REGULATORY COMPLIANCE OF DRUG SAFETY REPORTING IN CLINICAL TRIALS APPROVED BY THE PHARMACY AND POISONS BOARD OF KENYA

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DECLARATION OF ORIGINALITY FORM

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DEDICATION

I dedicate this work to my dear parents and family for their endless prayers and their belief in me.

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LIST OF ABBREVIATIONS AND ACRONYMS

CIOMS	Council for International Organizations of Medical Science
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
EU	European Union
GCP	Good Clinical Practice
ICF	Informed consent Form
IND	Investigational new drug
ICH-GCP	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice guidelines
IMP	Investigational medicinal product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
PPB	Pharmacy and Poisons Board
RCT	Randomized controlled Trial
SAE	Serious Adverse Event.
SUSARs	Suspected Unexpected Serious Adverse Reactions.
MeDRA	Medical dictionary for regulatory activities
UNESCO	United Nations Educational and Scientific Cultural Organisation

DEFINITION OF TERMS

Sponsor: A sponsor is an individual, company or organisation that takes responsibility for initiation, management and financing a clinical trial

Investigators: These are qualified individuals trained and experienced to provide important information to sponsors with regard to safety reporting. They are expected to observe, evaluate, manage and document all effects of treatment, including the reporting of adverse events.

Data and Safety Monitoring Board: This is an expert committee mandated to review on a regular basis the accumulating data from the clinical trial and ensure the continuing safety of participants and those yet to be enrolled.

Clinical trial protocol: It is a document that describes objectives, design, methodology, statistical considerations and organization of a clinical trial.

Adverse event: This is any untoward occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Serious adverse event (SAE): It is a serious adverse event and should be reported if it results in death, is life-threatening, requires hospitalization or results in prolongation of existing hospitalization, results in persistent incapacity, is a congenital anomaly or is a medically important event that may require medical or surgical intervention.

Suspected unexpected serious adverse reactions (SUSARs): This is a serious adverse event with a possible relationship to the study drug, and should be considered unexpected if the nature, severity or frequency of that event is not consistent with the information on the investigator's brochure.

Compliance monitoring: This involves ensuring receipt of appropriate, high-quality reports, submitted in accordance with specified timelines. The completeness of reporting across individual and cumulative safety reports is also assessed.

Clinical trials: A clinical trial is any investigation on human participants intended to discover or verify pharmacological and pharmacodynamic effect of an Investigational Medicinal Product (IMP) .Clinical trials study absorption, distribution, metabolism and

excretion of an IMP. Clinical trials provide the basis for regulatory approval for safe and effective medicine.

Good clinical practice (GCP): This is an international ethical standard for conducting, designing, reporting and recording trials involving human subjects.

Investigational new drug (IND): This is a term used by the United States of America to mean any substance for which Food Drugs Act (FDA) approval is being sought. A drug is considered new even if it has been in the market if a change is proposed in its use.

Investigational medicinal product (IMP): This is an active pharmaceutical ingredient which is being tasted in clinical trials. It includes products with marketing authorization but packaged in a different way from authorized form.

ABSTRACT

Background

Drug safety reporting in clinical trial is a continuous activity that goes throughout a products life cycle. Drug safety reporting compliance in clinical trials is important in identifying participant's safety concerns and protecting them from adverse events. Standards for drug safety reporting and managing adverse events in clinical trials are internationally accepted and have to be maintained during clinical trials. This study was conducted to establish if drug safety reporting in clinical trials complies with national and international guidelines.

Objectives

The study aimed to determine the compliance of drug safety reporting in clinical trials approved by the Pharmacy and Poisons Board of Kenya, with national and international clinical trials guidelines.

Methods

A retrospective cross-sectional study was conducted at Pharmacy and Poisons Board which is a regulatory body established under the Pharmacy and Poison's Act CAP 244 to regulate clinical trials**.** Clinical trial protocols and reports of adverse events submitted to Pharmacy and Poisons Board of Kenya from 2013 to 2017 were reviewed. Information was abstracted from the files using a checklist to determine if the clinical trial protocol and safety reports conform to the requirements set out by Pharmacy and Poisons Board (PPB) and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice guidelines (ICH-GCP). Data obtained was used to compute indicators that reflect the extent of compliance to regulatory requirements. Descriptive data analysis was done using STATA version 10 software.

Results

Out of the 69 clinical trial protocols analysed 63 (91.3%) were internationally sponsored trials compared to 6 (8.7%) that were locally sponsored trials. Twenty four clinical trial protocols were Phase I; Phase II were 23 while 22 were Phase III. A review

of the clinical trial protocols showed that 37 (53.6%) had an explicit objective on drug safety evaluation.

On safety reporting methods and pathways assessment; clinical trials protocols with provisions for safety reporting to local ethics research committee (ERC) were 69 (100%).Protocols that had provision for safety reporting to the sponsor were 53 (76.8%).Sixty (87.0%) protocols had provision for safety reporting to PPB. Protocols with provisions for sponsor to report to regulatory agencies outside Kenya were 42 (60.9%). Protocols that had a data collection tool with a case report form of reporting suspected unexpected serious adverse reactions (SUSARs) were 63 (94.0%).

Out of the 28 safety reports reviewed with respect to completeness and causality, 20 (70.4%) of the safety reports were complete while 8 (29.6%) of the safety reports were not complete as the patient code, age or type of suspected unexpected serious adverse reactions/serious adverse events (SUSAR/SAE) was not stated. Drug safety reports with age included were 94.4%. The type of suspected unexpected serious adverse reactions/serious adverse events (SUSAR/SAE) was stated in 38.9% of the safety reports. The start date of adverse event was stated in 5.6% of the safety reports and end date was included in 38.9% of the safety reports. Causality was stated as probable in 4 (12.5%) of the drug safety reports.

In relation to reporting timelines of serious adverse events (SAEs); 40 (58.8%) clinical trial protocols complied with PPB guidelines on reporting timelines to PPB of not later than twenty four hours. Fifty seven (82.4%) clinical trial protocols complied with PPB guidelines reporting timelines to sponsor of not later than twenty four hours. On description of reporting timelines of suspected unexpected serious adverse reactions (SUSARs); 6 (9.0%) clinical trial protocols complied with PPB guidelines of reporting timelines to sponsor of not later than seven calendar days with follow up reports within eight days.

Measures taken by the sponsor to mitigate serious adverse events were hospitalisation in which 22 (78.6%) of the safety reports had their clinical trial participants hospitalised. For 26(37.5%) studies the sponsor formed a data and safety monitoring board (DSMB) to conduct an interim data analysis and review emergent safety issues. In one case (1.6%), the clinical trial was terminated early as the study objective had

been achieved. Expedited reporting was done in 8 (11.6%) trials that showed a significant risk by the sponsor to the regulatory body.

Conclusion

The study identified gaps in drug safety reporting in clinical trials which different stakeholders can use to improve communication between themselves to ensure timely reporting of adverse events. There is need for a safety data base that will ensure safety reports are complete, quantification of adverse events and follow ups are done. There is need for the regulatory body to carry out more inspections of clinical trial sites to improve drug safety reporting.

CHAPTER 1: INTRODUCTION

1.1 Background

Clinical trials are distinct, well monitored and controlled systemic studies of medical treatments on human volunteer's .They are intended to discover or verify pharmacological and pharmacodynamic effect of an investigational medicinal product (IMP). Drug safety reporting is a continuous dynamic activity that never stops during a products life cycle. Reporting is important in identifying participant's safety concerns and protecting them from rare adverse events (1) . The clinical trial protocol outlines how adverse events will be reported and monitored. Provisions for actions to be taken in case of adverse drug reaction are also stated. An adverse event is any unfavourable and unintended symptom and which does not necessarily have to have a causal relationship with the test article (2) . There are different types of adverse events that can be encountered in clinical trials. Adverse events causes a change in the health of a participant which can be life threatening, a congenital defect like thalidomide effects or inability to conduct normal life activities (3) .A serious suspected adverse event may put a participant at risk calling for a medical or surgical intervention (4) .

In a clinical trial the participants are given a drug to investigate whether it is safe and effective. The trial gives data that is evidence based helping healthcare workers in decision making therefore directing resources to the strategy or treatment that give the best outcome (5) .

Regulation of clinical trials forms the basis of drug safety and public confidence in using drugs. The drug under investigation must first be tested in laboratory animals for potential toxicity before being tried in human beings. The regulatory body protects the study participants from harm and unethical practices (6).

Pharmacovigilance plays an important specialized role in clinical trials by ensuring that the drug are safe, effective and of quality before approval for use in clinical trials (9).The Pharmacovigilance unit develops safety reporting tools for adverse events that occur during clinical trial process and post marketing use. In Kenya an applicant makes an application to the clinical trial division and pharmacovigilance unit which is checked for completeness (8). The division protects study participants from significant harm and unreasonable risk.

Adverse events that participants suffer indicate potential risks the public face when using drugs. Risk benefit analysis of drugs is importance to ensure clinical safety. A safety data base enables one to assess, monitor and report any safety issues to the regulatory body(9). Over time there has been evidence that completeness of reporting of adverse event in clinical trials is not optimal and this problem has been growing over time. Clinical trial safety reports need to be clear, complete and transparent (10).

Clinical trials should be carried out following standards which include: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use- Good Clinical Practice guidelines (ICH-GCP),Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS), CONSORT additions for harms (for reporting outcomes of clinical trials) and Declaration of Helsinki ethical principles (11) .National and international standards are set to determine criteria for authorization and marketing of a drug. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human produced guidelines for planning, application, analysis, conclusion and safety reporting of clinical trials. Good clinical practice aims at ensuring safety, efficacy and quality of a drug. Approval to conduct clinical trials is based on ethical principles as stated in Declaration of Helsinki which includes respect for humans, benevolence and equity (5).

Adherence to these guidelines gives people a guarantee that their well being and health is paramount. When the rights of participants are safeguarded; there is credibility of clinical data. Most clinical trials focus on benefits and do not always assess adverse events within the framework of the study objectives and outcomes. This is partly due to shortcomings in the knowledge of researchers in carrying out research with regard to methods and policies of GCP or the likelihood that a true assessment of harms may compromise the research findings (12).

A clinical trial is an expensive process and benefits must outweighing risks before approval of a drug (9). Adverse event surveillance in clinical trials requires detection and reporting to the regulatory agency within acceptable time limits.

The reporting window depends on the seriousness of the event and the investigation of adverse events to establish a causality relationship with the drug under study. Adverse events are not well accounted for during clinical trials making it difficult to make an equilibrium between benefits and harm of an investigational drug. This may affect the

quality of clinical trials resulting in production of drugs that are less efficient to the population (12).

Safety of participants is based on protocol adherence, reporting on time and documenting of safety data, dealing with anticipated and unforeseen issues (13) .

Some aspects of data quality are important: accurateness, comprehensiveness and acceptance. Accurateness is checking if the data in a research is rational. Comprehensiveness ensures all vital data is obtainable or inaccessible. Acceptance associates to the duration between happening of an event and date of reporting (14).

Reporting of adverse events outcomes which are patient focused will produce accurate and efficient safety information during data collection. Monitoring of adverse events is of importance as this will support the participants and educate them on symptoms of any adverse events (15).

The national guidelines of clinical trials have safety reporting timelines which are specific after the sponsor ascertains that the adverse reaction fits reporting. Assessments of causality, expectedness and seriousness are done before submission of reports (8).

1.2 Problem Statement

Since the inception of clinical trial division in PPB there has never been a pharmacovigilance inspection to determine if the standards of clinical trial application and safety reporting comply with internationally accepted standards. There is no data that can guide policy change to improve the existing systems to international standards.

When participants suffer adverse events it points to the public the likelihood of harm when using the product. Clinical trials are carried out on selected populations and clinical safety is not absolute (9).In Kenya participants do not enjoy all round standard of care similar to counterparts in developed countries. Further in developed countries the best current interventions which may be locally available are used as standard care in clinical trials. The alternatives used in developing countries are usually inferior to international standards (6).

Despite the availability of requirements for requesting to carry out a study in Kenya, there is no data to indicate how many clinical trials attain the standards required in dealing with adverse events .Protocol violations may lead to the introduction of systematic, random, and design errors into a clinical trial study. Violations in clinical trials also lead to flawed trial conclusions and patient harm (16).The standards of

reporting should give accurate information on frequency and severity of adverse events (17). There are no standards to reliably establish drug safety reporting issues. Sponsors are also slow to submit drug safety reporting issues as they may not fully appreciate details in GCP.Drug safety reports in clinical trials are based on investigator brochure creating a reporting bias. Ten years ago (2009) the Kenyan Pharmacy and Poisons Board created a clinical trial division. The division has only two members making it under staffed; therefore there might be inadequate review of submitted clinical protocol applications. Given that in Africa many regulators lack sufficient training in the conduct of clinical trials, the regulatory oversight over the conduct of clinical trial may be inadequate. Therefore an inspection is required on the conduct of clinical trial especially with regard to pharmacovigilance of reporting. The problems that might exist with regard to pharmacovigilance of clinical trials may include inadequately developed protocols, underreporting, and failure to report on time. Lack of knowledge on pharmacovigilance reporting leads to failure to institute the necessary interventions. There is gross under-reporting and lack of adequately written SOPs and information. Information can also get lost and medicine investigations data may be keyed wrongly (14).

Selective reporting of findings brings about discrepancies between what was planned in a trial and what is eventually reported. This poses a threat to validity of evidence based healthcare (18).New information with a risk benefit analysis should be submitted to the PPB within fifteen days (8).Investigators aim at efficacy of the investigational medicinal product (IMP) fearing that reporting of adverse events may bring discredit and termination of clinical trials. The population eventually gets drugs that are less safe and more harmful (12). Errors in reporting generate many enquiries resulting in doubting of the efficacy and safety of drugs when is use by the public (19).

1.3 Study Justification

In Kenya the PPB is mandated by law to regulate clinical trials that are required to comply with drug safety reporting (8).There are few studies in Kenya on regulatory compliance of drug safety reporting during clinical trials. Data on compliance of safety reporting is important in improving patient and study participants' safety. The society is furnished with important information concerning adverse drug reactions and efficacy of drugs. This will improve the length of life and productiveness of the society. Safety

of clinical trial participants is dependent on timely reporting and recording drug safety information. Variability of drug response in our daily clinical practice is relative to the many observations made during clinical trials. Compliance of drug safety reporting in clinical trial will assist the prescribers predict and anticipate adverse drug reactions accordingly. This will improve clinical practice of prescribers by giving a drug of choice that is safe. Drug safety reporting is important as it will save the sponsors losses incurred due to drugs being withdrawn from market.

This will help the principal investigators and sponsors focus more on drug safety reporting issues and participant safety. There will be early detection of adverse drug reactions and measures taken before they progress to life threatening conditions. Drugs can be taken off the market due to safety issues that are not reported during clinical trials. An example is rosiglitazone that was withdrawn due to its association with increased heart attacks.

Participants are protected from severe adverse drug reactions and have improved drug safety. Drug safety reporting of SUSARS will improve the safety profile of medicines and new information will help in early detection of serious adverse drug reactions.

The study will establish gaps in clinical trials drug safety reporting which the regulatory agency can use to know areas that require capacity building and addition of staff members. Gaps in data timeliness and completeness of reports as well as problems in the existing practices of drug safety reporting will also be identified and regulatory actions taken.

1.4 Research Question

1. Do the applications to conduct clinical trials submitted to PPB comply with national guidelines and ICH-GCP international guidelines for drug safety reporting?
2. Do safety reports submitted to PPB conform to local and international regulatory guidelines for drug safety reporting of clinical trials?
3. What regulatory actions are undertaken by PPB and sponsors in response to drug safety reports?

1.4.1 Broad Objective

To determine the regulatory compliance of drug safety reporting during clinical trials approved by the Pharmacy and Poisons Board of Kenya

1.4.2 Specific objective

1 To determine whether clinical trial protocols submitted from 2013 to 2017 comply with drug safety reporting requirements outlined in the PPB and International guidelines.

2 To assess the drug safety reports for completeness and timeliness as stated in the national guidelines.

3 To identify measures taken by the drug regulatory board and sponsors to mitigate serious adverse events.

CHAPTER 2: LITERATURE REVIEW

2.1 International Standards of Safety Reporting

ICH-GCP guidelines require a researcher to ensure validity, comprehensiveness, clarity and timeliness of information reported to regulatory bodies in data collection forms. A clinical trial needs to have scientific value giving authentic information which is in line with set objectives (20) . Alteration of data collection forms must bear a date, be countersigned, and made clear without obscuring the original entry. Principal investigator should also hand in documented briefing of the position of research to international regulatory body. Safety reporting of serious adverse events (SAEs) needs to be done urgently to the sponsor (5). The investigative reports must distinguish participants by distinctive figures given to participants, personal identification numbers, and addresses. Adverse events need to be reported to the sponsor within the duration defined in protocol (5) . For deaths outlined in a report, the researcher ought to give the sponsor and regulatory board an autopsy reports and end stage written report.

If the trial is prematurely terminated the researcher must notify participants and offer them necessary treatment and ensure follow-up of participants. The IRB/IEC should be well informed and given an in-depth documented statement of the end stage. Upon completion of the clinical trial, the researcher should provide IRB/IEC with an abstract of the study's results (5) .Good clinical practice guidelines requires the investigator to know the correct use of product under investigation (5) .

The council for international organizations of medical sciences (CIOMS) was formed by WHO and UNESCO.It has a CIOMS I reporting form that covers worldwide reporting of adverse drug reactions based on Standardized MedDRA , organization of safety data from studies, regular drug safety updates, approaches for assessing benefits or risk and pharmacogenetics (21) .

2.2 Local standards of safety reporting

In Kenya the pharmacovigilance department started training regulatory experts in the year 2009.There are no developed local pharmacovigilance guidelines on drug safety reporting in clinical trials. The Kenyan government does not allocate enough funds to

ensure steady and sustainable support for pharmacovigilance inspections or activities in clinical trials.

According to clinical trial guidelines, the sponsor ought to issue reports of SUSARs to PPB in no more than seven calendar days on notification. Follow up reports must be submitted within additional eight calendar days. The PPB will need a summary of SUSARs/SAEs every six month throughout conduct of a clinical trial (4). The clinical trial department unit is responsible for drug safety surveillance which has the capacity of avoiding toxic drug effects while lowering healthcare costs (12).

Preclinical studies are needed to assure participants of their safety before getting marketing authorization of a drug. Safety evaluation of the investigational product is a vital component in a drug development cycle. The protocol elaborates safety reporting procedures specifically on expedited reporting of serious adverse events and annual safety reports which should be submitted annually. All fatal cases must be accompanied by a formal autopsy (8).

2.2.1 Drug safety reporting

Drug safety reporting is important in detecting participant safety issues. A protocol requires to a clear plan how adverse events will be followed and reported. Multicentre studies with large number of participants limits capacity of safety reporting by the investigators (1).

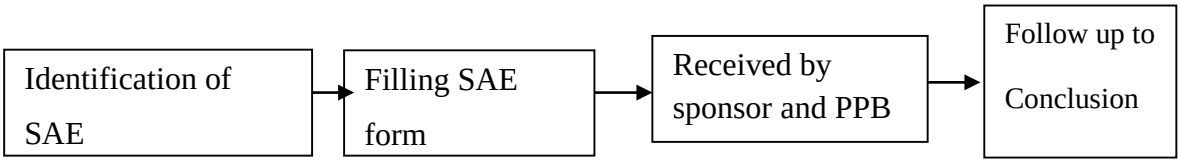

Figure 1: Reporting process flow chart

SAE are identified using a criteria set in the protocol and reported on a form which is sent to the sponsor by the principal investigator. The regulatory agency is also sent the report electronically. DSMB reviews clinical trials major concerns and ensures safety of study participants. SAEs are followed up to resolution and update reports provided to the regulatory agency (22).

2.2.2 Types of adverse drug reactions

Adverse drug reaction is any unintended response by a participant to an IMP associated with the dose administered. An adverse event is any untoward occurrence which is not necessarily associated with product. A serious adverse is life threatening and may result in death. It may require hospitalisation or extension of period in hospital. It may result in a birth anomaly or disability (22).A serious adverse reaction may be caused by the product under investigation. A suspected unexpected serious adverse reaction is not listed in investigator brochure and is neither consistent with safety information in terms of nature and severity (3).

2.2.3 Assessment of Causality

Causality is establishing if there is adequate relation of a product to an adverse event. It involves assessing periods of adverse events; rechallenge information, association with underlying ailments and biologic plausibility. Causality assessment is done on all reported cases by comparing rates of reports done in controls and test drug groups. For uncommon SAEs the investigator has to consider if the adverse event occurred after exposure to a drug and symptoms are related to adverse event (23) .

Causality assessment is based on history taken from the subject, clinical assessment of adverse events and lab results (24) . Causality is categorized based on certainty criteria in which there is a time relationship between drug intake and lab results with defined pharmacological action. Causality is likely if response to a withdrawal is normal. It can be unlikely to be causality if lab results and intake of a drug do not correlate over a period of time. Causality can be unassessable if information is contradictory and not clear (25) .

Adverse reactions are hardly particular for medicines with no characteristic tests and no rechallenge.The WHO-UMC causality was developed after consultations. It is a joint evaluation considering the clinical pharmacological details of the medical history and standard of recording of the study (25) .Pattern, severity, course of reaction and resolution on dechallenge are considered during causality assessment (24) .

2.2.4 Assessment of Safety Reporting

Safety reporting involves getting data from the participants which is then transferred to the PI who then reports to the regulatory body (26) . Assessment of safety in clinical trials may a primary objective, a co-primary objective or a secondary objective. In primary objective, analysis is based on a specific safety endpoint. In secondary objective, descriptive comparisons are commonly used to screen for any differences in AE(adverse events) rates between treatment groups (27) .Quality of data collected depends on the completeness and correctness of data reported. Ambiguous and non specific information should be minimized.

2.2.5 Completeness of Reporting

Investigators and sponsors record and report AE according to procedures described in the trial protocols. AEs are classified according to standardized scheme, such as MedDRA, System Organ Class and Preferred Term (27) . A complete report should have a summary of SAEs and SUSARs. The SUSAR/SAE SAE Log must have; Patient ID,age, category SUSAR/SAE, begin date of the SUSAR/SAE, End date of the SUSAR/SAE, cause for reporting the event as an SAE, association with experimental drug and outcome of the SAE (8) .

2.2.6 Time Frames of Safety Reporting

The Sponsor or the Principal Investigator should avail first reports of SUSARs to PPB soon in a period of seven calendar days of alert about the SUSARs. Follow through reports should be availed in an additional duration of eight days. The sponsors should also give a yearly safety report to PPB having all current available safety data received in the course of reporting duration (8). Principal Investigator should establish that the events are suspected adverse reactions, serious and unexpected ahead of giving an IND safety report (28).

2.2.7 Reporting Study End points

These are the outcomes that Principal Investigators are measuring to evaluate efficacy of a drug. Clinical trials evaluating outcome of medicine on disease associated with mortality or morbidity. The DSMB need to track as well as monitor endpoint information (28) . Cut off dates are specified in the protocols when subjects are no longer being enrolled for clinical trials and a site has been closed. However safety data due to toxicity that happens later may be reported and followed up.

2.2.8 Process of Safety Reporting

The SAE report is completed with detailed information such as laboratory results submitted by Principal Investigator to facilitate causality determination. Fatal occurrences are followed with an official autopsy report where available or an oral autopsy report.

Repeated adverse event to a drug is given urgent medical attention. Follow-up information is done by Principal Investigator. Copies of examination test results, laboratory results, or medical file progress notes are also submitted as additional information, clearly marked as update information with protocol number and participant number (8). Serious adverse events that are not study end points should be reported expeditiously and not as individual cases because they are uninformative as single cases. They should be checked at convenient time, and figures of events in individual arm of a controlled study correlated (4) .

2.2.9 Detection of ADR during clinical trials

Detection of ADRs can be by active or passive surveillance (12) .Adverse events can be detected by healthcare professionals during practice. Data on ADRs can also be collected by observing patients during clinical trials. Reviewing practice data retrospectively can be done manually or electronically by researchers (29) .

A valid individual case safety report (ICSR) should have an accountable reporter, single referable patient, a single suspect adverse reaction with at least one suspect drug. Accountable reporter characterized by qualification and referable patient is known by initials, patient identification number, and date of birth, age, or gender. The medicinal product is identified by name and the batch number. The report should specify the adverse event and its type as experienced. Reports must have include the oral text as used by the initial source or an exact translation (30).

2.2.10 Stakeholders in Safety Monitoring

In studies where DSMBs are selected, sponsors have to disseminate safety conclusions to the DSMB at work to inspect research of the experimental medicine. Safety monitoring objective in clinical trials is to establish, assess, minimize and accordingly handle risks. Timely communication the various stakeholders are important to establish participant safety in clinical trials. Sponsors are needed to do long term follow up of participants. ICF defines the details of the assessments, the recurrence and duration of follow-up.

2.2.11 Termination of Clinical Trials

Results of clinical trials have to be evidence based for them to be used in clinical practice. The difference phases of clinical trials influence termination. Phase 3 clinical trials are very expensive and require a lot of planning. The negative safety and efficacy decreases steadily from Phase 1 to Phase 3.Phase 4 trials is done after the drug is approved to be used in the market and seeks to get data on optimal use of the drug. Termination of clinical trials can be due to finance issues, wrong trial design, unavailable staff and precedence by other studies (31).

2.3 Conceptual framework.

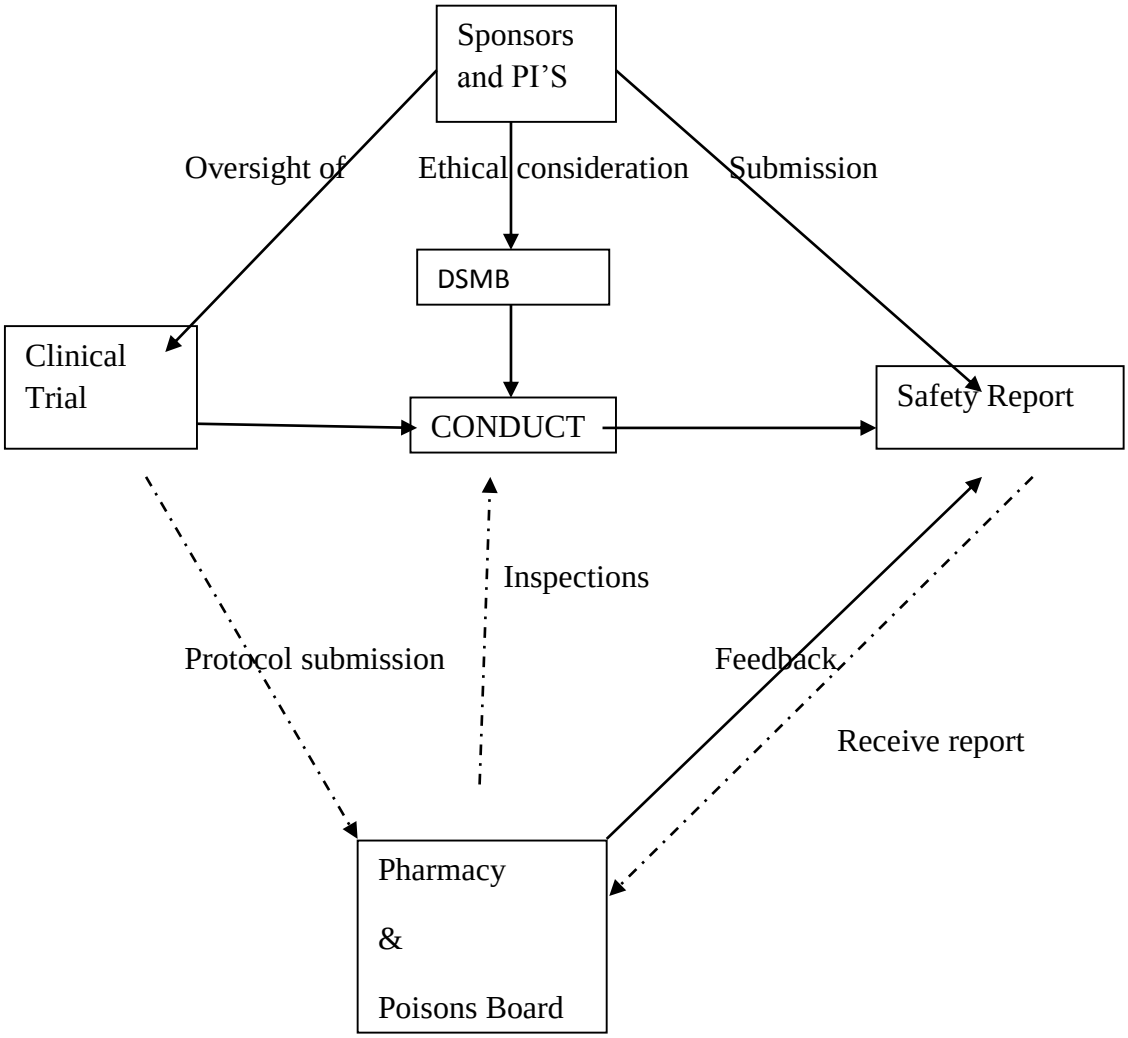

Figure 2: Conceptual framework

The sponsor and principal investigator have a responsibility to ensure participant safety. DSMB reviews and monitors clinical trials by looking into major concerns of adverse events reported. Safety reports are sent to the regulatory body which ensures participant safety. Prior to carrying out a clinical trial, protocols are submitted to the regulatory body for approval. PPB also does inspections at the sites where clinical trials are carried out.

CHAPTER 3: METHODS

3.1 Study Design

The study design was a retrospective cross sectional descriptive study of documentary materials. Approved clinical trial protocols and reports of adverse events submitted to Pharmacy and Poisons Board of Kenya from 2013 to 2017 were analyzed.

3.2 Study Site

The study was conducted at Pharmacy and Poisons Board which is a regulatory body established under CAP 244 to regulate research studies. Kenyan Pharmacy and Poisons Board through Experts committee on clinical trials reviews protocols submitted and provide response to applicants within thirty working days. There is a checklist for handing in documents to expert committee on clinical trials (ECCT) and guidelines for reporting serious adverse events (SAEs) and suspected unexpected serious adverse events (SUSARs).In addition the guidelines provides instructions regarding procedures for suspension of clinical trials. Kenyan Pharmacy and Poisons Board has a role to safeguard studies in Kenya concerning use of old drugs and new investigational drugs on participants adhere with National regulations to shield the participants (4).

3.3 Target Population

All clinical trial protocols submitted to Pharmacy and Poisons Board for approval and reports of SAEs and SUSARs reported between years 2013 to 2017.The study involved a review of clinical trial protocols approved by PPB starting the year 2013 to 2017 and adverse event reports submitted within the same time.

3.4 Inclusion Criteria and Exclusion Criteria

All approved clinical trial protocols that were being implemented or were to be implemented in Kenya were reviewed and included in the study. Reports of SUSARs reported between years 2013 to 2017 were also included. Inclusion criteria for clinical trial protocols were as follows:

- Clinical trial protocols for drugs conducted in humans.
- Protocols received and approved by PPB between 2013 and 2017.
- For a randomized controlled study.

- For Investigational Medicinal Product and new marketing approval or new use for the drug.

Permission was obtained from the regulatory body (PPB) to examine the documents. The archives officer was requested to supply at least five documents per day for perusal. Evaluation of the documents was done at the premises of PPB.

Exclusion criteria were as follows:

- Clinical trial done on medical devices and veterinary products.
- Strategies.
- Clinical trial protocols received before 2013 and after 2017.
- Phase 4 clinical trial or post marketing surveillance.
- Bioequivalence studies.
- Any other non-interventional studies.

3.5 Sampling Method

Universal sampling method was used because from anecdotal evidence there were few clinical trials protocols received. The Pharmacy and Poisons Board receives approximately three applications per month and thirty six per year. All archived protocols and safety reports from 2013 to 2017 were retrieved and reviewed.

The person responsible for archives was requested to give at least five clinical trial application documents daily. Using the eligibility check list in appendix 3 each document was scrutinized to determine if eligibility criteria have been met.

Universal sampling was conducted because expected sample size was small; no sample size computation was done.

3.6 Data Collection

Two data collection tools were used:

1. First tool was used to abstract information from the clinical trial protocol applications submitted to the PPB.It was designed to collect information on the

sponsor; if the sponsor was local or international; type of study in terms of phase; multisite study.

There was a checklist designed to determine if the safety reporting section meets minimal requirements (Appendix 1).

2. Second study tool was used to evaluate the submitted safety reports. The tool was designed to collect information on the sponsors and characteristics of the study. It was designed to determine methods used to submit the adverse event and if the reporting was done within the stipulated time frames; if assessment of causality was done; if appropriate mitigating action was taken by PPB and sponsors and type of drug involved. Adverse events reports were looked at with a focus on methods and timing of adverse event reporting, who was in charge of reporting, laboratory results, medical progress notes and duration of follow up of participants. This tool is presented in (Appendix 2).

3.7 Data Management

Codes were used as identifiers to ensure confidentiality of the information collected from the documents. All information collected by the researcher was kept under lock and key. Data was cleaned and entered within 24 hours in the Microsoft excel. Double date entry was conducted. Data was backed up every day. To ensure confidentiality, database was password protected and only the researcher had access to the data.

According to the Kenyan Law primary data from the study should be archived for ten years .The data will be archived in the department of Pharmacology and Pharmacognosy. The data collection instruments and other study materials used during study were kept under lock and key. At the end of the study it was handed over to department of Pharmacology and Pharmacognosy, University of Nairobi for storage. At the end of ten years, an application will be made to KNH/UoN-ERC for authority to destroy the data.

3.8 Data Analysis

Data collected was analyzed using STATA version 10 and proportions, percentages and pie charts generated to provide information on safety reporting and investigation of adverse events in clinical trials.

The data was coded and entered in Microsoft office excel then copied to Stata version 10.Descriptive data was analyzed quantitatively using descriptive studies and presented in form of percentages, proportions, pie charts and tables as appropriate. Categorical variables were summarized as proportions and percentages. Continous variables were summarized as standard deviation of mean if normally distributed. If not normally distributed they were summarized as median and interquartile range.

Inferential statistics was used to generate descriptive statistics and determinants of safety reporting in clinical trials were explored using Fischer's exact test against all variables. Tables to draw inferences with a level of significance of 5% were drawn. The null hypothesis is there is no difference in inclusion of expected serious adverse event or safety evaluation in locally and internationally sponsored clinical trials.

3.9 Variables

There was no single outcome variable but multiple variables serving as indicators of compliance to regulatory requirements. Some of these variables included proportion of Clinical trials applications that have explicit requirements for reporting to local regulator and procedures for causality assessment and seriousness. Proportion of protocols where the timeliness for reporting is specified, explicit laboratory and clinical procedures for detection of adverse events. Proportion for participant led reporting. Provision for description of mitigating strategies and proportion of protocols that have person responsible for pharmacovigilance reporting. The indicators used to assess the reports submitted included:

- The main reporting timeliness
- Percentage of complete reports
- Percentage of reports submitted electronically

3.10 Ethical considerations

Study approval was granted from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH-UON-ERC) via approval number P715/12/2017(Appendix IV). An administrative approval was granted by PPB following signing of a student confidentiality agreement (Appendix V).

3.11 Dissemination plan

The findings of the study will be disseminated to the medical library at University of Nairobi for accessibility to other students and staff at the University, Pharmacy and Poisons Board for implementation. Presentations of the findings will also be done in conferences and workshops. The study findings will be published in a peer reviewed open access journal once a manuscript is prepared.

CHAPTER 4: RESULTS

4.1 Characteristics of clinical trial protocols

A total of 69 clinical trial protocols and 28 safety reports that were submitted to PPB from 2013 to 2017.Sixty three clinical trials were internationally sponsored trials while six were locally sponsored trials. Phase 1 clinical trials were 34.7%, 33.3% phase 2 and 32.0% phase 3 clinical trials. Twenty nine clinical trials were conducted at multiple sites while thirty four were conducted on single site.

The characteristics of these studies are presented in Table 1.

Table 1 Characteristics of clinical trials applications approved by Pharmacy and Poisons Board for the period 2013-2017

	n	**%**
Types of sponsor		
International	63	91.3
Local	6	8.7
Phase of clinical trial		
Phase 1	24	34.7
Phase 2	23	33.3
Phase 3	22	32.0
Sites		
Multisite	29	49.3
Single site	34	50.7

4.2Characteristics of clinical trial protocols and safety reports on drug safety reporting

Clinical trial protocols that had explicit objectives on drug safety evaluation were 53.6%, 31.9% as primary objective and 21.7% as secondary objective. Clinical trial protocols with section on pre-clinical research information with regard to safety aspects were 89.7%. Clinical trial protocols with expected serious adverse stated were 84.1% and expected non-Serious adverse events listed were 7.3%. Clinical trial protocols which had previous experiences in using the test product in humans summarized in the trial protocol and investigator's brochure were 69.7%. Clinical trial protocols which had a section on pre-clinical research information with regard to safety aspects were 61 (89.7%). The findings are summarized in table 2 below.

Table 2 Characteristics of clinical trial protocols on drug safety reporting

Characteristics of clinical trial protocols	**n (%)**	**Comment**
Protocols that contain a section on pre-clinical research information with regard to safety aspects.	62 (89.7%)	PPB and ICH compliant
Protocols that do not contain a section on pre-clinical research information with regard to safety aspects.	7 (10.3%)	PPB and ICH non compliant
Protocols with explicit objectives on drug safety evaluation	37 (53.6%)	PPB and ICH compliant
primary objective	22 (31.9%)	
secondary objective	15 (21.7%)	
Protocols without explicit objectives on drug safety evaluation	32 (46.4%)	PPB and ICH non compliant
Protocols with stated expected SAE's	58 (84.1%)	ICH compliant
Protocols without stated expected SAE's	11 15.9%)	ICH non compliant

Protocols with expected non-serious adverse events stated Protocols without expected non-serious adverse events stated	5 (7.3%) 64 (92.7%)	ICH compliant ICH non compliant
Protocols with previous experiences in using the test product in humans summarized in the trial protocol and investigator's brochure Protocols without previous experiences in using the test product in humans summarized in the trial protocol and investigator's brochure	48 (69.7%) 21 (30.3%)	ICH compliant ICH non compliant

Twenty eight safety reports were available for study in which all the participants were accounted for. Follow up reports were submitted in 9 (32.1%) of the safety reports complying with PPB and ICH guidelines. No copies of publications affecting safety of the product and literature reports were submitted. Laboratory results were submitted in nine of the safety reports. This is shown in table 3 below.

Table 3 Characteristics of safety reports

Safety reporting requirement by guidelines	**n (%)**	**Comment**
All participants accounted for in safety report	28 (100%)	ICH compliant
Follow up reports submitted Follow up reports not submitted	9 (32.1%) 19 (67.9%)	PPB and ICH compliant PPB and ICH non compliant
Literature reports and copy of the publication affecting safety of product submitted	0 (0.0%)	Not compliant to PPB
Reports submitted through online system	26 (93.0%)	PPB compliant

Reports submitted by paper system or hard copies.	2 (7.0%)	PPB non compliant
Lab results submitted Lab results not submitted	9 (32.1%) 19 (67.9%)	PPB compliant PPB non compliant

4.3 Comparison of Inclusion of explicit objectives on drug safety evaluation in a clinical trial protocol

Out of 27 clinical trial protocols 14 (51.9%) had drug safety evaluation as a primary objective while 13 (48.2%) did not. Six (22.2%) placed it as secondary objective while 21 (77.8%) did not. The remaining clinical trial protocols did not define if drug safety evaluation was either a primary or secondary objective.

Table 4: Comparison of whether drug safety evaluation was a primary or secondary objective in clinical trial protocols

Drug safety evaluation as an objective	**Yes**	**no**
Primary objective	14 (51.9%)	13 (48.2%)
Secondary objective	6 (22.2%)	21 (77.8%)

Table 5: Comparison of safety evaluation objectives inclusion in clinical trials

Clinical trial aspect	Safety evaluation objective stated	Safety evaluation objective not stated	P value
a) Internationally sponsored clinical trials b) Locally sponsored clinical trials	26 (42.3%) 1 (16.7%)	37 (58.7%) 5 (83.3%)	0.235
a) Single site clinical trials b) Multisite clinical trials	13 (48.2%) 14 (51.9%)	22 (52.4%) 20 (47.6%)	0.462
a) Phase 1 b) Phase 2 c) Phase 3	24 (100.0%) 8 (34.8%) 7 (31.8%)	0 (0.0%) 15 (65.2%) 15 (68.2%)	0.001

Out of 69 clinical trial protocols 63 were internationally sponsored while 6 were locally sponsored. Five (83.3%) locally sponsored clinical trials did not have an explicit objective on drug safety reporting while 1 (16.7%) had an explicit objective on drug safety evaluation. Thirty seven (58.7%) of internationally sponsored clinical trials did not have an explicit objective on drug safety evaluation while 26 (42.3%) had an explicit objective on drug safety evaluation. The P value was 0.235 with a 5% level of significance therefore not statistically significant. This means that sponsoring of clinical trial did not affect inclusion of explicit objectives on drug safety evaluation.

Out of 69 clinical trial protocols 35 were single site while 34 were multisite. Twenty two (52.4%) single site clinical trials did not have an explicit objective on drug safety evaluation while 13 (48.2%) had an explicit objective on drug safety evaluation. Twenty (47.6%) multisite clinical trials did not have an explicit objective on drug safety reporting while 14 (51.9%) of multisite had an explicit objective on drug safety reporting. The P value was 0.462 with a 5% level of significance therefore not statistically significant. This means that the number of sites clinical trial did not affect inclusion of explicit objectives on drug safety reporting.

Out of 69 clinical trial protocols; 24 were Phase I; Phase II were 23 while 22 were Phase III. Twenty four (100.0%) of Phase I had an explicit objective on drug safety evaluation. Fifteen (65.2%) of Phase II did not have an explicit objective on drug safety evaluation while 8(34.8%) had an explicit objective on drug safety reporting. 15 (68.2%) of phase III did not have an explicit objective on drug safety reporting while 7 (31.8%) had an explicit objective on drug safety reporting. The P value was 0.001 therefore statistically significant with a 5% level of significance. This means that the phase of clinical trial affected including drug safety evaluation as an explicit objective.

4.4 Comparison of Inclusion of expected Serious adverse in clinical trials

Table 6: Inclusion of expected serious adverse event in clinical trials

Clinical trial aspect	**Expected serious adverse included**	**Expected serious adverse not included**	**P value**
a) Locally sponsored clinical trials b) Internationally sponsored clinical trials	2 (33.3%) 56 (96.6%)	4 (66.7%) 7 (3.4%)	**0.005**
a) Phase 1 b) Phase 2 c) Phase 3	19 (79.2%) 19 (82.6%) 20 (90.9%)	5 (20.8%) 4 (17.4%) 2 (9.1%)	0.600
a) Multisite b) Single site	31(91.2%) 27 (77.1%)	3(8.8%) 8 (22.8%)	0.103

Out of 69 clinical trial protocols; 58 of them had the expected serious adverse events included. 56 were internationally sponsored clinical trials while 2 were locally sponsored clinical trials. Seven (3.4%) of clinical trials which internationally sponsored did not include the expected serious adverse events. P value was **0.005** with a significance threshold set at 5% therefore statistically significant. This means the locally sponsored clinical trials were less likely to include the expected serious adverse events.

In terms of inclusion of expected serious adverse events there was no difference if Phase 1, 2 or 3 because 80-90% of the studies had included the expected serious adverse events. Phase 3 had the highest prevalence of including expected serious adverse events. In terms of failure to include the serious adverse events (11) 15.9% of the protocols did not comply and this is a serious omission.

In terms of clinical trial site; in multisite there was greater tendency to include the expected serious adverse events with 91.2% compliance. For single site there was reduced tendency to include expected adverse events with 22.9% noncompliance.

4.5 Methods of drug safety reporting

Clinical trial protocols should outline how adverse events will be reported by principal investigator and sponsor, their responsibilities to inform each other and the regulatory body. Twenty seven (96.9%) drug safety reports were sent via the online system while one (3.1%) was sent manually. Table 6 below show reporting methods and pathways reviewed. On safety reporting methods and pathways assessment; clinical trials protocols with provisions for safety reporting to local ERC were 69 (100%). Protocols that had provision for safety reporting to the sponsor were 53 (76.8%). Sixty (87.0%) protocols had provision for safety reporting to PPB. protocols had provisions for sponsor to report to regulatory agencies outside Kenya were 42 (60.9%). Protocols that had a data collection tool with a case report form of reporting SUSARs were 63 (94.0%). This is shown in table 7 below.

Table 7: Safety reporting methods and pathways assessment

Reporting Provision	Frequency (n %)	
	Provided	Not provided
Clinical trials protocols had provisions for safety reporting to local ERC	69 (100%)	0 (0%)
Clinical trials protocols had provision for safety reporting to the sponsor	53 (76.8%)	16 (23.2%)
Clinical trials protocols had provision for safety reporting to PPB	60 (87.0%)	9 (13.0%)
Clinical trials protocols had provisions for sponsor to report to ERC's and regulatory agencies outside Kenya	42 (60.9%)	27 (39.1%)
Clinical trials protocols had a data collection tool with a form of reporting SUSARs	63 (94.0%)	4 (6.0%)
Clinical trials protocols had provision for electronic method of reporting	65 (96.9%)	2 (3.1%)
Clinical trials protocols had provision for paper based method of reporting	2 (3.1%)	65 (96.9%)

4.6 Methods for detections and coding of ADRs

Participant laboratory results relevant to the adverse reaction were made for provision in 93.8% of the clinical trial protocols. Clinically identification of ADR was made for in 84.4% of the clinical trial protocols. Patient initiated ADR reporting was made for provision in 50.0% of the clinical trials. Coding method for ADR stated was stated in 4.7% of the clinical trial protocols. This is shown in figure 1.1 below.

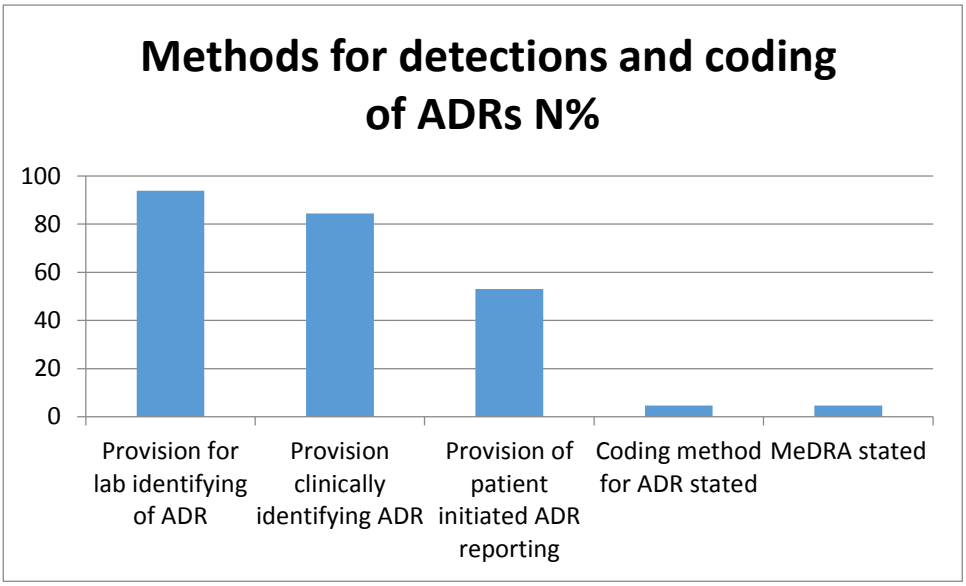

Figure 3: Methods for detecting and coding ADRs

4.7 Persons responsible for safety reporting

The Principal investigator reports adverse events to the sponsor who then reports to the regulatory board. Fifty three (76.8%) of the clinical trial protocols had a medical doctor as Principal Investigator, two (2.9%) a pharmacist, eleven (15.9%) a nurse .Sixty eight out of the sixty nine clinical trial protocols had the CV Of the Principal Investigator submitted.

Table 8 Categories of Principal Investigators

	Number of Protocols
Medical doctor	53 (76.8%)
Pharmacist	2 (2.9%)
Nurse	11 (15.9%)
Non medic	3 (4.3%)

4.8 Completeness and timeliness of drug safety reports

A total of 28 safety reports submitted to Pharmacy and Poisons Board were reviewed with respect to completeness, severity and causality. The nature of the adverse reactions

reported was in terms of severity. Safety reports with severity that was mild were 90.6%, 38.9% were severe and 50% were fatal**.**

Completeness of safety reports can be the qualitative or quantitative aspect of adverse events. Twenty (70.4%) safety reports were complete while eight (29.6%) were not complete as the patient code, age or type of SUSAR/SAE was not stated. Twenty six (94.4%) safety reports had age of the clinical trial participant included; 28 (100%) safety reports had all the participants accounted for and eleven (38.9%) had the type of SUSAR/SAE stated. Causality was stated as probable in 4 (12.5%) of the drug safety reports. This is presented in table 8 below**.**

Table 9: Completeness of SUSARs/SAEs received

Safety reporting	**n (%)**
Patient identification or code	22 (77.8%)
Age included	26 (94.4%)
All participants accounted for	28 (100.0%)
Type of SUSAR/SAE stated	11 (38.9%)
Causality	
Probable	4 (12.5%)
Unlikely	0 (0.0%)
Severity	
Mild	12 (40.6%)
Severe	10 (38.9%)
Fatal	6 (20.5%)

Severity highlights the intensity of adverse events following a scale for grading adverse events. It is classified as grade one (mild), grade two (moderate), grade three (severe) and grades four (life threatening). Mild means that the symptoms have minimal interference with routine social activities, moderate means symptoms cause higher than minimal interference with functional and social activities, severe means the symptoms cause inability to perform social and functional activities while life threatening the symptoms cause in-capabability to carry out self care tasks or death.

4.8.1 Reporting timelines of SAEs and SUSARs

On description of reporting timelines of SAEs; 40 (58.8%) clinical trial protocols complied with PPB guidelines of reporting timelines to PPB of not later than twenty four hours. Fifty seven (82.4%) clinical trial protocols complied with PPB guidelines reporting timelines to sponsor of not later than twenty four hours. On description of reporting timelines of SUSARs; 6 (9.0%) clinical trial protocols complied with PPB guidelines of reporting timelines to sponsor of not later than seven calendar days with follow up reports within eight days.

Table 10: Description of reporting timeliness of SAEs and SUSARs

TYPE OF ADR	AGENCY TO REPORT TO	Timelines as stated in guidelines	n (%)	Comment
SAE	PPB	Not later than 24 hours	40 (58.8%)	PPB Complied
		Did not specify	29 (41.2%)	Uncertain
	SPONSOR	Not later than 24 hours	57 (82.4%)	PPB Complied Not complied to ICH
		Not later than 7 days	4 (5.9%)	Not complied to PPB and ICH
		Did not specify	8 (11.7%)	Uncertain
SUSAR	SPONSOR	Not later than 7 days	6 (9.0%)	PPB complied
		Follow up reports within 8 calendar days	6 (9.0%)	PPB complied
		Did not specify	57 (82.0%)	Uncertain
	PPB	Did not specify	69 (100%)	Uncertain

4.9 Measures taken by the drug regulatory board and sponsors to mitigate serious adverse events.

Twenty two of the safety reports had their clinical trial participants hospitalised. Six safety reports had the adverse events resolving without hospitalisation. The hospitalisation of participants resulted in six deaths, seven resolved and nine had continuing serious adverse events. The deaths were due to drug induced liver injury and acute kidney injury. There were no reports of disability and birth defects as outcomes. There were five follow up reports submitted to the regulatory body. An independent data monitoring committee was formed for twenty two clinical trials. The IDMC recommended close follow up for a participant who had anaemia related to vaccines. The participant was also transfused with six units of blood. The deaths were mostly due to conditions secondary to the clinical trial. One participant who had seizures; death occurred during IV transfusion. The mild conditions like dizziness and headaches resolved.

The twenty eight safety reports were from nine clinical trials. Four were phase 1, five phase 2 and one was phase 3.

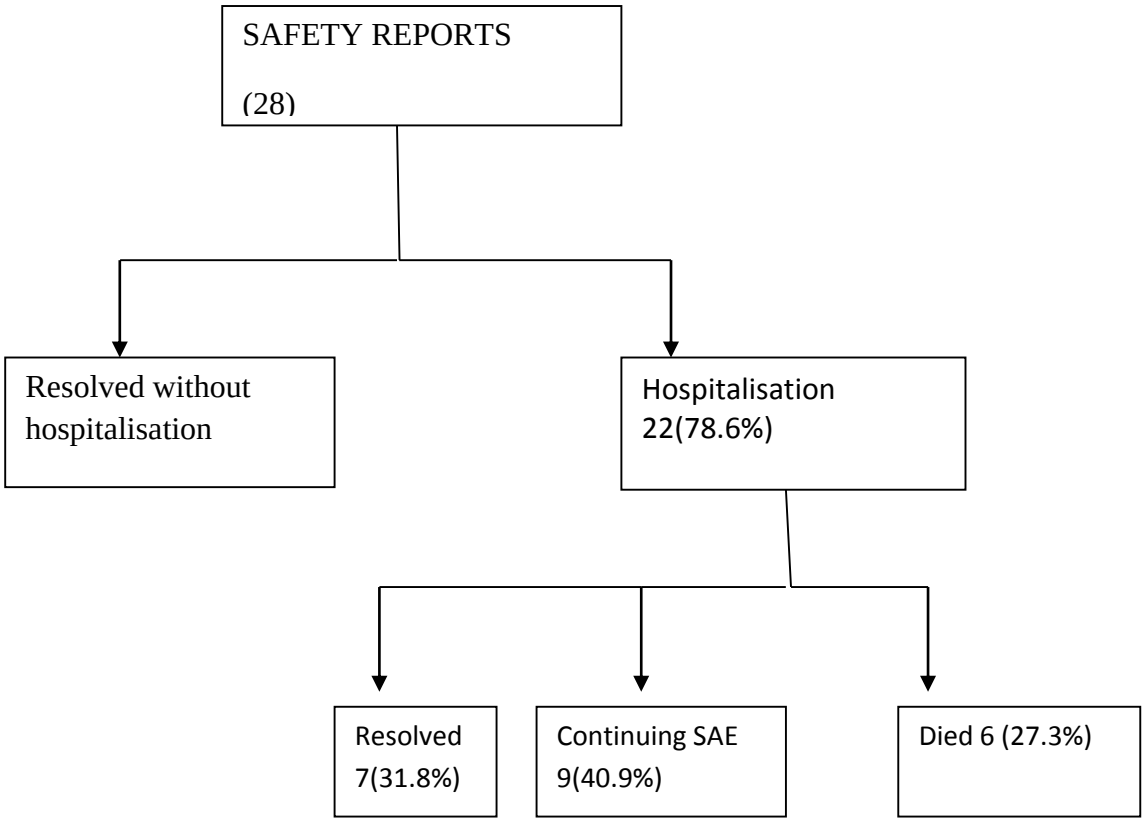

Figure 4: Measures taken to mitigate SAE'S

4.9.1 Actions taken by regulatory body and sponsors to mitigate adverse events

In response to a safety report the regulatory body may take different actions namely; temporal discontinuation of a clinical trial, termination of a trial or inspection. The study findings show that the regulatory body took one of these actions which was inspection of the clinical trial site. The sponsor can take different actions namely; stopping a clinical trial temporarily, submission of expedited reports, formation of DSMB, amending a clinical trial protocol or early termination of a trial. Only three of these actions were undertaken. In one case (1.6%) of the clinical trials were terminated early as the study objective had been achieved. For 26 (37.5%) studies the sponsor formed a DSMB to conduct an interim data analysis and review emergent safety issues. Expedited reporting was done in trials that showed a significant risk by the sponsor to the regulatory body in 8 (11.6%) of the clinical trials. Monitoring was done in 4 (5.8%) of clinical trials. This involved oversight of the quality of the trial to check if protocol is being followed, acceptability of data and success in keeping the participants in the trial.

This is shown in the table below.

Table 11 Actions taken by regulatory body or sponsor to mitigate adverse event

Action	**What is communicated**	**Undertaken by regulatory body or sponsor**	**(n) %**
Pausing a clinical trial	Reasons for the pause	Regulatory body	0 (0%)
Discontinuation of clinical trial for some participants	Reasons for discontinuation	Regulatory body	0 (0%)
Stopping a clinical trial temporarily	Reasons for the halt Scope of the halt Measure taken	Regulatory body/sponsor	0 (0%)

	Further actions planned Arrange continuing care and follow up of participants		
Inspection	Safety issues	Regulatory body	1 (1.6%)
Expedited reporting of SAE's	Safety issues	Sponsor	8 (11.6%)
Formation of DSMB to review data	Safety issues	sponsor	26 (37.5%)
Amending a trial	Details of safety issue Actions planned.	Sponsor	0 (0%)
Early termination of a clinical trial	Reasons for the early termination • Not able to show efficacy Measures taken Further actions planned	Sponsor	1 (1.6%)
Audit	Safety issues	Sponsor	0 (0%)
Monitoring	Safety issues	Sponsor	4 (5.8%)

CHAPTER 5: DISCUSSION, CONCLUSION, RECOMMENDATIONS AND LIMITATIONS

5.1 Safety evaluation as an objective in clinical trials

According to clinical trial guidelines in Kenya, safety evaluation parameters need to be specified in a clinical trial protocol. The methods, timing, recording and reporting adverse events need to be well specified to ensure proper safety evaluation (4) . According to ICH E2B guidelines safety variables should be collected as comprehensively as possible from clinical trial participants. This should be included in the clinical trial protocol and all adverse events reported whether or not they are related to the investigational product. The study shows that 37 (53.6%) of the clinical trials had safety evaluation as an objective.

Studies have shown that safety evaluation is a central component in all clinical trial phases and needs to be included in the study objectives. Clinical trials are carried out in human beings whose safety and well being has to be protected (32). The study revealed that Phase 1 studies were more likely to have an explicit drug safety evaluation objective as opposed to Phase 2 and Phase 3 clinical trial studies. This expected because Phase 1 studies are first studies done in humans therefore monitoring of adverse events is critical. Phase 2 and Phase 3 studies mainly focus on efficacy of the drug being tested. The sponsor has a responsibility to ensure safety evaluation of the investigational product. During pre clinical studies drug safety data is collected and feasibility of study determined.

Prior to a clinical trial being carried out in human beings, pre-clinical studies are done on animals in the laboratory to determine therapeutic and adverse events. This information is used to characterize the pharmacokinetics and pharmacodynamics of the product under investigation as well as the absorption, distribution, metabolism and excretion effects (9). In clinical trial information from earlier trials and other non clinical literature reviews will determine the method chosen to evaluate safety of product under investigation. Clinical trial protocols with section on pre-clinical research information with regard to safety aspects were 62 (89.7%).

According to ICH E2A and ICH E3 the occurrence of expected serious adverse events is important to be registered (33). Clinical trial protocols with expected serious adverse stated were 58 (84.1%).

Clinical trial protocols which had previous experiences in using the test product in humans summarized in the trial protocol and investigator's brochure were 48 (69.7%). This is important as it helps in predicting outcomes better with a reference point.

5.2 Methods of drug safety reporting and pathways assessment

A study was done in Cameroon by Akoh etal (2015) to establish surveillance of adverse events in clinical trials found that most clinical trials did not describe procedures for drug safety reporting (12) .These findings are very similar to present study that has described provision for safety reporting to the sponsor were 53 (76.8%). Sixty (87.0%) protocols had provision for safety reporting to PPB. Protocols had provisions for sponsor to report to regulatory agencies outside Kenya were 42 (60.9%). Protocols that had a data collection tool with a case report form of reporting SUSARs were 63 (94.0%).Well timed communication among stakeholders is important to ensure participant safety. The main goal of safety monitoring is to pick out, assess and manage risks (32). According to ICH guidelines; a clinical trial should be conducted after receiving favourable opinion from institutional review board (IRB) or independent ethics committee (IEC). Its main role is to safeguard safety and well being of participants in a clinical trial. The body should also review payments made to clinical trial participants and ensure it is documented in the informed consent form (34).

Safety reporting is significant in detecting participant safety issues and each clinical trial protocol should clearly state methods by which adverse events will be reported. Clinical trial protocol should outline how adverse events will be reported by sponsor and principal investigator, their responsibilities to inform each other and the regulatory body. Finding of present study indicate that 96.9% of drug safety reports we sent via the online system while 3.1% were sent manually.

High number of multisite centres complicates reporting pathways for adverse events. This frustrates protection of clinical trials participant safety because of high number of participants and unanalysed number of adverse events from a number of sites (1). Findings of present study showed that out of 69 clinical trial protocols 35 were single site while 34 were multisite.

5.3 Methods for coding and detection of ADRs

A study done by Irving et al.,(2017) to obtain real life data on safety of a treatment before market authorisation found that most of the systems had no ADRs coding criteria and lacked systems supporting detection of unknown ADRs (35) .Safety data should be embedded within every routine care visit. The trial design affects the frequency of safety data collection. Data on ADRs should be collected in a structured manner to understand causality.

Findings of present study indicate that coding method for ADR stated was stated in few of the clinical trial protocols. Coding is converting description of ADRs into universal medical terms with help of a drug dictionary called MeDRA (36) . Provision of patient initiated ADR reporting increases the number of reports received by the Principal Investigator. Participants also provide a more accurate and description of adverse event.

Almost all the clinical trial protocols had a provision for participant lab results for detection of adverse reaction. Clinically identification of ADR was made for in most of the clinical trial protocols. Patient initiated ADR reporting was made for provision in half of the clinical trials. These findings are very similar to a study done in Cameroon by Akoh etal (2015) which established that most clinical trials use active surveillance to detect adverse events.

5.4 Completeness and timeliness of safety reports

A study done in Korea (Kun Hyung et al.,(2014) found that completeness of reporting was suboptimal based on CONSORT statements (37) .This findings are consistent with present study in which 20 (70.4%) of the safety reports were complete while 8 (29.6%) of the safety reports were not complete. Most of the safety reports had age of the clinical trial participant included. All safety reports had all the participants accounted for and 11 (38.9%) had the type of SUSAR/SAE stated.

According to study done on consolidated standards of reporting, there was evidence of incompleteness in reporting over a lengthy period (10). Safety reports that are incomplete limit analysis of adverse events in a clinical trial.

On description of reporting timelines of SAEs; more than half of clinical trial protocols complied with PPB guidelines of reporting timelines to PPB of not later than twenty four hours. Fifty seven (82.4%) of clinical trial protocols complied with PPB guidelines

reporting timelines to sponsor of not later than twenty four hours. On description of reporting timelines of SUSARs; 6 (9.0%) clinical trial protocols complied with PPB guidelines of reporting timelines to sponsor of not later than seven calendar days with follow up reports within eight days. According to ICH guidelines all SAE's should be reported immediately to the sponsor except those that the investigator's brochure or protocol describes as not requiring immediate reporting (34). Reports of SUSAR's should be provided to PPB by the sponsor within seven calendar days of notification of SUSAR's with follow up reports being provided in a period of eight calendar days (4).

5.5 Measures taken by sponsors and regulatory body to mitigate adverse events

Fourteen of the safety reports had their clinical trial participants hospitalised. Eight of the adverse events resolved. Six of the adverse event reports resulted in death. Assessment of an adverse event is done by the Principal investigator in terms of severity and causality.

The findings from the study show that there was one clinical trial that was terminated early by the sponsor. The actions was taken because the sponsor achieved the objective of the before the set timelines. This was communicated to the regulatory body and ethical measures taken by doing follow ups to ensure safety of participants. Termination of a clinical trial can also occur due to change of study design as the protocol needs to changed altogether, ethical reasons, temporal suspension of funding, underpowered studies as end point is futile and non compliance (31).

The findings from the present study showed that 26 (37.5%) the clinical trials had a DSMB made up of a group of experts. The team consisted of a clinician, biostatician, medical ethicists, epidemiologist and an expert with prior DSMB experience. The sponsor initiates a safety monitoring process of participants corresponding with size, risk and complexity of the clinical trial (38). They look at the risk benefit ratio of the study and whether it is safe to continue or terminate a study. Suspension of a clinical trial occurs so as to protect safety of participants,reduce the cost of a study early if there is overwhelming evidence that the treatment is effective or ineffective and to avail treatment to participants (32). The number of meetings held by DSMB depends on safety concerns, unanticipated adverse events and data availability. DSMB is mainly needed for Phase III and multisite clinical trials with interventions that are risky to

participants. All participants in a clinical trial should be accounted for in a safety report. Reasons for exclusion from analysis should also be stated. Follow up reports of SUSARs should be provided within a further eight calendar days after initial reports.

Actions taken by regulatory body and sponsor are a safety measure to ensure participants well being. If a sponsor temporary pauses a clinical trial by interrupting treatment or suspending treatment; he has a responsibility to seek ethical review if necessary and notify the regulatory body within fifteen calendar days of the decision. A sponsor can amend a clinical trial because of a safety issue and notify the regulatory body of the actions planned within fifteen calendar days of being aware of the issue. A sponsor's decision to terminate a clinical trial early requires him to write a letter to the Ethics and Research Committee seeking ethical review of the action. The participants are informed and follow ups done to ensure their well being. The severity and number of life threatening adverse events should be given for every study arm (39). The sponsors have a responsibility of communicating safety information which is timely and streamlined to the regulatory body.

5.6 Conclusion

Drug safety reporting is a central component in clinical trials to protect and ensure safety of participants. Clinical trial protocols need to have a provision for safety reporting to PPB as the regulatory body. A gap was highlighted as 60 (87.0%) of the protocols complied with safety reporting to PPB. Slightly more than half the protocols had a data collection tool with a case report form of reporting SUSARs. A case report form allows for proper assessment and reporting in line with set standards. Investigations products carry risks as well benefits which should be well analysed before market authorisation. Locally sponsored clinical trials were less likely to include the expected serious adverse events as compliance to drug safety reporting. Phase 1 clinical trials had an explicit objective on drug safety evaluation as this is the sole priority of drug development cycle.

Completeness of safety reports is a major basis for causality assessment and early detection of adverse drug reactions. Twenty (70.4%) of the safety reports were complete while eight (29.6%) of the safety reports were not complete as the patient code, age or type of SUSAR/SAE was not stated.

Major gaps were highlighted on description of reporting timelines of SAEs; 40 (58.8%) of clinical trial protocols complied with PPB guidelines of reporting timelines to PPB of not later than twenty four hours. Fifty seven (82.4%) of clinical trial protocols complied with PPB guidelines reporting timelines to sponsor of not later than twenty four hours. On description of reporting timelines of SUSARs; 6(9.0%) of clinical trial protocols complied with PPB guidelines of reporting timelines to sponsor of not later than seven calendar days with follow up reports within eight days.

Measures taken by the sponsor to mitigate serious adverse events were hospitalisation. Six of the adverse event reports resulted in death. An independent data monitoring committee was formed for four of the clinical trial study which recommended close follow up for a participant who had anaemia related to vaccines. . In one case (1.6%) of the clinical trials were terminated early as the study objective had been achieved. For 26 (37.5%) studies the sponsor formed a DSMB to conduct an interim data analysis and review emergent safety issues.

The study revealed that drug safety reporting in clinical trials is inadequate and neglected.

5.7 Recommendations

The following are recommendations following findings of this study.

1. There is need to avail comprehensive drug safety reporting guidelines that match up to international standards to ensure clinical trials protocols submitted comply.
2. There is need for developing a safety data base that will help in quantification of adverse events and ensure follow ups is done.
3. Dedicate a stable and adequate budget for more inspections of clinical trial sites by the regulatory body.
4. Improve communication between different stakeholders in clinical trials to ensure timely reporting of adverse events.
5. There is need to conduct regular trainings for pharmacovigilance pharmacists to ensure safety reports are complete.

5.8 Study Limitations

The study was successfully carried out however clinical trial protocols done in years earlier than 2013 could not be accessed due to missing documents. Secondly no pilot study was done to validate the study.

REFERENCES

1. Shapiro BA. The Importance of Adverse Event Reporting. Aoron Shapiro, editor. Clin trials Retin Spec [Internet]. 2nd ed. 2013;(October):59. Available from: http://www.fda.gov

2. Cder F. Guidance for Industry and Investigators. Drug Saf [Internet]. 2012;(December):16. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/

3. Francisco S. Adverse Events in Clinical Trials. Clin Transl Sci Inst. 2014;1(1):1–30.

4. Kpkerich koskei F siyoi et al. Guidelines for applications to conduct clinical trial in kenya. In EXPERT COMMITTEE ON CLINICAL TRIALS; 2011. p. 40. Available from: www.pharmacyboardkenya.org%0AAn

5. Rosaliin A. Good Clinical Practices. Pan Am Heal Organ [Internet]. 2016;4. Available from: http://www.anvisa.gov.br/medicamentos/pesquisa/goodclinicalpractices_english.pdf

6. CIOMS. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Counc Int Organ Med Sci Int. 2002;1 to 52.

7. Mehta U HB. The importance of pharmacovigilance safety monitoring of medicinal products. Uppsala Monit Cent. 2002;38:1 to 52.

8. Pharmacy and Poisons Board kenya. Pharmacy and Poisons Board guidelines for conduct of clinical trials in Kenya. 2016.

9. Jesse A, Susan C E. Adverse event detection in drug development: Recommendations and obligations beyond phase 3. Am J Public Health. 2008;98(8):1366–71.

10. Turner L, Shamseer L, Altman DG, Weeks L, Peters J, Kober T, et al. Consolidated standards of reporting trials and the completeness of reporting of randomised controlled trials. Cochrane Database Syst Rev [Internet].

2012;(11). Available from: http://doi.wiley.com/10.1002/14651858.MR000030.pub2

11. Ghersi D, Askie L. International Standards for Clinical Trial Registries WHO Library Cataloguing-in-Publication Data. Int Clin trials. 2012;6.

12. Ebile A, Ateudjieu J, Ndikanae M MP. Assessing the detection , reporting and investigation of adverse events in clinical trial protocols implemented in Cameroon : a documentary review of clinical trial protocols. BMC Med Ethics [Internet]. 2015;1–9. Available from: http://dx.doi.org/10.1186/s12910-015-0061-5

13. Peter Ki le y M. Clinical trials in Ireland Regulatory Framework. Irish Med board [Internet]. 2006;10:1–29. Available from: http//www.imb.ie

14. Staa T-P Van, Klungel OH. Priority Medicines for Europe and the World "A Public Health Approach to Innovation." Prior Med Eur World "A Public Heal Approach to Innov [Internet]. 2013;25. Available from: http://www.who.int/medicines/areas/priority_medicines/BP8_4Data.pdf

15. Banerjee AK, Okun S, Edwards IR, Wicks P, Smith MY, Mayall SJ, et al. Patient-Reported Outcome Measures in Safety Event Reporting. Drug saf. 2013;36(10):1129–49.

16. Sweetman EA, Doig GS. Failure to report protocol violations in clinical trials. In BioMed Central Ltd; 2011. p. 214. Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-12-214

17. Moore R, Derry S, Aldington D, Pj W. Adverse events associated with single dose oral analgesics for acute postoperative pain in adults. Cochrane Database Syst Rev [Internet]. 2015;(10). Available from: www.cochranelibrary.com

18. Dwan K. Comparison of protocols and registry entries to published reports for randomised controlled trials. J Evid Based Med [Internet]. 2011;4(3):194. Available from: www.cochranelibrary.com%0AComparison

19. Danish health and medicines authority. Guide to individual case safety reporting. In Danish Health and Medicines Authority; 2015. p. 2 to 68.

20. Anant, Eugenijus D. International Ethical Guidelines for Health related Research Involving Humans. Counc Int Organ Med Sci [Internet]. 2016;4. Available from: www.cioms.ch

21. Sjölin-Forsberg G. Clinical trials to clinical practice. Clin Ther [Internet]. 2013;35(8):e129. Available from: http://linkinghub.elsevier.com/retrieve/pii/S014929181300790X

22. House H. Safety Reporting in Clinical Research Policy. Oxford Univ Hosp [Internet]. 2017;4:12. Available from: https://paratekpharma.com

23. Cobert B. Causality Asssessment. BLCMD Assoc [Internet]. 2013;(December):50. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072974.pdf 5

24. Regev A, Seef B, Aithal P WB. Causality Assessment for Suspected DILI During Clinical Phases of Drug Development. Drug saf. 2014;37(1):47 to 56.

25. Meyboom R EI. The use of the WHO-UMC system for standardized case causality assessment. Uppsala Monit Cent. 2005;(3):2–7.

26. Yang Wang. A Drug Safety Reporting System. PharmSUG. 2013;1–7.

27. WHO. Guidelines on clinical evaluation of vaccines. WHO Tech Rep [Internet]. 2004;(924):35–102. Available from: http://www.who.int/biologicals/publications/trs/areas/vaccines/clinical_evaluation/en/

28. Cder. Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA / BE Studies. 2012;(December).

29. Morimoto T, Gandhi K , Sege A , T C Hsieh BD. Adverse drug events and medication errors. Qual Saf Heal care. 2004;13(13):306–15.

30. European Medicines agency. Adverse Event Reporting Guidelines. 2013;(October):1–12.

31. Rodriguez MD, Roth FP. Why clinical trials are terminated. Dep Biol Chem

andMolecular Pharmacol Sch. 2015;1:1–22.

32. Yao B, Zhu L, Jiang Q, Xia HA. Safety Monitoring in Clinical Trials. 2013;(August 2014).

33. Practice G for good clinical. INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL. 2016;6(November).

34. Ddendum T. INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL. 2016;6(November). Available from: https://www.ich.org/.../Guidelines

35. Irving E, Bor R Van Den, Welsing P, Walsh V, Alfonso-cristancho R, Harvey C, et al. Collecting and reporting safety data and monitoring trial conduct in pragmatic trials. J Clin Epidemiol. 2017;

36. Kumar A, Khan H. Signal Detection and their Assessment in Pharmacovigilance. Open Pharm Sci J [Internet]. 2015;66–73. Available from: https://creativecommons.org/licenses

37. Kim KH, Kang JW, Lee MS, Lee J. Assessment of the quality of reporting in randomised controlled trials of acupuncture in the Korean literature using the CONSORT statement and STRICTA guidelines. 2014;1–8.

38. Research NH and M. Safety monitoring and reporting in clinical trials involving therapeutic goods. 2016;(November). Available from: www.nhmrc.gov.au/guidelines/publications/ea15

39. Ioannidis JPA, Lau J. Completeness of safety reporting in randomized trials. Jama [Internet]. 2001;285(4):437. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.285.4.437

APPENDICES

Appendix I: **Data tool collection form**

ABSTRACTION OF CLINICAL TRIAL PROTOCOL

Background information

1. Type of study

   Phase 1 Phase2 Phase 3

   □ □ □

   Pharmacological

   Others.

2. Sponsor:

   Local International

   □ □

3. Number of sites

   Multisite Single site

   □ □

CHECK-LIST FOR REVIEW OF PHARMACOVIGILANCE ASPECT OF THE CLINICAL TRIAL

	FINDINGS	COMMENTS
BACKGROUND AND GENERAL INFORMATION OF CLINICAL TRIAL PROTOCOL DRUG SAFETY REPORTING.		
Is there a section on pre-clinical research information with regard to safety aspects	Yes No	
Are there explicit objectives on drug safety reporting? If yes is it a primary or secondary objective?	Yes No	
Expected Serious adverse events listed/mentioned?	Yes No	
Expected NON-Serious adverse events listed/mentioned?	Yes No	
Are the previous experiences in using the test product in humans summarized in the trial protocol? and usually also detailed in the investigator's brochure.	Yes No	
Are the previous experiences in using the test article in human summarized in the investigator's brochure?	Yes No	
PERSONS RESPONSIBLE FOR DRUG SAFETY REPORTING		
Is the individual responsible for drug safety reporting explicitly stated?	Yes No	

If so, what are the qualifications of the PV person	PhD Masters Degree Diploma □ □ □ □	
What are the qualifications of the PI	Medical; pharmacist; non-medical; Nurse □ □ □ □	
Is the CV of the PI attached	Yes No	
Has PI conducted other clinical trials?	Yes No	
Is there a DSMB ?		
REPORTING METHODS		
Are there provisions for safety reporting to the local ERC	Yes No	
Are there provisions for safety reporting to the sponsor?	Yes No	
Are there provisions for safety reporting to the PPB?	Yes No	
Is there a provisions for the sponsor to report to the ERCs and Regulatory agencies outside Kenya		
Are the reporting systems electronic	Yes No	
If yes, what reporting system will be used?		
Is there a data collection tool that has a form of reporting SUSARs?	Yes No	
Does the form have a guide for causality assessment?	Yes No	
Does the form have a guide for assessment of severity?	Yes No	

Does the form have a guide for assessment of seriousness?	Yes No	
TIMELINES FOR REPORTING		
Are timelines for reporting to the ERC stated?	Yes No	
If yes what are the timelines for SUSAR?		
METHODS FOR DETECTIONS OF ADRS		
Is there a provision for lab identifying of ADR	Yes No	
Is there a provision clinically identifying ADR		
If there a provision of patient initiated ADR reporting	Yes No	
If yes, what is the reporting mechanism		
METHOD FOR CODING FOR THE ADRS		
Was coding method for ADR stated?	Yes No	
Was MeDRA stated?	Yes No	

DSMB Was DSMB present? Did they meet periodically? What action did they take? Suspend study Other recommendations □		

Appendix II: Check List for Completeness and Timeliness of Safety Reports

	YES	**NO**
Was patient Identification/code included?		
Was age included?		
Was type of the SUSAR/SAE stated?		
Was start date of the SUSAR/SAE stated?		
Was end date of the SUSAR/SAE stated?		
What was the listed severity of the adverse event? a) Severe (fatal or life threatening) b) Moderate (requires treatment or hospitalization) c) Mild (symptoms require no medical intervention)		
Was reason for reporting the event as SAE stated?		
Was causality assessment done? If yes was it: probable unlikely □ □		

Was outcome of the SAE stated? If yes was it : resolved death □ □ **Measures taken by regulator and sponsor** • Hospitalization • Discontinuation of medicines • Break randomization code • Formal investigation • Termination of study • Oversight visits		

Appendix III: Eligibility Checklist

Inclusion criteria

	YES	NO
Is drug for human use		
Was application received between 2013 and 2017		
Is it a randomized controlled trial		
Is it an interventional study		

Exclusion criteria

	YES	NO
Is the test article a vet product or device		
Is it a strategy		
Was the application received before 2013 or after 2017		
Was it a phase 4 or post marketing surveillance report		
Was it a non-interventional trial or bioequivalent study		

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

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
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Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/163

May 9, 2018

Irene Mokeira Nyambane
Reg. No.U51/82226/2015
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Irene

RESEARCH PROPOSAL – ASSESSMENT OF REGULATORY COMPLIANCE OF DRUG SAFETY REPORTING DURING CLINICAL TRIALS APPROVED BY THE KENYA PHARMACY AND POISONS BOARD (P715/12/2017)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is from 9th May 2018 – 8th May 2019.

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 serious 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) 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.

Protect to discover

For more details consult the KNH- UoN ERC website http://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 Chairperson, KNH-UON ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chairman, Dept. of Pharmacology and Pharmacognosy, UoN
Supervisors: Prof. George Osanjo, Dr. Stanley Ndwigah

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KENYATTA NATIONAL HOSPITAL
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Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/R /189

November 4, 2019

Irene Mokeira Nyambane
Reg. No. U51/82226/2015
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Irene,

Re: Approval of annual renewal - study titled 'Assessment of regulatory compliance of drug safety reporting during clinical trials approved by the Kenya Pharmacy and Poisons Board' (P715/12/2017)

Refer to your communication dated 31st October, 2019.

This is to acknowledge receipt of the study progress report and hereby grant annual extension of approval for ethical research protocol **P715/12/2017**.

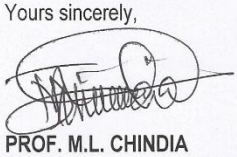
The approval dates are 9th May 2019 –8th May 2020.

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 **http://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 Director CS, KNH
The Chairperson, KNH-UoN ERC

Appendix V: 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 my study, I will gain access to certain information, which is proprietary to Pharmacy and Poisons Board and other interested parties.

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

(a) Not to use the Information for any purpose other than discharging my 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 any 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 to maintain confidentiality in my study could be grounds for immediate suspension of attachment with PPB and/or possible liability in any legal action arising from such breach.

I confirm that I 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.

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

All documents supplied to me 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

NYAMBANE IRENE MOKEIRA
(Student Name)

(Signature)

22nd February, 2018
(Date)