INSURANCE AND INDEMNITY COVERAGE FOR CLINICAL TRIALS OF MEDICINES IN KENYA

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DEDICATION

I dedicate this work to my family for their support during the study.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACRONYMS AND ABBREVIATIONS

CIOMS:	Council for International Organization of Medical Sciences
GCP:	Good Clinical Practice
ICH:	International Conference on Harmonization
KNH/UON-ERC:	Kenyatta National Hospital/University of Nairobi Ethics and Research Review Committee
PPB:	Pharmacy and Poisons Board
WHO:	World Health Organization
WMA:	World Medical Association

DEFINITION OF TERMS

Clinical trial-A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

Deductibles-This is the amount(s) that the insured agrees to pay in respect of all damages compensation and claimant's costs and expenses before the company shall be liable to make any payment.

Indemnity-This refers to a legally binding promise by which one party undertakes to accept the risk of loss or damage another party may suffer and/or compensate the other party for the loss or damage.

Insurance-This is a form of indemnity provided by an insurer under which the insurer agrees to indemnify the party purchasing the insurance policy in respect of certain specified losses and liabilities upon the occurrence of certain specified events.

No-fault insurance-This is a type of insurance where the entitlement to compensation is not linked to the ability to prove that a person's injuries were due to the fault of another.

Sponsor-A sponsor of a clinical trial is a company, institution or organization that takes overall responsibility of the clinical trial.

ABSTRACT

Background: Risk management is an important aspect in clinical trials due to the associated risk of injury to the study participants. There are both ethical and legal guidelines globally that are meant to ensure that there is compensation to study participants who are injured as a result of participation in clinical trials. Clinical trial insurance is one method of risk management that ensures that study participants are compensated for injury and study investigators are covered for liability that might arise in the course of the clinical trial. The Kenya Clinical Trial guidelines provide for the provision of indemnity cover and insurance during the conduct of a clinical trial. However, the guidelines do not provide a standard form of the clinical trial policy. This study was conducted to review the current clinical trial insurance arrangements and compensation mechanisms for clinical trial related injury in Kenya.

Objectives: The overall objective of the study was to evaluate the insurance and indemnity arrangements for clinical trials in Kenya, and assess knowledge among various stakeholders on the policies related to compensation of clinical trial related injury in Kenya.

Methodology: The study was conducted in two parts; a retrospective descriptive review of the insurance documents and informed consent forms attached to the clinical trial protocols submitted to Pharmacy and Poisons Board between 2011 and 2014 and a qualitative study involving in-depth interviews with key stakeholders involved in the ethical review and approval of clinical trials and an underwriter of clinical trial insurance. Quantitative data analysis was done using Statistical Package for Social Sciences (SPSS) and StataCorp. 2010. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP. For qualitative data analysis, an inductive approach to analysis was used focusing on emergent themes arising from the key informant interviews.

Results: Out of the 78 clinical trial applications reviewed 14(19.9%), 15 (19.2%), 24 (30.8%) and 25 (32.1%) involved Phase I, II, III and IV trials respectively. Sixty three (80.8%) of the clinical trials involved drugs registered in Kenya compared to 14 (17.9%) that involved investigational drugs. A review of the insurance documents showed that only eighteen (23.1%) of the clinical trial protocols reviewed had clinical trial insurance certificates attached with 28.2% of the protocols containing professional indemnity certificates for doctors. Eleven (61.1%) of the insurance certificates had both the "clinical trial insurance" and "product liability insurance" type of insurance indicated and thirteen (72.2%) of the insurance offered was of the no-fault type. Bivariate analysis showed that Phase I trials and trials involving investigational drugs were more likely to have clinical trial insurance.A review of the informed consent documents showed that fifty seven (73.1 %) of the protocols mentioned that compensation would be provided in case of trial related injury with medical care (85.2%) being the most common form of compensation provided. Majority of the interviewees (87.5%) indicated that there was insufficient knowledge on clinical trial insurance in Kenya while75% reported that medical care for injured participants was the most common form of compensation for clinical trial related injury that they were aware of.

Conclusion:

The proportion of clinical trial applications with clinical trial insurance that covers research participants was significantly low and some informed consent documents did not mention how compensation for research related injury will be provided. There is need for the development of clinical trial compensation guidelines and insurance requirements for clinical trials. There is also need to sensitize stakeholders involved in the conduct, ethical review and approval of clinical trials on insurance and compensation for research related injury.

CHAPTER 1: INTRODUCTION

1.1 Background to the study

The World Health Organization (WHO) defines a clinical trial for the purpose of drug registration as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes" (1). The development of new and useful pharmaceutical drugs through clinical trials is essential in order to improve the quality of therapeutics (2). Pre-approval clinical trials bring new drugs to the market and provide the information contained within each drug's prescribing information. This information concerning the drug's safety and therapeutic benefit guides treatment decisions at the individual patient level. Post-approval clinical trials provide additional information that may lead to changes to a drug's prescribing information over time as its use in clinical practice increases (3). There is huge demand for biomedical research on trial populations in developing countries which carry a high burden of diseases (4).

Risk of injury is inherent in any research and could be in the form of direct or indirect physical, psychological or economic harm (5). Studies have shown that clinical research participants often sign consents to participate in clinical trials with only modest appreciation of the risks associated with participation (6). In Phase one clinical trials the primary risk is death from the investigational product or death from malignancy progression or malignancy-related complications while other risks include acute toxicities or delayed toxicities (7). The risks in clinical trials expose the sponsors and investigators to various forms of liabilities arising from injury suffered by study participants.

Various risk mitigation strategies need to be employed in clinical trials to manage the risks. These compensation mechanisms for clinical trial related injury vary based on the policies and guidelines in different countries. Insurance is one of the methods of compensating research participants in the event of injury and it is meant to reinstate the subject to the position they were in prior to the incident. According to the World Medical Association Declaration of Helsinki, the investigator should "… include information regarding provisions for treating and/or compensating subjects who are

harmed as a consequence of participation in the research study in the study protocol" (8).

There are both ethical and legal obligations to be met to ensure that compensation is provided in the case of injury to participants in a clinical trial (9). Before participants can be enrolled in a clinical trial, the relevant ethics review committee must determine that the risks that the research poses to the participants are reasonable (10). Regulatory authorities also provide guidelines that stipulate legally binding obligations that must be met by investigators/sponsors of clinical trials. For example, the Pharmacy and Poisons Board (PPB), which is the pharmaceutical regulatory authority in Kenya, provides clinical trial guidelines that require submission of indemnity cover and insurance certificate for trial participants (11). However, these guidelines currently do not indicate either the minimum requirements for insurance in clinical trials or the type of compensation to be provided in case of trial related injury.

1.2 Statement of the Problem

Majority of the clinical trials in Kenya are conducted by research institutes, and the proportion of clinical trials conducted by multinational pharmaceutical companies is a small proportion of all clinical research conducted in Kenya. The main areas of research are HIV/AIDs, malaria and other infectious diseases.

The draft PPB Revised Guidelines on the Conduct of Clinical Trials in Kenya (2014) provide that participants must be insured against injuries arising from the conduct of the clinical trial and the insurance policy shall grant cover for compensation of study participants for injury which is causally linked to the clinical trial and must cover the liability of the investigator and sponsor without excluding any damage which may be attributed to negligence.

The guidelines, however, do not provide the specific requirements for indemnity cover and insurance in relation to clinical trials in Kenya. There is also no regulation regarding the limits of insurance for clinical trials. Furthermore, the clinical trial guidelines are not clear on the forms of compensation to be provided to research participants in the event of research related injury. This situation exposes the study participants to inadequate compensation in case of trial related injury and

investigators and sponsors vulnerable to civil suits for their role in the conduct of the clinical trial.

1.3 Study Justification

Compensation of participants for research related injury is an ethical and legal obligation for the sponsor of a clinical trial. Ethics review bodies require the clinical trial protocol to specify how compensation will be provided while clinical trial insurance is a requirement for all clinical trial applications made to the Pharmacy and Poisons Board of Kenya. It is important for ethics review committees and the regulatory body to critically examine the informed consent documents and clinical trial insurance policies to ensure that adequate compensation is provided to research participants in case of adverse events arising during the conduct of a clinical trial. There are no Kenyan guidelines that regulate the scope, type and magnitude of insurance policies that cover research participants. There are no similar studies done in Kenya and so the study findings will seek to highlight the current Kenyan situation regarding compensation and insurance in clinical trials.

1.4 Research Questions

1. What is the level of compliance of study protocols submitted to PPB to the guidelines to conduct clinical trials in Kenya regarding provision of indemnity cover and insurance certificate?

2. What are the elements included in the clinical trial indemnity cover and insurance certificate?

3. What are the forms of compensation provided for clinical trial-related injury in Kenya?

4. What are the views among stakeholders on the policies related to compensation for research related injury?

1.5 Objectives

1.5.1 Broad objective

The overall objective of the study was to evaluate the insurance and indemnity arrangements for clinical trials in Kenya.

1.5.2 Specific objectives

1. To compare the insurance and indemnity components of the clinical trial protocols submitted to PPB with the requirements stipulated in the PPB Guidelines for Applications to Conduct Clinical Trials in Kenya (2011).

2. To characterize the elements of insurance, indemnity and other forms of compensation for clinical trial related injury provided for in the clinical trial protocols submitted to PPB Kenya.

3. To explore the influence of selected clinical trial characteristics such as the phase of clinical trial, pharmaceutical classification of the medicine and category of clinical trial participants on the type, magnitude or scope of insurance cover provided for clinical trial related injury.

4. To assess knowledge among various stakeholders on the policies related to compensation of clinical trial related injury in Kenya as provided for in the PPB Guidelines for Applications to Conduct Clinical Trials in Kenya (2011).

1.6 Significance of the Study

The study findings will be beneficial to study participants as it will give insight into the current practices in terms of insurance policies put in place to compensate for injuries occurring due to participation in research. This will empower study participants to scrutinize the informed consent documents for provisions on compensation mechanisms put in place.

The study findings will be useful to ethics review committees, PPB and other clinical trial regulatory bodies in the region as it will give insight into current practices and the extent of adherence to available guidelines. It will also highlight any gaps that exist in terms of enforcement of guidelines and the need to develop research related compensation guidelines. The study will also assess the adequacy of existing insurance policies and elements of an insurance policy that ethics review committees need to review. The study findings will therefore contribute to an improvement of the current guidelines on compensation for research related injury.

The study findings will greatly benefit study sponsors and investigators as it will highlight their obligations towards minimization of research-related injury and adequacy of insurance policies currently in place.

CHAPTER 2: LITERATURE REVIEW

This chapter includes a review of studies done on compensation and insurance in clinical trials, guidelines and regulations from various countries.

2.1 Risks to Clinical Trial Participants

Participation in clinical trials has both benefits and risks. The benefits include receiving a new treatment before it is widely available while possible risks may include occurrence of physical, psychological, social and economic harm (12). Participation in clinical trials always carries some risk to the patient's health. Though rare, in some cases administration of a new treatment regimen, drug or biologic or use of an investigational device may result in injury or death (13).

Phase I trials are mostly done in healthy volunteers to obtain data on safety of investigational products such as medicines and vaccines or medical devices. Phase II trials are routinely carried out in patients to demonstrate therapeutic efficacy of medicines, immunogenicity of vaccines and to determine dose ranges and regimens. Phase III trials are large trials aimed at determining the efficacy and safety of the investigational product. Phase IV trials are done after the registration of the product for use by the general public and are used to monitor the effectiveness of the product in the general population and also collect information on adverse effects associated with widespread use (11).

The early phases of a clinical trial carry more risks. Healthy volunteers in Phase I trials are given an escalating dose of the potential drug to determine the maximum dose of the drug to induce the symptoms of toxicity. In some cases, this toxicity is irreversible (14). The primary risk from participation in a Phase I clinical trial is death from the investigational agent or death from malignancy progression or malignancy-related complications while other complications are acute or delayed toxicities (7). For example, in a Phase I clinical trial of TNG1412, a novel super-agonist anti-CD28 monoclonal antibody intended for the treatment of B cell chronic lymphocytic leukaemia and rheumatoid arthritis, all six healthy volunteers developed systemic inflammatory response and became critically ill after receiving a single dose of the drug (15).

2.2 Mitigation against risks to clinical trial participants

Financial compensation to research participants who get injured while participating in clinical trials is a relatively neglected subject particularly in developing countries (16). The International Ethical Guidelines for Biomedical Research Involving Human Subjects, Guideline 19 states that " Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap" (17).

International Conference on Harmonization (ICH) Guidelines 5.8.1 states "If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence" (18). ICH 5.8.2 states "The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s)".

Indemnity arrangements must be in place so that if anyone is harmed in a research study as a result of deliberate intent or negligence, those affected can receive compensation (19).

2.3 Legal and ethical principles

Civil liability to compensate a research subject participating in a clinical trial arises from breach of contract, negligence or strict liability as a producer or supplier of a defective product. Various countries have enacted legislation which dictate that clinical trial insurance be taken out in their country (20). Under French law, in research without individual direct benefit, the sponsor must always pay compensation to the injured research subject on a no-fault basis while in research with individual direct benefit, the sponsor must pay compensation unless the injury was not attributable to the negligence of the sponsor or other parties involved in the conduct of the trial. The law requires the sponsor to contact a private insurance (21).The South Africa Good Clinical Practice (GCP) Guidelines (2006) take a no-fault approach by providing that there is no need to prove negligence on the part of researchers or sponsors (22).

The informed consent process is designed to inform the research subject of the risks, rights and benefits of participation in a clinical research. The informed consent process arises from the principle of respect for persons that emerged from the Belmont Report that was issued in the United States in 1979. An individual is viewed as an autonomous agent and therefore, humans as research participants should be given an opportunity to choose whether they will participate in clinical research (23). By signing the informed consent document, it is assumed that a contract exists and all measures will be put in place to avoid harm from the investigational product (20). The informed consent document should clearly state that the research participant has a right to claim compensation in case of research related injuries (24). Limitation on the sponsor's obligation to compensate a research subject should be based only on a serious and unreasonable departure from clear research related instructions that cause the injury or harm in question (25).

The ethical principle of beneficence requires that investigators should always look to safeguard the welfare of the research participants. This principle therefore underpins the responsibility of the investigators/sponsors for the health care needs of any research participant injured in the course of the trial, and justifies compensation to cover the expenses of reparative healthcare. The ethical principle of justice raises the argument that compensation testifies reciprocity by the society to compensate participants for the risks they undertake for the benefit of society (21).The research subject should therefore claim compensation at least for major injuries. The obligation for compensation is based on the relationship between the participant and those responsible for the conduct of the clinical trial and this obligation reflects the moral principle of fairness (26).

Unfortunately, there have been reported incidents of the violation of ethical principles during the conduct of clinical trials. In 1996, there was an outbreak of cerebro-spinal meningitis in Kano State, Nigeria which mainly affected children. Pfizer recruited two hundred children to conduct research on its test drug Trovaflaxacin (Trovan), a quinolone antibiotic and some children later died during the trial. Pfizer was accused of not obtaining ethical clearance and failing to obtain informed consent and never informed the study participants that the drug was an experimental drug. Pfizer later agreed to pay compensation amounting to $75 million (27).

2.4 Compensation arrangements in practice

Research participants who suffer physical injury as a result of their participation in research project are entitled to equitable compensation for temporary or permanent impairment or disability (28). All those in charge of medical research should recognise the moral importance of compensation of the injured research participants as paramount (29). The informed consent document should explain to the research participants the compensation or treatment available in the event of trial-related injury (11). The KNH/UON ERC requires the sponsor to indicate in the Ethics and Research application form "…..who will be responsible for the treatment of physical injuries resulting from subject participation in study procedures" (30).

A review of policies for injuries to research participants in India showed that informed consent documents did not mention compensation for lost wages, disability, discomfort or death and compensation was mainly in form of medical care for adverse events paid for by the sponsor (12).

Under the United States Federal regulations, sponsors, particularly National Institute of Health (NIH) are not required to provide compensation for the treatment of research related injury for trial participants or allow grant funds to be used for appropriate insurance (31). For participants injured in US clinical trials many consent forms state that treatment for research related injury will be made available but costs are billed to the subject's insurance company (32). A study conducted by the Department of Health and Human Services in the USA found that most research institutions do not have policies that provide free care or compensation to injured participants (12). The USA Patient Protection and Affordable Care Act of 2010 requires group health plans and insurance issuers to provide coverage for routine care costs associated with participation in approved clinical trials (33).

The guidelines of the Association of the British Pharmaceutical Industry (ABPI) state that compensation should be paid, when on the balance of probabilities, the injury was attributable to the administration of a medicinal product under trial or any clinical intervention or procedure provided for by the protocol that would not have occurred but for the inclusion of the patient in the trial. The guidelines also state that no compensation should be paid for injury caused by other licensed medicinal

products administered to the patient for purposes of comparison with the product under trial (34).

2.5 Scope and valuation of compensation

2.5.1 Scope of compensation

Under the Indian Ethical Guidelines for Biomedical Research on Human Participants, research participants who suffer injury as a result of their participation in research are entitled to financial or other assistance to compensate them for any temporary or permanent impairment, disability or death. Participants may be paid for the inconvenience and time spent and should be reimbursed for expenses incurred in connection with their participation in research (35). The South Africa GCP guidelines specify that only damages for bodily injury may be claimed and therefore participants could only claim damages such as medical expenses, pain and suffering, loss of income, shortened life expectancy and incidental costs (22).

2.5.2 Valuation of injury claims

Compensation may depend on the kind of trial the participants are participating in. Volunteers participating in Phase I trials may have a stronger argument for compensation than patients participating in Phase III and Phase IV trials as the early phases are associated with uncertainty while in the latter phases, patients receive the same drugs they would receive in ordinary care (21).

Compensation for research related injury should be based on various factors like the participant's age, qualifications, years of productive life remaining and the need for medical and other care required as a result of injury (5). In Britain, assessment of the amount of compensation involves an assessment of the pain and suffering the individual has gone through as a result of injuries and the greater claims relate to sequential loss of earnings, the need for care, costs of aid and adaptations (36).

2.6 Insurance requirements for clinical trials

2.6.1 Indemnity and Insurance

Indemnity is the provision of a facility to ensure that in the event of an incident, compensation can be paid to reinstate the claimant to the same position that they were in prior to the incident. Indemnity is usually provided as a written assurance confirming that liabilities will be provided for.

Insurance is a contract or policy which requires a premium to be paid into a fund from which payment for compensation can be made in the event of a claim (9). Indemnity arrangements are required to cover each party in a clinical trial so that in the event of a claim the needs and rights of the clinical trial subject are accommodated.

2.6.2 Review of Insurance requirements for clinical trials in Various Countries

Insurance cover for participants in clinical trials is not mandatory in many countries but some countries require investigators and/or sponsors to have no-fault insurance cover to comply with good clinical practice (16). Insurance requirements for clinical trial insurance vary by country.

In South Africa, the Department of Health GCP guidelines requires researchers and sponsors of clinical trials to take out comprehensive insurance against injury and damage that participants may experience as a result of participation in clinical trials (22). The guidelines provide that participants may have a claim if it can be shown that a trial product or procedure was administered that caused serious bodily harm of an enduring character that would not have occurred but for participation in the trial.

In Brazil, clinical studies need a local insurance broker and the premiums and fees must be paid locally to the insurer while other Latin America countries require the sponsor to have a local presence in the country or appoint a local representative (37).

The Zambia clinical trial guidelines states that “All subjects must be satisfactorily insured against possible injuries that might arise during the conduct of a clinical trial. For all sponsor-initiated trials, a valid insurance certificate for the duration of the study must be provided prior to study initiation. For investigator-initiated trials, proof of current malpractice insurance that covers clinical trials must be provided” (38).

In Malawi, the guidelines prescribe the insurance documents that must be provided, the duration of the insurance policy and states that terms and conditions that appear to waive the rights of the participants should not be included in the policy (39).The guidelines provide that the insurance cover should cover the running period of the trial and a period of five years after the end of the trial. The guidelines state that an insurance of no-fault type must be obtained through a local insurance broker

operating and registered in Malawi. The authenticity of the insurance cover documents is assured by requiring them to be certified by a notary public.

In Japan, pharmaceutical companies buy three types of insurance namely; comprehensive liability insurance, healthy subject compensation insurance and insurance for clinical trials on patients that uses the adverse drug reactions injured party compensation system (40). The pharmaceutical companies take out liability insurance covering compensation for loss up to the highest amounts provided by the occupational accident compensation system and adverse drug reaction relief system. The companies are required to submit the proposed subject consent and information sheet and the certificate of insurance coverage to the institutional review board.

In a study done in India to examine if clinical trial insurance policies cover all contingencies that require reimbursement or compensation, all the policies studied had deficiencies and none had provision to pay full compensation if required and some had preconditions (41).

According to the EU Directive 2001/20, a clinical trial may be undertaken only if provision has been made for insurance or indemnity to cover the liability of the investigator or sponsor (21).

The Kenyan Guidelines for Application to Conduct Clinical Trials in Kenya (2011) require submission of Insurance and indemnity Certificate to cover compensation of clinical trial participants (11).

2.7 Conceptual framework

Clinical trials involving medicinal products are associated with the risk of injury to the research participants. There are both ethical and legal obligations that require that compensation be provided to the research participants in the event of injury. Sponsors and investigators have a responsibility of minimizing the risk of injury and should have compensation mechanisms in place in case of injury. Insurance in clinical trials seeks to mitigate the risks by providing compensation in case of injury. The Ethics and research review committee and PPB have a responsibility of ensuring that the insurance cover will be adequate to compensate the research participants.

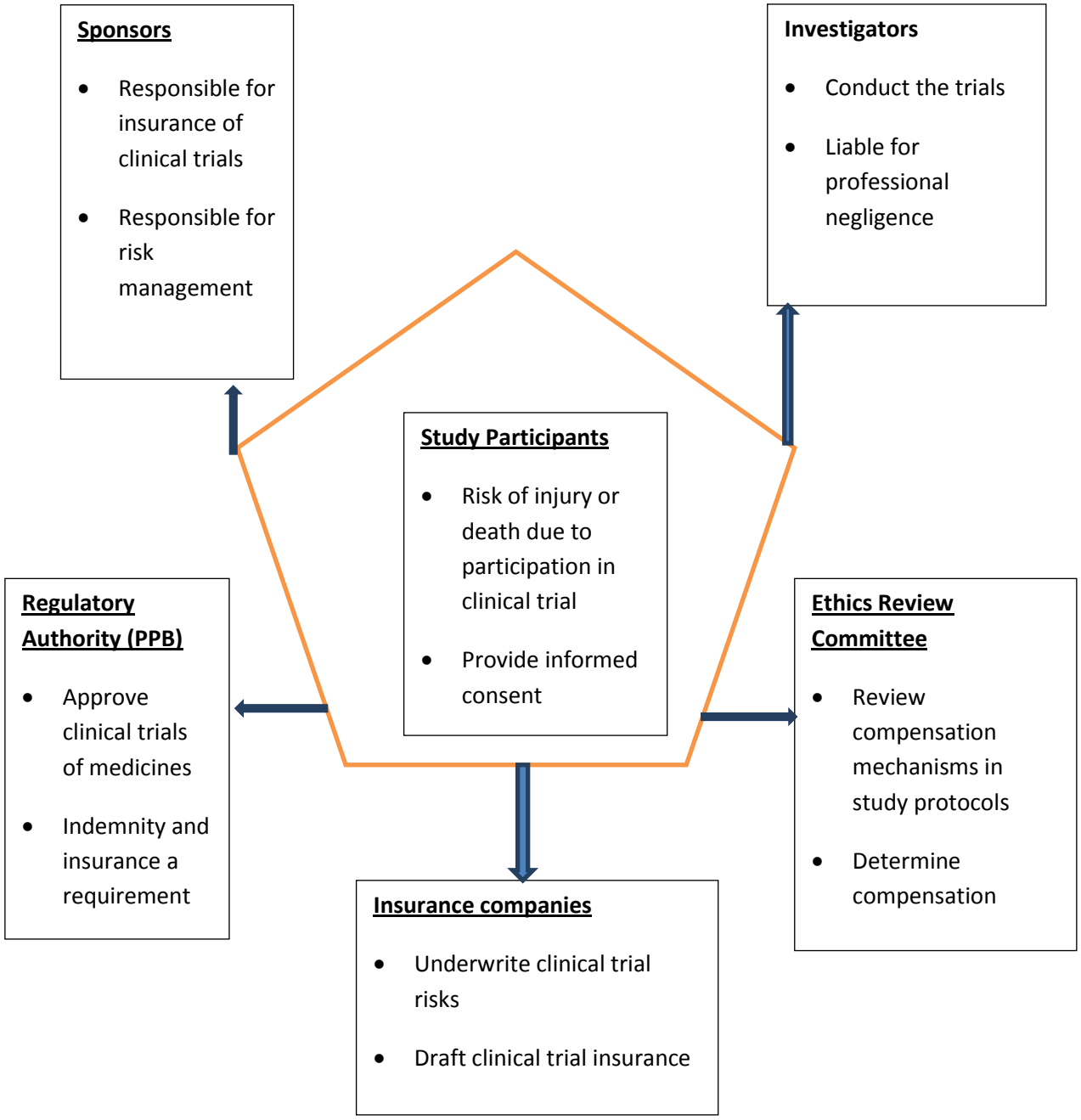

Figure 2.1: Conceptual framework showing the parties involved in Risk mitigation in Clinical Trials

CHAPTER 3: METHODOLOGY

3.1 Study Design

The study involved two components, as described below:

1. A retrospective descriptive review of the insurance documents and the informed consent forms of the protocols submitted to Pharmacy and Poisons Board in the period 2011-2014.

2. A qualitative study through semi-structured interview of key informants involved in the approval and conduct of clinical trials in Kenya. The interviews sought to assess knowledge on the policies related to compensation of clinical trial related injury in Kenya from the perspective of ethics review committee members, PPB expert committee on clinical trials, PPB personnel involved in review and approval of clinical trials, investigators in clinical trials and insurance risk managers in one insurance firm.

3.2 Study Site

The study was conducted at the PPB, KNH/UON ERC, KEMRI ERC and one insurance company (British American Insurance Company) involved in the underwriting of clinical trial insurance. British American Insurance Company was identified as an insurance firm that provides clinical trial insurance for local clinical trials through a fronting arrangement with global clinical trial insurance firms. PPB is the national drug regulatory authority established under the Pharmacy and Poisons Act Cap 244. The PPB has the mandate to ensure that clinical trials involving new investigational drugs and older drugs for new conditions, diseases or investigational devices in human participants are in compliance with national regulations including procedures to protect the safety of all participants. The role of the KNH/UON-ERC and KEMRI ERC is to review biomedical research in order to help safeguard the dignity, rights, safety and well-being of all actual or potential research participants.

3.3 Target Population

The study involved a review of clinical trial protocols submitted to PPB for investigational drug trial registration in the period 2011-2014.

The target interviewees comprised key informants derived from Ethical Review Boards at KNH/UON and KEMRI, British American Insurance Company and Pharmacy and Poisons Board.

3.4 Inclusion and Exclusion Criteria

All study protocols submitted to PPB for review between 2011 and 2014 were included in the review.

The inclusion criteria for key informant interviews were staff members in the three target groups who are most knowledgeable on insurance and clinical trials risk management. The interviewees comprised four target groups: members of the KNH/UON ERC, KEMRI ERC, PPB staff involved in review of clinical trials of medicines; British American Insurance Company staff involved in underwriting of clinical trials insurance; and a member of the PPB Expert Committee On Clinical Trials (ECCT).

3.5 Sample size and sampling techniques

A complete census of all randomized clinical trials study proposals submitted to PPB for review between 2011 and 2014 was carried out for this study. A total of seventy eight (78) clinical trial protocols (both electronic and manual) were available for review. This is the total number of protocols that could be accessed either in manual or electronic format.

Purposive sampling was used to identify participants from the target groups of key informants, i.e. from Ethical Review Boards, British American Insurance Company and Pharmacy and Poisons Board. Criterion sampling technique of the purposive sampling was used to identify interviewees from each target group, whereby the interviewees were involved in either the review of clinical trial applications at ethics review committees, ECCT and PPB, or in the underwriting of clinical trial insurance. Interviewee recruitment was continued until theme saturation was observed. This is the point where new themes or information stopped emerging from the data. Data was analyzed after every two interviewees to assess for theoretical saturation. Table 1 below shows the number of interviewees from each target group.

Table 3.1: Categories of Interviewees for Key informant interviews

Target Group	**Number interviewed**
Ethics Review Committees	5
Pharmacy and Poisons Board	2
British American Insurance Company	1
Total	8

3.6 Research instruments and data collection techniques

1. The first objective involved a review of the protocols for the presence of insurance documents. This was achieved through a data collection tool (Appendix 3).

2. The second objective involved a review of the insurance documents and informed consent forms attached. A data collection tool (Appendix 3) was used to collect the required data from the insurance documents. The elements to be included in clinical trial insurance policy were derived from countries with legislation on clinical trial insurance specifically the National Policy Requirements and Guidance for the Provision of Insurance cover for research Participants in Clinical Trials in Malawi (39), Legislation from various European countries and Australian Legislation on Clinical trial insurance. A data collection tool (Appendix 4) was used to collect data from the informed consent document.

3. The semi-structured interview of key informants was done using an interview guide (Appendix 6). The purpose of the study was explained to the interviewees and those who agreed to participate were requested to sign an informed consent form (Appendix 7). A pharmacist with a Bachelor of Pharmacy qualification was trained on the study and engaged as a research assistant to take notes during the interviews.

3.7 Data Analysis

Descriptive data analysis was carried out. To achieve the first objective, the presence of insurance documents is a categorical variable and so the proportion of clinical trial protocols with insurance documents attached was calculated. The second and fourth objectives were achieved through descriptive data analysis of the continuous and

categorical variables. For the continuous variables, the range was calculated. The categorical variables were expressed as proportions. Bivariate analysis comparing characteristics of clinical trials with and without clinical trial insurance was done using Pearson' s Chi-square test.P-values of 0.05 or less were considered statistically significant. Quantitative data analysis was done using Statistical Package for Social Sciences (SPSS) and StataCorp. 2010. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP.

For qualitative data analysis, an inductive approach to analysis was used focusing on emergent themes arising from the key informant interviews. Preparation for data analysis involved transcription of data, coding and indexing of responses. The thematic codes were developed using inductive coding. The concept of point of data saturation was used for data analysis. This is point at which no more themes emerged during the interviews.

3.8 Quality Assurance and Data Management

Data confidentiality was maintained by omitting the protocol number and title from the data collection forms. The data was kept under lock and key by the investigator. The names of the interviewees were kept confidential by the investigator. All the data was entered in the data collection forms and verification done for any missing information. The data collected from the study protocols was entered in Microsoft Office Excel (2010) and then copied to SPSS and Stata Version 10.Data cleaning and verification was done after data entry with any missing data checked in the data collection tools and entered. The data was backed up in an external hard disk and access restricted to the researcher.

3.9 Ethical considerations

Approval to carry out the study was granted by KNH/UON ERC on 27th March 2015 via approval number P78/02/2015 (Appendix 1). Administrative approval was granted by PPB after signing a Student Confidentiality Agreement (Appendix 2). All the information was collected from the clinical trial protocols submitted to the Pharmacy and Poisons Board and from key informants. Written informed consent was sought from the interviewees (Appendix 7). No information was collected on the title, sponsors or investigators in the clinical trials and all information obtained was treated in confidence. The data collection forms, soft copies of all data collected and

notes taken during the interviews will be destroyed within a period of two years after completion of the study.

3.10 Study Limitations

The study was limited to clinical trial protocols submitted to Pharmacy and Poisons Board for approval. Clinical trials conducted before development of the clinical trial guidelines were therefore not be studied. The desired number of interviewees was not achieved as some did not respond to requests to participate in the study while others cited lack of time for non-participation.

3.11 Dissemination plan

The study findings will be disseminated to the KNH/UON-ERC, KEMRI ERC, Pharmacy and Poisons Board, Kenyatta National Hospital and other stakeholders in the form of an executive summary. The study findings will also be published in a peer reviewed journal.

CHAPTER 4: RESULTS

This chapter contains the results obtained from the clinical trial protocols reviewed and the responses from the key informant interviews.

4.1.0 Characteristics of the clinical trial protocols

One hundred and five clinical trial applications were received at the Pharmacy and Poisons Board in the period 2011 to 2014. Seventy-eight (78) protocols were available for the study with the remaining protocols were not available, having been previously archived. Forty-nine (62.8%) of the clinical trial protocols studied related to 2013 and 2014 as they were also available in electronic form while twenty nine (37.2%) of the protocols related to 2011 and 2012. Table 4.1 below shows the basic characteristics of the study protocols that were reviewed.

Table 4.1: Characteristics of the clinical trial protocols

Year of submission to PPB		**2011**	**2012**	**2013**	**2014**	**Total**
Number of protocols reviewed		16	13	26	23	78
Phase of clinical trial	Phase I	4 (25%)	1 (7.7%)	6 (23.1%)	3(13.1%)	14
	Phase II	5 (31.3%)	-	5 (19.2%)	5 (21.7%)	15
	Phase III	4 (25%)	5 (38.5%)	8 (30.8%)	7 (30.4%)	24
	Phase IV	3 (18.7%)	7 (53.8%)	7 (26.9%)	8 (34.8%)	25
Investigational/Registered drugs	Investigational	3 (18.8%)	1 (7.7%)	4 (15.4%)	6 (26.1%)	14
	Registered	13 (81.2%)	12 (92.3%)	22 (84.6%)	16 (69.6%)	63
	Investigational/ Registered	-	-	-	1 (4.3%)	1
Multicentre trials		14 (87.5%)	11 (84.6%)	19(73.1%)	14 (60.9%)	58
Institution where the trial was carried out	Research centre	11 (68.8%)	10 (76.9%)	10 (38.4%)	6 (26.1 %)	37
	Hospital/Health centre/clinic	5 (31.3%)	3 (23.1%)	16 (61.6%)	17 (73.9%)	41

4.1.1 Phases of the clinical trials

The protocols were reviewed with respect to the phase of clinical trial. The distribution of the protocols with respect to the phase of clinical trial was 14(19.9%), 15 (19.2%), 24 (30.8%) and 25 (32.1%) for Phase I, II, III and IV respectively. The highest proportion of protocols involved Phase III and IV trials as shown in Figure 4.1.

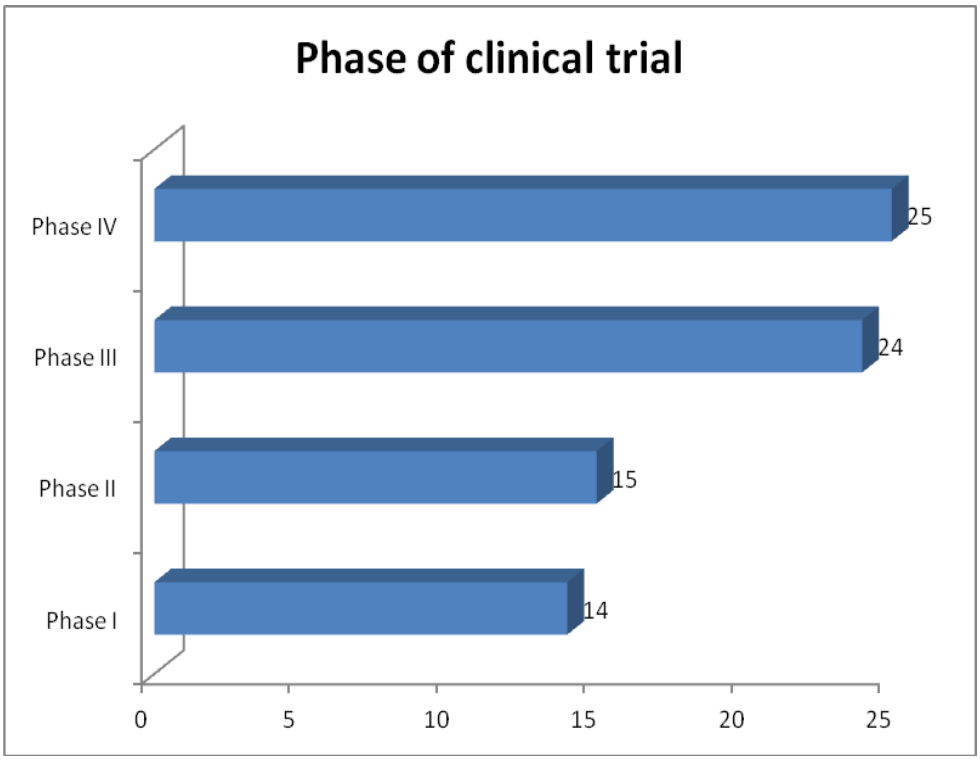

Figure 4.1: Phase of clinical trials

4.1.2 Investigational versus registered drugs

The clinical trials involved both investigational drugs and drugs already registered in Kenya. The clinical trials involving already registered drugs are meant for safety surveillance, exploring changes to indications, target population, dosage or new routes of administration. Sixty-three (80.8%) of the clinical trials involved drugs registered in Kenya compared to 14 (17.9%) that involved investigational drugs. One clinical trial involved both a registered and an investigational drug.

4.1.3 Pharmaceutical classification of the study drugs

The clinical trials studied involved fifteen different classes of pharmaceuticals. The highest proportion of the study drugs involved antiretroviral drugs (23.5%),

Antimalarials (14.3%), Vaccines (14.3%) and Antituberculosis drugs (11.8%) as shown in Figure 4.2.

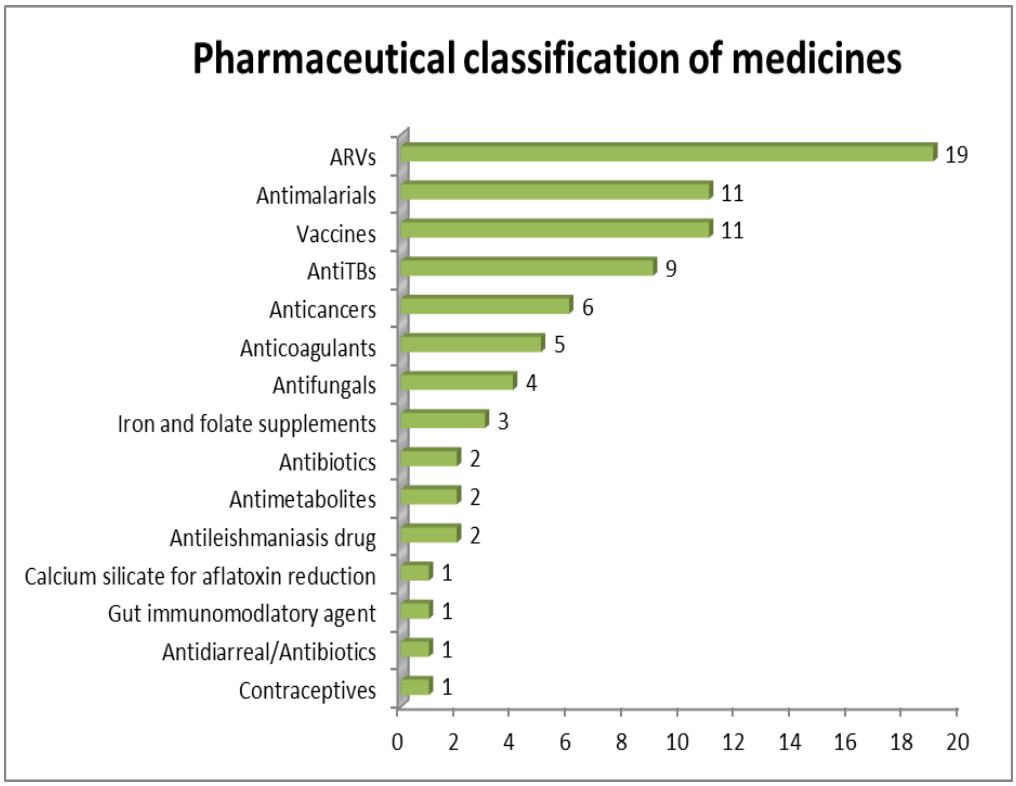

Figure 4.2: Pharmaceutical classification of study medicines

4.1.4 Number of clinical trial sites

Fifty-eight (74.4%) of the clinical trial protocols studied involved multicentre studies either within Kenya or in several countries while twenty (25.6%) were conducted in only one site in Kenya as shown in Figure 4.3.

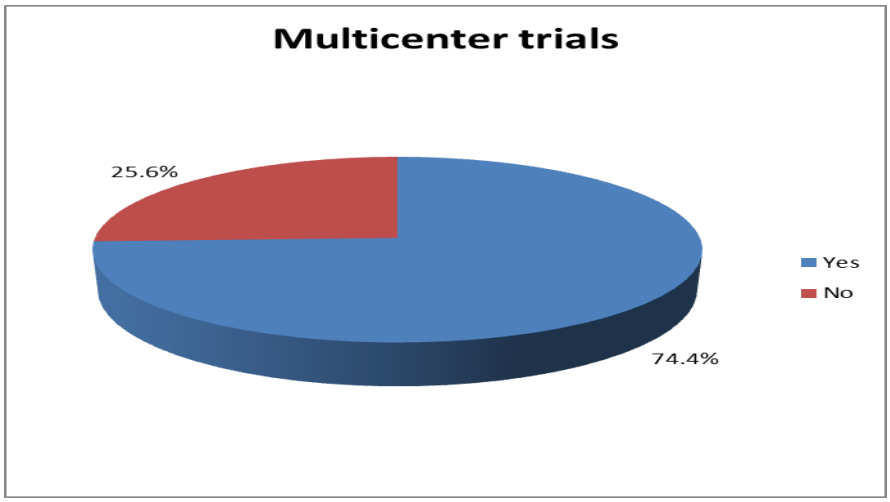

Figure 4.3: Multicentre trials

4.1.5 Institution where research was carried out

Fourty-one (53.0%) of the clinical trials were carried out in healthcare facilities (hospitals/clinics/health centres) while thirty-seven (47.0%) were carried out in research institutions. The research institutions were mainly Kenya Medical Research Institute (KEMRI) research centres.

4.2.0 Presence of insurance and/or indemnity in the clinical trial protocols

This section represents the findings regarding the presence of insurance certificate and indemnity cover documents. The PPB Guidelines to conduct clinical Trials in Kenya (2011) require the submission of indemnity cover for the investigators and insurance certificate for the participants.

4.2.1 Presence of clinical trial insurance

Eighteen (23.1%) of the clinical trial protocols reviewed had clinical trial insurance certificates attached; one protocol submitted in 2013 had both the insurance policy and certificate attached. The presence of clinical trial insurance was highest among protocols received in 2014 (30.4%). These findings are summarized in Table 4.2.

Table 4.2: Attached insurance documents

Year of Submission to PPB		**2011**	**2012**	**2013**	**2014**
Protocols with Clinical trial insurance certificate attached		4 (25.0%)	-	7 (26.9%)	7 (30.4%)
Protocols with insurance policy attached		-	-	1 (14.3%)*	-
Protocols with other documents that provided compensation attached	Professional indemnity certificate	1 (6.25%)	3 (23.1%)	7 (26.9%)	6 (26.1%)
	Letter of indemnity from sponsor	1 (6.25%)	1 (7.7%)	2 (7.7%)	-
	Letter on NHIF cover for participants	-	-	1 (3.8%)	-

*: also had an insurance certificate attached

4.2.2 Other documents that provided compensation for research related injury

Twenty-two (28.2%) of the protocols had other documents that provided compensation for trial related injury. These documents included a letter showing that indemnity would be provided for by the sponsor, Professional indemnity certificates for investigator and a letter showing that National Hospital Insurance Fund (NHIF) contributions would be paid for the participants. Table 4.2 above shows the other documents providing compensation to research participants.

Seventeen (77.3%) of the other documents providing compensation were professional indemnity cover certificates for the investigators. These were highest for protocols submitted in 2013 and 2014 (26.9% and 26.1% respectively)

4.3.0 Components of the clinical trial insurance

The insurance certificates were reviewed with respect to the type of insurance, no-fault type of insurance, duration of the policy, domicile country of the insurance company, applicable deductibles, limits of liability, number of participants covered and explicit reference to the clinical trial. The findings are presented in Table 4.3.

Table 4.3: Information obtained from the insurance certificates

Year of submission to PPB		**2011**	**2012**	**2013**	**2014**
Protocols with attached clinical trial insurance certificate		4 (25.0%)	-	7 (26.9%)	7 (30.4%
Type of insurance	Clinical trial insurance	4(100%)	-	6(85.7%)	7(100%)
	Product liability insurance	4(100%)	-	4(57.1%)	7(100%)
	Professional indemnity	-	-	-	2(28.6%)
Certificates indicating insurance to be of the No-Fault type		3 (75.0%)	-	1 (14.3%)	1 (14.3%)
Duration of the insurance policy	During trial period and 12 months after completion	-	-	1 (14.3%)	-
	Period of one year	4 (100%)	-	6 (85.7%)	7 (100%)
Local or foreign insurance company	Local	-	-	3 (42.9%)	2 (28.6%)
	Foreign	4(100%)	-	3 (42.9%)	4 (57.1%)
	Both local and foreign	-	-	1 (14.3%)	1 (14.3%)
Insurance certificates that indicate the number of participants covered		-	-	3(42.9%)	1(14.3%)

Limits of liability mentioned	Both aggregate and per claim liability	3 (75%)	-	7 (100%)	5 (71.4%)
	Aggregate liability	-	-	-	2 (28.6%)
	None	1 (25%)	-	-	-
Certificates that make explicit reference to the clinical trial		-	-	3 (42.9%)	4 (57.1%)

4.3.1 Type of insurance

Eleven (61.1%) of the insurance certificates had both the "clinical trial insurance" and "product liability insurance" type of insurance indicated. Two insurance certificates in 2014 had "professional indemnity" type of insurance also provided. This is presented in Figure 4.4. Clinical trial insurance indemnifies the insured (sponsor) against claims made in respect of injury to any trial participant arising out of participation in any clinical trial. Product liability insurance covers the liability arising out of bodily injury to a trial participant due to the use of defective products. Professional indemnity insurance protects a professional service provider against claims of negligence and breach of duty.

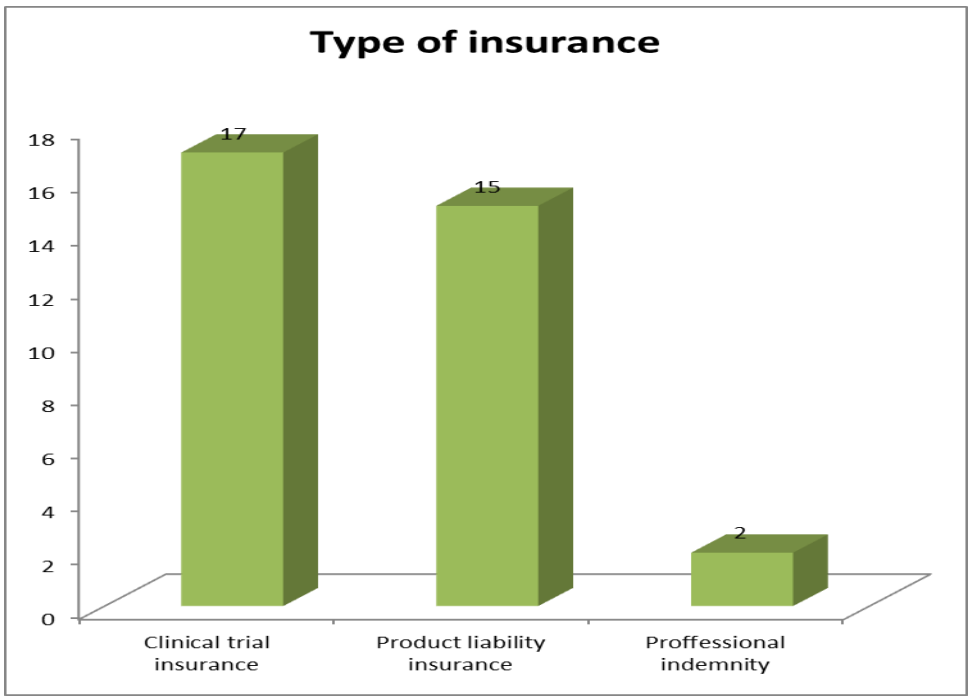

Figure 4.4: Type of insurance provided

Five (27.8%) of the insurance offered was of the no-fault type compared to 13 (72.2%) that was not of the no-fault type insurance as shown in table 4.3. No-fault type insurance is a type of insurance where the entitlement to compensation is not linked to the ability to prove that a person's injuries were due to the fault of another. In the case of clinical trials, this would mean that, in the case of injury, compensation would be due to the study participants despite the injury resulting from the negligence acts of the sponsor or investigators.

4.3.2 Duration of the insurance policy

Seventeen (94.4%) of the insurance certificates indicated a cover period of one year while the duration for one of the policies in 2013 was the running period of the trial and twelve months after the end of the trial.

4.3.3 Local or Foreign insurance company

The insurance certificates were reviewed as to the domicile country of the insurance company. Eleven (61.1%) of the clinical trial insurance was offered by foreign insurance companies (majority being offered by insurance companies from the United Kingdom), five (27.8%) by Kenyan insurance companies while two (11.1%) protocols had both a foreign insurance company and local insurance company certificates. This is shown in Figure 4.5.

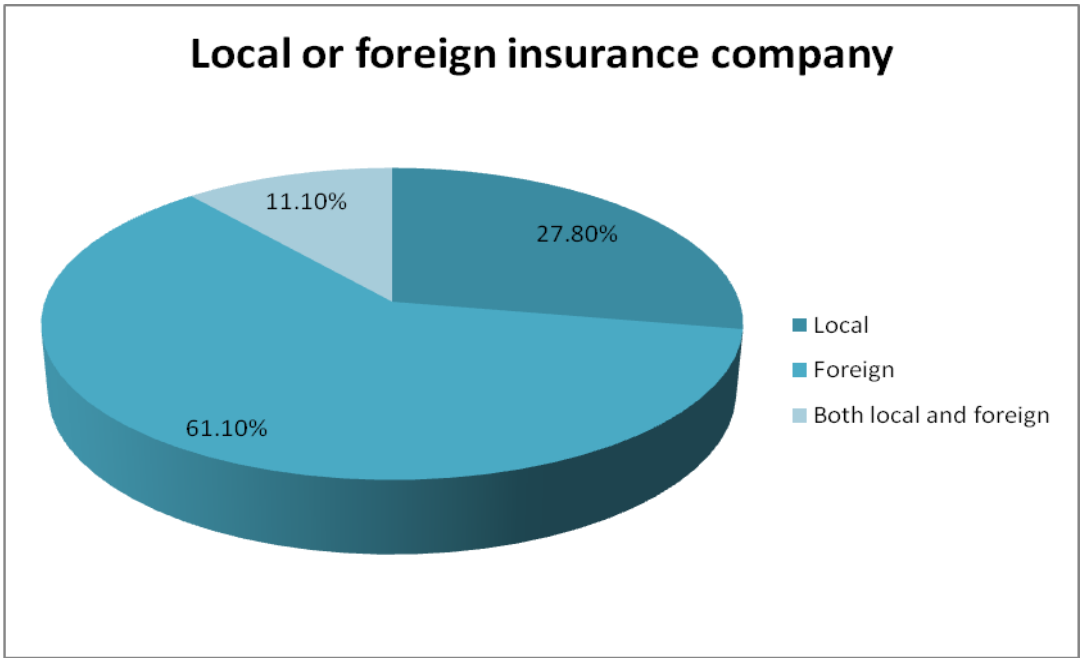

Figure 4.5: Local or Foreign insurance company

4.3.4 Explicit reference to the clinical trial

Seven (38.9%) of the insurance certificates indicated the specific clinical trial covered while majority (61.1%) of the insurance certificates did not make any reference to the title of the clinical trial covered. It was therefore not clear whether the insurance cover related to only one clinical trial.

4.3.5 Whether the insurance certificate indicates the number of participants covered

Only four (22.2%) of the insurance certificates indicated the number of participants covered which corresponded to the expected number of participants to be enrolled for the clinical trials. Majority of the insurance certificates (83.3%) did not indicate the number of participants covered by the insurance policy. In these certificates, it was not clear if the insurance covered an unlimited number of participants

4.3.6 Applicable deductibles

Nine (50%) of the insurance certificates showed the deductibles applicable during the payment of compensation. Deductibles refer to the amount(s) that the insurer agrees to pay in respect of all damages compensation and claimant's costs and expenses before the insurance company shall be liable to make any payment.

The value of the deductibles ranged from Ksh. 10,000 to Ksh. 3,750,000 while one protocol indicated that the deductible would be 5% per claim. Table 4.4 below shows a comparison of the deductibles and per claim liability for the nine insurance certificates showed the deductibles applicable during the payment of compensation. The percentage deductible per claim ranged from 0.04% to 5%.

Table 4.4: Comparison of deductibles and per claim liability

Deductible (Ksh.)	*Per claim liability (Ksh.)*	*Deductible (%)*
10,000	2,000,000	0.5
106,247	42,498,800	0.25
3,470,606	-	-
375,000	950,000,000	0.04
1,500,000	150,000,000	1
1,500,000	150,000,000	1
1,500,000	150,000,000	1
37,500,000	-	-
5% of indemnity limit	3000000	5

4.3.7 Limits of liability

Limits of liability refer to the maximum amounts that may be paid to the claimant (s). In per claim liability, the maximum compensation for every claim is fixed while in aggregate liability, the total amount that the insurer has to pay in case of multiple claims is specified.

Seventeen (94.4%) of the clinical trial insurance certificates indicated the limits of liability. Fifteen (83.3%) of the insurance certificates had both per claim and aggregate liability as shown in Figure 4.6.

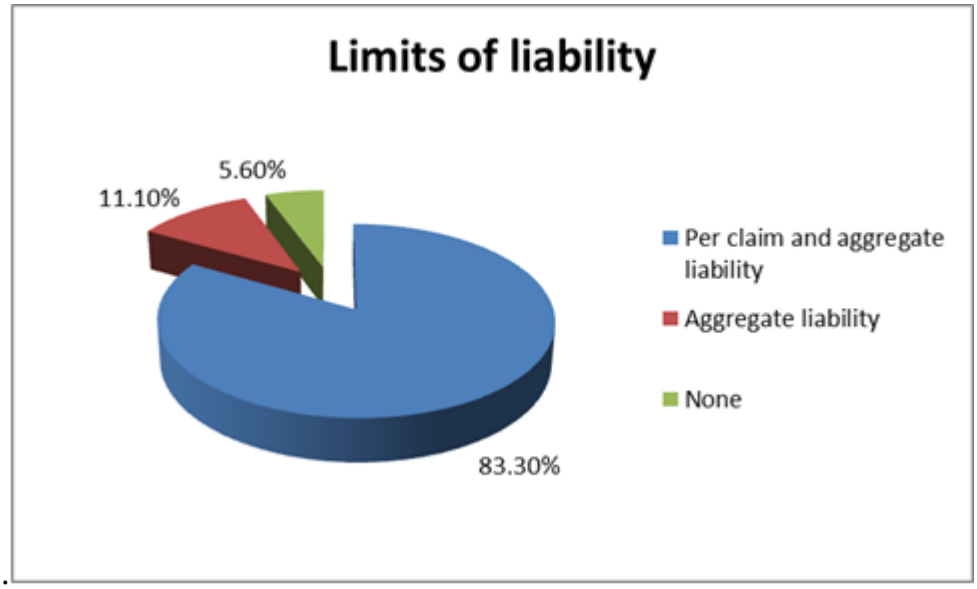

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Figure 4.6: Limits of liability

The per claim liability ranged from Ksh. 2,000,000 to Ksh.2,250,000,000 while the aggregate liability ranged from Ksh. 10,000,000 to Ksh. 1,500,000,000. Nine (50%) of the insurance certificates had similar figures for per claim and aggregate liability.

4.4.0 Information provided in the informed consent documents

The PPB Guidelines for Applications to conduct clinical Trials in Kenya (2011) requires the informed consent form to include an explanation on the compensation and/or treatment available to the participant in the event of trial-related injury.

A total of seventy-eight informed consent documents from clinical trial protocols submitted to PPB in the period 2011-2014 were studied to assess the information provided to trial participants regarding compensation for clinical trial related injury.

All the protocols reviewed had informed consent documents attached. Table 4.5 below shows the information obtained from the informed consent documents.

Table 4.5: Information provided by the informed consent documents (ICDs)

Year of submission to PPB		**2011**	**2012**	**2013**	**2014**
Number of ICDs reviewed		16	13	26	23
Number of ICDs that mentioned that compensation for research related injury would be provided		12 (75.0%)	8 (61.5%)	21 (80.8%)	16 (69.6%)
When would compensation be provided?	For Study related injury/illness	12 (100%)	8 (100%)	19 (90.5%)	14 (87.5%)
	Death	-	-	-	2 (12.5%)
	Side effects related to study drug	-	-	2 (9.5%)	-
Type of compensation that would be provided	Medical care	12 (100%)	8 (100%)	18(85.7 %)	9(56.3 %)
	Monetary compensation	-	-	1 (4.8%)	2(12.5%)
	Reimbursement of medical expenses	-	-	-	2(12.5 %)
Number of ICDs indicating sponsor would bear the expenses		12 (75.0%)	8 (61.5%)	19 (90.5%)	14 (60.9%)
ICDs that mention an insurance policy that covers trial related injuries		1(6.3%)	-	2(7.7%)	3(13.0%)
Information provided on an insurance policy that covers trial related injuries	The insurance coverage is provided by the sponsor	-	-	-	1 (4.3%)
	Study indemnity form mentioned	-	-	1 (3.8%)	-
	Medical expenses will be paid as per ABPI guidelines	-	-	-	1 (4.3%
	NHIF contribution paid for by the study	3 (18.8%	5 (38.5%)	-	-

4.4.1 Provision of compensation for research related injury

Fifty-seven (73.1 %) of the protocols mentioned that compensation would be provided in case of trial related injury while twenty one (26.9 %) did not mention any form of compensation.

4.4.2 Type of injuries/outcome to be compensated

Out of the fifty seven informed consent documents that mentioned compensation would be provided, 53 (93.0%) provided compensation for study related injury/illness while only 2(3.5%) mentioned that compensation would be provided in case of death. This is shown in Figure 4.7 below.

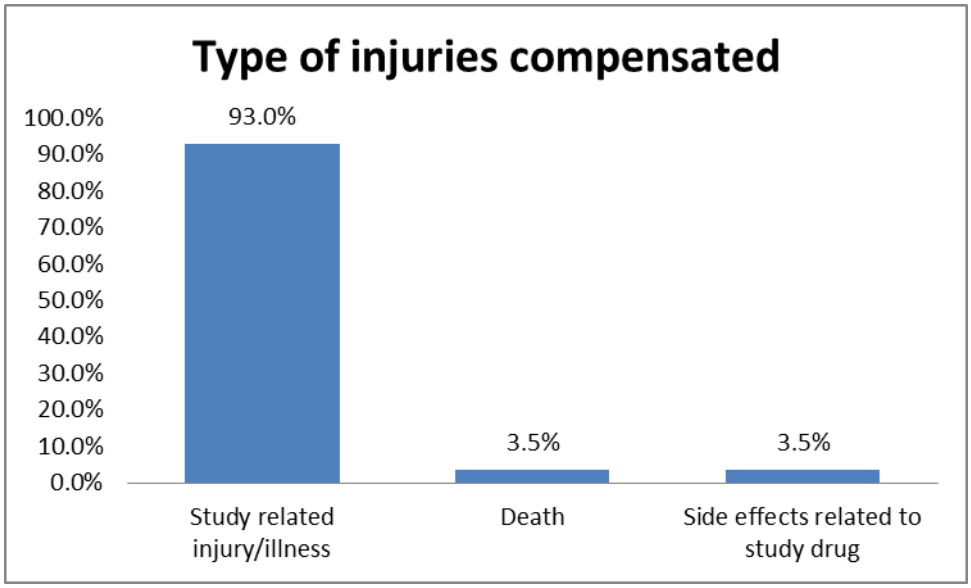

Figure 4.7: Type of injuries compensated

4.4.3 Type of compensation to be provided

Majority (82.5%) of the fifty seven protocols that mentioned compensation would be provided indicated that medical care would be provided for trial related injury. Other forms of compensation provided are as shown in Figure 4.8.

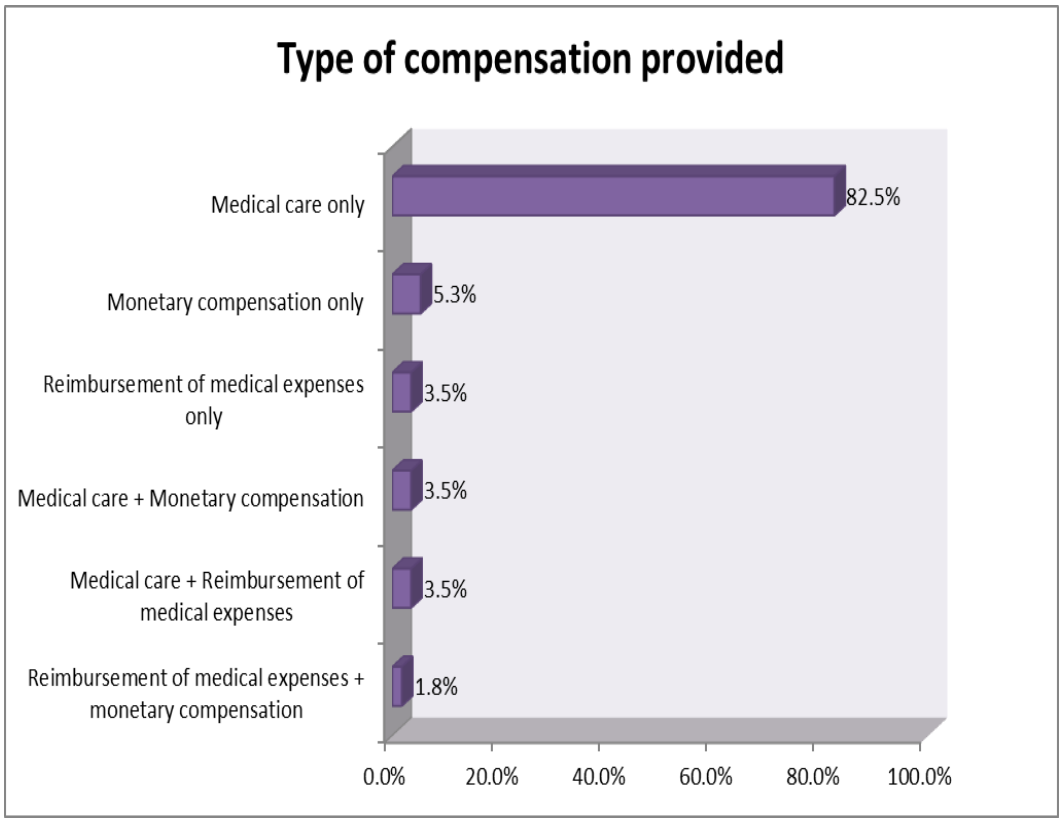

Figure 4.8: Type of compensation provided

4.4.4 Bearer of expenses associated with trial related injury

Fifty-three (67.9%) of the informed consent documents indicated that the sponsor would bear the expenses incurred in case of trial related injury while the rest did not specify who would bear the expenses.

4.4.5 Information provided regarding the presence of an insurance policy that covers participants

Only six (7.7%) of the informed consent documents mentioned the presence of an insurance policy that covers injuries sustained by trial participants. Eight (10.3%) of the ICDs mentioned that NHIF contributions for the participants would be paid for by the study sponsors. Three informed consent documents mentioned that a study indemnity form was attached to the protocol (1,1.3%), all medical expenses would be paid as per the Association of British Pharmaceutical Industries guidelines (1, 1.3%) and that insurance coverage was provided by the sponsor and compensation amount to be determined by the sponsor (1, 1.3%). This is presented in Figure 4.9.

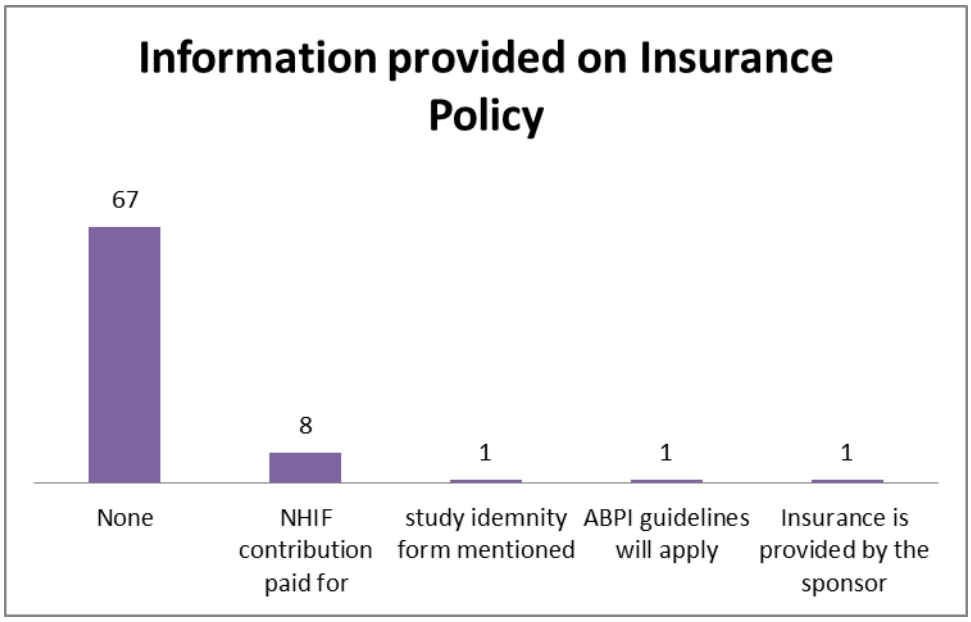

Figure 4.9: Information provided on an insurance policy that covers participants

4.5.0 Magnitude and scope of the insurance covers

The presence, scope and magnitude of clinical trial insurance could be influenced by the various characteristics of the clinical trial such as the phase of clinical trial, pharmaceutical classification of study medicines, category of participants, registration status of study medicines and number of study sites. Bivariate analysis was carried out to identify any association between these clinical trial characteristics and the presence of clinical trial insurance. The distribution of the variables across protocols with and without clinical trial insurance is summarized in Table 4.6.

The analysis showed that the proportions of clinical trials with clinical trial insurance varied significantly between the phases of clinical trials as well as between the registration status of the study medicines. There was no statistically significant difference with respect to the pharmaceutical classification of the medicines, category of participants, number of clinical trial sites and the institution where the trials were carried out.

Table 4.6: Characteristics of protocols with or without clinical trial insurance

Predictor Variable	No clinical trial insurance	Clinical trial insurance	p-value*
Phase of clinical trial			
Phase I	8 (57.1%)	6 (42.9%)	**0.024**
Phase II	11 (73.3%)	4 (26.7%)	
Phase III	17 (70.8%)	7 (29.2%)	
Phase IV	24 (96.0%)	1 (4.0%)	
Investigational vs registered			
Registered	54 (85.7%)	9 (14.3%)	**<0.001**
Investigational	6 (42.9%)	8 (57.1%)	
Investigational/Registered	-	1 (100.0%)	
Classification of medicines			
Contraceptives	1 (100%)	-	0.131
Antidiarreal/Antibiotics	1 (100%)	-	
Gut immunomodlatory agent	1 (50%)	1 (50%)	
Calcium silicate for aflatoxin reduction	1 (100%)	-	
Antileishmaniasis drug	2 (66.7%)	1 (33.3%)	
Antimetabolites	2 (66.7%)	1 (33.3%)	
Antibiotics	2 (66.7%)	1 (33.3%)	
Iron/folate Supplements	3 (100%)	-	
Antifungals	4 (100%)	-	
Anticoagulants	5 (83.3%)	1 (16.7%)	
Anticancers	6 (100%)	-	
AntiTBs	9 (90.0%)	1 (10.0%)	
Vaccines	11 (61.1%)	7 (38.9%)	
Antimalarials	11 (78.6%)	3 (21.4%)	
ARVs	19 (90.5%)	2 (9.5%)	

Participants category			
Adults	40 (78.4%)	11 (21.6%)	0.075
Children	12 (75.0%)	4 (25.0%)	
Pregnant women	1 (33.3%)	2 (66.7%)	
All ages	7 (87.5%)	1 (12.5%)	
Multicentre trial			
Yes	44 (75.9%)	14 (24.1%)	0.705
No	16 (80.0%)	4 (20.0%)	
Institution research is being carried out			
Research centre	31 (83.8%)	6 (16.2%)	0.172
Hospital/Health centre	29 (70.7%)	12 (29.3%)	

** Chi Square measure of association was used to assess the association between the predictor variables and the presence of clinical trial insurance.*

4.5.1 Phase of clinical trial

Phase I clinical trials were more likely to have clinical trial insurance (6, 42.9%) compared to Phase III trials (7, 29.2%), Phase II trials (4, 26.7%) and Phase IV trials (1, 4.0%).This showed that the phase of a clinical trial was a significant predictor (p=0.024) of the presence of clinical trial insurance. A majority of the Phase IV trials (24, 96%) did not have clinical trial insurance.

4.5.2 Investigational versus registered drugs

Clinical trials involving investigational medicines were more likely to have clinical trial insurance (8, 57.1%) compared to registered drugs (9, 14.3%).This difference was statistically significant (p<0.001).

4.5.3 Pharmaceutical classification, participants' category, number of trial sites and trial site

Clinical trials involving a gut immunomodulatory agent (1, 50%) and vaccines (7, 38.9%) were more likely to have clinical trial insurance compared to other classes of medicines. However, classification of medicines did not appear to be a significant predictor of the presence of clinical trial insurance (p=0.131).

Clinical trials involving pregnant women (2, 66.7%) were more likely have clinical trial insurance compared to those involving other categories of participants. However, there was no statistical significance between the participant's category and presence of clinical trial insurance.

The number of clinical trial sites (p=0.705) and institution where the clinical trial was carried out (p=0.172) were not a significant predictor of the presence of clinical trial insurance.

4.6.0 Knowledge among key informants on insurance and compensation in clinical trials

Eight (8) key informant interviews were conducted in the month of July and August, 2015.The interviewees included three (3) members of the KNH/UON ERC, two (2) members of the KEMRI ERC, one (1) member of the Expert committee on clinical trials, one (1) PPB staff and one (1) insurance underwriter.

Seven thematic codes were explored involving knowledge and views of key informants on insurance and compensation in clinical trials. The thematic codes generated are as follows:

1. Medical care as the form of compensation for clinical trial related injury.
2. Insufficient knowledge on clinical trial insurance.
3. Ethics review committee role in review of clinical trial insurance documents.
4. Insurance policy document to be attached to the clinical trial protocol.
5. Duration of insurance cover should be dependent on the specific clinical trial.
6. Different insurance requirements for different phases of clinical trials.
7. Provision of clinical trial insurance by a local insurance company.

The thematic codes generated in each interview are shown in Appendix 8.All the thematic codes were generated by the second interview and data saturation was reached by the seventh interview at which point each of the themes had been mentioned at least four times. The prevalence of the themes generated during the interviews is summarized in Table 4.7.

Table 4.7: Summary of thematic prevalence

Code Number	Theme	Number of interviewees with the theme	Thematic prevalence
1	Medical care as the most common form of compensation	6	75%
2	Insufficient knowledge on clinical trial insurance	7	82.5%
3	ERC has a role in the review of insurance documents	8	100%
4	Insurance policy document should be attached to the protocol	6	75%
5	Duration of insurance cover should be dependent on the study protocol	4	50%
6	Different insurance requirements for different phases of a clinical trial	5	62.5%
7	Insurance cover should be provided by a local insurance company	6	75%

Compensation mechanisms for clinical trial related injury in Kenya

Six of the interviewees (75%) reported that medical care for injured participants was the most common form of compensation for clinical trial related injury that they were aware of. One interviewee stated that "*ad hoc compensation mechanisms were in place depending on the principal researcher*". [Interviewee No.2]

Insurance as a means of compensating research participants was mentioned by four (50%) of the interviewees.

Knowledge on clinical trial insurance in Kenya

Majority of the interviewees (7, 87.5%) indicated that there was insufficient knowledge on clinical trial insurance in Kenya. There were various reasons given for this situation. The insurance underwriter explained that there was insufficient knowledge as this particular class of insurance is very new to the local market.

"Ethics review bodies don't have guidelines on the review of insurance policies for compensation" [Interviewee No. 2]

One interviewee stated that clinical trial participants are *"...not aware of their rights....."* [Interviewee No.4]

Role of Ethics Review committees in the review of insurance policy documents

All the interviewees stated that ethics review committees should review the insurance documents submitted during the ethics review process to ensure compensation is provided. Most interviewees stated that ERCs should ensure implementation of the guidelines regarding the presence of an insurance policy that covers participants.

Insurance documents that should be attached to the clinical trial protocol

Seventy-five percent of the interviewees proposed that the complete insurance policy document should be attached to the clinical trial protocol. The reasons given were that the insurance policy document is more detailed than the insurance certificate, it contains any exclusions and specific cover details and is best suited to confirm adequacy of the cover. However, one interviewee stated that only the insurance certificate should be provided since "*it is difficult for reviewers to analyse the contents of the insurance policy which is a technical document unless legal experts are hired*". [Interviewee No.5]

Duration of the clinical trial insurance policy

Fifty percent of the interviewees stated that the duration of the insurance cover should be dependent on the specific clinical trial being carried; three interviewees proposed that it should only cover the running period of the clinical trial. One participant stated that it is difficult to prove causality after the end of a clinical trial while another proposed that the insurance cover should be beyond the duration of the clinical trial by two years.

Insurance requirements for different phases of clinical trials

Majority (62.5%) of the interviewees proposed that there should be different insurance requirements for different clinical trial phases. The most common explanation given was that there are different risks associated with the different phases of a clinical trial.

"Phase IV trials should not be subjected to the insurance requirements since adverse effects would also occur during the clinical use of the medicines" [Interviewee No.5]

Clinical trial insurance provision by a local or foreign insurance company

Majority of the interviewees (75%) recommended that a local insurance company should be involved in the provision of clinical trial insurance either alone or as a local representative of a foreign insurance company. Majority of the interviewees felt that it would be easier to handle compensation claims. One interviewee suggested that capacity for local insurance companies to cover clinical trials should be enhanced.

CHAPTER 5: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1.0 Discussion

This study sought to assess the level of compliance to the guidelines regarding the provision of insurance for clinical trial related injury, explore various characteristics of the clinical trial insurance documents, review the forms of compensation provided in the informed consent documents and assess the awareness of stakeholders on the issues of compensation and clinical trial insurance.

The Pharmacy and Poisons Board (PPB) is the regulatory body mandated to approve clinical trials of medicines and medical devices in Kenya. The clinical trial protocols are submitted to PPB after prior review and ethical approval by relevant ethics review committees.

5.1.1 Presence of clinical trial insurance documents

This study shows that only 23.1% of the study protocols submitted to PPB for approval had clinical trial insurance documents attached, with 28.2% of the protocols containing professional indemnity certificates for doctors. This revealed low compliance to the PPB Guidelines for Application to Conduct Clinical Trials of Medicines in Kenya (2011) that require the submission of indemnity cover and insurance certificate that covers research participants (11). The guidelines are not adhered to by attaching professional indemnity certificates for doctors since these would only cover medical malpractice by the doctors but none of the other investigators in the clinical trial.

In many countries there is legislation for clinical trial insurance requirements. In the UK, most sponsors abide by the Association of British Pharmaceutical Industries (ABPI) Clinical Trial Compensation Guidelines that recommend that the sponsor's indemnity covers injury to clinical trial participants arising out of the administration of the product(s) under investigation or any clinical trial intervention or procedure provided for or required by the protocol to which the subject would not have been exposed to but for their participation in the clinical trial (9).

A study conducted in India by Thatte et al (12) found out that most of the insurance documents submitted to ethics review committees were insurance certificates with

only 16.67% of the documents with complete insurance policies attached. This is consistent with this study findings showing that 94.4% of the clinical trial insurance documents submitted to PPB are insurance certificates with only one protocol (5.6%) having both the insurance certificate and insurance policy enclosed. The complete insurance policy document contains more information on the preconditions for payment of liability claims which would enable ethics committees to review the adequacy of the insurance cover.

5.1.2 Components of clinical trial insurance documents

In the present study, 61.1% of the insurance certificates provide both clinical trial insurance and product liability insurance. In the Thatte et al study (12) product liability insurance was provided in 28% of the cases.

In the present study, 27.8% of the insurance policies were described to be of the no-fault type. In no-fault type of compensation trial participants are provided with compensation for research related injury without having to prove that the injury was caused by medical negligence or error on the part of the investigators or sponsor. No-fault compensation approach is a more sustainable method as it aims at providing compensation without ascribing blame and also enables participants to receive compensation in situations where negligence cannot be proved (42).

Bodily harm, death or any harmful effects and consequences arising from participating in a clinical trial may occur during the running period of the trial or long after the trial is completed. This necessitates insurance coverage and compensation during and after a trial is completed (39). In the UK, the Guidance on Insurance and Compensation in the event of injury in Phase I clinical trials (2012) recommends that the insurance cover continues in respect of any claims made for a minimum period of three years (43) while in Malawi, the guidelines require the insurance cover to extend for a period of five years after the end of a clinical trial (39). In Kenya, the guidelines do not mention provision of insurance that covers participants for a period after the end of the clinical trial. In a study conducted in India (41) most of the insurance policies reviewed were for a period of one year. Thatte et al (12) revealed the duration of the policies was one year or more depending on the study duration. The present study showed the duration of the policies as one year with the exception of one policy whose duration extends to

twelve months after the end of the clinical trial. It is assumed that the insurance covers were to be renewed annually during the running period of the trial.

Insurance policies specify the amount that may be paid to the claimants. The claim is usually based on per claim liability and aggregate liability. A study conducted in India by Ghooi and Divekar (41) showed some policies with both per claim and aggregate limits of liability while some only had aggregate liability and the value of per claim and aggregate liability similar for two policies. In the present study, majority of the insurance certificates (83.3%) indicate both per claim and aggregate liability and the value of per claim and aggregate liability was similar for 50% of the certificates.

In the UK, the Guidance on Insurance and Compensation in the event of injury in Phase I clinical trials (2012) provides a minimum level of cover of £5 million in aggregate per protocol for "first in man" studies with the cover reduced to a minimum of £2.5 million in aggregate per protocol in respect of other studies (43). In the study carried out by Ghooi and Divekar (41), the per claim liability ranged from Rs.1,500,000 (£ 14,857) to Rs.5,000,000 (£ 49,525) while the aggregate liability ranged from Rs.2 Cr (£ 198,100) to Rs.14 Cr (1,386,700). In the present study, the per claim liability ranges from Ksh. 2,000,000 (£ 12,400) to Ksh.2, 250,000,000 (£ 13,950,000) while the aggregate limits of liability range from Ksh. 10,000,000 (£ 62,500) to Ksh. 1,500,000,000 (£ 9,375,000). The minimum per claim liability is comparable to the amount in the Indian study but the maximum per claim liability is higher in Kenya as observed in this study.

The number of participants enrolled in a clinical trial influences the maximum amount payable per claim since the higher the number of research participants, the lower the amount payable per claim. In the present study, only 22.2% of the insurance certificates showed the number of participants covered by the insurance policy. This makes it difficult for the reviewers to assess the adequacy of the insurance for the participants. The specification of the number of participants covered would also ensure that investigators do not violate the terms of the insurance policy and expose participants to inadequate compensation.

Insurance companies usually insert a clause on the deductibles. This is the amount that is deducted by the insurance company to cover expenses incurred during the

processing of the claims. In the Ghooi and Divekar study (41) the amount of deductible ranged from Rs.100,000 (£990) to Rs.168,630 (£1,670) with one policy stating that the deductible to be 5% of every claim. In the present study, the deductibles ranged from Ksh. 10,000 (£62) to Ksh. 3,750,000 (£23,250) while one protocol indicated that the deductible would be 5% per claim.

In Kenya, the guidelines do not stipulate the location of the insurance company offering clinical trial insurance. In Malawi, the guidelines require that the insurance be taken out with a local insurance company or a local representative of a foreign company (39). Studies in Brazil need a local insurance broker as the premium and fees must be paid locally to the insurer while other Latin American countries require the sponsor to have a local physical presence or a local representative in the country (44). It is unclear whether an insurance policy stipulated by a company located outside Africa, with significant language and legal differences to the study countries , may work efficiently (45). The present study showed that 61.1% of the insurance policies are provided by foreign insurance companies mostly from the UK and 27.8% by local insurance companies.

Majority of the key informants interviewed in this study proposed that the clinical trial insurance be taken out with a local insurance company or a local representative of a foreign company to make the compensation logistics easier.

5.1.3 Magnitude and Scope of Clinical Trial Insurance

In the present study, 96% of the Phase IV trials do not have clinical trial insurance and majority of the stakeholders interviewed have proposed that there should be different insurance requirements for different phases of a clinical trial since the associated risks are different. The present study's findings also show that clinical trials involving investigational drugs were more likely to have insurance compared to those involving registered drugs. This could be due to these trials involving investigational agents being initiated by multinational pharmaceutical companies which abide by the requirement to have clinical trial insurance in their home countries, as well as the higher risks of adverse events associated with trials on investigational drugs.

The European Union Clinical Trials Regulation (2014) provides that insurance covering the investigator, the institution or product liability insurance will be

sufficient for low-intervention trials and sponsors are not obliged to provide specific insurance or indemnity compensation (46). Low intervention trials are defined in the regulations as clinical trials in which the investigational product is already authorized; its use in the trial is in accordance with the terms of the marketing authorization or its use is based on published scientific evidence of safety and efficacy; and the additional diagnostic or monitoring procedures do not pose more than minimum additional risk or burden compared to normal practice in a Member state.

The findings from the present study showed that only 38.9% of the insurance certificates have made explicit reference to the clinical trial covered. Making explicit reference to the proposed clinical trial in the insurance certificate would facilitate research participants enrolled in the study to make claims in case of trial related injuries from the insurance company that has insured the clinical trial.

5.1.4 Information on compensation provided by the informed consent documents

Ethics review committees should thoroughly review the informed consent document (ICD) to ensure that adequate compensation for research related injuries has been provided for and this fact is informed to the trial participants (42). The KNH/UON - ERC guidelines require the sponsor to indicate who is responsible for the treatment of physical injuries to research participants (30). As part of the informed consent process for research involving more than minimal risk, regulations of the US Department of Health and Human Services require that potential participants be told whether any compensation of medical treatments are available if injury occurs (47).

In a study of informed consent documents by Thatte et al (12) there was a gradual increase in the proportion of ICDs that provided details on compensation from 2003-2007 with 83% of the ICDs in 2007 providing details on compensation. In this study, 73.1% of the informed consent documents have provided details on compensation for research related injury.

Organizations conducting research should compensate any research participant who is injured as a direct result of participating in research, without regard to fault. Compensation should include at least the costs of medical care and rehabilitation

(48). In the study by Thatte et al (12), medical care was provided for trial related adverse events by most of the ICDs that mentioned compensation and two cases mentioned that monetary compensation of medical expenses incurred would be provided. This compares with the present study which shows that medical care is provided by 82.5% of the study protocols that mention compensation and 5.3% provide monetary compensation for medical expenses.

In the present study, only 7.7% of the informed consent documents have provided information on an insurance policy that covers research participants. This compares with the study in India (12) that showed that very few informed consent documents mentioned insurance (8% in 2004 increasing to 50% in 2007). The failure to mention the presence of an insurance policy leaves the participant unaware of the fact that he/she has been insured against adverse events occurring in the trial and the details of what is covered in the insurance in order to claim the same if required (42). The present study also revealed that 10.3% of the informed consent documents indicate that the trial participants' National Health Insurance Fund contributions would be paid by the sponsor to cover costs of medical care.

5.1.5 Knowledge among key informants on insurance and compensation in clinical trials

In the present study, most interviewees indicated that there was insufficient knowledge on clinical trial insurance among key stakeholders involved in the review and approval of clinical trials with the reasons given being lack of ethics committee guidelines for the review of the insurance documents, insufficient knowledge on clinical trial insurance in the local insurance industry and the technical nature of the insurance documents. This could have contributed to the low level of compliance with respect to clinical trial insurance.

In the Thatte et al study (12) in-depth interviews with key stakeholders revealed that there was lack of awareness among investigators and ethics committee members regarding the issue of compensation and both the investigators and ethics committee members relied entirely on the sponsors to make arrangements for payment and never went into the details. The ethics committee members cited paucity of time and lack of competence for not going through the compensation plan for research participants.

5.2.0 Conclusion

The number of clinical trial applications submitted to the PPB with clinical trial insurance certificates attached was significantly low (23.1%) while 28.2% of the protocols had professional indemnity certificates for doctors attached. The study revealed that a higher proportion of protocols submitted in 2013 and 2014 had clinical trial insurance certificates than those submitted in 2011 and 2012.

Majority (61.1%) of the insurance certificates provided for both "clinical trial insurance" and "product liability insurance" type of insurance and 27.8% of the insurance certificates indicated the insurance to be of the no-fault type. The duration of the insurance policies was one year for majority (94.4%) of the protocols and 61.1% of the insurance covers were provided by foreign insurance companies. The phase of a clinical trial and whether the trial involved a registered or investigational drug were found to influence the presence of clinical trial insurance.

The issue of compensation for clinical trial related injury was mentioned by most (73.1%) of the informed consent documents with medical care being the type of compensation provided in most of the clinical trials.

The study revealed that there is insufficient knowledge on clinical trial insurance among stakeholders involved in the review of clinical trials with majority of the interviewees aware of medical care as the most common form of compensation.

5.3.0 Recommendations

5.3.1 Policy changes

The Pharmacy and Poisons Board is in the process of reviewing the Clinical Trial guidelines and the findings of this study will be valuable in enriching the clinical trial insurance requirements. The following are recommendations based on the findings of this study:

1. There is need for strict enforcement of the guidelines to ensure that sponsors of clinical trials take out clinical trial insurance that covers trial participants in case of trial related injury.

2. The complete insurance policy document should be attached to the clinical trial application and a renewal certificate for the insurance policy submitted annually. An annual renewal insurance certificate will ensure that participants are insured during the entire duration of the clinical trial.

3. Due to the technical nature of the insurance documents, a standard form that summarizes the different aspects of the insurance policy needs to be attached to the clinical trial application to make it easier for the ethics committees and reviewers to assess the adequacy of the insurance covers.

4. There should be enhanced scrutiny by ethics review committees to ensure that all informed consent documents mention how compensation for research related injury will be provided. There is also need to sensitize ethics review committees on clinical trial insurance to ensure that adequate compensation is provided for clinical trial participants.

5. There is need for development of guidelines for compensation of research related injury and insurance requirements for clinical trials. The different phases of clinical trials expose trial participants to different levels of risks and therefore there should be different insurance requirements for different phases. However, the guidelines should not be so stringent as to hinder the conduct of clinical research in the country.

6. There is need to review the clinical trial insurance legal and regulatory framework to ensure more local insurance companies are able to develop insurance products to cover local clinical trials.

5.3.2 Future Research

This study's findings would form the basis for a study that will seek views from a larger and more representative group of stakeholders on the aspects of compensation in clinical research and recommendations that will help in the development of compensation guidelines.

There is need for research focussing on reports on research related adverse events submitted to PPB and Ethics Review committees and action taken by sponsors/investigators and the regulatory bodies.

A detailed study of the complete insurance policy documents would assess the adequacy of the insurance policies provided in local clinical trials and preconditions that are mentioned in the policies.

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APPENDICES

Appendix 1: KNH/UON Ethics and Research Committee Approval Letter

KENYATTA NATIONAL HOSPITAL APPROVED 27 MAR 2015 KNH/UoN-ERC P.O. Box 20723-00202 NRB

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Ref: KNH-ERC/A/140

27th March, 2015

Simon K. Wahome
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
University of Nairobi

Dear Simon

Research Proposal: Insurance and indemnity Coverage for Clinical Trials of Medicines in Kenya (P78/02/2015)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 27th March 2015 to 26th March 2016.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.erc.uonbi.ac.ke**

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chair, KNH/UoN-ERC
Supervisors: Dr. G.O. Osanjo, Dr. K.A. Sinei, Dr. E.M. Guantai

Appendix 2: Pharmacy and Poisons Board Student Confidentiality Agreement

REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

STUDENT CONFIDENTIALITY AGREEMENT

In the course of evaluation of your study, you will gain access to certain information, which is proprietary to Pharmacy and Poisons Board and other interested parties.

You shall treat such information (hereinafter referred to as "**the Information**") as confidential and proprietary to PPB or the aforesaid parties. In this connection, you agree:

(a) Not to use the Information for any purpose other than discharging your obligations under this agreement;
(b) Not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

I shall not communicate your observations and/or findings as well as any resulting recommendations and/or decisions of your work to any third party, except as explicitly agreed by PPB.

I understand that any information (written, verbal or other form) obtained during the performance of my duties must remain confidential. This includes all information about members, clients, families, employees and other associate organizations, as well as any other information otherwise marked or known to be confidential.

I understand that any unauthorized release or carelessness in the handling of this confidential information is considered a breach of the duty to maintain confidentiality.

I further understand that any breach of the duty to maintain confidentiality could be grounds for immediate dismissal and/or possible liability in any legal action arising from such breach.

You confirm that you have no situation of real, potential or apparent conflict of interest including financial or other interests in, and/or other relationship with, a party, which:

(i) May have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or

(ii) May have a vested interest in the outcome of evaluation of the application.

You shall promptly notify the Registrar, PPB of any change in the above circumstances, including if an issue arises during the course of your work.

All documents supplied to you in connection with this application shall be accepted in strict confidence and shall be held in safe and secure custody at all times.

I hereby accept and agree with the conditions and

Declaration:

I, the undersigned, do hereby agree to adhere to the provisions contained in this agreement.

I hereby declare that I have/~~do not have~~ (*delete what is NOT applicable*) a Conflict of Interest with the following application(s)/any of the applications that I have been requested to review (*delete what is NOT applicable*)

Reference number (s) of application (s) with which I have a conflict of interest

Simon K. Watkins

(Student Name)

(Signature)

06/05/2015

(Date)

Appendix 3: Data Collection Form the For Review of the Insurance Documents

1. Serial no…….
2. Does the protocol have attached insurance certificate

   YES ☐

   NO ☐

3. Does the insurance certificate indicate the insurance cover as being no-fault insurance?

   YES ☐

   NO ☐

4. What other documents that guarantees compensation is attached?

a. Letter of indemnity

b. Other……

   …….

   …….

5. Is the Insurance certificate certified by a notary public?

   YES ☐

   NO ☐

6. Who has initiated the clinical trial?

a. Sponsor

b. Investigator

c. Other……

7. Is the study a multicentre trial?

   YES ☐

   NO ☐

8. In which institution is the clinical trial being carried out?

   ……

9. Does the clinical trial involve an investigational drug or registered drug?

   …….

10. What is the pharmaceutical classification of the medicines being used in the clinical trial?

    ……..

11. What is the phase of the clinical trial?

a. Phase I

b. Phase II

c. Phase III

d. Phase IV

12. Does the insurance certificate make explicit reference to the proposed clinical trial?

    YES ☐

    NO ☐

13. Does the insurance cover all the centres involved in the trial for a multicentre trial?

    YES ☐

    NO ☐

14. What type of insurance is provided

a. Clinical trial insurance ☐

b. Product liability insurance ☐

c. Professional indemnity ☐

d. Other: _____

15. What is the duration of the insurance policy compared to the duration of the study?……..

16. Is the insurance cover provided by a local or foreign insurance company?

……

17. Does the insurance certificate indicate the number of participants covered?

YES ☐

NO

18. What are the terms and conditions enclosed in the insurance document that may waive the right of the research participant to compensation?

……..

…….

…….

19. Are there any deductibles applicable?

YES ☐

NO ☐

20. What are the categories of insured participants?

……

……

21. Does the insurance cover the following?

a. Death ☐

b. Permanent or temporary impairment ☐

c. Financial consequences directly attributable to participation in the trial ☐

d. Other……

22. What are the limits of liability?

a. Per claim liability ☐

b. Aggregate liability ☐

c. Value per claim and aggregate liability ☐

d. Other: _____

23. Are the limits of liability subject to review?

YES ☐

NO ☐

Comments: _____

Appendix 4: Data Collection Form for the Informed Consent Documents

1. Serial No……
2. Year of submission to PPB…….
3. Is compensation to be provided for research related injury?

   YES ☐

   NO ☐

4. Type of injury to be compensated

   ……

   ……

5. Type of compensation

   a. Reimbursement of medical expenses ☐

   b. Medical care ☐

   c. Monetary compensation ☐

   d. Other ☐

   If other, please specify: _____

   6. Who bears the expenses?

   a. Sponsor ☐

   b. Investigator ☐

   c. Other: _____

   7. Will payment be provided for the following in case of trial related injury?

   a. Lost wages ☐

   b. Disability ☐

   c. Discomfort ☐

8. When will compensation be provided?

a. If the injury is related to the study treatment

b. All types of injuries

c. Only if patient does not have medical insurance

d. Reimbursement only if the additional amount is not covered by participants medical insurance

e. Other: _____

10. Does the informed consent document mention an insurance policy that covers trial related injuries?

YES ☐

NO ☐

If yes, what information about the policy is provided?

…….....

.....

Appendix 5: Dummy Tables

Dummy Table 1: Elements of the Insurance document

Element/Characteristic	Data
Presence of insurance certificate	Yes-n,%, No-n,%
Multicentre trial	Yes-n,%, No-n,%
Reference to the specific study	Yes-n,%, No-n,%
Cover for multicentre trials	Yes-n,%, No-n,%
Type of insurance provided	Clinical trial insurance, product liability insurance, professional indemnity
Duration of the insurance policy	During the trial period, Some years after the end of the trial,Mean, standard deviation
Number of participants indicated in the policy	Yes-n,%, No-n,%
Enclosed terms and conditions	
Are there deductibles?	Yes-n,%, No-n,%
Categories of insured participants	
What is covered by the policy	Death, permanent or temporary impairment, Financial losses
Limits of the liability	Per claim liability-n,%, Value-Mean, Standard deviation Aggregate liability-n, %, Value -Mean, Standard deviation
Limits of liability subject to review	Yes-n,%, No-n,%

Dummy Table 2: Informed consent form characteristics

Characteristic	Data
Year of submission of protocol	2011, 2012, 2013, 2014
Compensation to be provided in case of injury	Yes-n,%, No-n,%
Type of injury to be compensated	
Type of compensation provided	Reimbursement of medical expenses, medical care, Financial compensation,
Who bears the expenses?	Sponsor, n,%, Investigator, n,%
Is compensation provided for the following?	Lost wages, n,% Disability, n,% Discomfort, n,%
When compensation provided	If the injury is related to the study treatment, All types of injuries, Only if patient does not have medical insurance, Reimbursement only if the additional amount is not covered by participants medical insurance
Insurance policy mentioned	Yes-n,%, No-n,%

Appendix 6: Semi-structured interview guide

Interviewee number:……

Designation:…….

Profession of interviewee……..

Institution……...

Role in clinical trial process.....

1. What are the compensation mechanisms for research related injury in Kenyan Clinical trials?

- Insurance policy?
- Letter of indemnity from sponsor?
- Medical care?
- Financial compensation?
- Other (please specify): _____

2. Is there sufficient knowledge on clinical trial insurance in Kenya? Explain your response:

3. Are the current guidelines regarding compensation for research related injury adequate? Explain your response:

4. Should there be a national policy governing the requirements for the provision of insurance cover for research participants?

   Which institutions should be involved in developing the policy?

5. Should ethics review committees review the insurance policy documents to ensure adequate compensation is provided?

6. What insurance documents should be attached to the protocol?

- Insurance policy?
- Insurance certificate?

- Others (please specify): _____

7. Should the insurance documents be certified by a notary public? If so, why?
8. Should there be need to prove causality before compensation is provided?
9. What are the types of clinical trial insurance available?
10. What elements should be included in the insurance policy?
11. Should no-fault insurance be recommended in Kenyan clinical trials?
12. What should be the duration of the insurance policy?

- Only during the running period of the trial
- Beyond the duration of the study (indicate by how many years)

13. Should professional liability for the investigators be covered by the insurance policy?
14. Should there be different insurance requirements for different phases of clinical trials? Explain your answer:
15. Should there be separate insurance covers for each site in a multicentre trial? If yes, why?
16. Who should be responsible for determining the quantum of compensation payable to injured research participants?

- Ethics review committee?
- Insurance company?
- PPB?
- Other (please specify): _____

17. Should terms and conditions which waive the rights of the research participant be included in the policy?
18. Should the insurance be provided by local or foreign insurance companies? Explain your answer:

Appendix 7: Informed Consent Form for Key Informant Interviews

Informed consent form for Participation in the Interview "Insurance and Indemnity Arrangements for Clinical Trials of Medicines in Kenya"

Principal Investigator:

Dr.Simon Wahome,

Masters Student, School of Pharmacy, University of Nairobi

Supervisors:

Dr. George Osanjo, School of Pharmacy, University of Nairobi

Dr.K.A. Sinei, School of Pharmacy, University of Nairobi

Dr. E.M. Guantai, School of Pharmacy, University of Nairobi

1. Information Sheet

This study is titled "Insurance and Indemnity Arrangements for Clinical Trials of Medicines in Kenya". Information regarding the study will be provided and I request that you willingly participate in the interview.

The study aims to assess knowledge among various stakeholders on the policies related to compensation of clinical trial related injury in Kenya, to determine the insurance and indemnity arrangements for clinical trials of medicines in Kenya and the forms of compensation provided for research related injury. The results of this study will help in identifying the types and adequacy of insurance and indemnity covers in place for research related injury and the level of adherence to the clinical trial guidelines. The study aims will be achieved through desk review of study protocols submitted to Pharmacy and Poisons Board for review and through interviews with key informants involved in the conduct, review and approval of clinical trial protocols and insurance underwriters of clinical trial insurance.

You are being requested to participate in this study due to your expertise in the conduct and ethical review of clinical trials in Kenya. This in-depth interview will involve use of probing questions and your responses will be recorded. Your

responses will be held confidentially and will not be taped. The interview will take about 45 minutes.

There are no expected risks due to your participation in this study. There might be no direct benefit from your participation but your contribution will lead to improvement in the guidelines regarding compensation of research participants for research related injury. There will be no reimbursements offered as a result of participating in the study.

The results of this study will be shared with all stakeholders involved in the conduct, review and approval of clinical trials of medicines in Kenya.

2. Certificate of Consent

I have read and understood the information provided regarding the study and my questions regarding the study have been addressed. I am willingly and consent to participate in this study.

NAME OF PARTICIPANT:……

SIGNATURE:……..

DATE:……...

Statement by the researcher:

I have provided all relevant information to the participant and answered all questions asked regarding the study. I have explained to the participant that his/her responses will be recorded in a note book and will not be taped. I confirm that information requested has been provided voluntarily.

A copy of this informed consent has been provided to the participant.

NAME OF RESEARCHER:……

SIGNATURE:……

DATE:…….

CONTACTS OF PRINICIPAL INVESTIGATOR:

For any questions regarding the study, please contact:

The principal investigator,

Dr. Simon Wahome

School of Pharmacy, University of Nairobi

P.O. Box 19676- 00202

Nairobi

Tel: 0722495650

Email address: simokanyoro@gmail.com

OR

CONTACT OF KNH/UON ERC:

Secretary, KNH/UON Ethics Review Committee,

P.O. Box 19676-00202,

Nairobi.

Tel: 020 2726300 Ext 44355

Email address: uonknh_erc@uonbi.ac.ke

Appendix 8: Summary of thematic codes generated per interviewee

	Thematic code 1	**Thematic code 2**	**Thematic code 3**	**Thematic code 4**	**Thematic code 5**	**Thematic code 6**	**Thematic code 7**
Interviewee number	Medical care as the most common form of compensation	Insufficient knowledge on clinical trial insurance	ERC has a role in the review of insurance documents	Insurance policy document should be attached to the protocol	Duration of insurance cover should be dependent on the study protocol	Different insurance requirements for different phases of a clinical trial	Insurance cover should be provided by a local insurance company
1	✓	✓	✓	✓			✓
2	✓	✓	✓	✓	✓	✓	✓
3	✓	✓	✓	✓	✓	✓	✓
4		✓	✓	✓	✓	✓	
5			✓			✓	✓
6	✓	✓	✓				
7	✓	✓	✓	✓	✓	✓	✓
8	✓	✓	✓	✓			✓
Response rate	75%	87.5%	100%	75%	50%	62.5%	75%