anyanwu et al, 2015). Kenya is currently recording neonatal mortality rate of 22 per 1000 live births, infant mortality rate of 39 per 1000 live births and under-five mortality rate of 52 per 1000 live births (KDHS, 2014). Apart from direct physical impacts, children with structural birth defects require costly medical care, which is limited in many developing countries (Conway et al, 2015).

2.7 Study justification and contribution to knowledge

Prevalence estimates of specific major external structural birth defects throughout childhood are grossly underestimated, and to the best of our knowledge, this is due to paucity of data in Kenya. However, Githuku et al., (2014) and Muga et al, (2009) in their studies estimated the prevalence spina-bifida and congenital abnormalities in AIC-Kijabe and Kenyatta hospitals in Kenya. This underscores the "silent" nature of this epidemic and underestimates its public health magnitude. To address this gap, we will estimate birth-defect specific prevalence to provide a snap shot of the extent of these defects in Kiambu county. This will demonstrate the additional health needs of these communities and provide insight to policy makers on the need for effective preventive and treatment strategies. These results may also be used by healthcare managers to assess effectiveness of health care interventions and inform allocation and distribution of resources for scaling-up effective healthcare services needed by women of reproductive age and children with these defects.

Many risk factors have been widely investigated, however, to the best of our knowledge, factors such as pre-gravid and post-gravid exposure to indoor smoke and pesticide, types of food, before and after conception iron-folic acid supplementation, trimester prenatal care began, and number of antenatal visits, have not been well investigated Kenya. Exposure assessments during the first trimester of gestation is of great importance, however, accurate ascertainment of early pregnancy exposures to modifiable risk factors is essentially a challenge of birth defects studies because of the difficulties in identifying women just before or in the first few weeks of gestation (Tinker et al, 2015). Increasing occurrence of these defects suggest prevalence of exposures few weeks to conception and few weeks after conception. Therefore, to address this gap, we will attempt to analyse the relationship between these two factors to these defects with a view of demonstrating possible preconception and early pregnancy maternal exposures to environmental teratogens. These results may suggest evidence and inform policy makers of the constant prevalence of risk factors among women of reproductive age in Kenya and suggest a new model for pre-conceptional and antennal care in Kenya. Additionally, the knowledge of the risk factors may be tailored to formulate specific interventions and inform risk-based surveillance of specific structural birth defects among women of reproductive age. Similarly, these results may help in assessing efficiency of preventive and control measures for these defects and provide insights to public health planners on the importance of implementing effective public health preventive and control strategies among women of reproductive age before and after conception countrywide.

Analyzing health sector to help understand economic costs, marginal effects, elasticity of health care spending and production costs of health services are aided by economic tools (Sengupta, 2016). However, to best of our knowledge economic tools are rarely used to understand health care market in Kenya. Cost analysis studies are not common in developing countries due to

inadequate costing capacity, expertise and costs data (Hendriks et al, 2014), and to the best of our knowledge, we are not aware of any study that estimated unit economic costs of these defects in Kenya. To address this gap, we will conduct a cost analysis of these defects from health care providers' perspective to estimate unit economic costs to highlight economic burden of birth defects with a view to guide policy and solicit government funding for their control. Additionally, non-monetary costs arising from these defects is not well documented in Kenya, however, to the best of our knowledge, few studies have estimated associated disability-adjusted life years. To bridge this gap, we will also estimate DALYs to inform policy of the unmet rehabilitative health needs of children living with disabilities related to structural birth defects. Similarly, we will endeavor to estimate proportionate changes in the quantities of health care given in relation to changes in demand for health care determinants to improve policy makers' understanding of health care market for birth defects. Similarly, to the best of our understanding, factors contributing to increased economic costs of structural defects have not been estimated in Kenya and we will attempt to estimate costs associated marginal effects.

Lastly, combined efforts by medical scientists, public health specialists and economists to understand the true burden of structural birth defects have not been demonstrated, largely in resource constraint countries. However, informed decisions on progressive healthcare investments undoubtably require evidence of public health and economic magnitude of these defects and their effects on social welfare. On this breath, we endeavour to simultaneously estimate the prevalence, assess risk factors and estimate the economic costs of these defects respectively in this study for this purpose.

2.8 Study objectives and research questions

Overall, this study seeks to determine epidemiology and economic burden of structural birth defects in Kiambu County, based on the following objectives and research questions: -

1. To estimate the prevalence of structural birth defects among children in Kiambu county. The corresponding questions will be: -
    a. How frequent are structural birth defects among children in Kiambu county?
    b. What are the marginal effects of sociodemographic factors on the frequency of structural birth defects among children in Kiambu county?
2. To identify risk factors associated with the occurrence of major external structural birth defects in Kiambu county. The corresponding questions will be: -
    a. Is there a significant association between age, level of education and/or infant sex with the occurrence of structural birth defects among children in Kiambu county?
    b. Is there a significant association between trimester prenatal care began and occurrence of major external structural birth defects among children in Kiambu county?
    c. Is there a significant correlation between structural birth defects and pesticide sprayed sources of food in Kiambu County?
    d. Is there a significant relationship between indoor smoke and structural birth defects in Kiambu County?
    e. Are planned preconception and post conception iron-folic acid supplementation by women of reproductive age significantly related to structural birth defects in Kiambu County?
3. To empirically determine the “shadow prices” of corrective health service for SBDs using Grossman’s theoretical model for demand of health and healthcare in Kiambu county
    a. What are the economic costs of SBDs among children in Kiambu county?

b. What are the marginal effects of sociodemographic factors on the economic costs of major external structural birth defects in Kiambu county?
c. What is the elasticity of health care spending for corrective health care costs of major external structural birth defects in Kiambu county?

2.9 Theoretical framework

Birth defect is a good measure of intrauterine, at birth and after birth child's health status because it represents adverse gestation outcomes, ill-health in later life cycles, and an indicator of socio-economic wellbeing of individuals, nation and worldwide, just like birthweight (Mwabu, 2009). Similarly, occurrence of SBDs indicates access, coverage and utilization of pre-gravid and early post-conception health services and prevalence of their risk factors among populations. Some of these SBDs are mediated by life-styles e.g. cigarette smoking, health system performance, e.g. antenatal care and folic acid-supplementation. SBDs-affected livebirths result into economic burden due to childhood morbidity, childhood mortality, life-long disability and reduced life expectancy, referred to as returns on health investment (ROI) (Wale, 2008). This theoretical foundation is underpinned on epidemiology social production of disease (Krieger, 2001), demand for health (Grossman, 1972) and demand for health capital models (Wagstaff, 1986).

Social production of disease model seeks explanations on causes of poor health arising from lifestyle behaviours and health system performance e.g. alcohol consumption particularly during the first eight weeks of gestation and utilization of antenatal care services respectively (Krieger, 2001). Grossman demand model on the other hand, elucidates correlation between health outcomes and socioeconomic predictors of individuals' health and demand for healthcare (Grossman, 1999; Grossman, 1972). Wagstaff, (1986), model of human capital demand also supports this philosophical standing and postulates health as a capital investment that depreciates or appreciates

over time, due to maternal aging, maternal education, price of medical care and wage rates. Our predictor variables, hypothesized to cause SBDs, affect health and health care demand will include maternal education, age, sub-county, occupation, parity, gestation age, nature of gestation (single/multiple), alcohol consumption, trimester prenatal care began, antenatal care visits, sex of child, indoor smoke, diet, birth order, marital status and pesticides. Mwabu, (2009) observes that variation in maternal behaviours determines child health, therefore, considering prevalence, risk factors and economic costs of SBDs as outcome variables of interest, analysis will be carried out using multiple linear regression models controlling for confounders and taking note of interacting variables. Additionally, Grossman (1972), estimated gross health-investment production function with medical care, education, gender and income per household using a two-stage least squares (2SLS), and wage rate, education, gender and family using reduced-form demand function for health by ordinary least squares (OLS) (Wale, 2008). Adopting this approach, these variables will also be examined econometrically as a function of investment (I) and consumption (Z) of market (income, education) and non-market (antenatal care, medical care, diet) goods. Therefore, from the above premise, SBDs production function will be derived from the following basic model: -

$$\mathbf{H=f\ (HC,\ Other\ Inputs;\ I_0)} \qquad \mathbf{(1)}$$

Where, H, HC and I_0 represent health-related outcome, healthcare and I_0 initial conditions respectively.

2.10 Conceptual framework

Founded on the above theoretical framework derived from epidemiology and economic theoretical underpinnings, our conceptual framework is based on empirical literature, illustrates hypothesized correlation of predictor variables, such as sex of child, maternal age, maternal level of education, trimester antenatal care began, indoor smoke, pesticides exposure, alcohol use, occupation, parity,

diet gestational age, residence, marital status, table salt and birth order of the child with specific structural birth defects expressed as health production function in the study analysis model. Intrauterine foetal structural birth defects development is a health production function hypothesised to directly or indirectly (proximate determinants) depend on the predictor variables and sometimes mediated or operating through predictors as shown in figure 1 below. Pre-gravid and/or post-gravid exposure to risk factors for structural birth defects, either as an individual consumption or investment produces birth defects of which some are structural in nature requiring substantial medical resources in their management.

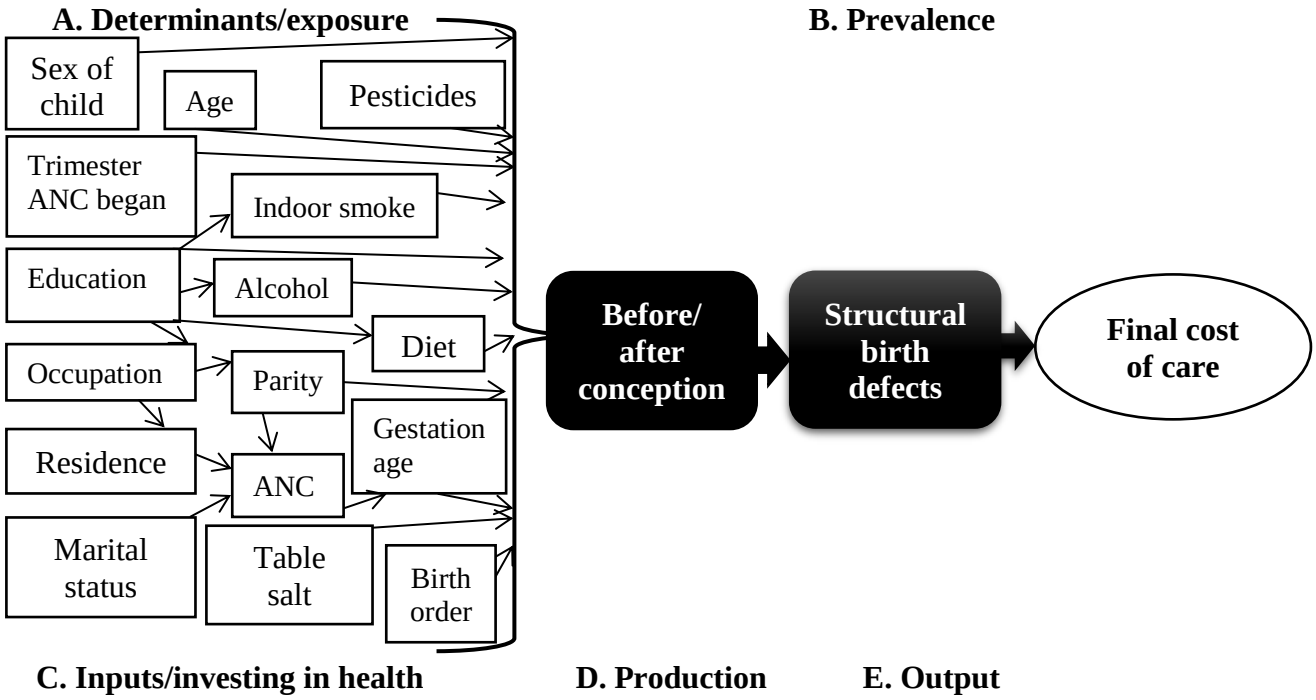

Figure 1: Conceptual framework

2.11 Study variables

Consideration the theoretical assertions and conceptual illustrations above, dependent variables of interest in this study will be specific structural birth defects, prevalence of specific structural birth defects, prevalence of specific risk factor for birth defects and economic costs of specific defect of structural birth defects, hypothesized to be influenced by maternal education, age, sub-county

(residence), occupation, parity, gestation age, nature of gestation (single/multiple), alcohol consumption, trimester prenatal care began, antenatal care visits, sex of child, indoor smoke, diet, birth order, marital status and pesticides.

2.11.1 Measurement and definition of response variables

Table 1 below illustrates definitions and measurement of response variables of interest.

Table 1: Response variables and their measurements

Variable types	Measurement of variable	Definitions and literature source	Statistical significance
Structural birth defect (nominal) *ssbd*	This will be specific structural birth defects considered outcomes of gestation	This will be specific major external structural birth defects captured and defined as nominal variable. Types of birth defects vary from place to place (Sahib, 2016).	This is statistically significant at 5% significance level
Economic costs (continuous) *eccost*	This will be a proxy for economic burden of structural birth defects	Will be the unit costs and DALYs captured as continuous variable and defined as discrete variable. Health care expenditure is highest among children (Bowles et al., 2014)	Statistically significant at 5% significance level
Prevalence of structural birth defects (continuous) *Prevsbd*	This will be a proxy for the public health burden of the defects	Will be the proportion of specific birth defects captured and defined as discrete variable. High prevalence of risk factors for birth defects increases their incidence accounting for regional and period variation in prevalence and patterns (Sahib, 2016).	Statistically significance at 5% level of significance
Prevalence of specific risk factors (continuous) *prevrf*	This will a proxy for the presence of teratogens 4- and 8-weeks after pregnancy	This will be captured as nominal variable and defined as continuous variable. Maternal age, education level, number of prenatal visits and parity are not significantly associated with knowledge of risk factors for birth defects (Bello et al., 2013).	Predictors statistically significant at 5% significance level

Source: Generated by the author

2.11.2 Measurement and definition of predictor variables

Table 2 below illustrates definitions and measurement of predictor variables of interest.

Table 2: Predictor variables and their measurements

Variables types	Variable measurement	Definitions and literature source	Statistical significance
Education (ordinal) *medu*	Education will be a proxy for maternal ability to understand health matters, i.e. birth defect risk factors and importance of timely first antenatal visit.	This will be the mother's level of education captured in completed years and defined as ordinal categorical variable from 0 to 3, where 0=no (0 years) education, 1=primary (8 years) education, 2=secondary (4 years) education and 3=tertiary (post-secondary) education recognised in Kenya. Reference category will be tertiary level of education. Women with appropriate education level for their ages and received antenatal care are likely to have better pregnancy outcomes than those who don't (Fraser et al, 1995). Tertiary maternal education level will be expected to positively influence reduction of birth defect because increased knowledge on risk factors and timely utilization of antenatal care (Ochako et al., 2011).	Secondary level of maternal education is statistically significant at 5% significance level
Age (continuous) *mag*	Age will be a proxy for maternal physiological maturity aiding intrauterine foetal development.	This will be the mother's years of life, captured in completed years and defined as ordinal categorical variable grouped from 15-49 years recognised as reproductive age for women. Reference category will be above 24 years of age when many women have completed tertiary education. Maternal age at birth of the last child is likely to increase use of fist antenatal care in first trimester (Ochako et al., 2011). Structurally malformed infants increase significantly and progressively in women aged at least 25 years (Hollier, 2000). Increased maternal age is expected to positively influence	Maternal age is statistically significant at 5% significance level

		incidence of birth defects (Lamichhane et al., 2016).	
Occupation (nominal) *occ*	Occupation will be a proxy for wage rate, household wealth index and socio-economic status.	Occupation will be defined as maternal and/or paternal full-time income generating activity. It will be captured as nominal categorical variable and defined as ordinal categorical variable grouped from 0 to 4, where 0=no occupation, 1=labourer, 2=semi-skilled, 3=skilled and 4=professional. Reference category will be professional occupation. Low socioeconomic status positively influences congenital birth anomalies (Tanriverdi et al., 2015). Affluent individuals spend more on health care, with a positive elasticity per-capita (Bustamante & Shimoga, 2018).	Elasticity per-capita is significant statistically among middle income countries at 5% level of significance
Gestation age (continuous) *gesage*	This will be a proxy for foetal maturity at birth	Gestation age will be completed weeks of intrauterine foetal life at birth. It will be captured as continuous variable and defined as ordinal categorical variable grouped in weeks of gestation as less than 24 weeks (abortion), 24-36 weeks (preterm gestation), 37-41 weeks (term gestation) and above 42 (postdate gestation). Reference category will be 37-41 weeks gestation. Congenital anomalies are more likely to occur in preterm than term births. Congenital anomalies were more than twice common among preterm than term births (Honein et al., 2009)	Preterm birth is statistically significant at 5% significance level
Alcohol consumption (nominal) *alc*	Alcohol consumption is a proxy for exposure to teratogenic agent	This will be maternal use of alcohol 4-before and/or 8-weeks after pregnancy. It will be captured as nominal variable and defined as one when used alcohol and zero otherwise. One will be the reference category. Maternal alcohol use during pregnancy is expected to positively	Alcohol is statistically significant at 5% significance level

		influence incidence of birth defects (Lamichhane et al., 2016).	
Antenatal care visits (discrete) *anc*	Will be a proxy for timely access and use of health services, i.e. iron-folic acid supplementation and health education	This will be number of antenatal care visits made by a pregnant woman. It will be captured as discrete variable and defined in this study as ordinal categorical variable grouped from 0 to 4, where, 0= no prenatal care visit, 1=one prenatal care visit, 2=two prenatal care visits, 3=three prenatal care visits and 4=four prenatal care visits. Reference category will be four prenatal care visits. First antenatal clinic visit in first trimester is likely to increase with maternal age at birth of the last child (Ochako et al., 2011).	First antenatal visit in first trimester is 5% level of significance
Nature of gestation (binomial) *nages*	Will be a proxy for single and or multiple pregnancy	This will be number of births at a single child birth captured as binomial variable and defined as one when single and zero otherwise. Single will be the reference category. Single pregnancy will be the reference category. Multiple pregnancy correlates to opposite sex with structural birth defects (Cui et al., 2005).	Twin pregnancy is statistically significant at 5% level of significance
Parity (discrete) *par*	Parity will be a proxy for the number of pregnancies for a woman of reproductive age	This will be null-parity or multiparity captured as discrete variable and defined as ordinal categorical variable. Null-parity will be the reference category. Certain birth defects are expected to occur in multiparous pregnancies. Parity is not significantly associated with specific and overall knowledge of women of risk factors for birth defects (Bello et al., 2013).	Parity is statistically significant at 5% level of significance
Trimester prenatal care began (continuous)	This will be a proxy for the date of first antenatal	This will be weeks of gestation at time of first antenatal clinic visit. It will be captured as discrete variable and defined in this study as continuous variable in weeks or months.	First antenatal visit in first trimester is

tpcbeg	clinic visits, use of iron-folic acid supplementation and health education.	The reference category will be 14 weeks of gestation. Women who used iron and folic acid in early pregnancies will be expected to have lesser risk for structural birth defects than who started late in pregnancy. Maternal age at birth of the last child is likely to increase use of fist antenatal care in first trimester (Ochako et al., 2011).	statistically significant at 5% significance level
Sex of the child (binomial) *sc*	Sex of the child will be a proxy for child's biological characteristics	It will be the biological description of the child, captured as binary variable and defined as one when male and zero otherwise. Male will the reference category. Sex variations in congenital anomalies exist between opposite-sex in twin births (Cui et al., 2005).	Sex of child is statistically significant at 5% level of significance
Iron-folic acid supplementation (nominal) *ifas*	This will be a proxy for mineral and multivitamin use at least 4-before and/or 8-weeks after pregnancy	This will use of iron and folic acid 4- weeks before and/or 8-weeks after pregnancy. Will be captured as binominal variable and defined in this study as one when IFAS and zero otherwise. One will be the reference category. Iron-folic supplementation reduces incidences of neural tube defects (Feldkamp et al., 2017).	IFAS is statistically significance at 5% significance level
Marital status (nominal) *ms*	A proxy for socio-economic support for women of reproductive age	This is the state of the mother living with a man as a husband. It will be captured as nominal variable and defined in this study as one when married and zero otherwise. Married status will be the reference category. Low socioeconomic status is expected to increase the risk for birth defects (Tanriverdi et al., 2015).	Low socioeconomic status is statistically significant at 5% significance level
Indoor-smoke (nominal) *idsm*	This will be a proxy for cigarette smoking and	This will be an exposure to air pollutants arising from indoor smoke 4 weeks before and 8 weeks after pregnancy due to use of charcoal and kerosene as domestic cooking fuel. It will be captured as nominal variable	Maternal passive-smoke is statistically significant

	ambient air pollution.	and defined as one when charcoal and zero otherwise, or one when kerosene and zero otherwise. One will be the reference category. Maternal passive-smoke during pregnancy is likely to positively increase occurrence some structural birth defects (Kummet et al., 2016; Leem et al., 2006).	for orofacial clefts formation at 5% level of significance
Cigarette smoking	This will a proxy for exposure to teratogenic agents	This will be active smoking by the mother when pregnant captured as nominal variable and defined as non-smoker, partial smoker and active smoker. Maternal smoking during pregnancy is likely to positively increase occurrence some structural birth defects (Kummet et al., 2016). Maternal smoking is positively associated with musculoskeletal defects, limb defects and clubfoot (Hackshaw et al., 2011).	Maternal active smoking is statistically significant at 5% significance level
Pesticides (nominal) *pest*	Pesticide will be a proxy for exposure to teratogens at least 4- weeks before and/or 8-weeks after conception	This will be maternal and/or paternal participation in spraying farms with pesticides 4 weeks before and 8 weeks becoming pregnant. It will be captured as binomial variable and defined as one when participated in farm spraying pesticides and zero otherwise. One will be the reference category. The prevalence of birth defects indicates exposure to teratogens such as pesticides and pharmaceutical agents (Lamichhane et al., 2016).	Pesticides exposure during pregnancy is statistically significant at 5% significance level
Birth order of child (ordinal) *bord*	This will be a proxy for physiological predisposition to formation of birth defects.	Birth order will be the position each child assumes among the siblings, captured as ordered categorical variable and defined in this study as one if first born and zero otherwise. One will be the reference category. First birth order will be the reference category. Higher birth order increases likelihood of maternal utilization	Last birth order is statistically significant at 5% significance level

		of fist antenatal services in the first trimester (Ochako et al., 2011).	
Diet (nominal) *dt*	This will be a proxy for adequate consumption of minerals and multivitamins	This will be the of source of minerals and vitamins from food. It will be captured as nominal variable in terms variety of foods eaten. Food rich in multivitamins during early pregnancy are expected to reduce occurrence of birth defects (Czeizel, 2004).	Maternal vitamin use during pregnancy is statistically significant at 5% significance level
Residence (nominal) *resd*	This will be a proxy for regional (subcounty) prevalence and risk factors variations	This will be the place of residence of the mother during pregnancy and birth of the child. It will be captured as nominal and defined as the county of residence during pregnancy and child birth. Prevalence of structural birth defects is likely to vary from region to region (Allagh et al., 2015). Birth defects are reported to be influenced by maternal residence during pregnancy (Lamichhane et al., 2016).	Regional prevalence variation is statistically significant at 5% significance level
Table salt *tbs*	Is a proxy for source of iodine	Will be captured as nominal variable and defined as one when used and zero otherwise. One will be the reference category. Inadequate iodine increases risks for some birth defects (WHO., 2010).	

Source: Generated by the author

2.11.3 Assessment of confounders

Confounding effects are likely to obscure the study results since predictors may be potentiated, mediated or operating through other factors. Therefore, based on the biological knowledge of the PI, residence, maternal age and parity will be considered as potential confounders in the regression analysis and assessed in the null, reduced and full models, where, a change of at least 30% of the regression coefficients will demonstrate the factor is indeed a confounder.

2.11.4 Assessment of interaction/effect modifiers

Similarly, interactions/effect modifiers will be assessed by adding the cross-product term ($X_1 \times X_2$) and examining its significance ($p<0.005$).

2.11.5 Specification of the study model

Birth defect as a good measure of foetal initial stock of health in utero, is a function of preconception and post conception environmental teratogenic exposures, socioeconomic and demographic factors, otherwise referred to as the determinants of birth defects arising from health consumption and investment. The defects resulting from this production function require substantial resources depending on their severity, in this respect, the model specified here is structurally stated as a multiple regression model where SBDs, unit costs, DALYs, YLL, YLD, risk factors and "shadow prices"/elasticities of health care spending on corrective health care services for structural births will be hypothesised to depend on the predictor variables above. The multiple regression structure will be generally stated as:

$$\mathbf{Y=\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots\ldots + \beta_K X_K + \varepsilon.} \qquad \mathbf{(2)}$$

Where, Y, is the outcome/dependent variable, X's, are the independent variables, β's, are the partial slope coefficients of the parameters, and, ε, is the stochastic error term. From population regression function (PRF) expressed in equation (2), a sample regression function (SRF) will be expressed as: -

$$\mathbf{y=\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots\ldots + \beta_K X_K + \varepsilon.} \qquad \mathbf{(3)}$$

The regression function, $\mathbf{\beta_0 + \beta_1 X_1 + \beta_2 X_2}$ gives the explained variation in the outcome variables, whereas stochastic/random error term **ε.** gives the unexplained variation in the outcome variables resulting from natural/biological variation among observational units, measurement error in

response variable and other extraneous factors influencing the response e.g. unknown confounders. Therefore, the following regression model will be specified as: -

$$\mathbf{y=\beta_0 + \beta_1 medu + \beta_2 mag + \beta_3 occ + \beta_4 gesage + \beta_5 alc + \beta_6 anc + \beta_7 nages + \beta_8 par + \beta_9 tpcbeg + \beta_{10} sc + \beta_{11} ifas + \beta_{12} ms + \beta_{13} idms + \beta_{14} pest + \beta_{15} bord + \beta_{16} tbs + \beta_{17} resd} \quad \mathbf{(4)}$$

Where y will be the outcome variable of interest, i.e. specific structural birth defects ***(ssbd),*** prevalence of specific structural birth defects ***(prevsbd)***, prevalence of specific risk factor for birth defects **(*prevrf)*** and economic costs of specific defect of structural birth defects ***(eccost)*** *as* outcome variables. These variables will be considered in binomial regression, multiple linear regression, 2SLS and OLS regression analyses. On the other hand, predictor variables will include: - ***medu*** representing maternal education level, ***mag*** representing maternal age, ***occ*** representing maternal and/or paternal occupation, ***gesage*** representing gestational age, ***alc*** representing alcohol use, ***anc*** representing antenatal care visits, ***nages*** representing nature of gestation, ***par*** representing parity, ***tpcbeg*** representing time prenatal care began, ***sc*** representing sex of child, ***ifas*** representing iron-folic acid supplementation, ***ms*** representing marital status, ***idms*** representing indoor-smoke, ***pest*** representing pesticides, ***bord*** representing birth order, ***tbs*** representing table salt and ***resd*** representing residence. The data will be analyzed using binomial regression and linear regression models in addition to 2SLS and OLS models.

2.11.6 Analysis assumptions

The assumptions for this study will include: - linearity (linear relationship between the variables), independent paired observations, homoscedasticity (variance of the subpopulations is equal), the independent variable(s) is measured without error (fixed and discrete) and normality (the error term is normally distributed with $\mu=0$ and a variance, σ).

CHAPTER THREE: METHODOLOGY

3.1 Study design

Descriptive cross-sectional and case-control study designs will be adopted in this study to determine epidemiology and economic burden of structural birth defects in Kiambu county from 1st January 2014 to 31st December 2018. First and foremost, a descriptive cross-sectional design at 14 hospitals will be used to estimate prevalence of structural birth defects in Kiambu county and at 2 specialized hospitals to estimate economic costs of structural birth defects in Kiambu county, followed by a hospital-based case-control design at 2 specialized hospitals to identify the determinants of these defects in Kiambu county. The rationale for choosing descriptive cross-sectional study design is because it is the best optimal choice for estimating population attributes, such as prevalence and economic costs for purposes of making point estimate statistical inferences, i.e. hypothesis testing and confidence interval estimations. On the other hand, the rationale for the choice of hospital-based case-control study design is because, birth defects are rare, latent and having several risk factors, therefore is the is the most efficient methodology option for identifying associated exposures. Additionally, hospital-based study has been preferred because of easy access to cases and controls, thus increasing reliability and validity of the study results for countywide and countrywide generalization. Lastly, case-control design has been chosen because of difficulties in identifying women just before pregnancy and/or first few weeks of gestation, thus collecting exposure data retrospectively by asking them about preconception and conception exposures during hospital visits will improve generalizability of the results.

3.2 Study sites

This study will be carried out in 14 level-4 and above hospitals in Kiambu county, which was a district in the former central province. There will be 12 public and 2 faith-based hospitals, where

11 level-4 hospitals will be Lari in Lari sub-county, Kiambu in Kiambu sub-county, Nyathuna in Kabete sub-county, Tigoni in Limuru sub-county, Lussigetti in Kikuyu sub-county, Wangige in Kabete sub-county, Gatundu in Gatundu South sub-county, Ruiru in Ruiru sub-county, Karuri in Kiambaa sub-county, Igegania in Gatundu North sub-county and Kihara in Kiambaa sub-county. Kiambu county consists of 12 sub-counties/ constituencies, i.e. Githunguri, Kiambaa, Kabete, Limuru, Lari, Gatundu north, Gatundu south, Ruiru, Kikuyu, Juja, Thika and Kiambu, each with at least a level-4 and above hospital apart from Githunguri and Juja. Its health department is organised into six tiers, i.e. community health services (tier 1), seventy dispensaries (tier 2), twenty-four health centres (tier 3), twelve level-4 county hospitals (tier 4), Thika level-5 county referral hospital, in addition to faith-based and private health facilities of different tiers. Level 4 hospitals coordinate within county referrals because of their capacity provide comprehensive medical and surgical services. Home, dispensaries and health centres births with defects are likely to be referred to level-4, 5 and 6 hospitals, either directly, or through level-4,5 and 6 hospitals. These hospitals offer clinical care and are the first referral hospitals forming integral part of the county's health system. The services provided in these facilities include curative, preventive, promotive and rehabilitative health services. Each of these hospitals has a capacity of at least 100 beds, in addition to new-born units (NBU) and maternity (LWD) units recording averagely20 births daily of which 1-2 have some form of birth defects. Thika level-5 county referral hospital will be included because of its tertiary hospital status, in addition 2 faith-based specialized referral hospitals for structural birth defects, i.e. AIC CURE Internationallevel-4 and AIC Kijabe level-6. All these facilities are approximately 10 to 60 kilometres from Nairobi capital city. AIC Kijabe hospital has affiliate satellite clinics across the country where, children are followed-up by nurses and physiotherapists following surgery and adjacent to it is AIC CURE International hospital,

approximately 60 kilometres northwest of the capital city of Nairobi. Apart from the specialised faith-based hospitals, health workers in these other hospitals have no additional specialised training on structural birth defects besides skills and knowledge acquired during trainings at different levels. Nevertheless, this study will be conducted at level 4,5 and 6 hospitals in the county because of their infrastructural and human capacity to accurately define and provide at least some medical and surgical treatment to newborns with these defects. The county is more than 60 percent urbanised, with its capital in Kiambu town and is considered one of the wealthiest counties, with a population of 1,623,282. It is a leading innovative commercial hub in Kenya and borders Nairobi county to the south, Muranga and Nyandarua counties to the north, Nakuru and Kajiado counties to the west.

3.3 Study population

This study targets all children born in Kiambu county during the study period from 1st January 2014 to 31st December 2018. Source population randomly derived from the study population during the study period will be children with structural birth defects born to resident women of Kiambu. This will be helpful in achieving internal and external validity of the study results for purposes of generalization to entire county's population. The results will act as a pointer to the "silent epidemic", economic burden and prevalence of the risk factors and inform policy on prevention and treatment strategies aimed at reducing economic burden of these defects in the entire country.

3.4 Eligibility criteria, case definition and case ascertainment

Cases eligible for this study will be defined as live-births (singleton/multiple) of at least 28 weeks gestation, with at least a clinically obvious external SBDs of any body organ and/or system, and/or ascertained by a medical specialist(s) born to a resident mother of Kiambu county during the study

period (1st January 2014 – 31st December 2018), born at home and/or any of the participating hospitals and/or received/receiving care at the hospitals participating in the study. The systems/organs defects will include central nervous system (neural tube defects), musculoskeletal system (reduction deformities, gastroschisis, omphalocele), orofacial defects (cleft lip with palate, cleft lip without palate), genitourinary defects (hypospadias, epispadias), eye defects (anophthalmia, microphthalmia) and ear defects (anotia and microtia).These defects will be included in this study because they are easy to recognize visually or through physical examination by any trained healthcare provider at birth or shortly after birth and case ascertainment is less likely to be affected by regional differences in referral and medical treatment compared to other anomalies. Additionally, they have been considered for this study because they have significant impact on individuals' physical health and health care services. Any child born with minor birth defects born to a Kiambu county resident and/or non-resident woman, and/or any child born with other forms of birth defects in/out of Kiambu county and/or any child whose parent will have not signed informed consent or completed the structured interviewer-administered questionnaire will be excluded from this study.

3.5 Controls definition and ascertainment

Controls will be defined as children with no birth defect(s) born to a resident mother of Kiambu county and receiving child health services at the 2 specialized referral hospitals during the study period from 1st January 2014 to 31st December 2018. Cases will be matched to controls by age in the ratio of 1: 2 during data collection and analysis. Any child born to a non-resident mother will be excluded from this study, in addition to those, whose parents will have not signed informed consent or completed the structured interviewer-administered questionnaire. The specialized

referral hospitals have been considered for recruitment of cases and controls because of providing various child health services, in addition to corrective surgeries for structural birth defects.

3.6 Sample size determination and sampling techniques

3.6.1 Sample size determination for prevalence study

A descriptive cross-sectional design at 14 hospitals will be used to estimate prevalence of structural birth defects in Kiambu county. The following statistical formula will be used to determine the sample size at 14-hospitals and 2-specialized hospitals: -

$$\boldsymbol{n = Z_{\alpha}^{2} pq / L^{2}}$$

Where, n, will be the desired sample size, $\boldsymbol{Z_{\alpha}}$, will be the value of Z_{α} required for confidence $1-\alpha$: Z $\alpha/2=196$, p will be a priori estimate of the proportion assumed at 50%, q=1- p and L will be the precision of the estimate (also called "allowable error" or "margin of error") equals half the desired length confidence interval, i.e. 5%.Therefore, from the equation above, our sample size for the descriptive cross-sectional study will be computed as follows: -

$$n = \frac{1.96^{2} \times 0.5 \times 0.5}{0.05^{2}}$$

$$n = \frac{3.8416 \times 0.25}{0.0025}$$

$$\boldsymbol{n = 384}$$

3.6.2 Sampling techniques for prevalence study

The figure 1 illustrates referral channels for children born alive with external structural birth defects in Kiambu county and demonstrates how numerator data will be collected for purposes of computing prevalence estimates. Additionally, for clarity, the figure includes costing and case-control sampling strategies because we will stepwise collect data beginning with lower-level facilities to higher-facility levels.

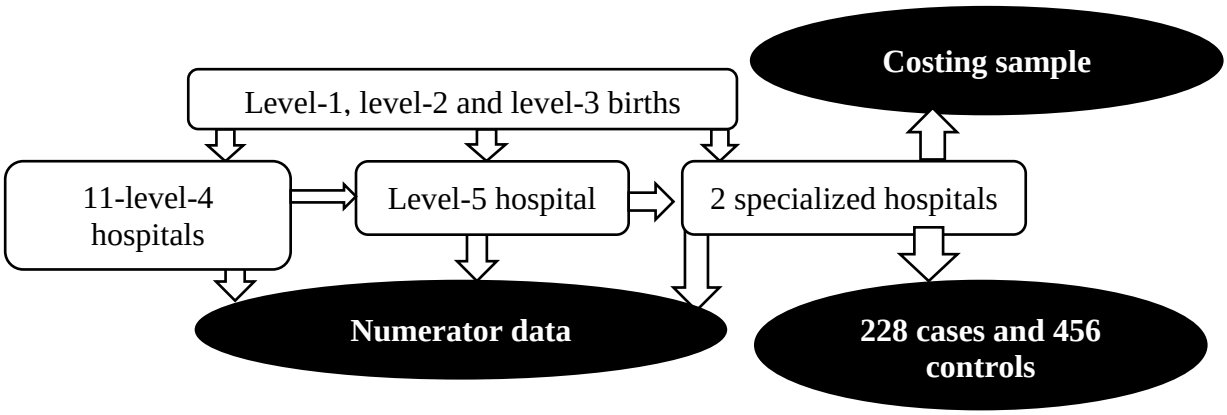

Figure 2: Data collection strategy

Different referral channels exist for children born with structural birth defects, births taking place at home, dispensaries and health centers may be referred to level-6 hospitals through level-4 and level-5 hospitals or directly from where the birth took place. Therefore, numerator data will be systematically collected from level-4 to level-5 and, finally at the 2 faith-based specialized referral hospitals during the study period, 1st January 2014 to 31st December 2018. The number of live births at each of the fourteen hospitals will be computed for the three-year period of study, i.e. from 1st January 2014 to 31st December 2018 and divided by 36 months to obtain average monthly live births at each of the hospitals. This will help in computing the proportion each hospital contributes to the sample size of 384. The proportion for each hospital will multiplied by 384 to obtain the sample size for each hospital. Files of a live births in each hospital during the study period will be retrieved by the hospitals' medical records officers and reviewed by research assistants for cases of structural birth defects. Every case of structural birth defect recorded in excel spread sheet by research assistants using anonymous identification codes. The files will then be refiled to filing cabinets by the hospitals' medical records officers. Cases entered in the excel spreadsheet will act as the sampling frame for each hospital, where the first sample will be selected using random numbers table and creating a sampling interval number of cases in the sampling

frame by the proportional desired sample size for every hospital, the subsequent samples will be selected using systematic random sampling technique.

3.6.3 Sampling techniques for costing study

One month per year during the study period from 1st January 2014 to 31st December 2018 will be chosen randomly using lottery techniques and all cases of major structural birth defects in the month will be listed in epi-data software.

3.6.4 Sample size determination for case-control study

Desired sample size will be determined as specified by Kelsey et al, (1996) for case-control study as follows: -

$$\boldsymbol{n = \left(\frac{r+1}{r}\right)\frac{\left\{(\bar{p})(1-\bar{p})\left(Z_{\beta}+Z_{\alpha}\right)^{2}\right\}}{(p_1-p_2)^2}}$$

Where $\boldsymbol{n}$ will be the sample size in the case group**, r**=2, will be the ratio of controls (unexposed) to cases (exposed), $\boldsymbol{p_1}$ will be the proportion of children born with major external structural birth defects whose mothers will have not attended 4 antenatal care visits (the proportion of cases exposed), $\boldsymbol{p_2}$ will be the proportion of children born with major external structural birth defects whose mothers will have attended at least 4 antenatal care visits (proportion of controls exposed), set at 57% (Fontoura, 2014), $Z\alpha$ representing the desired level of statistical significance level (1.96) and Z_{β} representing the desired power (-0.84) will be the required values which specify the 2-tailed confidence level (95%) and statistical power (80%) desired respectively. The odds ratio (OR) for the antenatal care visits as the primary exposure will be approximated at 2.0 (universally acceptable), $\boldsymbol{(p_1-p_2)^2}$, will the effect size, i.e. the difference in proportions and $\boldsymbol{(\bar{p})(1-\bar{p})}$ will be a measure of variability. Given the above statistical formula: -

$$\boldsymbol{p_{1\,(cases\ exposed)} = \frac{ORp_{2(controls\ exposed)}}{p_{2(controls\ exposed)}(OR-1)+1}}$$

$$\boldsymbol{p_{1\,(cases\ exposed)}} = \frac{2.0(0.57)}{0.57(2.0-1)+1}$$

$$\boldsymbol{p_{1\,(cases\ exposed)}} = \mathbf{0.726}$$

$$\bar{\boldsymbol{p}} = \frac{p_1 + rp_2}{r+1}$$

$$\bar{\boldsymbol{p}} = \frac{0.726 + \{(2)(0.57)\}}{2+1}$$

$$\bar{\boldsymbol{p}} = \frac{1.866}{3} = \mathbf{0.622}$$

$$\boldsymbol{p_{2\,(controls\ exposed)}} = \mathbf{0.57}$$

Further, given the above statistical formula and the figures above,

$$\boldsymbol{n} = (3)\frac{\{(0.622)(1-0.622)(0.84+1.96)^2\}}{(0.726-0.57)^2}$$

$$n = (3)\frac{\{(0.622)(0.378)(7.84)\}}{0.024336}$$

$$n = (3)(76) = \mathbf{228}$$

Therefore, $\boldsymbol{n = n_1(cases)}$ =**228** and $\boldsymbol{n_2(controls)} = rn_1 = 2(228) = \mathbf{456}$

3.6.5 Sampling techniques for case-control study

Self-weighted representative samples for cases and controls will be determined through probability proportional to size approach from 2 specialized referral hospitals. First, two sampling frames of children born with at least a major external structural birth defects stated in section 2.2 above will be created from pediatrics medical records in each of the 2 specialized participating hospitals. The number of birth defects listed in the sampling frame above will be divided by the number of defects for each hospital to determine proportional contributions of each hospital to the total sampling frame. Sample size for each hospital will be determined by multiplying the proportional contribution of each hospital by 228 (computed sample size for cases) in section 3.6.4 above. The

number of cases in the line list for each hospital will be divided by the desired sample size for each facility to determine sampling intervals. The sampling frames for each facility will be entered in an epi-data software where, first sample will be chosen using random numbers tables, followed systematically using the predetermined sampling intervals until desired sample sizes are attained.

Similarly, two sampling frames of children attending or receiving child health services at the two hospitals stated in section 3.2 above will be created from medical records in each of the 2 specialized participating hospitals. The number of controls listed in the sampling frame above will be divided by the number of controls for each hospital to determine proportional contributions of each hospital to the total sampling frame. Sample size for each hospital will be determined by multiplying the proportional contribution of each hospital by 456 (computed sample size for control) in section 3.6.3 above. The number of controls in the line list for each hospital will be divided by the desired sample size for each facility to determine sampling intervals. The sampling frames for each facility will be entered in an epi-data software where, first sample will be chosen using random numbers tables, followed systematically using the predetermined sampling intervals until desired sample sizes are attained. Cases will be matched to controls during data collection in the ratio of 1:2 by age to reduce recall bias. The reason for choosing this sampling technique is to ensure representativeness of the study population and improve the precision of the overall estimates.

3.7 Study procedures

The University of Nairobi supervisors having reviewed the proposal, the proposal will be submitted to KNH-UoN Ethics Review Committee for approval and submitted to the University of Nairobi Graduate School for full registration as PhD student of the University. Another approval will be sought from National Commission for Science, Technology and Innovation (NACOSTI)

to be able to access the study area, i.e. Kiambu county. Similarly, I will seek approval and clearance from Kiambu county health department to access the hospitals, in addition to approval and clearance of the 14-hospitals' management to access the study respondents, medical records and hospital records. Before embarking on data collection exercise, five research assistants who attained at least Diploma in health-related courses, preferably nursing or clinical medicine will be identified, recruited and trained on the essential concepts of data collection using structured interviewer-administered questionnaires, secondary data review from hospital records and medical records, obtaining consent from research participants, and ethical procedures in research. At least 10% of the questionnaires will be pretested, in addition to a mock-trial of retrospective review of medical and hospital records from participating hospitals. Lastly, a status conference will be held with the research assistants to share experiences and challenges and make necessary corrections to ensure study results' reliability and validity.

The Principal Investigator will take lead in data collection, data cleaning and formatting. Files of children treated for birth defects in these hospitals during the study period will be retrieved by the hospitals' medical records officers and reviewed by research assistants for cases of structural birth defects. Active files will be tracked by medical record officers and data abstracted from the point of use and left there. Cases will be live-births (singleton/multiple) of at least 28 weeks gestation, with at least a clinically obvious external SBDs of any body organ and/or system, and/or ascertained by a medical specialist(s) born to a resident mother of Kiambu county during the study period, born at home and/or any of the participating hospitals and/or received/receiving care at the hospitals participating in the study. Numerator data for the prevalence study consisting of live-births with structural defects will be abstracted retrospectively by research assistants from MOH 333, NBU and pediatric medical records during the study period, from 1st January 2014 to 31st

December 2018, whereas, the denominator will consist of the number of live births reported or projected by Kenya National Bureau of Statistics by years from 1st January 2014 to 31st December 2018. Information abstraction from medical records will include maternal education, age, sub-county (residence), occupation, parity, gestation age, nature of gestation (single/multiple), alcohol consumption, trimester prenatal care began and antenatal care visits, sex of child. Interviewer-administered questionnaire will also be used to obtain information including maternal education, age, sub-county (residence), occupation, parity, gestation age, nature of gestation (single/multiple), alcohol consumption, trimester prenatal care began, antenatal care visits, sex of child, indoor smoke, diet, birth order, marital status and pesticides. Every case of structural birth defect recorded in excel spread sheet by research assistants using anonymous identification codes, similarly, eeconomic cost inputs from health provider's viewpoint will be gathered by retrospective review of pediatric medical records and hospital logs respectively, in addition to administering pretested structured interviews to health care workers and managers by research assistants. Active files will be tracked and reviewed at points of use, whereas, retrieved files will be refiled to the cabinets by the hospitals' medical record officers Lastly, exposure data will be gathered by administering-pretested structured interviews to cases and controls by the research assistants. Cases entered in the excel spreadsheet will act as the sampling frame for each hospital, where the first sample will be selected using random numbers table and creating a sampling interval number of cases in the sampling frame by the proportional desired sample size for every hospital, the subsequent samples will be selected using systematic random sampling technique. Data will be audited for quality (DQA) using Epi-info software and exported to Stata software 11.2 for final analyses.

3.8 Statistical analysis

Data will be entered in epi-data manager software, with the outcome variable of interest being SBDs, Unit costs, DALYs, YLL, YLD and elasticities of health care spending on corrective health care services for structural births. Predictor variables of interest will include maternal education, age, residence, occupation, parity, gestation, alcohol consumption, trimester prenatal care began and antenatal care visits. Data will be checked for double entries, missed data will be verified/deleted, cleaned, formatted and audited for quality (DQA) using EPIINFO version 7 (U.S Centres for Disease Control and Prevention, Atlanta, GA, USA). This will ensure data completeness and accuracy, and exported to STATA version 11.2 (Stata corporation, College Station, Texas, 77845, USA) for final analyses and results will be presented in graphs, tables and narrative summaries as follows: -

3.8.1 Descriptive analysis

3.8.1.2 Categorical variables

Qualitative variables will be summarized in proportions/percentages and results presented in graphs, tables and narratives summaries.

3.8.1.3 Birth-defect specific prevalence estimation

Prevalence of specific structural birth defects will be calculated by dividing the numerator (number of cases of specific structural birth defects in the county each year) by the denominator (number of live births in the county reported/projected by the Kenya National Bureau of Statistics) yearly during the study period, 1st January 2014 – 31st December 2018. The numerator for this study will be live-births (singleton/multiple) of at least 28 weeks gestation, with at least a clinically obvious external SBDs of any body organ and/or system, and/or ascertained by a medical specialist(s) born to a resident mother of Kiambu county during the study period from 1st January 2014 to 31st

December 2018, born at home and/or any of the participating hospitals and/or received/receiving care at the hospitals participating in the study.

3.8.1.4 Continuous variables

For descriptive statistics, continuous variables, i.e. total economic costs, unit economic costs and DALYs will be summarized by using mean at 95% CI, median, inter-quartile range (IQR), histograms and boxplots.

3.8.1.4.1 Estimation of total costs and unit costs

Costs from intermediate and indirect cost centres will be allocated to final/direct cost centres to provide total costs. This will be used to compute unit economic costs of specific SBDs by adding all final/direct costs and dividing the total costs by the number of final/direct cost centres to find the average cost of healthcare service and expressed in U.S. dollars.

3.8.1.4.2 Estimation of DALYs

The burden of disease of structural birth defects will be computed using established techniques, universal and life-tables specific to country based on the Global Burden of Disease (GBD) study and the World Health Organization. DALYs will be computed based on life expectancy-tables and estimated disability weights for selected structural birth defects published by WHO and GBD. DALYs will be computed as the sum of YLL due to SBDs and YLD related to SBDs. YLD will be the product of the life expectancy at birth with the defect and the disability weight (DW) provided by GBD study and WHO endorsed scales. The sum YLL will be the number of deaths (N) multiplied by the standard life expectancy (L) at the age at which death occurs, whereas, sum of YLD will be the number of incident cases in that period multiplied by the average duration of the disease and a weight/disability weight (DW) factor that reflects the severity of the disease on a scale of 0 (perfect health) to 1 (dead).

3.8.1.4.3 Sensitivity analysis

Due to uncertainty arising from data required for economic evaluation and sampling, this uncertainty will be handled by carrying statistical analysis for the estimates and hypothesis for the total costs, unit costs and DALYs.

3.8.1.4.4 Discounting for differential timing

Capital costs will be discounted for differential timing at 3%, assuming 3 years life-line for equipment, 4 years for motorbikes/vehicles and 30 or 20 years based on building materials and allocated to final cost centres.

3.8.2 Binomial logistic regression analysis

In view of observations made in conceptual framework, 2.10, and model specification, 2.11.5, above, the model specified here will be stated as a binomial logistic regression model. The occurrence of specific external structural birth defects will be hypothesised to depend on maternal education, age, residence, occupation, parity, gestation, alcohol consumption, indoor pollution, iron-folic acid supplementation, trimester prenatal care began and antenatal care visits. The logistic regression model will be expressed as:

$$\mathbf{P(y=1|x) = \beta_0 + \beta_1 X_I + \beta_2 X_2 + \ldots\ldots\ldots\ldots + \beta_K X_K.} \qquad \mathbf{(5)}$$

Where, y, is will be the binary outcome/dependent variable taking the values zero and one, X's, are the independent variables, β's, are the partial slope coefficients of the parameters, and, ε, is the stochastic error term. Binomial regression model violates the assumption of homoscedasticity and normality. It will always be true that, P(y=1|x) =E (y|x) in a binary logistic regression model expressed in equation (5).

3.8.2.1 Marginal effects estimation

Binomial logistic regression model fitted with specific structural birth defects as the outcome variable of interest, categorised as one when present and zero otherwise and regressed against predictor variables of interest controlling for potential confounders for maximum likelihood estimation (MLE).

3.8.2.2 Odds ration estimation

Logistic regression model will be used to calculate odds ratios at 95% confidence interval (CI) controlling for potential confounders. Residence, maternal age and parity will be considered potential confounders/effect modifiers and evaluated in this model. Lastly, overall, significance of this model will be determined through likelihood ratio test (LRT).

3.8.3 Linear regression analysis

From the observations made in the conceptual framework, 2.10, and model specification, 2.11.5, above, the model specified here will be stated as a linear regression model. The economic costs (shadow price health) of specific external structural birth defects will be hypothesised to depend on maternal education, age, residence, occupation, parity, gestation, indoor pollution, iron-folic acid supplementation, alcohol consumption, cigarette smoking, sex of child, trimester prenatal care began and antenatal care visits. The linear regression structure will be generally stated as follows:

$$y=\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots\ldots + \beta_K X_K \qquad (6)$$

Where, y, is the outcome/dependent variable, X's, are the independent variables, β's, are the partial slope coefficients of the parameters, and, ε, is the stochastic error term.

3.8.3.1 Marginal effects estimations

Linear regression analysis will be conducted to estimate marginal effects of the predictors on shadow prices of health among children with these defects.

3.8.3.2 Empirical determination of the "shadow prices" or elasticity, E_d of corrective health care costs

Based on the Grossman's model for health and heath care demand, econometrically, prevalence, unit costs and DALYS associated with specific birth defects will be considered as health status of the child, fitted into a multiple regression model and hypothesized to depend on the study predictor variables. Applying logarithms in both sides of the regression equation, the demand for health and health care will be econometrically estimated using two-stage least squares (2SLS) and ordinary least squares (OLS) models.

$$\Delta y=\beta_0 + \Delta\beta_I X_I +\Delta\ \beta_2 X_2 +.....+\Delta\beta_K X_K + \varepsilon. \qquad (7)$$

3.8.4 Detection and reduction of collinear predictor variables

Collinearity between variables will be detected by computing variance inflation factor (VIF), given by: -

$$\mathbf{VIF} = \frac{\mathbf{1}}{\mathbf{1} - \boldsymbol{R_X^2}}$$

Where R_X^2 is the coefficient of determination from regressing the variable about to enter the model on the other variable in the model, and computed VIF greater than 10 indicates collinearity. Therefore, the variable will be removed from the model or note will be taken of reduced precision of the regression coefficients during interpretation. Lastly, overall significance of this model will be determined through multiple partial F-Test.

3.8.5 Evaluating assumptions of multiple linear regression model

Homoscedasticity: Homoscedasticity will be examined by plotting the standardised residuals against the predicted $\boldsymbol{y}$ values; and a scatter of points resembling a horizontal band seen in homoscedasticity. However, if its heteroscedastic (variance not constant), a fanning (increased

variance with larger predicted values) or conning (decreased variance with larger predicted values) patterns will result. Heteroscedasticity will be corrected by log-transforming the outcome variable.

Normality of the residuals: To examine normality of the residuals, we will plot a histogram of the residuals or a normal probability plot (aka Quantile-Quantile [Q-Q]) of the residuals. For normally distributed residuals, the Q-Q plot will be approximately a straight line at 45^0 to the horizontal. However, if residuals will be skewed to the right or left (based on the histogram), then Q-Q plot will curve below 45^0 or above 45^0 respectively. Non-normality will be corrected by log-transformation of the outcome variable.

Linearity of predictor-outcome association: This will be examined by plotting residuals against each continuous predictor variable, with horizontal smooth line suggesting linearity. Non-linearity will be resolved by adding a power term of $\boldsymbol{X}$ (e.g. quadratic) or log-transforming the $\boldsymbol{y}$ variable or categorising the continuous variables.

3.9 Minimizing bias

Information bias and selection bias to include referral, ascertainment, admission rate and hospital-control biases are likely to occur in this study. Pretesting interviewer-administered questionnaires will increase validity and reliability of the results, whereas, matching controls to cases by age and choosing recent cases (occurring in 5 years) will reduce selection bias and recall bias. Limited data sources from exclusive secondary data abstraction, may lead to ascertainment bias and result into over-ascertainment or underestimation of certain defects, however, this will be minimized by passively ascertaining cases by reviewing data diagnosed made by medical specialists, administering structured questionnaires, and verifying cases using hospital discharge summaries. Access and utilization of specialized services due close hospitals proximity may lead to overrepresentation or underrepresentation of exposed cases from specific communities in a

hospitalized population, however, this will be avoided by pooling data from the two hospitals for analysis rather than separately analyzing data for the individual hospitals. Multiple and associated defects may have higher admission rates (berkson bias) than isolated or single defects, thus will be reduced by analyzing these defects in categories as multiple, associated, isolated and single defects. Similarly, overrepresentation of exposed controls may occur if the disease among the control group is related to the exposure of interest, that will be minimized by selecting controls with no known form of defects and/or patients with a variety of admission diagnosis other than genetic or syndromic defects for use as controls. Confounders will be controlled for in the regression models, whereas, sensitivity and statistical analyses to reduce uncertainties in costing methodologies and ensure robustness of costing results, in addition to discounting capital costs for differential will carried out.

3.10 Ethical considerations

Ethical consideration will include privacy, confidentiality, security, psychological discomfort and informed consent. Privacy being the right of an individual to control access, use and declaration of any health information that can potentially identifies him or her, unique identifiers will be assigned to each case. Confidentiality refers to the right of an individual to have any health information that may identify him or her secured and out of sight of unauthorised people, therefore, case files will be made inaccessible to unauthorised persons unless express authority is given by the PI, in addition to only aggregated reports shared with the hospitals' and county's officials and RA signing confidentiality agreement before the study begins and will be periodically reminded. Security referring to safeguards and practices of technology and administration aimed at protecting data against unauthorised disclosure, modification or destruction, personal information will be stored in a secured in laptops secured with alphanumerical passwords. Psychological discomfort

and fear for stigmatization are likely to occur during interviews, therefore study participants will be assured and informed that the study is solely intended for academic purposes. Lastly, signed informed consents will be obtained from the study participants after comprehensible explanation of the study merits and demerits and being free to opt out at any time in addition to non-benefit participation. Ethical approval will also be sought from Kenyatta National Hospital and University of Nairobi Ethics and Research Committee, Kiambu county government and participating hospitals.

3.11 Limitations for this study

Administering structured questionnaires will be expensive and time consuming, uncertainty on educational level and professional knowledge of the interviewer and participants. Confounding information may be scanty, information of potential confounders may not be enough, miscoding and wrong data entry is likely to occur when extracting data from registers. Medical records may lack of information about individuals changing their exposure status over time and obtained data may be incomplete and invalid. Information about consanguinity marriages may be difficult to collect, whereas, prevalence estimate precision may decrease because of hospital-derived numerator data, rather than population-derived data, in addition to exclusion of perinatal deaths and terminated pregnancies secondary defects. Lastly, costing results may not be generalizable to other settings because of differences in costing analysis techniques and perspectives.

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APPENDICES

Appendix 1a: Parent participant information consent form (English version)

(To be administered in English or any other appropriate language e.g. Kikuyu and Kiswahili translations in 1b and 1c)

Title of Study: "The Epidemiology and Economic Burden of Structural Birth Defects in Kenya: A Case of Kiambu County".

Principal Investigator: MR. AGOT, GEORGE NYADIMO

Institutional affiliation: University of Nairobi, School of Public Health

Course: Candidate of Doctor of Philosophy Degree in Public Health (PhD.)

Co-Investigators and institutional affiliation:

1. **DR. MARSHAL, M. MWEU,** BVetMed; PGDip. (Epidemiology); MSc. (Epidemiology); PhD. (Epidemiology); Lecturer, Epidemiology and Biostatistics, School of Public Health, University of Nairobi
2. **PROF. JOSEPH, K. WANG'OMBE,** BA; MA; PhD. (Health Economics); Professor of Health Economics and Policy Development, School of Public Health, University of Nairobi

Introduction:

I would like to tell you about a study being conducted by the above listed researchers. The purpose of this consent form is to give you the information you will need to help you decide whether to be a participant in the study. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to be in the study or not. This process is called 'informed consent'. Once you understand and agree to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in a medical research: i) Your decision to participate is entirely voluntary ii) You may withdraw from the study at any time without necessarily giving a reason for your withdrawal iii) Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities. We will give you a copy of this form for your records.

May I continue? **YES / NO**

This study has approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol No. _____

WHAT IS THIS STUDY ABOUT?

The researchers listed above are interviewing mothers whose children were born with structural birth defects in Kiambu county between 1st January 2014 to 31 December 2018. The purpose of the interview is to find out the how frequent are these defects and what are the factors likely to cause them in Kiambu count. Participants in this research study will be asked questions about their socio-economic background, obstetrics history and demographic characteristics. There will be

approximately 726 participants in this study randomly chosen. We are asking for your consent to consider participating in this study.

WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH STUDY?

If you agree to participate in this study, the following things will happen: You will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately 30 minutes. The interview will cover topics such as level of education, marital status, occupation, age, sex of your child with the defect, birth order of the child with birth defect, alcohol use, indoor smoke, pesticide exposure among others. After the interview has finished, if you require counseling, I will provide a trained a counsellor in a private and comfortable room for you.)

We will ask for a telephone number where we can contact you if necessary. If you agree to provide your contact information, it will be used only by people working for this study and will never be shared with others. The reasons why we may need to contact you include clarifying some of the information you will have given and not clear to me.

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify you in a password-protected computer database and will keep all our paper records in a locked file cabinet. However, no system of protecting your confidentiality can be full-proof secure, so it is still possible that someone could find out you were in this study and could find out information about you.

Also, answering questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview.

It may be embarrassing for you to ask some questions; however, we will do everything we can to ensure that this is done in private. Furthermore, all study staff and interviewers are professionals with special training in these examinations/interviews. Also, some information about the child may be stressful and not easy to recall, however, I request you provide the most correct responses to the best of your ability.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

You may benefit by receiving free counselling when needed and health information as necessary. We will refer you to a hospital for care and support where necessary. Also, the information you provide will help us better understand the frequency, risk factors and costs of these defects. This information is a contribution to science and policy formulation on prevention, control, rehabilitation and treatment of children born with structural birth defects.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

Not at all, you will not be asked to pay anything for participating in this study and you will not be refunded any money for participating in this study.

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page. For more information about your rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke. The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to participate in research is voluntary. You are free to decline participation in the study and you can withdraw from the study at any time without injustice or loss of any benefits.

CONSENT FORM (STATEMENT OF CONSENT)

Participant's statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study. I understand that all efforts will be made to keep information regarding my personal identity confidential. By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study: **Yes / No**

I agree to provide contact information for follow-up: **Yes/No**

Participant printed name: _____

Participant signature / Thumb stamp _____Date _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher's Name: _____Date: _____

Signature _____

Role in the study: _____ [i.e. study staff who explained informed consent form.]

For more information contact **0721589544** at **any time** from **8.00am to 5.00pm**

Appendix 1b: Parent participant information consent form (Kikuyu language version)

Title of Study: "The Epidemiology and Economic Burden of Structural Birth Defects in Kenya: A Case of Kiambu County".

Principal Investigator: MR. AGOT, GEORGE NYADIMO

Institutional affiliation: University of Nairobi, School of Public Health

Course: Candidate of Doctor of Philosophy Degree in Public Health (PhD.)

Co-Investigators and institutional affiliation:

3. **DR. MARSHAL, M. MWEU,** BVetMed, PGDip. (Epidemiology); MSc. (Epidemiology); PhD. (Epidemiology); Lecturer, Epidemiology and Biostatistics, School of Public Health, University of Nairobi
4. **PROF. JOSEPH, K. WANG'OMBE,** BA; MA; Ph.D. (Health Economics); Professor of Health Economics and Policy Development, School of Public Health, University of Nairobi

Kiambiriria:

Bomu ino niya gukumenyithia iguru ria uthuthuria uratongorio ni ataramu acio magwetetwo hau iguru na guguteithia kwamura kana niukunyitanira nao. Igua wimuitikirie kuria kiuria ogiothe kigii bata, ugwati kana uguniki, ihooto ciaku witamwirutiri, okindu ogiothe kigii uthuthuria uyu kana waga gutaukiruwo ni ciururia iria cii bomu-ini ino. Twacokia chioria ciaku chiothe ginya uiganire ,wi mwitikirie kurega kana gwitikira kunyitatanira naithui uthuthuriani uyu. Thutha wagwitikira kunyitanira naithui, nitugukuria na gitio waandike ritua riaku bomu-ini ino.

Ni ubatairie gutaukirwo ni motaaro maya megii uthuthuria wa urigitani:

i. Kunyitani na uthuthuria uyu ni kwenda gwaku
ii. Noo urege guthii na mbere na uthuthuria uyu o hindi o yothe
iii. Kurega gwaku gutikugiria ugwate utungata wa urigitani thibitari ino kana ingi o yothe

Nitugukuhe kopi ya bomu ino wiigire. Tuthii nambere? **Aca kana iini**

Uthuthuria uyu nimwitikirie ni kamitii ya uthuruia thibitari ya Kenyatta National Hospital-University of Nairobi No……

UTHUTHURIA UYU NI WA KII?

Ataramu aria maguetetuo, nimakuhoya uhuro kumwa kuri atumia aria mahetwo twana ciana mawathe ma iringu cia mwiri,thini wa kaunti ya kiambu kwambiria mweri wa Januari 2014 kinya Dicemba 2018. Gitumi kia utuiria uyu nikumenya mawathe maya monekanaga maita maiganai na kihumo kiamao. Erutiri nimakorio ciuria ciigii uciari na muturire wao, Nitugucagura andu matanyihire 726 hatari kubuata mutaratara kumacagura.

NII MAUNDU MARIKU MAKUHANIKA WETIKIRA KUNYITANIRA NA UTHUTHURIA UYU?

Niukorio ciuria ni mutaramu muri o eri kwa ihinda ritakirite ndagika mirongo itatu. Niukurio ciuria ciigii githomo giaku, kihiko, wira, miaka, mwana uria ugikoruo na wathe aciarirwo ri, unyui wa njohi na maundu mangi maigi. Thutha ucio ungubatara mutarani inukaheo nigetha muarie nake. Nitukoya namba ciaku cia thimu nitondu hari maundu tugibatara gutaririo tutanyitite wega. Namba iyo igatumika o uthuthuriani uyu.

NIKURI NA UGUATI OWOTHE UKONAINIE NA UTHUTHURIA UYU?

Thuthuria wa urigitani uyu winauhoti wa kurehe thina wa meciria, muturire na mwiri. Kiyo nigikiragwo kunyihanyihia moguati maya. Uguati umue munene wagukoruo thini wa uthuthuria uyu nikuaga hitho, no nitukuiga maundu maria ugatuira mahitho ouria kwahoteka. No urege gucokia ciuria iria ungigua ni cia thoni kana iria ingituma wiigwe utari nathayu. Ataramu aya ni andu athomu na mena ugi wa kuigana wigii maundu maya. Ningi nouremwo nikuririkana maundu megie mwana, ningukuria na gitiyo ugerie kuheana uhoro uria wiwama.

NIKURII NA UGUNIKI KUNYITANIRA NA UTHUTHURIA UYU?

Nouteithike na kuheo utaro wa tuhu na maundu megii ugima wa mwiri na notugutume thibitari kuria ugiheo uteithio uria wagiriire. Nigii uhoro uria ugutuhe niugututeithia kumenya, muigana wa mawathe na moguati maria warehaga mawathei. Uhoro uyu niuguteithiriria guthondeka mitaratara ya kugiriririria na kurigita ciana iria ciciarituo na mawathe.

NI KURI MARIHI?

Gutiri marihii.

CIURIA

Ugigakoruo na cioria thutha-ini nouhure thimu kana wandike ndumiriri nguhi kuri namba iyo yandikitwo hau thi. Ungienda kumenya maingi megie ihoto ciaku cia kunyitanira na uthuthuria uyu no unyitanire na muikariri giti wa kamitii ya Kenyatta National Hospital-University of Nairobi Ethics and Research. Namb ya thimu ni, 2726300 EXT 44102, email uonknh_erc@uonbi.ac.ke . Athuthuria aya nimagagucokeria marihii mothe megie waraniria uyu.

MATUA MAKU NI MARIKU?

Kwirutira ni wendi waaku na wina kihoto kia kuiyeheria o hindi oyothe ungienda.

CIUGO CIA KWIRUTIRA

Nithomete uhoro wa BOMU ino kana gathomeruo. nigite na mweke wakuaririria na mutarani na ngacokerio ciuria ciakwa na ruthiomi gumenya. Nindaririo mogwati na mawega ma uthuthuria uyu na ninjui unyitaniri wakwa uthuthuriani uyu niwirutiri wakua na ingienda no ndiyeherie o hindi o yothe. Ninjui unyitaniri wakwa niukuiguo nanjira ya hitho. Guikira kirora bomu-ini ino tikuga nindateyaniria ihoto ciakua tamwirutiri.

Nindetikira kunyitanira tahini wa utuiria: **iini / aca**

Nindetikira gutariria uria iginyitikana niundu wa riria ndabatarikana: **iini / aca**

Riitwa……..

Kirore/thairi ……..Tariki……

CIUGO CIA MUTHUTHURIA

Nii muthuthuria nindariirie maundu mothe kuri munyitaniri uyu wandikituo hahaiguru na ninjui niataukirwo naakwirutira gwake ni kwiyendera gwake

Ritwaa ria muthuthuria …….. Tariki……

Kirore/thairi ……

Wira wa muthuthuria ……

FORM YA RUTHA

Niundu wa uhoro makiria hura thimu **0721589544** mathaa-ni ma **thaigiri cia kiroko** kinya **thaa ikumi na imwe hwaini**

Appendix 1c: Parent participant information consent form (Kiswahili version) -Fomu ya kibali ya wazazi wanaohojiwa

Mada ya utafiti: Epidemologia na Mzigo wa Kiuchumi Kutokana na Kasoro Kimuundo Kuzaliwa Nchini Kenya. Uchunguzi kifani wa Kaunti ya Kiambu

Mtafiti Mkuu: MR. AGOT, GEORGE NYADIMO

Kitaasisi Uhusiano: Chuo Kikuu Cha Nairobi, Idara ya Afya ya Umma**.**

Kozi: Mgombea Shahada ya uzamivu katika Afya ya Umma

Wachunguzi Wenza

1. **DR. MARSHAL, M. MWEU,** BVetMed, PGDip. (Epidemiology); MSc. (Epidemiology); PhD. (Epidemiology); Lecturer, Epidemiology and Biostatistics, School of Public Health, University of Nairobi
2. **PROF. JOSEPH, K. WANG'OMBE,** BA; MA; Ph.D. (Health Economics); Professor of Health Economics and Policy Development, School of Public Health, University of Nairobi

Dibaji:

Ningependa kukueleeza kuhusu utafiti unaofanywa na watafiti waliotajwa hapo awali. Nia ya hili fomu ya kibali ni kukupatia habari unayohitaji kukusaidia kuamua kama utakuwa mmoja wa wale watakaohusika/watakaohojiwa katika utafiti huu.

Uko huru kuuliza maswali kuhusu dhamira ya utafiti huu, nini kitakachofanyika au kitakachojiri ukihusika kwenye utafiti huu, uwezekano wa hatari au faida, haki zako kama aliyejitolea na mambo mengineo kuhusu utafiti huu ama fomu hili amabalo inawezekana kuwa sio mwafaka. Tutakapo jibu maswali yako kadiri ya kuridhika kwako, unaweza kuamua kama utahusika katika utafiti huu au la. Hii inajulikana kama Kibali Kielezi.

Unapoelewa na kukubali kuwa katika utafiti huu, nitakuomba utie sahihi yako kwenye fomu hili Unastahili uelewe msingi na nia ya utafiti kwa kila mtu anayehusika katika uchunguzi huu wa kimatibabu: -

i) Uamuzi wako wa kuhusika katika utafiti huu ni wa hiari wala sio kulazimishwa

ii) Unaweza jitoa kwa utafiti huu saa yoyote bila kuwa na taswishi yoyota au kutoa sababu zozote zakutohusika. Utaenedele kupokea huduma kutoka unapojitoa katika utafiti huu

Naweza kuendelea? **NDIO/HAPANA**

Utafiti huu unapewa idhini na Hospitali kuu ya Kenyatta kwa Ushirikiano na Chuo Kikuu cha Nairobi, Kamati ya Maadili na Utafiti, Itifaki Nambari _____

UTAFITI HUU UNAHUSU NINI?

Watafiti waliotajwa hapo awali wanawahoji wazazi (mama) ambao Watoto wao walizaliwa na aina za kasoro kimuundo katika Kaunti ya Kiambu kati ya Januari mosi mwaka wa elfu mbili na kumi na sita na desemba tarehe thelathini na moja mwaka wa elfu mbili na kumi nane (1-januari-2014 hadi 31-desemba-2018).

Madhumuni ya mahojiano hay ani kujua jinsi ya mara kwa mara ya kasorokimuundo hutokea kwazo katika Kiambu Kaunti

Watafiti katika utafiti huu wataulizwa maswali kuhusu kijamii na kiuchumi, historia ya magonjwa ya kina mama na tabia ya idadi ya watu. Kutakuwa na idadi ya watu takribani mia saba ishirini na sita (726) washiriki katika utafiti huu ambao wamechaguliwa bila taratibu yoyote .
Tunakuomba kibali ya kushiriki katika utafiti huu.

NI NINI KITAKACHOFANYIKA/KITAKACHOJIRI UKIAMUA KUSHIRIKI KATIKA UTAFITI HUU

Ukishiriki katika utafiti huu, mambo yafwatayo yatafanyika: -
Utahojiwa na mhoji aliye hitimu katika sehemu binafsi, pahali ambapo utakuwa uko starehe iliuweze kujibu maswali. Mahojiano yatachukua takribani nusu saa na itazingatia maswala yanayo husiana na masomo yako, habari ya ndoa yako, kazi au uajiri wako, miaka yako, jinsia ya mtoto wako aliye na kasoro za kimuundo, wakati wake wa kuzaliwa kwa jamaa yenu, matumizi au la ya pombe, matumizi ya dawa za wadudu au hata shambani,
Tutakapomaliza mahojiano, na kutambulike kuwa unahitaji mshauri, utapewa mshauri aliye hitimu ambaye atakushauri kwenye mazingira ya utulivu na starehe
Tunahitaji utupatie namabari ya simu ambayo tutatumia kwa mawasiliano na wewe wakati utahitajika. Namabri hiyo itatumika na wafanyikazi wa utafiti huu peke yake na hautapeanwa kwa watu ambao hawahusiki na utafiti huu. Mawasiliano yetu yatakuwa yanahusiana na kutaka maelezo Zaidi kuhusu mambo mtakayo jadili na wahoji, mambo ambayo yanataka maelezo Zaidi.

JE? KUNA HATARI, MADHARA AU USUMBUFU YANAYO HUSISHWA NA UTAFITI HUU?

Utafiti wa kimatibabu ina uwezekano wa kuleta hatari za kisaikologia, ujamii, hisia na za kimwili.
Kuna haja ya kufanya vyote viwezekanavyo ili kupunguza uwezekano wa kutoea kwa hatari hizi
Haswa katika utafiti huu, kuna uwezekano wa kupoteza ubinafsi wako. Tunakuhakikishia kuwa tutaweka siri vyote ambavyo utatueleza katika mahojiano yetu. Tutatumia nambari ya siri kukutambulisha katika tarakalishi na rekodi ya makaratasi yetu ya mawasiliano yatawekwa salama kamatika kabati iliyofuungwa kwa unasaha.
Ingawa tumejaribu kuhakikisia usalama wa habari utakayotupa, kuna uwezekano kuwa watu wanaweza tambua kuwa ulishiriki katika utafiti hu una kupata habari hizi.
Kuna maswali ambayo yanaweza kukusumbua kujibu, una uhuru wa kukataa kujibu maswala kama haya, hata kujiondoa kwa hii mahojiano.
Maswala yanaweza kuulizwa kwa njia ya siri, wahoji wamehitimu na wakuelekeza ipasavyo.
Unhimizwa kutoahabari za kweli kuhusu mtoto hata ingawa tuna tambua kuwa mambo mengine yanaweza kuleta fedheha and yana ugumu wa kukumbuka.

JE? KUNAO FAIDA KATIKA KUSHIRIKI KWENYE UTAFITI HUU?

Unaweza kupata faida ya kupewa ushauri wakati wowote unapohitaji, kuna uwezekano wa kupelekwa hospitalini kwa kupewa usaidizi Zaidi wa kimatibabu. Habari utakayo toa itasaidia kuelewa marudio, hatari na gharama ya kasoro kimuundo hizi. Habari hizi zitachangia ukuuzi wa sayansi na utafiti katika fani hii as katika kudhibiti, kuzuia na kukarabati na matibabu ya kasoro kimuundo duniani.

JE? KUNA GHARAMA YA KUSHIRIKI KWENYE UTAFITI HUU?

La, hasha. Hakuna gharama yoyote kushiriki katika utafiti huu, na hauta regeshewa pesa zozote kushiriki utafiti huu.

JE? UKIWA NA MASWALI BAADAYE, UTAFANYAJE?

Ukiwa na maswali kuhusu kushiriki utafiti hii, tafadhali piga simu au tuma ujumbe mfupi kwa wafanyekazi wa utafiti kwa nambari zilizopo hapa chini.

Kwa maelezo Zaidi huhusu haki zako kama mshiriki wa utafiti huu, unaweza kuwasiliana na katibu au mwenyekiti , Kenyatta National Hospital-University of Nairobi kamati ya Maadili na Utafiti simu namabri. 2726300 Ext. 44102 barua pepe: uonknh_erc@uonbi.ac.ke. Wafanyikazi wa utafiti watakulipa kwa gharama uliyoipata kwa kupiga simu inayohusiana na utafiti huu.

JE? UNA UCHAGUZI MWINGINE KUHUSU KUSHIRIKI UTAFITI HUU

Uamuzi wako kushiriki utafiti huu ni kwa hiari yako, uko na uhuru wa kuhusika katika utafiti hu una unaweza kujitoa katika kushirikimkwa utafiti huu kwa saa yoyote bila ukiukaji wa haki au hata kupoteza faida za utafiti huu.

FOMU YA KIBALI (TAARIFA YA KIBALI)

Taarifa ya mshiriki wa utafiti

Nimesoma fomu hii ya kibali au nilisomewa taarifa hii.

Niliweza kujadiliana kuhusu utafiti huu una mshauri utafiti. Waliweza kujibu mawali kwa lugha niliyoelewa. Nimeelezwa kuhusu hatari na faida za utafiti huu. Nimefahamu na kuelewa kuwa kuhusika kwangu katika utafiti huu ni kwa hiari yangu na pia nafahamu kuwa naweza kujiondoa saa yoyote ile nipendavyo. Nimekubalikuwa jitihada zote zita fanya ilikuwezesha na kuweka habari kuhusu utambulisho binafsi kuwa siri.

Kwa kutia sahihi fomu hii ya kibali, jija poteza haki zangu za kisheria kama mshiriki wa utafiti huu.

Nimekubali kushiriki katika utafiti huu: **Ndiyo/hapana**

Nimekubali kupeana namabari za mawasiliano kutumika katika siku zizajo: **Ndiyo/hapana**

Jina la Mshiriki: _____

Sahihi ya Mshiriki / alama ya kidole gumba au stamp _____tarehe _____

Taarifa ya Mtafiti

Mimi, niliyeweka sahihi hapa chini, nimeeleza kwa kina habari kuhusu utafiti huu kwa mshiriki wa utafiti huu aliye tajwa hapo juu na naamini kuwa mshiriki ameelewa na kwa hiari yake ametupa kibali chake kuhusu utafiti huu

Jina la Mtafiti: _____tarehe: _____

Sahihi _____

Jukumu katika utafiti huu: _____ [yaani, wafanyikazi walioeleza kuhusu fomu ya kibali.]

Kwa maelezo Zaidi, piga simu kwa nambari **0721589544** wakati wowote kutoka saa mbili asubuhi hadi saa kumi na moja jioni

Appendix 2: Consent form for health workers

Study Title: "The Epidemiology and Economic Burden of Structural Birth Defects in Kenya: A Case of Kiambu County

Study ID…….

Date……

Participant ID……

Hello, this a verbal consent and my name is **MR. GEORGE NYADIMO AGOT, I'm a PhD. Candidate at the University of Nairobi, School of Public Health, College of Health Sciences**. I'm required by the University to carry out a research and write thesis report on the same and this the reason for this study. The purpose of this study is to determine the epidemiology and economic burden of structural birth defects. You have been chosen at random to be in a study about epidemiology and economic burden of structural birth defects in Kiambu county. This study involves research whose purpose is to assess the prevalence, determinants and economic costs of structural birth defects. This will take about 30 minutes of your time. This study will solely be used for academic purpose and not for any other reason, your participation is voluntary, and you are free to opt out any time, there is no reward for participating in this stud and all the information in this study will be kept in confidence and no one will be allowed to access it fully or partially without express authority from the author There are no foreseeable risks or benefits to you for participating in this study. There is no cost or payment to you. If you have questions while taking part, please stop me and ask. We will do our best to keep your information anonymous or confidential, but we cannot guarantee absolute anonymity or confidentiality. If you have questions about this research study, you may contact the principal investigator **MR. GEORGE NYADIMO AGOT** at **0721589544**. If you feel as if you were not treated well during this study, or have questions concerning your rights as a research participant call The Secretary/Chairperson KNH-UoN ERC on Tel. No. 2726300 Ext 44102. Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop. May I continue?

I certify that I have consented the participant (code no.) _____

Researcher's name: _____

Signature: _____

Date: _____

Appendix 3: Consent form for health mangers

Study Title: "The Epidemiology and Economic Burden of Structural Birth Defects in Kenya: A Case of Kiambu County

Study ID…….

Date……

Participant ID……

Hello, this a verbal consent and my name is **MR. GEORGE NYADIMO AGOT, I'm a PhD. Candidate at the University of Nairobi, School of Public Health, College of Health Sciences**. I'm required by the University to carry out a research and write thesis report on the same and this the reason for this study. The purpose of this study is to determine the epidemiology and economic burden of structural birth defects. You have been chosen purposely because of managerial roles and responsibilities you have in this facility to be in a study about epidemiology and economic burden of structural birth defects in Kiambu county. This study involves research whose purpose is to assess the prevalence, determinants and economic costs of structural birth defects. This will take about 30 minutes of your time. This study will solely be used for academic purpose and not for any other reason, your participation is voluntary, and you are free to opt out any time, there is no reward for participating in this stud and all the information in this study will be kept in confidence and no one will be allowed to access it fully or partially without express authority from the author There are no foreseeable risks or benefits to you for participating in this study. There is no cost or payment to you. If you have questions while taking part, please stop me and ask. We will do our best to keep your information anonymous or confidential, but we cannot guarantee absolute anonymity or confidentiality. If you have questions about this research study, you may contact the principal investigator **MR. GEORGE NYADIMO AGOT** at **0721589544**. If you feel as if you were not treated well during this study, or have questions concerning your rights as a research participant call The Secretary/Chairperson KNH-UoN ERC on Tel. No. 2726300 Ext 44102. Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop. May I continue?

I certify that I have consented the participant (code no.) _____

Researcher's name: _____

Signature: _____

Date: _____

Appendix 4: Structured, pretested, interviewer-administered questionnaire

Study Title: "The Epidemiology and Economic Burden of Structural Birth Defects in Kenya: A Case of Kiambu County

Date……

Study ID……

Instructions

- **i.** This questions is to be admimistered by the research assistants to mothers with children with SBD (cases) and controls
- **ii.** Fill in the the correct responses in spaces provided in the questionnare
- **iii.** Tick the correct response for each multiple choice question

Part One: Socio-demographics

1. Maternal age? (in completed years) …….
2. Maternal birth order? ……..
3. Maternal sub-county of birth/origin…….
4. Maternal sub-county of residence in Kiambu county?
5. Education level
   a. Primary
   b. Secondary
   c. Tertiary
   d. None
6. Occupation ……..
7. Marital status
   a. Married
   b. Not married
   c. Separated
   d. Divorced
   e. Widowed

Part Two: Child characteristics

1. Age of the child with the defect……...
2. Sex of the child with the defect
   a. Male
   b. Female
3. Date of birth of the child with defect (date/month/year) ……..
4. Birth order of the child with defect ……..
5. Place of birth of child with defect
   a. Home
   b. Dispensary/health centre
   c. Hospital

d. Others

6. Name of birth defect……..
7. Any of your children with a birth defect and name of the defect if any……..

Part Three: Maternal characteristics

1. Date of last menstrual period……

2. Planned pregnancy
   a. Yes
   b. No

3. Started IFAS at least 4-weeks before last menstrual period
   a. Yes
   b. No

4. Started IFAS 8 weeks after last menstrual period
   a. Yes
   b. No

5. Number of pregnancies so far ……

6. Number of the child birth with the defect ……..

7. Started ANC visits before 8^{th} week after last menstrual period
   a. Yes
   b. No

8. Started ANC visits after 8^{th} week after last menstrual period
   a. Yes
   b. No

9. Number of antenatal clinic visits during the pregnancy with the defect
   a. Zero
   b. Less than four
   c. More than four

10. Nature of pregnancy?
   a. Single
   b. Multiple

11. Nature of child birth
   a. Before term
   b. At term
   c. Others specify

12. Name of chronic illness
   a. Diabetes
   b. Hypertension

c. Epilepsy
d. Others

13. Names of drugs used during the pregnancy with the defects
a. ……..
b. ……..

Part Four: Environmental characteristics

1. Fuel for domestic cooking during pregnancy
a. Charcoal
b. Kerosene stove
c. Firewood
d. Cooking gas
e. Others

2. Sprayed farms with pesticides during pregnancy
a. Yes
b. No

3. Got domestic foods from pesticide sprayed farms during pregnancy
a. Yes
b. No

4. Cooking place during pregnancy
a. Kitchen without a window
b. Kitchen with a window
c. Open place

5. Source of domestic water during pregnancy
a. Piped
b. River
c. Borehole
d. Others

6. Used shifted ugali flour during pregnancy
a. Yes
b. No
c. Others

7. Alcohol consumption 3 months before last menstrual period
a. Yes
b. No

8. Alcohol consumption 8 weeks after last menstrual period
a. Yes

b. No

9. Smoked cigarettes 3 months before last menstrual period
   a. Yes
   b. No

10. Smoked cigarettes 8 weeks after last menstrual period
   a. Yes
   b. No

11. Describe your typical meal per day
   a. Breakfast……..
   b. Lunch……
   c. Supper……..

Part Five: Knowledge on birth defects

1. Is acquired by a woman when pregnant?
   a. Don't know
   b. Yes
   c. Yes

2. Is acquired by an infant before birth?
   a. No
   b. Yes
   c. Don't know

3. Cause?
   a. Miscarriage
   b. Premature birth
   c. Still birth
   d. Don't know
   e. Others specify

4. Infected individuals can transmit the defects?
   a. Don't know
   b. Yes
   c. No

5. Some birth defects can be prevented?
   a. Don't know
   b. Yes
   c. No

6. Some birth defects can be treated in the hospitals

a. No
b. Yes
c. Don't know

7. Severity of the defects can be reduced by hospital care?
a. Yes
b. No
c. Don't know

8. Severity of the defects can be reduced by herbal medicine?
a. Yes
b. No
c. Don't know

9. Severity of the defects can be reduced by witch doctors' care?
a. Yes
b. No
c. Don't know

Part Six: Knowledge on risk factor and prevention

1. Alcohol use by a pregnant woman increases the chances of giving birth to an infant with birth defect
a. No
b. Yes
c. Don't know

2. Multivitamins use by pregnant woman reduces the chance of giving birth to an infant with birth defects
a. No
b. Yes
c. Don't know

3. Use of multivitamins by a pregnant woman few weeks to pregnancy reduces the risk of giving birth to an infant with birth defects
a. Don't know
b. Yes
c. No

4. Use of certain out-of-counter medicines by pregnant woman can cause birth defects
a. No
b. Don't know
c. Yes

5. Smoking cigarettes by a pregnant woman increases the chance of giving birth to an infant with birth defect

a. No
b. Yes
c. Don't know

6. Overweight by a pregnant woman increases the chance of giving birth to an infant with birth defect
a. No
b. Yes
c. Don't know

7. Consumption of iodinated salt in early pregnancy reduces chances of giving birth to an infant with a defect
a. No
b. Yes
c. Don't know

8. Causes of birth defects include (tick correct answers)
a. Supernatural powers
b. Giving birth to many children
c. Immoral behaviour
d. Curse
e. Poor health of a pregnant woman
f. Forbidden food eaten during pregnancy
g. Others specify

9. Which foods are known to cause birth defects ……?

Appendix 5: Direct accounting/micro-costing technique

Study Title: "The Epidemiology and Economic Burden of Structural Birth Defects in Kenya: A Case of Kiambu County

Date……

Research Assistant code……

Hospital code…….
Department……**Defect(s)**……**Date**……
Instructions

i. Identify all direct and indirect medical resources used for each child with a specific structural birth defect in all the departments in each hospital using the line items shown in the table below
ii. Measure all direct and indirect medical resources used for each child with a specific structural birth defect in all the departments in each hospital using the line items shown in the table below
iii. Write the names of all defects for any child with multiple birth defects

Line items	**Grouped line items**	**Total**
1. Labour/staff Salaries including benefits General medical practitioner's consultation fee General medical practitioner's procedure fee Medical specialist consultation fee Medical specialist procedure fee Surgeon procedure fees Surgeon consultation fee Nursing general care fee Nursing specialist care fee Physiotherapist fees Occupational therapist fee	**Personnel costs**	
2. Facility operations/administration Telephone charges Fax charges Electricity charges Water charges Stationary requirements Office materials and supplies	**Administrative costs**	
3. Building and vehicles Vehicle	**Transport costs**	

Vehicle maintenance Vehicle insurance Building (rental value) consider building materials		
4. Consumables Drugs Laboratory supplies Consumables Linen	 **Pharmacy costs** **Laboratory costs** **Kitchen costs** **Laundry costs**	
5. Furniture and equipment Laboratory equipment Operating theatre equipment Furniture Medical equipment Medical supplies		
	Total costs	

Appendix 6: Healthcare provider semi-structured interview guide

Study Title: "The Epidemiology and Economic Burden of Structural Birth Defects in Kenya: A Case of Kiambu County

Instructions to the respondent

i. Please sign for me this consent if you accept to participate in this study
ii. Fill in the the correct responses in spaces provided in the questionnare
iii. Tick the correct response for each multiple choice question

Date……

Study ID……

Questionnaire

1. What is your qualification? **……**
2. When did you complete your pre-service training? ……..
3. When did you complete post-basic training? ……
4. **For surgeons only to answer** (How long do you take to perform surgery of children with the following defects?)
    i. Spina bifida
    ii. Gastroschisis
    iii. Omphalocele
    iv. Orofacial defects
    v. Hypospadias
    vi. Epispadias
    vii. Anophthalmia
    viii. Microphthalmia
5. How long have you been working in this hospital?.....
6. On average, how many children with structural defects do you operate on each day?.....
7. What is your gross monthly salary?.....
8. How much would you be paid for operating on such patients in private hospitals?.....
9. How long does it take to perform surgeries on these patients?.....
10. How long does it take to discharge them home?.....

Appendix 7: Data abstraction tool

Study Title: "The Epidemiology and Economic Burden of Structural Birth Defects in Kenya: A Case of Kiambu County"

Instructions to the research assistants

i. Thus form is for recording information reviewed from files of children with confirmed cases of structural birth defects included in the study
ii. All fields should be filled completely and correctly
iii. File ID must be filled serially from 001 onwards

Date……

Study ID……

Variables	ID……	ID……..	ID..……..	ID…….	ID…..
Education					
Age					
Subcounty					
Occupation					
Parity					
Gestation age					
Nature of gestation					
Alcohol use					
Trimester prenatal care began					
Antenatal visits					
Sex of child					
Indoor smoke					
Birth order					
Marital status					
Diet (list) i. Breakfast ii. Lunch iii. Dinner					
Pesticides exposure					

Appendix 8: Work plan

Study Title: "The Epidemiology and Economic Burden of Structural Birth Defects in Kenya: A Case of Kiambu County

Study ID……..

Time	Proposal development	Ethical approval	Data collection	Data analysis	Thesis defence	Thesis writing/ submission	Findings dissemination
Sept 2017 - Sept 2018							
Oct -Dec 2018							
Jan-Jun 2019							
Jul-Dec 2019							
Jan-Feb 2020							
Mar-Jun 2020							
Jul-Dec 2020							

Appendix 9: Dissemination plan ftom July to December 2020

Study Title: "The Epidemiology and Economic Burden of Structural Birth Defects in Kenya: A Case of Kiambu County

Study ID…….

Time	First publication in public health/medical journal	Second and third publication in public health/medical journal	First presentation in scientific conference and county health department	Second presentation in scientific conference and hospitals	Third presentation in scientific conference and health facilities
Jul 2020					
Aug 2020					
Sept 2020					
Oct 2020					
Nov 2020					
Dec 2020					

Appendix 10: Study budget

Study Title: "The Epidemiology and Economic Burden of Structural Birth Defects in Kenya: A Case of Kiambu County

Study ID……..

Description, quantification and valuation of items for the study budget

Printing and binding of 4 copies of PhD proposal books @ 1,500/= each **(6,000/=)**	One-time ethical approval for the research proposal 10,000/= **(10,000/=)**	One-time training of 5 research assistants (tea, lunch and transport) @ 2,000/= per person **(10,000/=)**	Per-diem for 5 research assistants @5,000/= per person per day for 60 days **(1,500,000/=)**	Transport for 5 research assistants @1,500/= per person per day for 60 days **(450,000/=)**	Printing and binding of 10 copies of the PhD Thesis books @ 2,000/= each **(20,000/=)**	**Total Cost (Kenya shillings)**
Purchase of laptops 2 pcs @100,000/= (**200,000/=)**	Other approvals **50,000/=**	Purchases of Stata Software @ 20,000/= each (**20,000/=)**	Purchase of PDF Software @ 20,000/= each (**20,000/=)**	Purchase Antivirus 3pcs @ 2,000/= each (**6,000/=)**	Microsoft word 2 30,000/= each (**30,000/=)**	
Dissemination of study findings in 1 scientific conference @ 30,000/= **(30,000/=)**	Dissemination of study findings in 1 scientific conference @ 30,000/= **(30,000/=)**	Dissemination of study findings in 1 scientific conference @ 30,000/= **(30,000/=)**	Publication in 2 public health/medical journals @10,000/= **(100,000/=)**	Publication in 1 public health/medical journal @10,000/= **(100,000/=)**	Incidental participants @200/= for 500 participants **(100,000/=)**	
236,000/=	**90,000/=**	**60,000/=**	**1,720,000/=**	**556,000/=**	**150,000/=**	**2,812,000/=**