ASSESMENT OF THE EFFECTIVENESS OF METFORMIN IN PREVENTING PREDNISONE-INDUCED HYPERGLYCEMIA AMONG HEMATOLOGICAL CANCER PATIENTS AT KENYATTA NATIONAL HOSPITAL.

Lucy Akinyi Ochola, B.Pharm

U56/87314/2016

UNIVERSITY OF NAIROBI

November 2018

Declaration of Originality

Name of Student:	Lucy Akinyi Ochola
Registration Number:	U56/87314/2016
College:	College of Health Sciences
School:	School of Pharmacy
Department:	Pharmaceutics and Pharmacy Practice
Course Name:	Master of Pharmacy in Clinical Pharmacy
Title of Work:	Assessment of the Effectiveness of Metformin Prevention of Prednisone-Induced Hyperglycaemia in Haematological Cancer Patients at Kenyatta National Hospital

DECLARATION

I, Lucy Akinyi Ochola, declare that,

1. I understand what Plagiarism is and I am aware of the University's policy in this regard.

2. I declare that this research dissertation is my original work and has not been submitted elsewhere for examination, award of a degree or publication. Where other people's work or my own work has been used this has properly been acknowledged and referenced in accordance with the University of Nairobi's requirements.

3. I have not sought or used the services of any professional agencies to produce this work.

4. I have not allowed, and shall not allow anyone to copy my work with the intention of passing it off as his/her own work.

5. I understand that any false claim in respect of this mark shall result in disciplinary action in accordance with University Plagiarism Policy.

Signed…………………………… Date……………………………..

LUCY AKINYI OCHOLA - U56/87314/2016

Approval by Supervisors

This dissertation has been submitted for review with our approval as University Supervisors and co-investigators:

1. Dr. David Nyamu (B.Pharm, M.Pharm)

Lecturer, Department of Pharmaceutics and Pharmacy Practice

Signature………………………….. Date………………………….

2. Dr. Eric M. Guantai (PhD)

Lecturer, Department of Pharmacology and Pharmacognosy

Signature………………………….. Date………………………….

3. Dr. Irene Weru (B.Pharm, M.Pharm,)

Deputy Chief Pharmacist, Kenyatta National Hospital

Signature………………………….. Date………………………….

Dedication

I dedicate this dissertation to the anchor and rock of my life, my heavenly Father, Lord and Saviour, Jesus Christ for His blessed favour and amazing grace from conception to its fulfilment. I would be nothing without Him as my Lord, for the journey I have walked has solely been guided and led by His wondrous love and mercies towards me.

I thank my beloved parents. Thank you dear Dad for your continual support and understanding which nurtured this idea to its realization. Lastly, I dedicate the entire project to my dearest and awesome mother, whose ideation and overwhelming support can never be repaid.

Acknowledgements

Table of Contents

List of Figures and Tables

List of Figures

List of Tables

Abbreviations and Acronyms

a.a - Amino Acids

A.O.R- Adjusted Odds Ratio

AL- Acute Leukaemia

ALL- Acute Lymphoblastic Leukaemia

ALT- Alanine aminotransferase

AML- Acute Myeloid Leukaemia

AMPK-Adenosine Monophosphate Activated Protein Kinase

AST- Aspartate aminotransferase

ATP- Adenosine Triphosphate

AUC- Area under the Curve

BGL- Blood Glucose Levels

BL-   Burkett's Lymphoma

BMI- Body Mass Index

C.O.R- Crude Odds Ratio

CBG- Capillary Blood Glucose

CDASH-Clinical Data Acquisition Standards Harmonization

CHOP- Cyclophosphamide, Doxorubicin, Vincristine, Prednisone

CI- Confidence Interval

CLL- Chronic Lymphocytic Leukaemia

COPMAP- Cyclophospamide/Vincristine/Prednisone/Methotrexate/Cytarabine/Procarbazine

COPP- Cyclophosphamide/Vincristine/Prednisone/Procarbazine

CP- Chlorambucil/Prednisone

CRF- Case Report Form

CVS- Cardiovascular

CVP- Cyclophosphamide/Vincristine/Prednisone

DLBCL- Diffuse large B-cell Leukaemia

DM-   Diabetes Mellitus

DPP- Diabetes Prevention Program

DSMB-Data Safety Board Management

FBG- Fasting Blood Glucose

FFAs- Free Fatty Acids

FPG- Fasting Plasma Glucose

GLUT- Glucose Transporters

GU- Genitourinary

HbA1C-Hemoglobin A1C

HDL-C-High Density Lipoprotein Cholesterol

HDS- High Dose Steroid

HGP- Hepatic Glucose Production

HL- Hodgkin's Lymphoma

HOMA- Homeostatic Model Assessment

HR- Hazard Ratio

ICU- Intensive Care Unit

IFG- Impaired Fasting Glucose

IGT- Impaired Glucose Tolerance

IM- Intramuscular

IR- Insulin Resistance

KNH- Kenyatta National Hospital

LDL-C- Low Density Lipoprotein Cholesterol

MM- Multiple Myeloma

mmol/L- Millimoles per Liter

mTOR- Mammalian Target of Rapamycin

NHIF- National Hospital Insurance Fund

NHL- Non Hodgkin's Lymphoma

NLPHL-Nodular lymphocytic predominant Hodgkin's lymphoma

OGTT- Oral Glucose Tolerance Test

OHAs- Oral Hypoglycaemic Agents

ORs- Odds Ratio

PDN- Prednisone

PID- Patient Information Document

PIH-   Prednisone-Induced Hyperglycaemia

PPG-   Post Prandial Glucose

R- Rituximab

RA-   Rheumatoid Arthritis

RCT-   Randomized Control Trial

SD-   Standard Deviation

SE- Standard Error

SIDM- Steroid-Induced Diabetes Mellitus

SIH-   Steroid-Induced Hyperglycaemia

SLL- Small Lymphocytic Leukaemia

SUs-   Sulphonylureas

T2DM- Type 2 Diabetes Mellitus

TGs-   Triglycerides

Operational Definitions of Terms

Covariates- A statistical variable that changes in a predictable way and can be used to predict the outcome of a study

C-peptide- A by-product of insulin production whose test is carried out to find out how much insulin the body produces so as to differentiate between type 1 and type 2 diabetes

Diabetes Mellitus- A chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced

Disposition index- The product of insulin sensitivity times the amount of insulin secreted in response to blood glucose levels

Fasting Blood Glucose- Blood glucose levels determined in blood after an overnight fast of 8 hours.

Glucometabolic- Relating to the metabolism of glucose

Gluconeogenesis- The biosynthesis of glucose from non-carbohydrate precursors.

Glucose intolerance- A condition in which blood glucose levels are higher than normal levels upon fasting or following a carbohydrate-rich meal or ingestion of a glucose test solution but not high enough to be diagnostic of diabetes mellitus

Glucose tolerance- The ability of the body to absorb and use a relatively large dose of glucose.

Glycogenolysis- The biochemical breakdown of glycogen to glucose

High-dose steroid- A prescribed dose of steroid that is more than 30mg per day of prednisone or its dose equivalent.

Hyperglycaemia- A condition characterized by an excessive amount of circulating blood glucose levels.

Hyperglycaemic-range diabetes- The levels of blood glucose characterized by fasting glucose greater than 7.0mmol/L and postprandial glucose levels greater than 11.0 mmol/L 2 hours after meals.

Hyperinsulinemia- A state characterized abnormally high levels of insulin in your body

Insulin resistance- A condition in which a given concentration of insulin produces a less than expected biological effect in insulin sensitive tissues

Insulin sensitivity- Ability of insulin to decrease plasma glucose levels by suppressing its production in the liver and stimulating its uptake in insulin-sensitive tissues.

Lactic acidosis- A state characterized by persistently increased blood lactate levels (usually >5 mmol/L) in association with metabolic acidosis.

Postprandial blood glucose- Blood glucose levels determined in blood 2 hours after a meal.

Postprandial hyperglycaemia- An exaggerated rise in blood sugar following a meal characterized by a blood glucose level exceeding 7.8 mmol/L 2 hours after a meal.

Pre-diabetes- A condition characterized by the presence of blood glucose levels that are higher than normal but not yet high enough to be classed as diabetes

Prednisone dose equivalent- express doses of different glucocorticoids in mg prednisone calculated by using the relative potencies.

Prednisone-induced hyperglycaemia- A clinical condition resulting from impaired insulin action, secretion and/or destruction of β-cells in patients using steroids

Pre-prandial hyperglycaemia- A blood glucose level before meals above normal range (4.4-7.2mmol/L) but not enough to be classified as diabetes

Steroid-induced Diabetes Mellitus- An abnormal increase in blood glucose associated with the use of corticosteroids in a patient with or without a prior history of diabetes mellitus.

Steroid-induced hyperglycaemia- A clinical condition resulting from impaired insulin action, secretion and/or destruction of β-cells in patients using steroids

β- cell dysfunction- The impairment of normal functioning β-cells to produce adequate insulin as well as the loss of β-cell mass

β- cell function-Ability of the pancreatic β-cells to produce the appropriate amount of insulin hormone to maintain normal circulating blood glucose levels.

Abstract

Background: Steroid-induced hyperglycaemia is a common side effect of prednisone therapy among cancer patients. The prevalence, pattern, effects, monitoring, and treatment have been described in studies. Few studies have demonstrated the beneficial effect of metformin in preventing hyperglycaemia. Metformin's preventative effect on prednisone-induced hyperglycemia in haematological cancer patients was investigated in low resource settings.

Objectives: The overall goal of the study was to assess the effectiveness of metformin in the prevention of prednisone-induced hyperglycaemia among haematological cancer patients at Kenyatta National Hospital.

Methods: A prospective randomized controlled trial of 24 cancer patients on high-dose prednisone was carried out at the Kenyatta National Hospital for 4 weeks. Eligible patients were randomized to either the intervention group receiving standard care plus metformin 850mg once daily for two weeks followed by 850 mg twice daily for another two weeks or the control group receiving the standard care. All participants had random baseline glucose levels were determined. The primary outcome was the presence or absence of prednisone-induced hyperglycaemia and patients had their fasting and 2-hour postprandial blood glucose monitored once weekly for the 4 weeks. All the analysis was done using STATA software version 13.0. Analysis of data was done using modified intention to treat analysis. The primary outcome, the presence or absence of prednisone-induced hyperglycaemia was dichotomized and expressed as proportions, with comparison across groups done using Fishers' exact test. Comparison of inter-group variability of mean blood glucose differences was done using Mann-Whitney U test while within-patient comparison of single and double dose metformin within the treatment group utilized the Wilcoxon-Signed Rank test. Absolute and relative risk reductions alongside odds ratio was computed and reported along with their 95% confidence intervals estimates. A p value of <0.05 was considered as statistically significant. Logistic regression was employed to assess for the association between predictor variables and prednisone-induced hyperglycaemia.

Results: Eighteen of the 24 randomized patients completed the study (11 control and 7 treatment). The proportion of the control subjects that progressed to pre-diabetes using the fasting and 2-hour postprandial glucose estimates was 72.7% (95% CI 45.5-90.9%) and 54.5% (95% CI 27.3-81.8%)

respectively. In contrast, the proportion of the treatment group was 14.3% (95% CI 0-42.9%) using fasting glucose, with no pre-diabetes being detected using the 2-hour postprandial glucose estimate. Comparative analysis of the mean fasting glucose in the 2 arms found no significant difference. However, statistically significant differences in mean 2-hour postprandial glucose in the 2 arms were noted in week 2 (p=0.0144), week 3 (p=0.0095) and week 4 (p=0.0074) of the study, where the treatment group presented with lower mean glucose values. Double dose (1700mg) metformin was more effective in lowering blood glucose than single dose(850mg), though this was not statistically significant using both fasting and 2-hour postprandial glucose (p=1.0000 and p=0.4531 respectively).

Conclusion: The effectiveness of metformin in reducing the risk of prednisone-induced hyperglycaemia was significant. A prospective long-term study with a larger sample size can be employed to more conclusively elucidate the effectiveness of metformin in preventing steroid-induced hyperglycaemia.

CHAPTER ONE: INTRODUCTION

1.1 Background to the Study

The burden of cancer in Kenya has significantly increased, making it the 3rd leading cause of deaths in the country, accounting for 7% of the overall national mortality (1). The prevalence of haematological malignances in sub-Saharan Africa has increased and has largely contributed to morbidity and mortality across all age groups (2–4). The commonly encountered blood cancers are Acute Leukaemia (AL), Non-Hodgkin's Lymphoma (NHL), Hodgkin's Lymphoma (HL) and Multiple Myeloma (MM). These blood cancers accounted for 8.7% and 9.9% of incident cancer diagnoses and cancer deaths in 2008 respectively (2). Most of these blood cancers require chemotherapy, in which prednisone (PDN) serves as a cornerstone in their management.

However, PDN use is associated with the adverse effect of hyperglycaemia (5–8). Steroid-induced hyperglycaemia (SIH) and steroid-induced diabetes mellitus (SIDM) are outcomes associated with high dose and/or long-term prednisone use (9–12). SIH can reach an incidence of up to 46% in patients, with an increase in blood glucose levels of up to 68% compared to baseline (7,13). In cancer patients, SIH has a significant effect on survival. It represents a risk of increased all-cause mortality and hospital stay among patients (14). Unfortunately, the hyperglycaemic side effect is not adequately managed in this patient population (15), reducing their relapse-free interval and survival rates while increasing acute complications like infections and impaired immune function (14).

Studies done have shown that SIH and SIDM may be averted by use of metformin. These have demonstrated its efficacy, tolerability, and safety. For example, Bostrom *et.al* showed metformin's safety and effectiveness in controlling SIH in children with acute lymphoblastic leukaemia (ALL) (16). The median administered metformin daily dose of 1000mg in participants with median blood glucose levels of 15.8mmol/L showed significant control of hyperglycaemia with no observed hypoglycaemic episodes or toxicities (16). A study by Seelig *et.al* found a beneficial effect of metformin on glycaemic control in adults and viewed it as a promising drug for preventing the metabolic side effects of systemic steroid therapy(17). In addition, studies have verified its beneficial use in cancer patients in that it increased progression-free survival time in ALL (18) as well as lowered risk of malignancy (19–23).

1.2   Problem Statement

Oral systemic steroid use has a demonstrated association with an increased risk of developing diabetes due to SIH (10,15). For instance, a local study at Kenyatta National Hospital (KNH) identified a prevalence of 61.5% of SIH among patients on prednisone therapy (15). Moreover, the study reported a higher prevalence of pre-diabetic states, namely impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), compared to other similar prevalence studies conducted (15,24,25). Twenty-five percent of the participants in the local study were on prednisone-based treatment for malignancies (15). PDN-based regimens have increased the incidence of SIH in haematological malignancies. For instance, studies done on ALL patients reported an incidence of SIH between 10-56%, depending on the glucose levels defined (26,27) and an incidence of DM of 15.7% in patients on prednisone-based therapy (28).

Thus, the use of prednisone in haematological cancers is associated with hyperglycaemic effects which have a significant effect on survival due to increased risk of all-cause mortality and hospital stay (27,29). Patients diagnosed with ALL who had hyperglycaemia had a shorter median survival (29 months vs. 88 months; $p<0.001$) (27). Nevertheless, follow up on prednisone-induced hyperglycaemia is not a common standard of practice for these patients. The patients are not adequately managed as appropriate guidelines are yet to be established for diagnosing and treating SIH and SIDM in order to prevent the complications associated with hyperglycaemia (7). Hence, patients are likely to develop diabetes, which adds on to their comorbidities and to the overall health burden in the country.

1.3   Purpose of the Study

The aim of this study was to establish the potential efficacy of metformin as a form of prophylactic intervention in preventing prednisone-induced hyperglycaemia (PIH) among haematological cancer patients at KNH.

1.4   Objectives

1.4.1 Broad Objective

To assess the effectiveness of metformin in the prevention of prednisone-induced hyperglycaemia among adult haematological cancer patients receiving high-dose prednisone at Kenyatta National Hospital

1.4.2 Specific Objectives

1. To determine the incidence of pre-diabetes and diabetes among adult haematological cancer patients receiving prednisone-based regimens with no metformin prophylaxis of prednisone-induced hyperglycaemia

2. To assess the effectiveness of Metformin in preventing prednisone-induced hyperglycaemia among adult haematological cancer patients receiving high-dose prednisone.

3. To compare the postprandial and fasting blood glucose levels achieved by single versus double daily metformin dosing among adult haematological cancer patients receiving high-dose prednisone.

1.5   Research Questions

What proportion of patients without metformin treatment progress to pre-diabetic and diabetic states while receiving prednisone-based regimens for the management of haematological cancers?

Does metformin lower the incidence of hyperglycaemia among adult patients with haematological cancers on prednisone-based chemotherapy at KNH?

Do the postprandial blood glucose levels change significantly among patients receiving single-daily versus double-daily metformin doses?

1.6   Rationale of the study

Cancer patients on high-dose steroids (HDS) require close monitoring, due to the high risk of developing SIH. Currently, there are no consensus guidelines for the management of SIH. There is no evidence yet to confirm which drugs are more effective in achieving adequate glycaemic control and lowering complications rates in patients with SIH (7,12,30). It is prudent then that efforts be made to identify the drugs that would effectively minimize hyperglycaemic episodes in patients receiving high-dose steroids, and which would also potentially offer great benefit for these patients (30).

Metformin enhances insulin sensitivity thereby preventing the glucometabolic side effects during systemic steroid therapy (21). Its usefulness as a preventive agent in patients at high risk of developing diabetes has been demonstrated. Male and female participants taking low dose metformin at 500mg per day, effectively reduced the progression rate of impaired glucose

tolerance (IGT) to diabetes, thus reducing the risk of developing diabetes mellitus (DM) by 31% (31). Also, metformin has been found to confer added benefits of reduced risk of cancer in general and in specific populations via several mechanisms (21). It offers off-target beneficial effects to patients with malignancies (16,18). These off-target effects include the inhibition of AMP-activated protein kinase (AMPK), targeting of the mammalian target of rapamycin (mTOR), potential protection from anthracycline cardiotoxicity and improved progression-free survival (32–34). Patients using metformin during chemotherapy were 5.4 times less likely to die and/or relapse (18).

As such, it was useful to assess the effectiveness of metformin as a preventive agent of SIH in cancer patients on prednisone therapy. The study aimed to address the literature gap in which evidence is lacking on the effectiveness of metformin in preventing PIH in African patients with cancer. In addition, the identification of a low-cost effective intervention such as metformin for preventing PIH would be advantageous in the affected populations in our resource-limited setting.

1.7 Research Hypothesis

Null hypothesis: There will be no difference in the proportion of patients developing prednisone-induced hyperglycaemia while receiving metformin treatment with those receiving standard care among haematological cancer patients receiving prednisone-based therapy at KNH

Alternate hypothesis: There will be a difference in the proportion of patients developing prednisone-induced hyperglycaemia while receiving metformin treatment with those receiving standard care among haematological cancer patients receiving prednisone-based therapy at KNH

1.8 Significance of the study

This study aimed to evaluate metformin as an effective and affordable drug interventional measure that could potentially help decrease the burden of prednisone-induced hyperglycaemia in haematological cancer patients at KNH. This would be in relation to reduced incidences of prednisone-associated hyperglycaemia morbidity and mortality via prevention or delay in the progression of development of SIH to diabetes, reduction in hospitalizations and hospital stays. Ultimately, this will improve the patients' quality of life and their general outcome as well as offer potential benefits across all populations using prednisone therapy. It will ensure glycaemic control in susceptible populations by means that are readily available, cost-effective and safe.

1.9   Delimitations

The study area was limited to the population of haematological cancer patients, aged 18 years and above. This is because the safety and efficacy of the intervention under study have been evaluated in ages within this range. The interest of high-dose prednisone in haematological cancer patients does not limit the extent of participants that are managed using high-dose prednisone. This population is vast, depending on the condition being managed.

The study was conducted in KNH, which represents a small sample of haematological cancer patients in the region and country as a whole. The set-out objectives were focused on evaluating the effectiveness of the intervention, metformin, to reduce prednisone-induced hyperglycaemia. It did not identify the similarity of effect in other types of steroids neither did it expound the effect of other hypoglycaemic agents on prednisone-induced hyperglycaemia. This, therefore, did not allow for the comparative assessment of effect.

1.10   Conceptual Framework
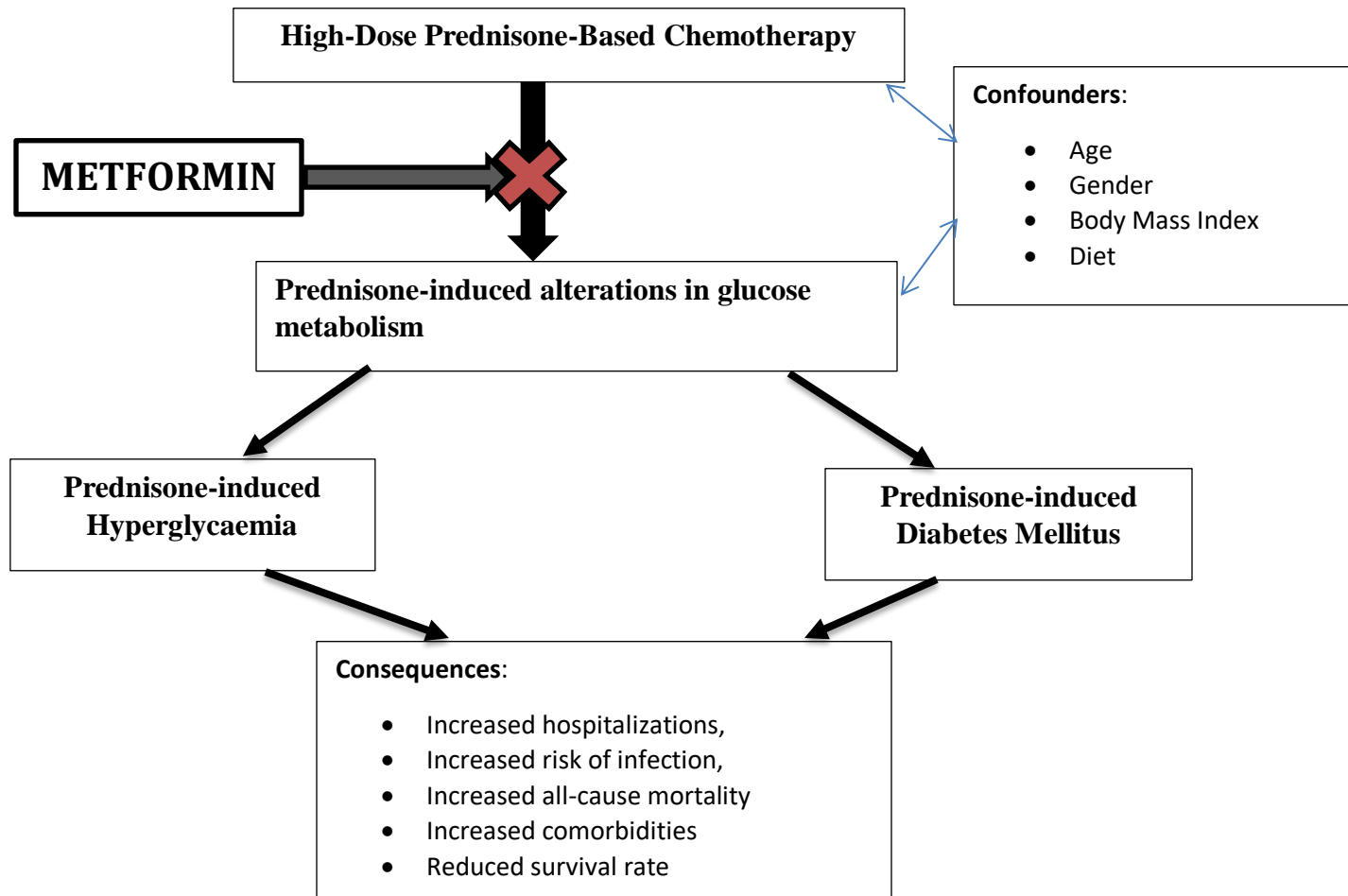
Figure 1: Conceptual Framework

The predictor variable in the theoretical framework is high-dose prednisone-based therapy. Its use will lead to the most common outcome variable which is prednisone-associated glucometabolic side effects. The alteration in glucose metabolism will predispose the patient to prednisone-induced hyperglycaemia, which precedes the onset of prednisone-induced diabetes mellitus when unmonitored. This ultimately results in increased all-cause morbidity and mortality, reduced patient survival rate, increased risk of infection and increased hospitalizations.

This strong association is affected by confounding variables, namely age, diet, medication and body mass index. Metformin, an oral hypoglycaemic agent is hypothesized to counteract the induction of prednisone-induced hyperglycaemia by preventing the glucometabolic side effects associated with prednisone use.

CHAPTER TWO: LITERATURE REVIEW

2.1 Burden of Haematological Cancers

Globally, cancer accounted for 8.8 million deaths in 2015, with developing countries contributing an estimated 70% of the mortality (1). In Kenya, cancer ranks third as a major cause of morbidity and mortality (1). It significantly contributes to the burden of non-communicable diseases, accounting for 7% of the overall national mortality. The annual incidence of cancer is nearly 37,000 new cases with an annual mortality of over 28,000 (1). Among the cancers, haematological malignancies play a major role in the causation of morbidity and mortality (35). The blood cancers include Lymphomas like Non-Hodgkin's and Hodgkin's, Leukemias, and Multiple Myeloma. These collectively accounted for nearly 10% of the overall regional cancer burden and 9.9% of cancer deaths in sub-Saharan Africa (35). Studies have shown a specific increase of some classes of blood cancers like NHL, and to a lesser extent HL, across the region especially in the advent of HIV (2).

Haematological cancers in the recent past have been on the increase. In Kenya for instance, the leukemias have shown to be a major health issue over the years with an increasing incidence (4). Epidemiological studies in Western Kenya indicate a pattern of haematological cancer distribution similar to that described across sub-Saharan Africa (6). In patients aged 19 years and below between 2006-2010, newly diagnosed malignancy depicted NHL as the most common type of cancer (34%), followed by ALL (15%) then Hodgkin's lymphoma (8%) (36). To augment, Agwata *et.al* comments in a 10-year ALL retrospective review that mortality was the most commonly occurring treatment outcome, with 110 deaths, giving a case fatality rate of 64.3% among paediatric ALL cases in KNH (3).

2.2 Prednisone-based chemotherapy in blood cancers

Steroids are consumed by 0.9% of the general population at any given point in time and almost a quarter of this fraction may need to use them for a duration of greater than 6 months (37). Prednisone, an exogenous corticosteroid, is a cornerstone in the management of haematological malignancies. Its vast use is primarily founded on its role as an anti-inflammatory and immunosuppressive agent based on its high glucocorticoid activity (38). In addition, its availability as an oral formulation, low cost of purchase and high potency advocates for its wide applicability (15,38).

Prednisone has been the corticosteroid most commonly used in haematological cancers. In ALL therapy, it is administered for 4 consecutive weeks in combination with Vincristine, an anthracycline, L-asparaginase, and intrathecal chemotherapy (39). In KNH, the regimen frequently used entails a dose of PDN of 40mg/m²/day per oral for 28 days in 3 divided doses, with gradual tapering of the drug to zero in 7 days (40). Multiple myeloma has been managed using standard intermittent chemotherapy courses of PDN and Melphalan for several years (41). Prednisone is given in daily oral doses for four days, at a dose of 60 mg/m² after breakfast. These intermittent courses induce remission in about 40% of newly diagnosed patients (41).

For the lymphomas, the CHOP regimen (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) has become the gold standard in management (42). CHOP is currently the protocol of choice for induction of remission in Burkitt's lymphoma at KNH. Prednisone plays a crucial part in this regimen and is administered at a dose of 40mg/m² orally daily for 4 weeks then tailed off to zero from week 5 (40). In Hodgkin's lymphoma, PDN is given at a dose of 40mg/m² per oral from days 1-14, as part of a combined treatment regimen. This is given per cycle every 21days, for a total of 6 cycles (40). A different chemotherapy combination regimen from CHOP used in Hodgkin's therapy still maintains the use of PDN 40mg/m2 per oral from days 1-5. This other regimen entails rest days between days 14 - 21, then repeat of the cycle from day 1, with a minimum of six courses (40).

2.3 Prednisone-Induced Hyperglycaemia

2.3.1 Mechanism of Prednisone Impairment of Glucose Metabolism

Prednisone antagonizes the effects of insulin on glucose metabolism. It inhibits insulin-mediated hepatic glucose release, reduces peripheral glucose uptake via reduced translocation of glucose transporters types (GLUT) to the cell membrane and reduces insulin receptor binding affinity. Prednisone glucometabolic effects are caused by increased peripheral and hepatic insulin resistance, β-cell mass dysfunction, increased glucose intolerance, impaired suppression of hepatic glucose production (HGP), reduced insulin secretion in response to hyperglycaemia and reduced number of insulin receptors (43). These glucometabolic effects occur at various stages of the insulin signalling cascade via different mechanisms, resulting in glucose intolerance.

Firstly, PDN triggers post-receptor defects by dysregulating GLUT 4 transporters in skeletal muscle cells, which contribute to the uptake of almost 80% of postprandial glucose and storage

(37,44). This results in decreased expression and migration of GLUT 4 transporters, leading to a subsequent reduction of around 30-50% and 70% of insulin-stimulated glucose uptake and glycogen synthesis respectively (37). Secondly, it increases protein catabolism, leading to increased levels of serum amino acids (a.as). Lastly, it enhances lipolysis resulting in increased serum free fatty acids (FFAs) and triglycerides (TGs) which reduces entry and storage of intramuscular (IM) glucose (44). Furthermore, studies have also validated that the elevation in blood glucose levels (BGL) seems to be attributable to decreased peripheral uptake and/or glucose clearance as well as increased hepatic glucose-6-phosphatase activity (45). This eventually results in the impairment of glucose tolerance.

Increased insulin resistance (IR), which can be as high as 60-80%, occurs due to reduced insulin sensitivity and secretion (37,46). This largely contributes to PDN-induced glucose intolerance. Its manner of presentation is similar to that in type 2 diabetes mellitus (T2DM). Insulin resistance correlates linearly with the dose and type of steroid treatment. Yasuda *et.al.* demonstrated that the observed differing degrees of IR was associated with reduced insulin binding affinity instead of a decrease in insulin receptor number for the different steroids including hydrocortisone, dexamethasone and prednisone (47). Increased IR, hyperinsulinemia, is detected both in the liver and in peripheral sites, leading to high basal glucose production and glucose impairment respectively (48). Prednisone also impairs insulin hepatic and peripheral sensitivity as well as induces β-cell dysfunction which influences fasting blood glucose (FBG) and postprandial glucose (PPG) (44,49).

In a separate additive mechanism, chronic PDN exposure also induces a state of hyperinsulinism. This arises from the body's compensation to induced IR and progressive loss of β-cell function (44). Pagano *et.al* observes this in his study where an average PDN dose administered for 7 days induced insulin IR depicted by reduced peripheral glucose utilization and increased HGP in healthy participants. Fasting sugar levels were also high, in spite of the increased levels of serum insulin, denoting insulin resistance (50). Other supporting studies include that done by Hoes *et.al* assessing the effect of chronic steroid (PDN dose equivalent) users and naive patients with rheumatoid arthritis (RA). It was determined that impaired insulin sensitivity and β-cell dysfunction could explain the resultant impaired metabolic state. This was consistent with other RA population studies which proved a correlation between steroid exposure and insulin resistance as well as

related predictability of diabetes (51). The observed IR depends chiefly on the type of steroid and the prescribed dose (46).

Prednisone administration will negatively impact β-cell function depending on the dose, duration of exposure and susceptibility of the exposed population (44). Prednisone facilitates this via a reduction in expression of GLUT 2 transporters and glucosidase receptors. The resultant β-cell dysfunction signifies a loss in glucose sensitivity and inhibition of insulin production and secretion (8,45) which may influence progression from IR to SIH (52). Raalte *et.al* demonstrated that both acute and chronic PDN therapy in varying low and high doses of 7.5–80 mg respectively resulted in impairments of both insulin and c-peptide release, in response to a physiologic glucose load (53,54). This was illustrated in a study that assessed the effects of acute PDN exposure in healthy men. Single dose 75mg PDN and 2-week dosage of PDN 30mg per day both exhibited a dysfunction in β-cell parameters. The acute prednisone dose markedly increased area under the curve (AUC) glucose with unaltered c-peptide secretion (53). Meanwhile, chronic periods of PDN therapy like 6–15 days leads to the adaptation of β-cell functionality in compensation to the steroid-induced peripheral IR (53,55–57). Thus, blood glucose levels will likely remain near the normal values even with the different levels of hyperinsulinemia, depending on the amount of corticosteroid administered (58). Ultimately, the end result is reduced insulin synthesis and decreased β-cell mass from apoptosis induction (59).

The above-mentioned mechanisms result in PDN-induced IR and a resultant state of hyperinsulinism. Normally, this would elicit a compensatory counter-regulatory mechanism in healthy individuals via increased insulin production to maintain a euglycemic state (60). Unfortunately, susceptible populations with steroid-induced reduction in insulin sensitivity or with concomitant inflammatory states lack the normal counteractive effect, leading to hyperglycaemia. Nonetheless, the development of PIH is improbably related to the prior existence of underlying disease as healthy individuals on observation in experimental studies also display dysfunctionality in glucose metabolism (30). Pagano *et.al* presents an emphasis on this point in that healthy volunteers given PDN for 1 week noted a 50% reduction in insulin sensitivity upon assessment using insulin clamp methodology (50). All the described illustrates PDN glucometabolic effects independent of dosage and the duration of exposure (53,54)

2.3.2 Pattern of Prednisone-Induced Hyperglycaemia

Intermediate-acting corticosteroids such as PDN exhibit a peak effect of action of 4-6 hours. The distinct profile is a marked increase in postprandial glucose which optimizes 8-12 hours post-PDN exposure (7). Burt *et.al* findings confirm the predominant increase in BGL in the afternoon and evening, suggesting that these times were most appropriate for screening and treatment implementation (61). This is supported by Uzu *et.al* who diagnosed DM in 40.5% of renal failure patients on HDS using postprandial hyperglycaemia (24). Additionally, a retrospective study showed 47% of patients with post-lunch plasma glucose levels of >11.1mmol/L while having normal FBG. The population included non-diabetic patients using 0.75mg/kg PDN in primary renal disease (48). The glucose effect of single dose PDN occurs predominantly in the afternoon and evening with minimal impact on FBG (61). Prednisone once-daily morning administration is associated with higher BGL in the day, values of >15 mmol/L, and commonly unaffected FBG values (38). The greatest impact is seen on postprandial glucose levels as compared to FBG levels (61). Therefore, the best diagnostic sensitivity of PIH is postprandially.

The development of PIH will be observed within 1-2 days of PDN initiation in about 94% of the cases (11). In observed cases, 50% of the time, the occurrence of SIDM was seen between the second and fourth week (62). Acute administration of PDN is likely to cause the most profound impact in the 2-4th week of therapy (62). Kwon *et.al* notes that upon administration of steroid doses equivalent to 40mg per day for 2 days or more, inpatients will develop SIH (63). Hyperglycaemia related to PDN use can either be transient or persistent. Short term PDN treatment usually results in the attainment of transient hyperglycaemia. Persistent hyperglycaemia will mainly occur upon administration of daily divided doses (44,64). The transient hyperglycaemic effect induced by PDN is usually reversible upon reduction of dose, but this is not applicable to all cases (60). Even with the possibility of reversibility, reports demonstrate that transient increases in serum BGL are associated with acute inflammatory processes and endothelial dysfunction in non-diabetic and diabetic patients (46). The disposition index in healthy participants was constant while susceptible populations showed failure to compensate, leading to hyperglycaemia (44).

2.3.3 Prevalence of Prednisone-Induced Hyperglycaemia.

Steroids are the drugs most commonly implicated in the development of drug-induced hyperglycaemia in both healthy and susceptible populations (9,42). This side effect has been

recognized for over 50 years (8). Several types of research have supported this observation. One such reports an incidence of SIH of 11.1mmol/L in hospitalized patients without a known prior history of diabetes (13). Oral steroids like prednisone have been associated with a 2% incidence of SIDM in patients (10). Further studies indicate a causation of diabetes of up to 46% incidence in patients with no previous history of hyperglycaemia prior to steroid treatment initiation, and an associated increase of BGL of 68% from the initial baseline values (7,13). More than half of patients receiving HDS in the hospital setup develop hyperglycaemia, with at least an occurrence of 86% incidence of first onset hyperglycaemia. Forty-eight per cent of these record an average blood glucose level of 7.78mmol/L (11).

A population-based study of 11,000 patients assessed the risk of SIH. It established SIH risk to be directly proportional to increased daily steroid dose. Odds ratios (ORs) for hyperglycaemia were 1.77, 3.02, 5.82 and 10.34 for 1–39 mg/day, 40–79 mg/day, 80–119 mg/ day and ≥120 mg/day of hydrocortisone-equivalent, respectively (61). In corroboration, Hwng *et.al* found approximately 40% of all cases were new-onset SIDM or steroid exacerbated T2DM for inpatient consults, constant with the 56% rate noted at other institutions (8,13). Furthermore, an assessment of PDN pulse therapy in Pemphigus management revealed that 19 of the 21 patients developed SIH after the first pulse. Thirty-six per cent of these patients developed SIDM after 8 weeks (65). Darjani *et.al* holds the position that baseline FBG levels prior to treatment are a strong predictor of SIDM (65). The rate of SIH in many studies is reported as 30-40% (62). Nonetheless, the precise prevalence of hyperglycaemia secondary to PDN therapy is unknown, posing a challenge in healthcare (12).

2.4 Effect of Prednisone-Induced Hyperglycaemia on Patients

2.4.1 General Effects of Prednisone-Induced Hyperglycaemia

The effects of PDN-induced hyperglycaemia bear adverse outcomes in the affected populations. Hyperglycaemia affects immune function by impairing the activation of neutrophils, increasing lymphocyte apoptosis, inhibiting T-cell proliferation and glycosylating immunoglobulins and complement factors (66,67). Episodes of acute hyperglycaemia result in increased hospitalizations, higher rates of infection, poor wound healing, dehydration, acute hyperglycaemic syndrome, increased risk of intensive care unit (ICU) admissions and higher mortality rates (27). Moreover, a 22 year follow up study on healthy non-diabetic men showed elevated fasting sugar levels being

associated with higher cardiovascular (CVS) mortality rates. The associated 53% mortality gave a higher relative mortality risk in the men grouped with the highest BGL (68). Also, adverse outcomes of PIH like immunosuppression predisposes patients to infections and dehydration. This tends to incline one to diabetic emergencies like hyperosmolar, hyperglycaemic states (12).

Furthermore, hyperglycaemia is a risk factor for cancer–related mortality, with noticeable negative consequences on the survival of patients with small lung and breast cancer (69). Rowbottom's *et.al* findings confirm that long-term steroid use worsens the prognosis for cancer patients. The study revealed that hyperglycaemia led to hospitalization in 23% of monitored genitourinary (GU) cancer patients. Thirteen out of 19 patients without prior DM demonstrated high BGL. Fifteen per cent of these demonstrated hyperglycaemia with random blood sugar (RBS) >27.8mmol/L while another 15% had RBS in the range 15-27.8mmol/L. Upon hospitalization, 2 of the former proportion of patients were initiated on oral hypoglycaemic agents (OHAs) whereas 2 of the latter succumbed to multiple organ failures. Most hospitalized patients were discharged upon reduction of steroid dose (29). Harris *et.al* reported a hyperglycaemia prevalence of 58.9% of patients (53 of 90) in a study of 3 cohorts of cancer patients on steroid therapy. No significant differences of the mean BGL for the 3 treatment groups of 9.4 ± 4.6 mmol/L was observed. Seventeen of 90 (18.9%) patients had DM- range hyperglycaemia. The criteria for a new diagnosis of DM was met by 13.3% (12 of 90) of the patients who experienced DM-range hyperglycaemia (14).

The main risk factors associated with SIH are cumulative dose and the type of steroid (43,44,70). Others include the treatment duration, age, body mass index, mode and route of steroid administration, family history, race/ethnicity, concomitant use of medication, Down syndrome (8,9,13,24,37,46,62). Zeng *et.al* illustrates that steroid dose and increased age were crucial factors in predicting the 31.5% SIDM prevalence seen in their study (71). The presence of more than one risk factor increases the frequency of SIH (72). High-risk patients noted are those who are overweight/obese, elderly, patients with Acanthosis nigrans and previous gestational DM. An existing history of known IGT or impaired fasting glucose (IFG), as well as exposure to causative drugs, poses an increased risk.

All these PDN-induced hyperglycaemic effects are regardless of whether the hyperglycaemia is transient or persistent. Persistent hyperglycaemia has been shown to adversely affect patient prognosis. Thus, hyperglycaemia in patients requires prompt management. A reduction in the rate

of developing complications and mortality has been observed upon the management of transient hyperglycaemia (73,74). The difference in types, doses, regimens, modes of administration and dosage schedules of steroids are factors that contribute to the onset and degree of hyperglycaemia. A common practice is the administration of high-dose PDN as 1mg/kg/day for 1-3 months in the management of certain health conditions (13,37). Studies have shown that low dose of daily oral PDN administration, 6 mg for 7–10 days or 7.5 mg for 14 days induced a deterioration in glucose homeostasis, although to a lower magnitude than imposed by the high PDN dose 30 mg (55,75). High cumulative or daily GC dose was associated with T2DM patients with RA (49).

2.4.2 Detrimental Effects of Prednisone-Induced Hyperglycaemia in Haematological Cancers. Identification of hyperglycaemia as a potential risk factor in the development of cancer is rising and it is closely associated with poor treatment outcomes (14). According to Duan *et.al,* hyperglycaemia contributes to the growth of malignancy via induction of cell proliferation, inhibition of apoptosis, facilitating metastasis as well as chemotherapy resistance (76). Studies have observed an increased risk of cancer mortality in adults with previously impaired glucose tolerance as compared to normal tolerance (77). In haematological patients, the occurrence of hyperglycaemia is of great concern due to the immunosuppressed states, the risk of infection and the risk of hyperglycaemia from steroids, stress and other chemotherapeutic agents. Steroid-based therapy has led to increased cases of SIH and SIDM in these patients. The exact incidence of SIDM in the therapeutic management of haematological cancers has most likely been underrated. Case series suggest values as high as 40% (62).

The studies that have been carried out in specific groups of haematological cancers have yielded comparable results. To elucidate, a prospective study in recently diagnosed haematological cancer patients without DM and initiated on HDS was conducted. Gonzalez *et.al* assessed the impact of continuous versus cyclic dosage regimens of PDN. The continuous cycle included ALL patients receiving PDN 100mg/day for first 6 weeks while the cyclic cycle included NHL patients given 100mg once daily PDN for 5 days followed by 15 days off in one cycle, repeated for 5 cycles. All 32 patients were analysed at 8 weeks using serum insulin levels, FPG and 2-hour postprandial capillary glucose tests. The results indicated an incidence of FPG ranging from 5.6-17.72 mmol/L in 68.7% of patients (22 of 32), with a 34.3% incidence respectively seen in both pre-diabetes and

DM category. The 10 cases without fasting hyperglycaemia were on cyclic PDN. Those who developed hyperglycaemia had a significantly higher cumulative dose of prednisone (62).

The mean value of serum insulin increased over time, though it was not statistically different in the 2 groups as observed by Gonzalez *et.al*. Postprandial hyperglycaemia by week eight showed an incidence of 15.6% (5 out of 32 cases), in which 3 also had a fasting plasma glycaemia ≥7.00 mmol/L. Fifty-four per cent of the 11 patients in the pre-diabetic state were characterized as so in the first week. Five cases of the 11 of 32 cases showed SIDM occurred between the second and fourth week (9.25 ± 2.90 mmol/L) while the remaining 6 occurred afterwards (7.37 ± 0.40 mmol/L). Pre-diabetes was reported in 11 cases who did not develop DM. Continuous PDN scheme was identified as a risk factor for developing DM (Odds ratio (OR) 2.0 95% CI 1.29-3.1). An incidence of 100% of fasting glycaemia was seen in the continuous PDN scheme versus 50% on cyclic PDN scheme. Of these 7 and 4 cases developed DM respectively, with 5 of the 7 cases occurring in the 2nd-4th week. This study found FBG to be more sensitive than postprandial, a contradiction to other studies. However, the participants who developed DM on continuous and cyclic PDN both had a significant increase in insulin secretion compared with those who did not (62).

According to Vidler's *et.al* pilot study, an overall incidence of SIH and SIDM of 44% was noted. Thirty-four out of the 83 enrolled haematological cancer patients were prescribed for high-dose steroids. Thirty percent of the patients without previously known diabetes developed SIDM. A total of 15 patients, including 8 with pre-existing DM, on HDS developed SIH/SIDM that warranted management (6). Other published studies reveal an incidence of 10-56% of hyperglycaemia during the induction phase of acute leukaemia, depending on the defined BGL criteria (27,72,78,79). Koltin *et.al* remarks on an incidence of 15.7% SIDM in ALL patients (28). Likewise, Pui *et.al* observed that 41 of 421 ALL patients developed hyperglycaemia during remission induction on PDN and L-asparaginase (26). It was noted that the frequency of transient hyperglycaemia during the induction phase in ALL therapy was up to 20% (80,81). Matias *et.al* reported hyperglycaemia among adult AL hospitalized patients submitted to a remission induction as frequent. Patients presenting with even low threshold hyperglycaemia (fasting glucose> 5.5mmol/L) were at an increased risk of complicated infections and mortality (82). Relatedly, overt hyperglycaemia has been associated with reduced overall survival and reduced relapse-free

survival (79). This is supported by Weiser *et.al* who found that hyperglycaemic patients had a shorter survival with an increase in infective complications (27).

Consistency is reported across the other types of blood cancers. Ali *et.al* study found that hyperglycaemia was associated with increased hospital mortality in acute myeloid leukaemia (AML) patients, even after adjusting for covariates. The rise in mortality was evident at even levels of mild hyperglycaemia (6.1-8.3 mmol/L) (78). Brunello *et.al* supports the findings of impaired glucose function. He noted abnormal glucose values at baseline in 44% of 349 NHL patients. Dysglycemia over the treatment course was observed in 70% of the NHL patients (83).

Prednisone is indicated in the management of diseases with an inflammatory component. The inflammation induced β-cell effects will interfere with corticosteroid modulation of β-cell function (51). To add on to PIH, inflammatory disease states can themselves independently impair glucose metabolism. These states induce β-cell dysfunction via indirect mechanisms (63). The concomitant occurrence of SIH and inflammatory states may worsen CVS effects. Increased CVS mortality has been observed with fluctuating BGL. This is linked to increased endothelial dysfunction, increased pro-inflammatory cytokine production, increased low-density lipoprotein cholesterol (LDL-C) as well as increased oxidative stress. These bring about macrovascular complications with associated disease progression (59).

2.5 Management of Prednisone induced hyperglycaemia

A commonly employed steroid treatment schedule is based on transient use. This is typified by initial high-dose steroid with gradual tapering upon disease improvement (38). Moderate to severe hyperglycaemia occurs initially accompanied by rapid changes in glycaemia. Thus, the hyperglycaemic effect is depicted as temporary depending on treatment duration (7,38,58). Normalization of blood sugar levels is expected in non-diabetic patients upon discontinuation of PDN use. However, this does not usually pan out hence such patients require close follow up in relation to the high risk associated with developing SIH and SIDM (12). Blood glucose levels can be expected to increase roughly 4 to 8 hours post oral steroid administration. In guiding the appropriate therapeutic interventions, capillary blood glucose (CBG) monitoring is paramount (5). The study recommends once daily CBG monitoring for high-risk patients.

Individualization of glycaemic targets for SIDM patients is recommended. Nonetheless, most patients are recommended to have FBG and 2-hour PPG targets of 4.0-7.0 mmol/L and 5–10

mmol/L, respectively (5,84). Guidelines advocate monitoring blood glucose parameters of the first PDN dose within 8 hours (38). Others suggest monitoring for 48 hours post-PDN initiation as almost 94% of PIH occur during this period (7,38). A post-lunch prandial hyperglycaemia offers the best diagnostic sensitivity upon PDN administration, especially as a single morning dose (7). It is prudent to search for PIH during the second, fourth and sixth week of exposure to high doses of steroids. This finding is consistent with other results that have identified most cases of DM in the early stages of exposure to corticosteroids (24,85). Though these offer an appropriate laid out monitoring regimen, it needs extensive resources to accord all susceptible populations with home glucose testing kits.

Delayed diagnosis was seen in most SIDM patients due to lack of clinical symptoms. Donihi *et.al* observes that 24% of patients receiving HDS undergo no glucose monitoring (13). A strong association of steroid use and high prevalence outcomes has been observed in studies. Conventional diagnostic tests used do not adequately estimate the level of PIH. Fasting glucose measurement can undervalue the real impact of PIH. Haemoglobin A1C levels may be suitable if patient PDN use is more than 2 months rather than with recent use (30). Oral glucose tolerance test (OGTT) may be unsuitable for diagnosis as its done in fasting patients, which inadvertently underestimates the increase in glucose observed in afternoon and evening (37). Notwithstanding information regarding pathophysiology, pattern, intensity, onset, frequency, diagnosis and monitoring is limited (30). Also, prospective studies assessing the effectiveness of preventive interventions and comparisons of different treatment modalities is lacking. Consensus guidelines for optimal management of SIH are needed. The tendency in the development of new-onset hyperglycaemia in susceptible patients is not pre-empted and addressed accordingly (30).

Divergent consenting views exist in regard to the treatment of SIH. A practical point of view entails considering therapy when pre-prandial and postprandial capillary glucose levels are 7.7 and 11.1 mmol/L respectively (30). Consideration points in management would depend on the duration of use particularly if greater than 4 weeks, the severity of SIH, prednisone dosage frequency and concomitant underlying conditions. The choice of medication is influenced by multiple factors like type of steroid, the presence of comorbidities and severity of SIH (12). Oral hypoglycaemic agents chosen should target hyperglycaemia and have a rapid onset of effect. These are initiated with the presence of high BGL of 9-15mmol/L (12).

Second generation sulphonylureas (SUs) are the mainstay therapy used to manage mild postprandial hyperglycaemia (30,37). They are selected due to their rapid onset of action. Usually, doses are given at lunch hour to target postprandial hyperglycaemia. Short and long-acting SUs like gliclazide and glimepiride respectively have been used for once daily and daily divided PDN doses respectively (86). However, SUs present a disadvantage in that they do not specifically target postprandial BGL and prolonged use is associated with high hypoglycaemic risks (30,46). Furthermore, these agents exert effect based on adequacy of β-cell function. The latter is impaired in PDN therapy. Additionally, the insulin-secreting function will result in hyperinsulinemia. High levels of circulating insulin may promote cancer cell proliferation and tumour growth (87,88). Higher endogenous insulin levels have been linked to an increased risk of certain cancers (89). This worsens the prognosis in inflammatory states. The negative effect of hyperinsulinemia is increased when administered HDS is being tapered down and when steroids are given for short durations.

Insulin is administered on a weight basis when blood glucose levels are persistently high or >15mmol/L (73). The insulin regimen chosen is influenced by the raised glucose parameters, whether FBG or PPG as well as the dosage characteristics of the steroid. Unfortunately, laboratory studies have demonstrated that insulin levels may have direct effects in vitro on growth, proliferation and resistance to apoptosis of cancer cells (90). Insulin can promote tumorigenesis through a direct effect on epithelial tissues acting on the insulin/insulin-like growth factor family of receptors (91), or indirectly by affecting the levels of other modulators, such as insulin-like growth factors, sex hormones, and adipokines (92). Hyperinsulinemia from exogenous insulin and SUs adversely affects prognosis in cancer patients and is an independent risk factor for several types of neoplasms (93). To add on, debates ensue on insulin dose adjustment when tapering down steroids. Some decrease both by similar percentages while other reduce dose by half the tapered steroid dose (5,7). This unresolved state tends to prolong the effects of the insulin administered.

2.6 The Role of Metformin in Preventing Prednisone-Induced Hyperglycaemia

2.6.1 Mechanism of action of Metformin in PIH

Metformin suppresses in vitro and in vivo endogenous HGP via activation of the insulin receptor, mainly insulin receptor 2 (94,95). This leads to a reduction in FBG, with subsequent reductions HPG levels (95,96). It also directly improves insulin's sensitivity in both hepatic and peripheral

tissues like skeletal muscles (95,96) thus promoting insulin-stimulated glucose uptake and utilization by peripheral tissues. Moreover, it is not associated with hypoglycaemia unlike other OHAs as it doesn't affect insulin production. These effects are caused by activation of adenosine monophosphate-activated protein kinase (AMPK) and improving insulin sensitivity (97).

AMPK is a principal energy metabolism regulator and mediates several metabolic hormones (98). Activation of AMPK leads to suppression of cellular dependent adenosine triphosphate (ATP) metabolic processes like gluconeogenesis with the concurrent promotion of catabolic processes like glycolysis (23,99). The glucose-lowering properties of metformin are mediated through AMPK restoring cellular energy levels. This is accomplished by phosphorylating regulatory proteins that cause stimulation of glucose uptake into muscle tissues as well as inhibition of gluconeogenesis in the liver. Evidence has shown that steroid therapy led to changes in the activation of AMPK in Cushing's syndrome patients and in vitro in human adipocytes. Profoundly, these effects were reversed with metformin in human adipocytes. These indicate the likelihood of converse effects conferred by steroids and metformin in the AMPK signalling pathway, as well as the overruling of steroid effect by metformin (100,101). Supporting studies demonstrate that steroid-related increase in glucose levels can be prevented with an AMPK activator (102).

2.6.2 Efficacy of Metformin in Preventing Prednisone-Induced Hyperglycaemia

Seelig's *et.al* 4-week trial investigated metformin's effect in preventing the development of systemic steroid-induced metabolic side effects in newly steroid initiated non-diabetics. The treatments included prednisone ≥7.5 mg or an equivalent steroid for at least 4 weeks. The baseline steroid doses across the groups were 35mg/day and 30mg/day for metformin and placebo respectively. Twenty of the 34 patients were randomized to receive 850mg of metformin at increasing dose schedules. Initially, they took 1 tablet for one week, then 2 tablets for 3 weeks. The results obtained showed no difference between baselines 2-hour area under the curve (AUC) glucose concentrations in the metformin group but increasing values in the placebo group. Also, changes in FBG were different across the groups whereas no changes in haemoglobin A1C (HbA1C) values were noted. Metformin prevented worsening of glucose metabolism upon correct timing with PDN therapy initiation. The study found that metformin prevented an increase in 2-hour glucose AUC. This indicated glucose tolerance preservation. In addition, there was improved insulin resistance and reduced FBG (17).

Consistently, a study by Bostrom *et.al* commented on the safety and efficacy of metformin in hyperglycaemia-induced from treatment of childhood ALL. The BGL were controlled by metformin monotherapy in 12 of 17 patients, without the need for insulin. The median dose administered was 1000mg/day (500-2000mg) or 28mg/kg/day (14-64mg/kg/day) for a median of 6 days (2-46 days). Interestingly, 1 of the patients who had developed hyperglycaemia during relapse re-induction was effectively controlled using metformin alone without the need for insulin. The same patient who had been diagnosed before the study had required insulin during induction therapy for hyperglycaemia. Three of the patients given insulin therapy due to high BGL were eventually weaned off insulin to metformin alone. Only 1 patient required continued insulin use all through for hyperglycaemia control (16).

The Diabetes Prevention Program (DPP) carried out a large study of 3,234 pre-diabetic patients. Participants on 850 mg twice daily metformin reduced their risk of developing diabetes by 31 % for both men and women, a value higher than the placebo's group. It was shown to be effective in restoring normal FBG values (103). Moreover, no significant safety issues were identified (104). In a similar comparative study, metformin still retained its effectiveness in a much smaller dose (500 mg/day) than used in the DPP (1,700 mg/day). It was noted that in lower doses (500 mg) of metformin effectively reduced the progression rate from pre-diabetes to diabetes in the Asian Indian population. The absolute reduction in the study was 14.5 per 100, higher than the DPP reduction of 7.2 per 100 (31,103). Similarly, a meta-analysis showed the benefits of metformin in pre-diabetic and/or high-risk patients. It demonstrated a reduction of new-onset diabetes by 40%, with an absolute mean reduction of 6% during a 1.8 year trial period. Additional benefits of improved insulin resistance, lipid profiles and weight were also illustrated (105). Research shows a reduction of 5.3% of TGs as well as 5.6% of LDL-C with metformin use. It also modestly improves high-density lipoprotein cholesterol (HDL-C) by about 5% (106).

In cancer patients, the accrued benefits and efficacy of metformin are also illustrated. Libby's *et.al* prospective cohort study observed a reduced overall and cancer-associated deaths in new users of metformin. A 37% reduced risk of cancer was noted, even after adjusting for confounding. The largest cancer risk reduction was seen with the highest dose of metformin of 850 mg twice daily. Incident cancer diagnosis was 8% in the metformin cohort compared with 11% in non-users during a 10 year follow up (19).

In regard to glucose metabolism, the fasting and postprandial insulin levels in DM patients showed a consistent decrease. This signified a preserved pancreatic compensatory function with enhanced sensitivity to insulin (95,96). Trials document a consistent decline in FBG by 3.3-3.9 mmol/L with metformin therapy. In a large double-blind, prospective study involving 289 diet-treated patients with type 2 diabetes with FBG of 13.3 mmol/L, metformin reduced the fasting glucose levels by 2.9 mmol/L (107). These decreases were independent of age, ethnicity, duration of diabetes, body mass index, or fasting and glucose-stimulated plasma insulin or c-peptide levels. Approximately 25% of T2DM patients on metformin monotherapy achieved a fasting plasma glucose level of less than 7.8 mmol/L (108). It is however speculated that the decrease in FBG from baseline levels is associated with initial FBG values (108). The FBG shows a decrease within 3-5 days upon initiation of metformin treatment and reaches a nadir in 1-2 weeks.

Similarly, a study by Garber *et.al* assessed the efficacy of different Metformin dosages in 451 patients with FBG $\geq$10mmol/L. Benefits were observed with doses as low as 500mg, while maximal advantages were accrued with higher daily doses. The mean differences in FBG from baseline values exceeded the placebo by 1.05- 4.6 mmol/L at 500-2000mg doses respectively (109). The maximal glucose-lowering effect of between 80-85% was seen with a daily metformin dose of 1500mg. The hypoglycaemic action of metformin increased linearly, even at very high fasting plasma glucose levels >16.7 mmol/L (108).

2.6.3 Benefits of Metformin Therapy in Cancer Patients

Metformin is associated with reduced cancer morbidity and mortality (19,21,22). Preclinical studies implicate that metformin can inhibit the growth of cancer cells in vitro and in vivo (23). The anti-cancer effects of metformin may be linked to direct action of metformin on the AMPK signalling pathway, rather than its clinical effects on insulin sensitivity and hyperinsulinemia (110) and other target sites like the mammalian target of rapamycin (mTOR) (32). Furthermore, targeting of mTOR has been shown to be beneficial in childhood ALL management (33). Additionally, metformin may also confer protection from anthracycline-associated cardiotoxicity in combination chemotherapy regimens (34). Observational studies have reported decreased cancer incidence and cancer-related mortality in diabetics receiving standard doses of metformin (1500 to 2250 mg/day in adults) (19,21,23,111). A meta-analysis of 5 observational studies showed that metformin is associated with a 31% statistically significant decrease in cancer risk compared

with other diabetic treatments (23). Subsequent reduction of cancer risk in diabetics is associated with metformin's increasing protective effect upon higher dose exposure (21).

Several other studies have associated metformin use with a reduced incidence and risk of cancer in diabetic populations (19,20,22). In a study assessing the occurrence of cancer in 1,340 T2DM patients with no malignant histories, metformin exposure was associated with a decreased cancer incidence (OR 0.46 [95% CI 0.25–0.85], p=0.014) in both men and women. The mean daily dose of metformin given was 16-18.5mg/kg/day. In comparison, sulphonylureas did not show any reduction in incidence (OR 0.75 [0.39– 1.45], p=0.40) (111). Likewise, Ruiter's *et.al* study of 3552 patients demonstrated that metformin use in 1590 patients was significantly associated with a lower risk of specific and general cancers as compared to the use of SU derivatives in 1962 patients (20). Metformin monotherapy carried the lowest risk of cancer. In comparison, the adjusted hazard ratio (HR) was 1.08 (95% CI 0.96–1.21) for metformin plus sulfonylurea, 1.36 (95% CI 1.19–1.54) for sulfonylurea monotherapy, and 1.42 (95% CI 1.27–1.60) for insulin-based regimens. Adding metformin to insulin reduced progression to cancer (HR 0.54, 95% CI 0.43–0.66). Those on insulin or insulin-secreting agents were more likely to develop solid cancers than those on metformin, and combination with metformin abolished most of this excess risk (22). Vu *et.al* described the benefit of increased progression-free survival in ALL patients on metformin (18). In addition, metformin monotherapy has also been associated with a reduction in macrovascular complications like stroke or myocardial infarction (23,112).

The pharmacokinetic properties of metformin additionally offer a unique advantage with use. Its negligible protein binding, lack of hepatic metabolism and achievement of steady-state concentrations that rarely exceed 5ug/ml even at maximum doses advocates for its safety in cancer patients. The risk of lactic acidosis which occurs with high concentrations is low, especially when there is adequacy of renal function. Acidosis was rare in adult diabetic patients and was never directly attributable to metformin (113). Similarly, Salpeter *et.al* systematic review found no cases of fatal and non-fatal lactic acidosis in 70,940 patient years of metformin use (114). Even upon occurrence, studies indicate a low risk of acidosis which was noted only in 1.6% patients who had overdosed on metformin (115)

In summary, most literature on PIH effects lack an assessment of measures that can be taken to prevent the anticipated glucose intolerance. A recent study by Seelig *et.al* offered the basis of using

metformin to prevent glucometabolic deterioration in newly initiated steroid therapy. The study like most has yet to assess the effectiveness of metformin in high dose steroid conditions, especially with associated inflammatory states.

CHAPTER THREE: METHODS

3.1 Research Design

The study design was a two-armed, single-centre, prospective randomized controlled trial (RCT) to assess the level of effectiveness of metformin in preventing prednisone-induced hyperglycaemia among haematological cancer patients on prednisone-based regimens at KNH. The RCT study design was chosen as it provided the most rigorous conditions for comparing the level of effectiveness of metformin as an intervention. The predictor variable in this study was prednisone-based chemotherapy in haematological cancers while the outcome variable of interest was prednisone-induced hyperglycaemia. The experimental arm and control arm involved participants who were randomly assigned to receive metformin or standard care respectively. The RCT design also provided the desired means of realizing the specific objectives aforementioned by enabling the determination of the incidence of pre-diabetic and diabetic states of PIH in the control group.

3.2 Study Site

The study was carried out at the adult haemato-oncology clinic (clinic 23) and ward 8C at the Kenyatta National Hospital in Nairobi. This centre was identified as the study setting due to its establishment as the biggest public health teaching and referral facility in Kenya, which offers comprehensive cancer care treatment and has a high flow of patients in need of these specialized services. According to records, 30 or more new cancer patients are reviewed on a weekly basis, with concurrent admissions and treatment (116). Moreover, the site has established protocols and standard of practice that eases follow up of patients. Thus, it offered an ideal location for accessing the required sample size, with a good representation of the intended target population as well as for monitoring treatment course.

3.3 Study Population

The study population were patients diagnosed with haematological cancers, aged 18 years and above, being managed on steroid-based chemotherapy at KNH. These patients had been prescribed high-dose prednisone as part of the standard chemotherapy regimen and were most likely to develop hyperglycaemia during the treatment duration (10,38), making them an ideal target population. Evidence indicates that greater than half of the patients on HDS develop hyperglycaemia, with an incidence of 86% of at least one episode of hyperglycaemia and 48% of patients presenting a mean blood glucose $\geq$ 7.8mmol/L (11). In addition, the incidence of

haematological cancers is on the rise, which fostered the need for addressing hyperglycaemia in this patient population (4).

3.4 Eligibility Criteria

The eligibility criteria used was based on the detailed inclusion and exclusion criteria specified below. It incorporated the use of patient records and interviewing of participants by the principal investigator to identify the below-mentioned criteria. To ensure consistency with other studies, a rigorous literature review was undertaken to help in the formulation of the inclusion and exclusion criteria that were employed.

3.4.1 Inclusion Criteria

Inclusion criteria included patients that were presently on or had been initiated on high-dose prednisone-based chemotherapy (>30mg/day) (117) with haematological cancers (Leukaemias, Lymphomas and Multiple Myeloma), patients who had postprandial blood glucose readings that indicated no hyperglycaemia prior to enrolment in the study, patients aged 18 years and above, patients who had adequate renal function prior to enrolment to the study with a serum creatinine levels of <150umol/L and/or estimated glomerular filtration rate (eGFR) of >30mL/min per 1.73m² , patients who had adequate electrolyte balance particularly serum lactate levels <5 mmol/L, patients who showed willingness to comply with the study protocol and signed an informed consent, and patients who had normal haemoglobin reference values from full hemogram tests.

The inclusion criteria defined above was based on the knowledge of the pharmacokinetics of metformin, which is primarily excreted in urine unchanged thus needs adequate renal function. The inclusion of patients presently on HDS allowed the determination of metformin effectiveness in already exposed patients, as long as it allowed adequate follow up during the study period. The low likelihood of occurrence of lactic acidosis associated with metformin use dictated the inclusion criteria depicted above. The use of normal ranges of haemoglobin values ruled out the presence of vitamin B_{12} deficiency which typically presents as megaloblastic anaemia. Thus the safety concern of metformin-associated depletion of vitamin B_{12} was appropriately addressed. Selection of patients on high-dose prednisone-based chemotherapy was based on previous literature review that it largely predisposed the patient to hyperglycaemia. The choosing of patients that were willing and able to comply with the study protocol ensured minimal loss to follow up over the study period.

3.4.2 Exclusion Criteria

The exclusion criteria ruled out patients on prednisone treatment for any other indication other than haematological cancers, patients who had pre-existing diagnosed diabetes mellitus, patients who had been recently exposed or were awaiting radiocontrast procedures, patients who had recent exposure (less than 3 months) to metformin, patients who had more than one cancer where the additional cancer was non-haematological, patients on medication that may have contributed to hyperglycaemia like thiazide diuretics, beta-blockers, protease inhibitors, statins, niacin, phenytoin, atypical antipsychotics, oral contraceptives and L-asparaginase, pregnant patients, patients who had significant electrolyte disturbances, patients who had tissue hypoxia like cardiac or respiratory insufficiencies, patients who consumed three or more alcoholic drinks per day, patients who had concurrent severe illness and patients who had been on any other antidiabetic therapy.

The exclusion criteria was carefully chosen based on the need of assessing the true effect of metformin in preventing hyperglycaemia in prednisone use. Exclusion of exposure to radiocontrast material, patients who had significant electrolyte disturbances, patients who had excessive alcohol consumption and patients who had concurrent severe illness was centred on the relative contraindication of metformin use in such patients. The exclusion of pregnant patients was limited to the fact that studies had not ascertained the use of metformin safely in this population. Patients on antidiabetic therapy like insulin or sulphonylureas, may have been inclined to having lower blood glucose levels thus confounding the assessment of metformin's effect. Patients who had hypoxic states were excluded due to the high risk of occurrence of lactic acidosis.

3.5 Sample Size Estimation

The estimated sample size was based on the alternate hypothesis that there will be a statistically significant difference in the proportion of patients who would develop prednisone-induced hyperglycaemia among participants receiving metformin and those who did not. Numbers used in determining the sample size were estimated based on previous studies conducted in similar populations. An observational study examining the prevalence of SIH in patients undergoing cancer therapy detected a hyperglycaemia prevalence of 58.9% (14).

A study by Bostrom *et.al* showed the effectiveness of metformin in controlling SIH in AL patients on induction therapy. Out of the 13 patients who qualified for and received metformin alone, 8 had

excellent blood glucose control with levels never exceeding 11.1 mmol/L. Of the remaining 5 patients, 4 had controlled blood sugar levels but experienced days when blood glucose >11.1mmol/L, while one patient failed metformin therapy and required insulin. Thus, the proportion of patients who achieved adequate glucose control (blood glucose values never exceeded 11.1mmol/L) on metformin alone (without the need for additional insulin) was 61.5% (8 out of 13 patients who qualified for metformin only) (16). The effect size of interest in the study was, therefore, an expected SIH proportion reduction of 61.5% in the metformin group relative to the control group. Consequently, we estimated that the proportion of patients with SIH in the metformin group would fall by a similar margin that is from the estimated 58.9% in the control group down to 22.7%.

The sample size was calculated using the formula by Chan *et.al* for randomized controlled trials with a dichotomous outcome of interest (118). A conventionally acceptable level of α of 0.05 for a two-sided test and a 1-β power of study of 0.8 was chosen. This level of potential error and statistical power were considered acceptable in health care research as the minimum acceptable chance of obtaining a false positive and false negative results respectively, to demonstrate the effects of the intervention. The formula used in estimating the sample size was:

$$n \text{ (size per group)} = c \; x \; \frac{\pi1(1-\pi1)+\pi2(1-\pi2)}{(\pi1-\pi2)^2}$$

where c= 7.9, the conventional multiplier for β at 0.80

   $\pi1$=proportion estimate in group 1= 0.589 (58.9%)

   $\pi2$=proportion estimate in group 2= 0.227 (22.7%)

   $\pi1 - \pi2$= effect size of the intervention= 0.362 (0.589 - 0.227)

Thus, the estimated target sample size to determine the effect of the intervention at 5% significance and a power of 90% was:

$$n = c \; x \; \frac{\pi1(1-\pi1)+\pi2(1-\pi2)}{(\pi1-\pi2)^2}$$

n= 7.9 x [0.589(1-0.589) + 0.227(1-0.227)]

   $(0.362)^2$

$$n = 25.2$$

Thus, a minimum of 25 patients in each arm was required, entailing a total of 50 patients for the study. Accounting for an expected 10% loss to follow up, the final sample size estimated about 56 patients in total.

3.6 Participants Recruitment Process

The recruitment process targeted eligible patients at KNH hemato-oncology clinic 23 and ward 8C. Patients were identified and assessed for preliminary eligibility by the attending physician. Those who qualified for enrolment were duly notified of the study by either the attending physician or were called upon by the principal investigator based on information obtained from medical records. They were referred to the principal investigator who duly informed them of the details of the study which included the basis and need of the study, the interventions that were to be administered, the duration and follow up of the study, the tests that were to be administered, the expected outcome and benefit of the study, the risks associated, the possible side effects expected and unexpected during the study as well as ethical considerations. The Informed Consent Form (Appendix 3) contained all the relevant aforementioned information. All patients willing to comply with the study protocol were enrolled in the study upon signing the informed consent. Patients unwilling to participate continued with their provided treatment. Any patients in doubt were allowed time to deliberate on possible participation and all queries raised regarding the study and related issues were suitably addressed.

Patients who agreed to participate in the study were assigned a study identification number and proceeded for physical examination, capillary blood glucose and any other required laboratory tests for example full hemogram, serum creatinine and serum lactate tests to definitively establish their eligibility. A structured eligibility assessment form (Appendix 5) was used to guide the process of assessing eligibility. After qualification for eligibility, these patients were given a unique patient information card (PID) (Appendix 4) and proceeded to the research coordinator, the oncology pharmacist, where they received their chemotherapy management as well as were assigned to a study arm that received either standard treatment or metformin. All study participants were issued with PIDs bearing a unique alphanumerical code. This card was used to identify and track the patients during the study period.

3.7 Randomization

All eligible participants who met the eligibility inclusion criteria and willingly consented to take part in the study were included in the study sample. A restricted method of randomization was applied to assign each participant to either the control or intervention arm. This prevented selection bias as well as minimized the effect of confounding variables.

3.7.1 Allocation Sequence

The technique used was permuted block randomization. Participants were randomly assigned to receive either control (standard care) or intervention (metformin). The randomization scheme used was generated by the research biostatistician and consisted of a sequence of blocks such that each block contained a 1:1 ratio of patient allocations across treatment groups. The sequence of allocations within each block was in random order, with each block having a different random sequence. The equality of the patient allocations across treatment groups within each block ensured a balance in numbers between the two arms upon the completion of each block, with random blocks of size 2 and 4 being used by the biostatistician.

3.7.2 Allocation Concealment

The generated randomized allocation sequence and block sizes were concealed by the biostatistician. He created sequentially numbered sealed opaque envelopes, each containing a slip with a code that designated which of the two interventions assigned was to be received by each participant. This facilitated allocation concealment. The sealed envelopes were securely and confidentially provided to the research coordinator (the oncology pharmacist) at KNH. The patient allocations were known only to the oncology research pharmacist as the level of blinding included both the participants and the outcome assessors.

3.7.3 Allocation Implementation

The research coordinator (oncology pharmacist) at KNH was responsible for assigning the generated allocation sequence to the participants of the study. She was responsible for opening the sealed envelopes assigned as per the patient information card (PID) (Appendix 4) and determined to which study arm the participant was allocated to. She was also responsible for the dispensing of the treatment (metformin) to the interventional arm of the study group as per the provided protocol (Section 3.9.1).

3.8 Treatment of Participants

Upon enrolment into the study, participants were allocated to either of the two arms, based on the concealed randomization process described above.

3.8.1 Control group (Standard treatment)

The control group received the standard care offered at the study site for the study duration of 4 weeks per participant. This involved the prescribed chemotherapy management for their illness as well as any additionally prescribed treatment. This included proton pump inhibitors for example omeprazole and calcium tablet supplements. These are usually administered to prevent peptic ulcer disease and osteoporosis respectively.

3.8.2 Treatment Group (Metformin)

The treatment group received the above described standard treatment as well as additional treatment with metformin. Metformin was initiated at a dose of 850mg once daily for the first two weeks, with adjustment upwards to 850mg twice daily for the remaining study duration. The dosing strength of 850 mg metformin was selected based on a precedent observed in similar studies which illustrated that high doses of metformin (1000-2000mg daily) have a greater glucose lowering effect as well as an associated protective effect among cancer patients (7–11). In addition, it has also been demonstrated that 80-85% of the maximal glucose-lowering effect by metformin is observed with a daily dose of 1500mg (119). The dosing schedule of administering metformin as an initial dose of 850mg daily with an upward titration to 1700mg daily is based on a standard product information guide as well as from observations from literature review (31,120). These highlighted that initiating participants with smaller doses of metformin with gradual increment after a 2-week period reduces the incidence of gastrointestinal side effects to the participants (120). The metformin brand procured was the innovator drug Glucophage 850 mg tablets from Merck Pharmaceuticals.

3.8.3 Intervention Implementation

An oncology research pharmacist was responsible for the treatment during the study duration of 4 weeks per participant. The pharmacist was responsible for the treatment management of both the control and intervention arms of the study. The research pharmacist was a qualified and licensed Master of Pharmacy (Clinical Pharmacy) degree holder, with at least 1 year of clinical experience at KNH. She ensured that both the standard care and metformin were administered to the study

participants. She oversaw the dispensing of the interventions as well as the issuance of respective instructions to both groups. All the attendant instructions provided across the groups were uniform to avoid the possibility of co-interventions. The control arm received the provided standard care over this period. The interventional arm was instructed on how and when to take the medications.

The pharmacist bore a drug record schedule on the dispensing of metformin (Appendix 6). This was used to document the number of tablets and the time the tablets were taken for each participant in the interventional arm. This not only helped in assessing participant compliance and adherence to treatment protocol but ensured blinding as only the research coordinator (oncology pharmacist) was aware of who was receiving the intervention. Any participant from the clinic setup was given the designated number of tablets to consume until their next follow up visit.

During the study period, all the participants were provided with standardized monitoring and care by the research coordinator and principal investigator. They all equally received the recommended tests required during this period as per the prescribed treatment as well as the study protocol (Section 3.9).

3.9 Patient Follow Up

Participants were made aware of scheduled follow-up visits from the onset of the study as well as via reminders from calls and/or text messages. They were each followed up for a period of 4 weeks. The study duration of 4 weeks was adequate based on review of previous studies investigating the development of prednisone-induced hyperglycaemia. These studies sufficiently provided evidence illustrating that the occurrence of prednisone-induce hyperglycaemia could be demonstrated as early as 48 hours after initiation of high dose prednisone therapy in 94% of patients (11). Acute prednisone administration would probably cause the most profound impact in the 2-4th week of therapy and that upon administration of steroid doses equivalent to 30mg per day (which is the dose administered to this target population) for 2 days or more, inpatients would develop SIH (62,63).

The patients were assessed on the first day of enrolment into the study (Day 1) and every 7 days during the study period (Days 8, 15, 22 and 29). Blood sugar testing for each of the participants was done using the above-described schedule by an enrolled and blinded research nurse. The research nurse was a qualified and licensed degree holder, who had been adequately trained to offer healthcare services. The capillary blood glucose levels were measured at day 1 of recruitment

and every 7 days thereafter. The nurse was responsible for determining and recording both the observed fasting and postprandial (2 hours after lunch meal) capillary BGL readings. The amount of blood drawn for capillary BGL was a droplet of blood (3-5 microliters). Prior to the day of blood sugar testing, participants were encouraged to fast overnight for 8 hours via telephone and /or face to face communication.

Fasting blood glucose levels were obtained in the morning. The 2-hour postprandial capillary BGL was taken after lunch, with lunch being provided to these participants. The lunch provided to all patients was the same standard healthy meal sourced from the KNH cafeteria to minimize variation in meals that could have possibly introduced an element of confounding. The standard aseptic technique observed in the measurement of blood glucose was observed. This included the use of gloves by the nurse in cleaning the intended site by an alcohol swab and pricking the finger using a single-use sterile lancet needle. The nurse underwent training on the use of the study glucometer to ensure that the correct standard procedure was observed in accordance with the investigator study protocol and manufacturer's instructions. This ensured that the sampling technique was appropriate and all the readings obtained are valid.

At each follow up visit, the participants had a physical assessment done which incorporated monitoring of vital signs as well as a capillary BGL test by the research nurse, a refill of tablets from the dispensing pharmacist (the intervention group) and an interview with the principal investigator and/or research assistant who assessed the occurrence of any adverse and/or side effects as well as provided any additional instructions. In addition to the above described, laboratory tests were carried out on Day 22 of the follow-up visits. These required the determination of serum creatinine levels, serum lactate levels, and specific liver function tests aspartate and alanine aminotransferases (AST and ALT). This entailed drawing of 3-5 millilitres of venous blood from all the study participants. These were carried out in the laboratory facilities of KNH at the expense of the principal investigator. All the obtained results were recorded in the designed case report form (CRF) (Appendix 7).

The laboratory results obtained were subjected to scrutiny by the established Data Safety Management Board (DSMB) monitoring of any irregularities. Upon determination of any such irregularities, the DSMB comprising of the two oncology medical officers and oncology nurse deliberated on the findings and determined the most appropriate course of action to be taken for

the affected participant. They were joined by the oncology pharmacist who presented the patient data in the CRFs for the DSMB review. Any intervention undertaken on any participant based on the laboratory results or any findings found in the scheduled follow up visits were at the expense of the principal investigator.

All patients were advised on the monitoring parameters to be checked in terms of hyperglycaemia symptoms and the possible metformin-associated side effects, with the relevant provision of contact details given to each participant to call in case of emergency. This information was also provided in the participant information sheet (Appendix 2) as well as the patient information card (Appendix 4). Patients exhibiting mild side effects were managed according to standard procedure while those presenting with more severe adverse events to metformin were discontinued for safety purposes based on the recommendations of the DSMB.

The principal investigator made due effort to minimize loss to follow up by contacting and reminding the participants prior to the scheduled follow up visit days (Day 8, 15, 22 and 29) via text messages and phone calls.

3.10 Blinding

During the study, the persons that were blinded included the principal investigator, the research nurse, the research assistant, and the supervisors. Only the oncology research pharmacist was unblinded. The study encompassed the following blinding procedures:

Firstly, the generated random allocation sequence of participants into either the intervention or standard treatment arm was concealed all through the study and was known only to the research biostatistician. Secondly, the research coordinator, the oncology pharmacist, was the sole person responsible for implementation of the allocation sequence as well as dispensing metformin to the participants. No other research personnel/ co-investigator was aware of the assignment of participants to either of the two arms and the subsequent administration of the intervention drug.

Thirdly, the enrolled research nurse was blinded and was not privy to the allocation of participants to the two arms. The nurse was responsible for the determination of the participants' physical assessment during follow up visits as well as the measurement and recording of blood glucose reading in the CRF (Appendix 7). The CRF's were confidential and the oncology research pharmacist was in charge of their safekeeping. Fourthly, the principal investigator and the research

assistant were blinded, and the interviews were done on participants' during follow-up visits by them only entailed questioning of the participant well-being and the occurrence of any side effects. In the event of the occurrence of any side effects, the study participants were referred to the DSMB for review and the appropriate medication therapy management. This minimized the risk of possible unblinding of the principal investigator and research assistant.

It was noted that, due to the absence of a suitable placebo, it may not have been possible to blind the study participants. However, as the main outcome measure (blood glucose levels) was an objective measure that was determined by a blinded research nurse, the risk of information bias during outcome determination was minimal.

3.11 Research Instruments

The data capturing tool used in the study was the CRF (Appendix 7), designed to collect all pertinent participant data and all relevant observations made during the study. The CRF was consistent with the FDA's Clinical Data Acquisition Standards Harmonization (CDASH) standards (121). It contained relevant personal information regarding patient demographics, medical history, current diagnosis and treatment, concomitant medications, physical assessment parameters, adverse reactions and their management and all glucometer readings. A patient information card (Appendix 4) was developed to document the type and name of the treatment administered, the occurrence of any symptomatic side effects as well as the symptoms to be watched out for during the study period. A drug entry form (Appendix 6) was designed to indicate the number of metformin tablets administered as well as the time of taking the medication for the intervention group. Other research instruments included the participant information sheet, the informed consent form and the eligibility assessment form. These were provided in Appendices 2, 3 and 5 below.

The research equipment used included a glucometer with its respective measuring strips, lancing device and lancets. The glucometer used was On-Call Advance® (Acon Diabetes Care Manufacturer), which has a BGL test range of 1.1-33.3mmol/L and a memory storage of 300 results with dates and time. These were acquired from an authorized seller to facilitate monitoring of postprandial and fasting blood glucose levels on a given schedule. Other consumables used were latex examination gloves and sterile surgical swabs for the purposes of capillary finger prick test.

3.12 Validity and Reliability

The validity of the blood glucose testing machine was determined using the manufacturer's control solution as per the manufacturer's instructions. The contents of the CRF had been harmonized in accordance with the standards of the FDA's CDASH. This allowed its reliability and credibility in the study.

3.13 Data Collection Techniques

The sources of data used in the study included data obtained from patient medical records and/or files, data from interviewing the patients and/or relatives when assessing for the eligibility criteria and during follow up visits as well as information from laboratory test results performed through the course of the study. All relevant data were recorded into each participants' respective CRF (Appendix 7). The data collected was entered and cross-checked by the principal investigator. This was then later followed by subsequent recording into a secured electronic study database. The electronic database used was Microsoft Excel, which was password protected. Information collected on the PID was handwritten by the participant while medication administration information was recorded into the Drug Entry Form (Appendix 6) by the oncology research pharmacist.

The data variables collected in the CRF during the study included participants' baseline characteristics, all relevant medical history, physical assessment parameters, specified laboratory tests, the number of tablets administered and the time they were taken as well as all the participants' blood glucose readings at the specified intervals. The baseline characteristics and history were obtained from medical records and from each individual participant. The information on physical assessment was obtained from the enrolled and qualified research nurse while the laboratory results were obtained from the relevant tests done at the laboratory in KNH.

Physical assessment was done at baseline for all enrolled participants by the research nurse. The parameters observed were recorded in the CRF. It included vital signs like pulse, heart and respiratory rate, temperature, blood pressure, weight and height. This ensured patient safety and eligibility to take part in the study with no unnecessary imposed patient risk. It also allowed for capturing of baseline characteristics that were later be used in assessing the patients' comparability between the groups.

3.14 Data Management and Analyses

Physical data obtained were securely kept under lock and key by the principal investigator and the research coordinator throughout the study period. Upon completion of the study, the data obtained was transferred into a secure electronic database which was password protected. These were then transferred to STATA for data analyses. The STATA version used was version 13.0 data analysis and statistical software.

The method that was used in analysis of collected data was the modified intention to treat analysis. This necessitated the inclusion of patients who successfully reached Day 22 of the protocol and successfully had their laboratory and capillary BGL measured. This meant that all patients who successfully reached day 22 of the study as described above were analysed in the group to which they were randomized. This criterion was based on the fact that the participants' status was unlikely to change after the 22nd day. Patients lost to follow up before Day 22 were excluded from analysis.

The baseline characteristics were expressed as percentages for categorical variables while glucometer values and other continuous variables were presented as means and standard deviations. The outcome of interest which was the presence or absence of PIH (defined as a 2-hour postprandial BGL of >7.8mmo/L or a fasting BGL of >5.6mmol/L) was determined using incidence rates of pre-diabetes and diabetes among the study participants. This dichotomous variable was expressed as proportions (percentages) and was compared across groups using the Fishers' exact test. The Mann-Whitney U test was used to compare the medians of continuous variables across the 2 groups while the Wilcoxon-Signed Rank test was used for within-patient comparison of BGL for individual participants in the treatment group using single and double daily metformin dosing. Measures of association of absolute and relative risk reductions, as well as odds ratio due to metformin intervention on BGL, was calculated across both groups, with their respective 95% confidence intervals estimates. A p value of <0.05 was determined as statistically significant.

Multivariate logistic regression model was employed in assessing the association between study predictor variables and the development of PIH, after adjustment for confounding variables like age, gender and body mass index (BMI).

3.15 Ethical Considerations

3.15.1. Independent Human Research Ethics Committee Approval

Ethics approval for this study was sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON-ERC) before the commencement of the study. The ethical approval reference number was P143/03/2018(Appendix 1)

3.15.2. Informed Consent

The patients were required to sign an informed consent (Appendix 3) for participation in the study. They were offered all the adequate oral and written information about the purpose, nature, possible risks and benefits of the trial. Patients were also notified of the freedom to discontinue from the trial at any given time if they chose to. The patients were accorded the opportunity to ask questions and allowed as much time as they required to consider the information provided.

3.15.3. Confidentiality

Participant confidentiality was strictly held in trust by the research personnel. This confidentiality was extended to cover testing of blood glucose samples as well as clinical information relating to participants. The study protocol, documentation, data and all other information generated was held in strict confidence. No information concerning the study or the data was released to any unauthorized third party. All evaluation forms and/or reports and other records related to the trial that left the site were identified only by the participant identification number to maintain participant confidentiality. Clinical information was not released without written permission of the participant, except as necessary for monitoring by KNH/UoN-ERC.

3.15.4. Safety and Monitoring

Participant safety was monitored throughout the course of the study by ensuring provision of all the relevant safety information in the participant information sheet as well as providing the necessary contact details for communication in case of an emergency. The relevant laboratory tests were done for all participants on day 22 and at any point in the study in which such was deemed necessary. The principal investigator and the co-investigators were trained in good clinical practice, to ensure that patient safety was observed by the recruited research team.

A DSMB comprising of two oncology medical officers and oncology nurse deliberated on any emergent health issues and advised on the best and most appropriate course of action in any

required instance. They were joined by the oncology pharmacist who presented the patient data in the CRFs for this review when required. Any study participants found to have developed hyperglycaemia during the study was managed by the attending physician, in accordance with the ascribed standard procedures. This involved the issuance of hypoglycaemic agents, prescribed accordingly by the attending physician or the reduction of prednisone dose. The participant was discontinued from the study based on the development of the outcome of interest. They continued with their normal chemotherapy treatment as well as any standard care treatment that may have applied.

All adverse reactions reported were recorded on the CRF (Appendix 7) as well as the Adverse Reaction Reporting Form, with major ADRs being reported to KNH/UoN-ERC within 48 hours.

3.15.5 Financial Implications

All the costs of the study excluding the normal chemotherapy and routine laboratory tests for the patients were covered by the principal investigator and the KNH Research and Programs Department. Any additional cost like extra transport charges above the set reimbursed fee incurred by the participant upon follow up visits were reimbursed by the principal investigator. A transport compensation fee of Ksh.300 plus a healthy standard lunch were offered during the follow-up visits.

CHAPTER FOUR: RESULTS

4.1 Participants Enrolment

Over a 12 week duration (25th June 2018 to 10th September 2018), a total of 39 potential participants were screened, and 27 were enrolled for the study as per the eligibility criteria. The 12 participants were excluded on the basis that a proportion of them had been switched to a non-prednisone containing regimen at the time of the study. Also, a proportion of these patients were still undergoing investigations to determine the definitive cancer diagnosis.

From those enrolled, 3 study participants retracted their consent and withdrew from the study, leaving 24 patients who were successfully randomized to participate. During the study period, 6 participants were lost to follow up, in the ratio of 2:1, 4 from the treatment arm and 2 from the control arm respectively. The loss to follow up was attributed to the demise of 3 patients while another 2 were lost on the basis of change of treatment protocol and relocation to a distant region thus unavailable for ample follow up. A further one patient was discontinued from the study due to the discovery of pre-existing diabetes mellitus that had been undocumented and the patient was unaware. The study thus was successfully completed with 18 study participants. This is highlighted in a consort flow diagram below:

```
            ┌──────────────────────┐
            │ 39 patients screened │
            └──────────┬───────────┘        ┌────────────────────────┐
                       │──────────────────→ │ 12 failed to meet the  │
                       │                    │ eligibility criteria   │
                       ↓                    └────────────────────────┘
            ┌──────────────────────┐
            │ 27 participants      │
            │ enrolled             │
            └──────────┬───────────┘        ┌────────────────────────┐
                       │──────────────────→ │ 3 withdrew consent     │
                       │                    │ from the study         │
                       ↓                    └────────────────────────┘
            ┌──────────────────────┐
            │ 24 patients          │
            │ randomized           │
            └─────┬──────────┬─────┘
                  ↓          ↓
       ┌──────────────┐  ┌──────────────┐
       │ 11 Treatment │  │ 13 Control   │
       │ Group        │  │ Group        │
       └──────┬───────┘  └──────┬───────┘

┌────────────────────┐         ┌────────────────────┐
│ 3 participants lost │         │ 2 participants lost │
│ to follow up; 1     │         │ to follow up        │
│ participant was     │         └────────────────────┘
│ disqualified (DM)   │
└────────────────────┘
       ↓                   ↓
┌──────────────────────┐  ┌──────────────────────┐
│ 7 successfully       │  │ 11 successfully      │
│ completed study      │  │ completed study      │
└──────────────────────┘  └──────────────────────┘
```
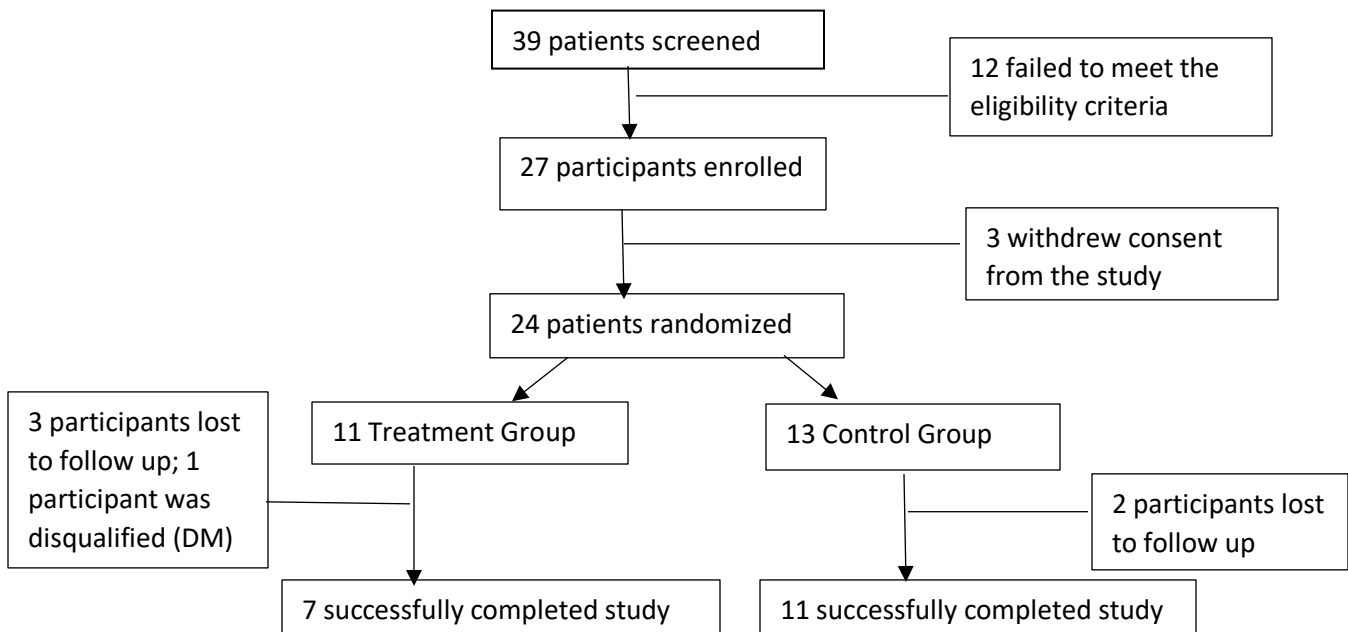
Figure 2: Consort Diagram showing Enrolment of Study Participants and reasons for Non-participation

4.2 Participants Baseline Characteristics

The baseline socio-demographic characteristics of the study participants are described in Table 1 below.

Table 1: Participant Socio-Demographic Characteristics per Intervention Assignment

Variable	Category	Overall (N=24)	Control (n=13)	Treatment (n=11)	P-Value
		n (%)	n (%)	n (%)	
Study Arm	Control	13(54.2%)	-	-	-
	Treatment	11(45.8%)	-	-	
Age(years)	Mean±SD; Median; Range	49.5±16.6; 51.5; 20-77	46.4±18.4; 48.0; 24.0-77.0	53.3±14.1; 53.0; 20.0-70.0	0.2963
Sex	Female	6(25.0%)	4(66.7%)	2(33.3%)	0.4101
	Male	18(75.0%)	9(50.0%)	9(50.0%)	
Height(m)	Mean±SD; Median; Range	1.7±0.0; 1.7; 1.6-1.82	1.7±0.0; 1.7; 1.7-1.8	1.7±0.1; 1.7; 1.6-1.8	0.3989
Weight(kg)	Mean±SD; Median; Range	62.7±7.6; 63.0; 49-85	64.0±4.7; 65.0; 53.0-70.0	61.2±10.1; 60.0; 49.0-85.0	0.1040
BMI(kg/m²)	Mean±SD; Median; Range	21.0±2.2; 21.2; 17.0-28.1	21.3±1.2; 21.3; 19.2-22.9	20.7±3.0; 20.3; 17.0-28.1	0.2116
Ethnicity	Kalenjin	1(4.2%)	1(100.0%)	0(0.0%)	0.1385
	Kamba	4(16.7%)	1(25.0%)	3(75.0%)	
	Kikuyu	12(50.0%)	6(50.0%)	6(50.0%)	
	Luhya	2(8.3%)	1(50.0%)	1(50.0%)	
	Luo	2(8.3%)	1(50.0%)	1(50.0%)	
	Meru	3(12.5%)	3(100.0%)	0(0.0%)	
Family History of Cancer	No	19(79.2%)	11(57.9%)	8(42.1%)	0.4146
	Yes	5(20.8%)	2(40.0%)	3(60.0%)	
Type Cancer (n=5)	Colon	1(20.0%)	1(100.0%)	0(0.0%)	0.5000
	Leukaemia	1(20.0%)	0(0.0%)	1(100.0%)	
	Prostate, Abdominal	1(20.0%)	0(0.0%)	1(100.0%)	
	Throat	2(40.0%)	1(50.0%)	1(50.0%)	
Family History Diabetes	No	23(95.8%)	13(56.5%)	10(43.5%)	0.4583
	Yes	1(4.2%)	0(0.0%)	1(100.0%)	
Smoking History	No	14(58.3%)	8(57.1%)	6(42.9%)	0.5267
	Yes	10(41.7%)	5(50.0%)	5(50.0%)	
Alcohol History	No	18(75.0%)	9(50.0%)	9(50.0%)	0.4101
	Yes	6(25.0%)	4(66.7%)	2(33.3%)	

The study involved 18 participants, randomized as 54.2% (n=13) in the control arm and 45.8% (n=11) in the treatment arm. The mean age of the participants was 49.5±16.6 years. The treatment group had a slightly higher mean age as compared to the control group (53.3±14.4 vs 46.4±18.4

years), but there was no statistically significant difference in age between the 2 arms (p=0.2963). The ratio of men (n=18) was three times that of women (n=6). The distribution of males was equal in the 2 arms whereas females across the two arms had a distribution of 66.7% (n=4) and 33.3 % (n=2) in the control and treatment arms respectively. However, this difference in the distribution of sex was not statistically significant (p=0.4101). The incidence of a history of alcohol intake, smoking, family-related diabetes and cancer was not significantly different between the two arms. A majority of the patients were of Kikuyu ethnicity, followed by Kamba ethnicity, though the difference in the allocation between the two groups was not statistically significant (p=0.1385).

Table 2: Participant Clinical Characteristics per Intervention Assignment

Variable	Category	Overall (N=24) n (%)	Control (n=13) n (%)	Treatment (n=11) n (%)	P-Value
Cancer Diagnosis	ALL	1(4.2%)	0(0.0%)	1(100.0%)	0.3322
	BL	1(4.2%)	1(100.0%)	0(0.0%)	
	CLL	7(29.2%)	4(57.1%)	3(42.9%)	
	DLBCL	8(33.3%)	4(50.0%)	4(50.0%)	
	NHL	1(4.2%)	0(0.0%)	1(100.0%)	
	NLPHL	1(4.2%)	1(100.0%)	0(0.0%)	
	Refractory HL	1(4.2%)	1(100.0%)	0(0.0%)	
	Relapsed DLBCL	1(4.2%)	0(0.0%)	1(100.0%)	
	Relapsed SLL	1(4.2%)	0(0.0%)	1(100.0%)	
	Relapsed NHL	1(4.2%)	1(100.0%)	0(0.0%)	
	SLL	1(4.2%)	1(100.0%)	0(0.0%)	
RVD Status	Negative	18(75.0%)	9(50.0%)	9(50.0%)	0.4101
	Positive	6(25.0%)	4(66.7%)	2(33.3%)	
Treatment Regimen	CHOP	7(29.2%)	3(42.9%)	4(57.1%)	0.4813
	COPP	1(4.2%)	1(100.0%)	0(0.0%)	
	CP	6(25.0%)	4(66.7%)	2(33.3%)	
	CVP	1(4.2%)	0(0.0%)	1(100.0%)	
	Prednisone	1(4.2%)	0(0.0%)	1(100.0%)	
	R-CHOP	5(20.8%)	4(80.0%)	1(20.0%)	
	R-COPMAP	1(4.2%)	0(0.0%)	1(100.0%)	
	R-CVP	2(8.3%)	1(50.0%)	1(50.0%)	
Cycle of Treatment	1	8(33.3%)	6(75.0%)	2(25.0%)	0.4900
	2	6(25.0%)	2(33.3%)	4(66.7%)	
	3	2(8.3%)	0(0.0%)	2(100.0%)	
	4	5(20.8%)	3(60.0%)	2(40.0%)	
	5	2(8.3%)	1(50.0%)	1(50.0%)	
	6	1(4.2%)	1(100.0%)	0(0.0%)	

*ALL- Acute lymphoblastic leukaemia, *DLBCL- Diffuse large B-cell leukaemia, *CLL- Chronic lymphocytic leukaemia, *BL- Burkett's lymphoma, *NHL-Non-Hodgkin's lymphoma, *HL- Hodgkin's lymphoma, *NLPHL-Nodular lymphocytic predominant Hodgkin's lymphoma, SLL-Small lymphocytic leukaemia

*CVP-Cyclophosphamide/Vincristine/Prednisone, *CHOP-Cyclophosphamide/Doxorubicin/Vincristine/Prednisone, *CP-Chlorambucil/Prednisone, *COPP-Cyclophosphamide/Vincristine/Prednisone/Procarbazine, *R-Rituximab, *COPMAP-Cyclophospamide/Vincristine/Prednisone/Methotrexate/Cytarabine/Procarbazine

The above Table 2 shows the study participants clinical characteristics. As indicated, the inherent clinical patient characteristics depicted no statistically significant difference in retroviral disease

(RVD) status, height, weight and the body mass index of the study participants in the control and treatment arm. Clinically, the cancer most commonly observed in both arms was NHL, especially the subtypes of Diffuse Large B-cell Leukaemia (DLBCL) (n=8) and Chronic Lymphocytic Leukaemia (CLL) (n=7). Only 2 cases of HL were identified to be prednisone-based regimens. However, in the randomization, no statistically significant difference was found across the 2 arms in regard to cancer diagnosis (p=0.3323).

The most common prednisone containing treatment regimen was CHOP (n=7), with or without Rituximab (R-CHOP, n=5), which had a total of 12 patients. The second most used regimen was Chlorambucil/Prednisone (CP) (n=6), followed by Cyclophosphamide/Vincristine/Prednisone CVP (n=1) with or without Rituximab (R-CVP, n=2). The difference in allocation based on treatment regimen was not statistically significant between the 2 arms (p=0.4813). Most study participants were in the first (n=8), second (n=6) and fourth (n=5) cycles of treatment, receiving a prednisone dosing frequency that was often in daily divided doses of three (n=13) or two (n=9) times daily. The differences in the cycle of treatment and prednisone dosing frequency were not statistically significant across the 2 groups (p= 0.4900 and 0.5194 respectively). The prednisone-related variables of the study participants per group have been outlined in Table 3 as follows:

Table 3: Participant Prednisone-Related Variables per Intervention Assignment

Variable	Category	Overall (N=24)	Control (n=13)	Treatment (n=11)	P-Value
		n (%)	n (%)	n (%)	
Total Daily Prednisone dose(mg)	150	1(4.2%)	0(0.0%)	1(100.0%)	0.4746
	105	2(8.3%)	1(50.0%)	1(50.0%)	
	100	5(20.8%)	3(60.0%)	2(40.0%)	
	90	2(8.3%)	1(50.0%)	1(50.0%)	
	80	2(8.3%)	0(0.0%)	2(100.0%)	
	60	10(41.7%)	8(80.0%)	2(20.0%)	
	50	1(4.2%)	0(0.0%)	1(100.0%)	
	40	1(4.2%)	0(0.0%)	1(100.0%)	
Duration of Prednisone therapy (days)	14	8(33.3%)	5(62.5%)	3(37.5%)	0.2007
	7	2(8.3%)	0(0.0%)	2(100.0%)	
	5	14(58.3%)	8(57.1%)	6(42.9%)	
Prednisone total dose Divided per day(mg)	50.0	4(16.7%)	2(50.0%)	2(50.0%)	0.1808
	40.0	3(12.5%)	0(0.0%)	3(100.0%)	
	35.0	3(12.5%)	2(66.7%)	1(33.3%)	
	30.0	5(20.8%)	4(80.0%)	1(20.0%)	
	25.0	2(8.3%)	0(0.0%)	2(100.0%)	
	20.0	7(29.2%)	5(71.4%)	2(28.6%)	
Prednisone Frequency Schedule	o.d	1(4.2%)	0(0.0%)	1(100.0%)	0.5194
	b.d	9(37.5%)	5(55.6%)	4(44.4%)	
	t.d.s	13(54.2%)	8(61.5%)	5(38.5%)	
	q.i.d	1(4.2%)	0(0.0%)	1(100.0%)	

o.d-once daily, b.d-twice daily,* t.d.s-three times daily,*q.i.d-four times daily

The most commonly encountered total daily dose of prednisone amongst the groups was a total dose of 60mg (n=10, 41.7%), followed by 100mg (n=5, 20.8%) respectively. These were distributed as 80% (n=8) and 60% (n=3) for the control arm and 20% (n=2) and 40 %(n=2). This difference in the total daily prednisone dose was not statistically significant between the 2 groups (p=0.4746). The divided daily total prednisone dose schedule most encountered among the participants was 20mg (n=7, 29.2%) and 30mg (n=5, 20.8%). These various divided doses were not significantly different between the 2 groups (p=0.1808). The duration of prednisone use most encountered amongst the participants was 5 days (n=14, 58.3%), which was observed in 57.1% (n=8) of the subjects in the control group and 42.9% subjects (n=6) in the treatment group. It was followed by a 14-day prednisone use (n=8, 33.3%), which was observed in 62.5% of the subjects (n=5) in the control group and 37.5% subjects (n=3) in the treatment group. These differences in

the prednisone duration of use were not statistically significant between the two groups (p=0.2007).

Generally, the two study arms were comparable with respect to sociodemographic (Table 1) and clinical (Table 2) and prednisone-related (Table 3) characteristics thus providing reasonable assurance that the randomization was performed successfully. The physical baseline characteristics were determined and were outlined in Table 4 below. The difference in baseline measures between the two groups was not statistically significant except for baseline body temperature (p=0.0458) and pulse rate (p=0.0062).

Table 4: Participant Physical Baseline Characteristics as Per Intervention Assignment

Baseline Measures	Allocation		
	Controls (n=11)	Treatment (n=7)	P-Value
	Mean±SD	Mean±SD	
Temperature (⁰C)	36.1±0.7	35.4±0.7	**0.0458**
Systolic (mmHg)	128.7±9.8	132.0±13.6	0.4953
Diastolic (mmHg)	80.0±9.5	69.1±12.5	0.0809
Respiratory rate(breaths/min)	19.0±1.4	17.9±1.1	0.1031
Pulse rate(beats/min)	91.9±10.4	76.0±9.5	**0.0062**
Creatinine(umol/L)	84.9±21.3	74.1±22.0	1.0000
AST(units/L)	20.7±8.5	25.4±14.3	0.5490
ALT(units/L)	18.4±8.3	22.0±11.3	0.3857
Glucose level (mmol/L)	5.5±1.5	4.6±0.8	0.1708

*ALT-Alanine aminotransferase, *AST-Aspartate aminotransferase

4.3 Loss to Follow-Up
The participants' completion status at the end of the study was that 18 successfully completed the study, with 6 participants being lost to follow up. The baseline socio-demographic and clinical characteristics of the patients lost to follow up are tabulated below in Table 5:

Table 5: Socio-Demographic Characteristics of Participants lost to follow-up

Variable	Category	Overall (N=6)
		n (%)
Arm	Control	2(33.3%)
	Treatment	4(66.7%)
Age	Mean±SD; Median; Range	48.8±18.6; 20-77
Sex	Female	2(33.3%)
	Male	4(66.7%)
Height	Mean±SD; Median; Range	1.7±0.1; 1.6-1.75
Weight	Mean, Median, SD, Range	64.0±12.2; 49-85
BMI	Mean±SD; Median; Range	21.9±3.6; 17-28.1
Ethnicity	Kalenjin	1(16.7%)
	Kamba	1(16.7%)
	Kikuyu	2(33.3%)
	Luo	1(16.7%)
	Meru	1(16.7%)
Family History of Cancer	No	6(100.0%)
Family History Diabetes	No	5(83.3%)
	Yes	1(16.7%)
Smoking History	No	4(66.7%)
	Yes	2(33.3%)
Alcohol History	No	3(50.0%)
	Yes	3(50.0%)

The distribution across the 2 arms was such that 33.3% (n=2) in the control arm while 66.7% (n=4) were in the treatment arm. The male sex had a higher incidence in this group (n=4) than the female sex (n=2). The median age of this group was 48.8±18.6 years. The loss to follow up had arisen from patient absenteeism or unfortunate sudden demise. Three of the 6 study participants lost to follow up had unfortunately succumbed during the study period. One was male, from the control arm while the other two were male and female respectively from the treatment arm. These patients had been in good health, according to physical assessment parameters and laboratory results. However, they developed acute complications and succumbed within a short period of time, each at different time points of the study. This was notified to the principal investigator upon doing weekly routine follow up via telecommunication. One of the female participants enrolled in the treatment arm was discontinued midway from the study upon the realization that she had undiagnosed diabetes, and the continuous blood sugar monitoring had helped in that identification.

It was noted that this was the only patient in the study who had a family history of diabetes. The finding was immediately reported to the attending physician who evaluated the participant and initiated anti-diabetic treatment. Table 6 below outlines the clinical characteristics of the participants lost to follow up.

Table 6: Clinical Characteristics of Participants lost to follow-up

Variable	Category	Overall (N=6)
		n (%)
Cancer Diagnosis	ALL	1(16.7%)
	DLBCL	4(66.7%)
	SLL	1(16.7%)
RVD Status	Negative	5(83.3%)
	Positive	1(16.7%)
Treatment Regimen	CHOP	1(16.7%)
	Prednisone	1(16.7%)
	R-CHOP	3(50.0%)
	R-COPMAP	1(16.7%)
Cycle of Treatment	1st	3(50.0%)
	2nd	3(50.0%)
Prednisone dose	100mg	1(16.7%)
	80mg	2(33.3%)
	60mg	2(33.3%)
	50mg	1(16.7%)
Duration Prednisone	14 days	1(16.7%)
	7 days	1(16.7%)
	5 days	4(66.7%)
Prednisone Dosing Schedule	40mg	2(33.3%)
	32.5mg	1(16.7%)
	25mg	1(16.7%)
	20mg	2(33.3%)
Prednisone Frequency	b.d	3(50.0%)
	t.d.s	3(50.0%)

*ALL- Acute lymphoblastic leukaemia, *DLBCL- Diffuse large B-cell leukaemia, SLL-Small lymphocytic leukaemia, *CHOP-Cyclophosphamide/Doxorubicin/Vincristine/Prednisone,*R-Rituximab, *COPMAP-Cyclophospamide/Vincristine/Prednisone/Methotrexate/Cytarabine/Procarbazine, *b.d-twice daily, t.d.s-three times daily

The clinical attributes of the patients lost to follow up were that most of the patients (n=4, 66.7%) had been diagnosed with DLBCL, with 50 % of the total number been prescribed for the treatment

regimen of R-CHOP (n=3). These patients were due for the next cycle of treatment following their previous 1st or 2nd cycle of treatment (n=3,50% respectively), using mostly the total daily dose of either 60mg (n=2,33.3%) or 80 mg (n=2,33.3%), divided into a daily dosing schedule of 20mg (n=2,33.3%) or 30mg (n=2,33.3%) for either a common dosing frequency of twice (n=3,50%) or three (n=3,50%) times daily.

4.4 Incidence of Prednisone-Induced Hyperglycaemia

The incidence of prednisone-induced prediabetes and diabetes amongst the study participants was determined using the fasting and 2-hour postprandial BGL readings.

4.4.1 Incidence of Prednisone-induced Diabetes

Prednisone-induced diabetes was defined as determinations of blood glucose level measurements of either fasting or 2-hour post-prandial glucose tests greater than 7.0mmol/L or 11.1 mmol/L respectively. The diagnosis of diabetes requires at least 2 separate readings of blood glucose readings of fasting plasma glucose at or above 7.0 mmol/L, HbA1C $\geq$6.5%, a 2-hour value in an OGTT at or above 11.1 mmol/L, or a random plasma glucose concentration $\geq$11.1 mmol/L in the presence of symptoms (122). None of the study participants was determined to have developed prednisone-induced diabetes as per the standard diagnostic criteria.

Repeated BGL measurements at different time points showed variations in the results obtained. Some of the study participants' blood glucose readings obtained could fall under the classification of prednisone-induced diabetes (fasting or 2-hour postprandial blood glucose levels greater than 7.0mmol/L and 11.1mmol/L respectively). However, none of the patients had repeat separate clear-cut diabetic-defining blood glucose values. Similarly, none of these participants presented with any symptomatic clinical criteria used in the diagnosis. Thus, they were not classified as having developed prednisone-induced diabetes.

4.4.2 Incidence of Pre-Diabetes among the Participants

Prednisone-induced pre-diabetes was evaluated by categorizing the participants into 2 blood glucose levels classes of fasting blood glucose levels of lesser or equal/greater than 5.6mmol/L and a 2-hour postprandial blood glucose of lesser or equal/greater than 7.8mmol/L. Participants having readings less than the cut-off of the relevant test were classified as having no pre-diabetes while those having at least one BGL reading (either fasting or 2-hour postprandial) with an equal or higher value than the respective cut-off were classified as being pre-diabetic or diabetic.

Table 7 below shows the FBG and 2-hour PPG observed measurements that were categorized as pre-diabetes among the study participants found to have developed at least one incidence during the study period.

Table 7: Blood Glucose Readings of the Participants who developed Pre-Diabetes

Group	FBG(mmol/L)				2-hour PPG(mmol/L)			
	Day 8	Day 15	Day 22	Day 29	Day 8	Day 15	Day 22	Day 29
Control	4.5	**6.9**	3.8	4.6	6.1	7.4	5.0	5.8
Control	**6.3**	5.0	5.4	4.2	**9.3**	7.6	7.3	4.9
Control	**5.8**	**5.6**	5.0	5.1	6.8	7.6	7.6	**8.2**
Control	**6.4**	3.1	4.6	4.6	6.2	5.8	5.5	7.0
Control	4.0	4.2	3.8	**8.3**	5.0	**10.1**	6.0	6.9
Control	**5.6**	**6.6**	**12.5**	**5.9**	7.1	**13.3**	**19.3**	7.6
Control	**9.0**	**6.1**	5.2	**5.8**	**11.6**	**13.5**	7.3	6.4
Control	4.2	**6.3**	**6.1**	5.0	5.1	6.9	6.2	5.1
Control	4.3	4.8	5.5	4.6	**9.4**	4.9	5.7	5.8
Treatment	3.5	5	**5.6**	5.2	5.3	6.9	7.3	7.2

*Fasting blood glucose defined by blood glucose levels≥5.6 mmol/L
**2-hour postprandial blood glucose defined by blood glucose levels≥7.8mmol/L

The incidence of prednisone-induced hyperglycaemia, which was categorized as pre-diabetes among the study participants is shown in Table 8 below:

Table 8: The Incidence of Pre-Diabetes among the Study Participants

Measure	Group	n	Percentage (%)	95% C.I		Total (N)
				Lower	Upper	
Fasting BGL	Control	8	72.7	45.5	90.9	11
	Treatment	1	14.3	0.0	42.9	7
2-hour Postprandial BGL	Control	6	54.5	27.3	81.8	11
	Treatment	0	0.0	0.0	0.0	7

The above table 8 demonstrates a comparison of the fasting and 2-hour postprandial blood glucose results in the control and treatment groups. It was observed that using the FBG measurements, the control group had an incidence of prediabetes of 72.7% (CI 45.5%-90.9%), with 8 of the 11 subjects developing a pre-diabetic state. The treatment group had an incidence of only one of the 7 subjects developing a pre-diabetic state, representing a proportion of 14.3% (CI 0%-42.9%).In using the 2-hour PPG measurements, only the control group had participants who developed pre-

diabetes. The proportion of this subjects was 54.5% (CI 27.3%-81.8%), which represented 6 of the 11 participants.

4.4.3 Characteristics of Participants who developed Pre-diabetes
The socio-demographic and clinical characteristics of the participants who developed pre-diabetes are shown in Table 9 and 10 below:

Table 9: Socio-Demographic and Physical Characteristics of the Participants Who Developed Pre-Diabetes

Patient Number	Sex	Age (years)	Group	BMI(kg/m²)	Blood Pressure(mmHg)		RVD Status
1	F	25	Control	22.5	118	80	Positive
2	M	70	Control	20.9	127	79	Negative
3	M	48	Control	22.6	141	89	Positive
4	F	32	Control	19.2	123	81	Negative
5	M	49	Control	21.9	105	64	Negative
6	M	68	Control	22.9	148	72	Positive
7	M	61	Control	21.0	115	72	Negative
8	M	39	Control	21.3	105	72	Negative
9	F	32	Control	1.7	114	76	Negative
10	M	66	Treatment	21.7	118	57	Negative

The table above shows that 9 of the 11 study participants in the control group developed pre-diabetes and only 1 participant in the treatment arm who developed an episode of pre-diabetes. This was observed by a high BGL reading in either the FBG or 2-hour PPG tests. Of these 9 participants, 3 were female (n=33.33%) while 6 (n=66.67%) were male. The mean age of the participants who developed pre-diabetes was 47.1±16.5 years while the mean BMI was 21.3±1.3 kg/m². The mean systolic and diastolic blood pressures were 121.8±14.9 and 76.1±7.2 mmHg respectively. The proportion of participants with a negative RVD status was 66.67% (n=6) while that with a positive status was 33.33% (n=3).

In terms of clinical attributes, CLL was the most commonly encountered diagnosed cancer in the participants who developed pre-diabetes (n=4, 44.44%), followed by DLBCL (n=3, 33.33%). One of the patients with HL developed pre-diabetes (n=1, 11.11% each). The treatment regimen with

the highest frequency in this cohort was CP (n=4, 44.44%). It was followed by R-CHOP (n=2, 22.22%), and its variant without rituximab, CHOP (n=1. 11.11%). The other regimens encountered in this group were R-CVP (n=1. 11.11%) and COPP (n=1. 11.11%). These study participants were mostly in the 3rd cycle of treatment (n=4, 44.4%), followed by the 2nd and 4th cycles of treatment (n=2 each, 22.22% each) and lastly the 6th cycle, which had 1 participant (n=1, 11.11%). These clinical attributes described tally with the observed clinical characteristics of the 1 participant in the treatment group who developed pre-diabetes. This participant had been diagnosed with CLL and was on the CP treatment regimen. These are demonstrated in table 10.

Table 10: Clinical Characteristics of the Participants Who Developed Pre-Diabetes

Patient Number	Diagnosis	Group	Treatment regimen	Treatment Cycle	PDN Dose (mg)	Duration of Use (days)	Dosing Schedule (mg)	Frequency (per day)
1	DLBCL	Control	CHOP	4	100	5	50	2
2	CLL	Control	CP	4	60	14	20	2
3	DLBCL	Control	R-CHOP	1	105	5	35	3
4	CLL	Control	CP	2	60	14	30	2
5	CLL	Control	CP	1	60	14	20	3
6	Relapsed NHL	Control	R-CVP	1	100	5	50	2
7	CLL	Control	CP	6	60	14	20	3
8	DLBCL	Control	R-CHOP	2	60	5	20	3
9	Refractory HL	Control	COPP	1	90	14	30	3
10	CLL	Treatment	CP	2	60	14	20	3

In respect to prednisone-related parameters, the mean total daily dose amongst this group was 77.22±20.78 mg. Most study participants had been prescribed a total daily dose of 60mg (n=5, 55.56%), followed by 100mg (n=2, 22.22%). The other prednisone daily doses encountered were 90mg and 105mg (n=1, 11.11% each). The duration of use that was most frequently prescribed in this group was 14 days (n=5, 55.56%), closely seconded by a 5-day duration (n=4, 44.44%). The dosing schedule used commonly in these participants was 20mg (n=4, 44.44%), followed by 30mg and 50mg (n=2 each, 22.22% each) then lastly 35mg (n=1, 11.11%). In relation to the dosing, the

frequency most encountered was thrice daily dosing (n=5, 55.56%) and two times daily dosing (n=4, 44.44%).

The participant in the treatment group was in the 2nd cycle of treatment and was receiving a total daily dose of 60mg prednisone, administered as 20 mg three times daily dosing. This finding is agreeable with that of a majority of the participants in the control group who developed pre-diabetes.

4.5 The Effectiveness of Metformin in Preventing Prednisone-Induced Hyperglycaemia.
The effectiveness of metformin as a prophylactic measure in preventing PIH was evaluated by comparing the incidence of PIH between the 2 study groups, as well as assessing the degree of effectiveness of metformin in preventing PIH by comparing the mean differences in BGL in the 2 study groups.

4.5.1 Comparison of the Incidence of Prednisone-Induced Hyperglycaemia
The comparison of the 2 study groups showed a significant difference in the occurrence of PIH among the participants. The incidence of the participants who developed PIH using the fasting and 2-hour postprandial BGL was graphically represented in figure 3 below:
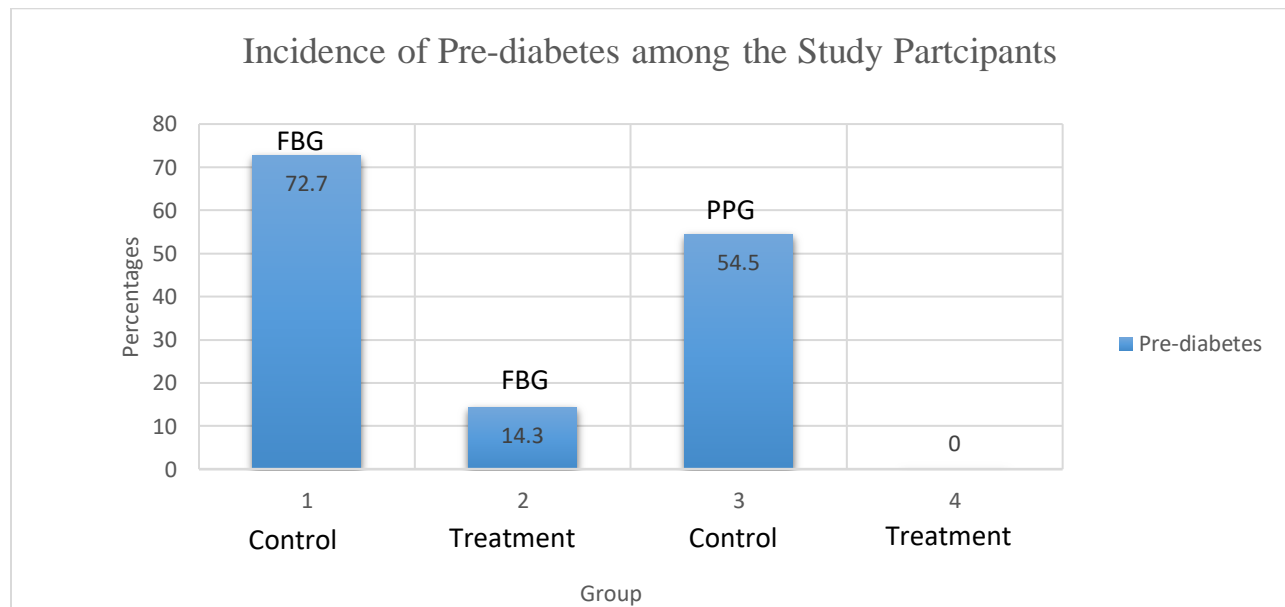
Figure 3: Bar-graphs representing the incidence of fasting and 2-hour postprandial blood glucose levels pre-diabetes among the participants

The incidence of pre-diabetes among the control group using FBG and 2-hour PPG readings was 58.4% and 54.5% higher than the treatment group respectively. It was also observed that in each week, at least 1 participant in the control arm developed a pre-diabetic state. This contrasts with the treatment arm in which only one episode of PIH was determined in 1 participant during the entire study period while using the FBG glucose readings. No participant in the treatment group had developed PIH while using the 2-hour PPG measurements. The effectiveness of metformin as an intervention was further determined using measures of association between the treatment group (exposed) versus the control group (unexposed). Table 11 below highlights the proportion of study participants who developed PIH (identified as pre-diabetic states) in the 2 arms of the study. It also indicates the risk difference and ratio between the 2 groups at 95% confidence interval (CI) as well as the odds ratio.

Table 11: Measures of Association for Metformin Intervention among the Study Participants

Participants	Controls (Unexposed)	Metformin (Exposed)	Total	P-value
Pre-Diabetes (Cases)	8	1	**9**	
Non Pre-Diabetes (Non-cases)	3	6	**9**	
Total	11	**7**	**18**	
Risk	0.727	0.143	0.5	**0.0498**
	Point Estimate	**95% C.I**		
Absolute Risk Reduction	0.584	0.097	1.072	
Relative Risk Reduction	0.804	0.236	0.949	
Risk Ratio	5.09	1.31	19.79	
Odds Ratio	16	1.30	194.64	

The risk of developing prednisone-induced hyperglycaemia in the treatment group was 58.4% less than the control group. Subsequently, the use of metformin tablets reduces the risk of developing prednisone-induced hyperglycaemia by 80.4% (95% CI 23.6%-94.9%) of the baseline risk in the control group. In addition, unexposed subjects (control group) are 5 times as likely to develop prednisone-induced hyperglycaemia as the treatment group. The calculated crude odds ratio found that the participants in the control group had 16 times the odds of developing pre-diabetes than those in the treatment group.

In estimating the degree of the effectiveness of metformin in lowering BGL levels in patients receiving high dose prednisone, the mean BGL levels of the study participants using the fasting and 2-hour post-prandial blood glucose readings were tabulated below (Table 12):

Table 12: The primary outcome of median blood glucose readings in the study arms using the Mann–Whitney U test

Blood Glucose Measurement(mmol/L)	Control Median(IQR)	Treatment Median(IQR)	P-value
Baseline Random blood glucose	5.3 (4.3-6.4)	5.0 (3.8-5.2)	0.1595
Day 8 Fasting blood glucose	5.1 (4.3-6.3)	4.3 (4.2-4.7)	0.0845
Day 15 Fasting blood glucose	5.0 (4.7-6.3)	4.6 (4.4-5.2)	0.2205
Day 22 Fasting blood glucose	5.2 (4.6-5.5)	4.7 (4.1-4.9)	0.0769
Day 29 Fasting blood glucose	5.0 (4.6-5.8)	4.8 (4.4-4.9)	0.4660
Day 8 2-hour Postprandial blood glucose	6.2 (5.1-9.3)	5.4 (5.3-6.4)	0.4680
Day 15 2-hour Postprandial blood glucose	7.4 (5.7-10.1)	5.2 (4.7-6.1)	**0.0144**
Day 22 2-hour Postprandial blood glucose	6.2 (5.5-7.3)	5.0 (4.4-5.5)	**0.0095**
Day 29 2-hour Postprandial blood glucose	6.9 (5.8-7.6)	4.4 (4.3-5.4)	**0.0074**

The baseline random BGL of the study participants at enrolment was 5.5±1.5mmol/L in the control group and 4.6±0.8mmol/L in the treatment group. The difference in the random baseline blood sugar was not statistically different between the 2 groups (p=0.1595). During the study period, a mean difference in the fasting and 2-hour postprandial blood glucose values amongst the control and treatment arms was observed all through. The lowest and highest mean differences in FBG of the control versus the treatment arm during the 4-week duration was 0.5mmol/L and 1.2mmol/L respectively. The 2-hour PPG had the lowest and highest mean differences in blood glucose readings over the 4 week period as 1.2mmol/L and 2.6 mmol/L respectively. Comparative analysis of the fasting blood glucose in the 2 arms found no statistically significant difference in the mean fasting blood glucose levels. However, statistically significant differences in mean blood sugar readings were seen with the 2-hour PPG, in week 2 (p=0.0144), week 3 (p=0.0095) and week 4 (p=0.0074) of the study. The treatment arm had a lower mean fasting glucose level compared to the control arm in all the blood glucose readings obtained during the study. This has been depicted in the figures 4 and 5 below:
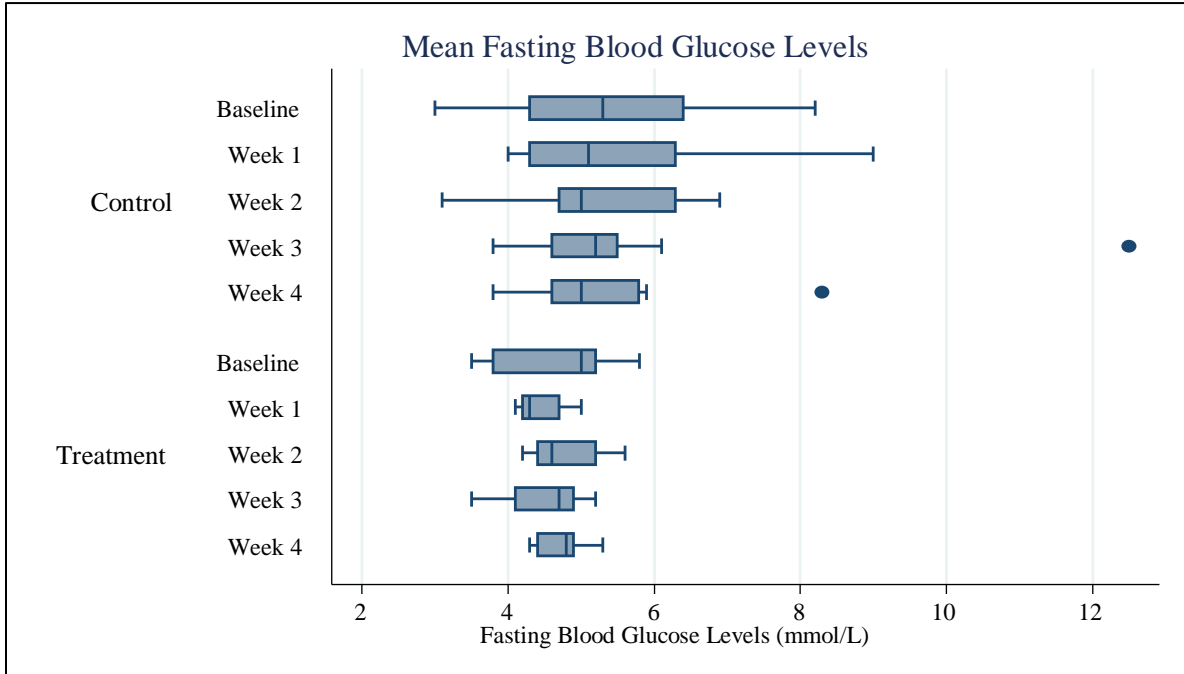
Figure 4: A box and whiskers plot showing the differences in fasting blood glucose levels between the 2 study groups.
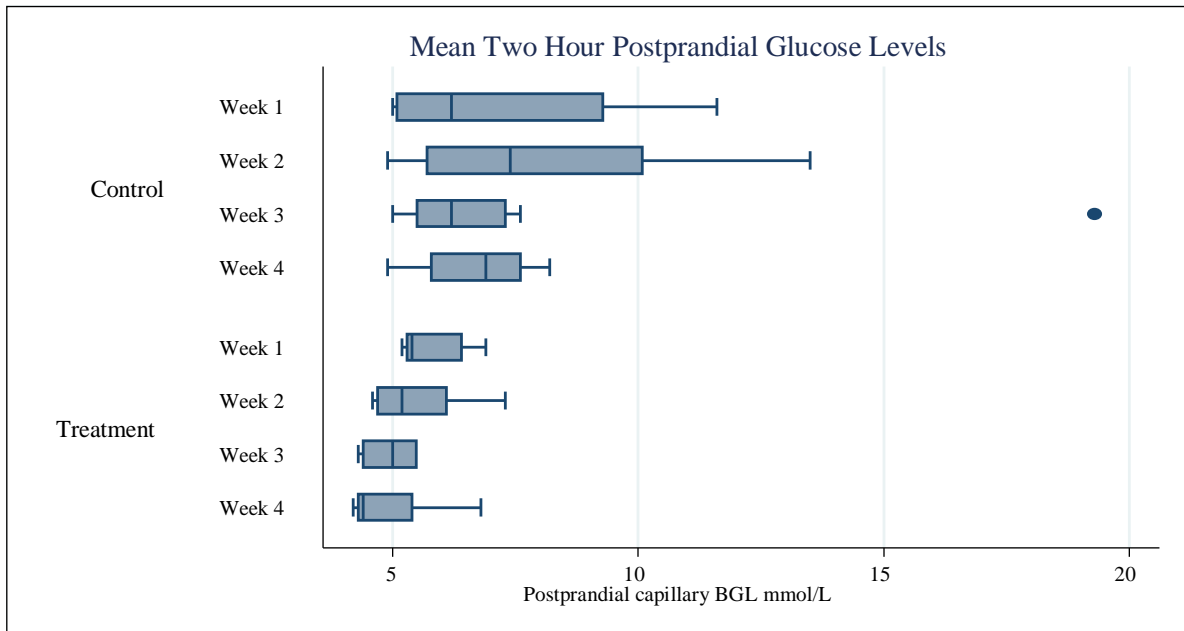
Figure 5: A box and whiskers plot showing the differences in 2-hour postprandial blood glucose levels between the 2 study groups

The control group had significantly higher fasting and 2-hour postprandial blood glucose readings than the treatment group in the 4-week study duration. In the FBG readings, the control group had the highest BGL value as 12.5mmol/L, much exceeding the pre-diabetic and diabetic diagnostic readings of >5.6 and >7.0mmol/L respectively. The treatment group, on the other hand, had 5.6mmol/L as its highest value during the study period. Other high BGL readings identified in the control group were 9.0 and 8.3mmol/L. This denoted the development of PIH in these group of patients.

In evaluation of the mean 2-hour post-prandial blood glucose readings, the treatment arm had significantly lower BGL values compared to the control group. None of the values in the treatment arm exceeded the defined PIH 7.8mmol/L cut off point, unlike the control arm which had several readings exceeding the cut-off. The highest value observed in the control arm was a PPG level of 19.3mmol/L, followed by subsequent high values of 13.5, 13.3, 11.6 and 10.1 mmol/L, just to mention a few. The treatment arm had its highest PPG reading at 7.3 mmol/L, with a majority of the patients having a PPG of <5.0mmol/L for most times during the study period. This is supported by the statistically significant p-values seen in the differences in the mean 2-hour PPG observed.

4.5.2 Effectiveness of Single versus Double Dose Metformin in the Treatment Arm
In comparison of the effectiveness of single versus double dose metformin, only one incidence of PIH was detected using the fasting BGL with the use of single-dose metformin 850 mg tablet per day. No such incidence was detected using the double dose metformin 850mg tablets. The degree of the effectiveness of single versus double daily dosing metformin tablets in lowering BGL levels in patients receiving high dose prednisone in the treatment arm was highlighted in Table 13 below:

Table 13: Comparison of the effectiveness of single versus double dose metformin 850mg in the treatment arm

Measure	Single (850mg)		Double (1700mg)		Mean Difference	P-Value
	Mean±SD (mmol/L)	Median(IQR) (mmol/L)	Mean±SD (mmol/L)	Median(IQR) (mmol/L)	Mean±SD (mmol/L)	
Fasting Blood Glucose	4.8±0.5	4.6 (4.4-5.2)	4.7±0.3	4.8 (4.4-4.9)	0.06±0.5	1.0000
2-hour Postprandial Blood Glucose	5.5±1.0	5.2 (4.7-6.1)	5.0±0.9	4.4 (4.3-5.4)	0.5±0.9	0.4531

The treatment group did not exhibit any statistically significant difference in the mean fasting BGL (p=1.0000) and in the 2-hour postprandial BGL (p=0.4531) while taking single-dose versus double-dose metformin. The mean differences of single versus double dose metformin demonstrated variation in both the fasting and 2-hour postprandial BGL. This is depicted by the observed BGL mean differences values of 0.06±0.5mmol/L in FBG glucose readings and 0.5±0.9 mmol/L in 2-hour PPG glucose readings. The differences in the individual study participant blood glucose levels for both the fasting and 2-hour postprandial readings are illustrated graphically below in figures 6 and 7:
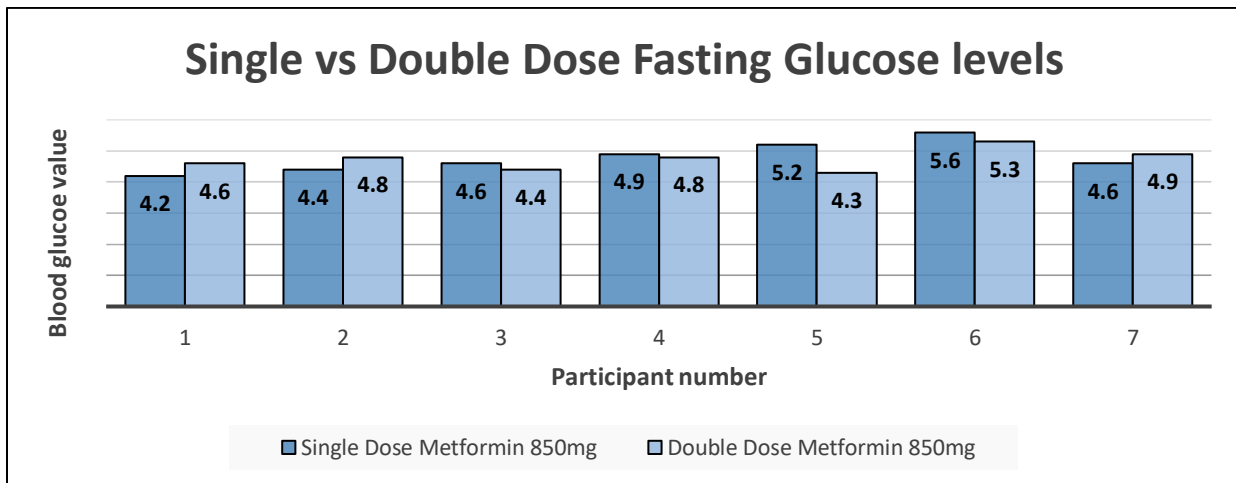
Figure 6: Individual participant fasting blood glucose using single vs double metformin in the treatment arm

As illustrated in the above figure, individual study participants in the treatment arm exhibited varied results in fasting BGL values while on single and double dose metformin 850mg tablets. Some participants showed a decrease in FBG (n=3, 57.1%) while others showed an increase (n=3, 42.9%) when the metformin dose was double to 1700mg per day.
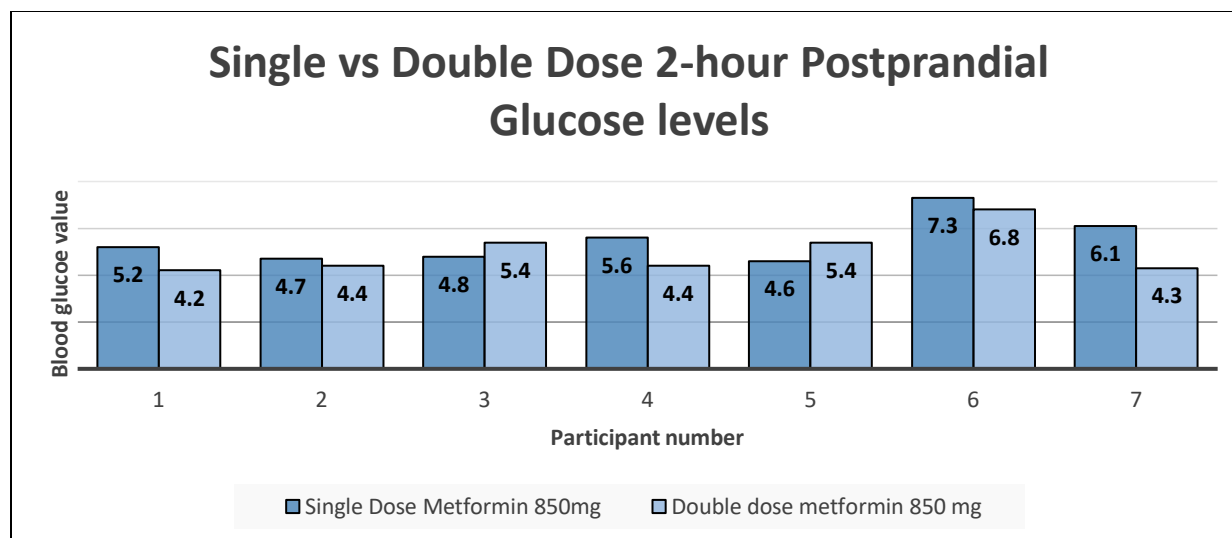
Figure 7: Individual participant 2-hour postprandial blood glucose using single vs double metformin in the treatment arm

In reference to the 2-hour PPG glucose values, most participants exhibited a reduction in BGL (n=5, 71.4%), with a few showing an increase (n=2, 28.6%).

4.6 Participant Laboratory Parameters

The study participants had laboratory tests done on the 3rd week of the study to determine the presence of any derangements, as well any laboratory parameter changes from the baseline values. The tests that were carried out on the participants were serum creatinine levels, liver function tests (AST and ALT) plus serum lactate levels. The comparison between the two groups in terms of their initial and final creatinine and LFTs are outlined in Table 14 below:

Table 14: The Differences in Serum Creatinine and Liver Function Tests in the Study Arms.

Laboratory Parameter	Control		Control	Treatment		Treatment	P-Value
	Initial	After	Change	Initial	After	Change	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Serum Creatinine(umol/L)	84.9±21.3	88.5±24.9	3.6±24.9	74.1±22.0	103.1±23.4	29.4±20.5	**0.0400**
AST(Units/L)	20.7±8.5	21.9±11.7	1.2±12.9	25.4±14.3	20.3±8.6	-5.1±19.7	0.4800
ALT(Units/L)	18.4±8.3	28.0±27.9	9.6±29.3	22.0±11.3	26.0±19.2	4.0±13.6	0.7200

The results indicated no statistically significant difference in the liver function tests between the control and treatment groups (p=0.4800 and 0.7200). Both groups had an increase in serum creatinine levels, though the treatment group had higher values than the control. This difference in the change in serum creatinine levels between the 2 arms was statistically significant (p=0.0400). Nonetheless, the high values observed in the treatment group still lie within the normal serum creatinine range (60-130umol/L).

Analysis of serum lactate levels was also done in the 3rd week to determine the incidence of the side effect of lactic acidosis usually associated with metformin use, especially in the onset of a decline in kidney function. The values that were obtained were represented below (Table 15):

Table 15: Serum Lactate Tests Results in the 2 Study Groups

Serum Lactate (umol/L) (Range- 0.5-2.22)				
Participant No	Treatment Arm	Participant No	Control Arm	P-value
1	1.53	1	1.34	**0.4586**
2	1.59	2	1.96	
3	1.24	3	1.73	
4	**3.49**	4	**2.88**	
5	**2.58**	5	**2.25**	
6	2.07	6	1.75	
7	**2.48**	7	2.08	
		8	**2.42**	
		9	1.76	
		10	1.65	
		11	1.28	
	Mean±S.D=2.14±0.78		**Mean±S.D=1.92±0.47**	

The serum lactate levels determined showed no statistically significant difference between the control and treatment arms. The values showed a higher mean serum lactate level in the treatment arm of 2.14±0.78umol/L whereas the control arm had a mean serum lactate level of 1.92±0.47 (p=0.4586). A similar number of patients in both groups was determined to have higher than the normal range serum lactate levels. In the treatment group, the proportion of participants with above normal lactate values were 42.8% (n=3). The control group had a proportion of 27.3% (n=3) participants with higher than the normal serum lactate levels. The difference in these proportions was not statistically significant (p=1.0000)

4.7 Incidence of Adverse Effects

Among the study participants, there were no recorded nor reported side effects throughout the study period except for 1 patient. Since the participants were followed up and assessed physically once weekly and also received regular check-ups via telecommunication, no side effect went undetected during the study period. The only noted incident was that of 1 patient in the treatment group, who had developed mild diarrhoea at week 3 when the dose of metformin 850mg had been titrated upwards from once to twice daily. The study participant informed the research nurse, who closely monitored and followed up the patient. Fortunately, the incident resolved spontaneously after 2 days. The patient did not report any other side effect.

4.8 Inferential Analysis

Inferential statistical analysis was carried out to determine the association between baseline predictor variables and the development of PIH.

4.8.1 Bivariate Logistic Regression

Bivariate logistic regression analysis was done and Table 16 below highlight the odds ratio and 95% CI, and the associated p-value of this regression as follows:

Table 16: Bivariate Logistic Regression using Participant Baseline Characteristics

Parameter	FBS				PPG			
	C.O.R	95% C.I.		Sig.	C.O.R	95% C.I.		Sig.
		Lower	Upper			Lower	Upper	
1. Arm-Control	16.0	1.3	194.6	**0.0296**	UD	UD	UD	0.9989
2. Sex-Male	1.0	0.1	9.2	1.0000	1.67	0.13	20.58	0.6904
3. BMI	3.2	1.2	8.9	**0.0258**	2.04	0.85	4.88	0.1093
4. Age	1.0	0.9	1.1	0.8364	1.03	0.96	1.10	0.3669
5. Random baseline glucose	0.7	0.4	1.6	0.4565	1.90	0.78	4.62	0.1560
6. Smoking history	0.4	0.1	2.7	0.3472	1.40	0.20	10.03	0.7377
7. Alcohol history	0.4	0.0	5.9	0.5341	1.00	0.07	13.87	1.0000
8. RVD Status	0.6	0.1	4.6	0.6006	1.50	0.18	12.78	0.7106
9. Cycle of treatment	2.5	0.4	16.9	0.3472	2.00	0.26	15.38	0.5054
10. Total daily dose	1.6	0.2	10.8	0.6297	1.43	0.18	11.09	0.7330
11. Duration of PDN therapy	0.2	0.0	1.8	0.1580	0.17	0.02	1.42	0.1011
12. PDN divided daily total prednisone dose	1.6	0.2	10.8	0.6297	1.43	0.18	11.09	0.7330
13. PDN dosing frequency	0.6	0.1	4.2	0.6297	0.20	0.02	2.26	0.1937

*UD-Undetermined; *C.O.R-Crude Odds Ratio,* PDN-Prednisone

Key: Cycle of treatment: 4-6 vs 1-3, Total daily dose (mg) : >90 vs ≤90, Duration of prednisone therapy (days) :> 7 vs ≤7, Prednisone total dose divided schedule (mg) : >30 vs ≤30, Prednisone dosing frequency (per day): ≥2 vs <2

The odds of developing PIH was statistically significant with the independent predictor variables of arm (control) and BMI using the FBG measure. It was observed that the odds of developing PIH in the control group was 16 times the odds of developing PIH in the treatment group (p=0.0296). Body mass index showed a positive association that was statistically significant (p=0.0258), indicating that every unit increase in BMI was associated with 3 times the odds of developing PIH. The variables of random baseline glucose levels, smoking and alcohol history and RVD status showed negative associations which were not statistically significant using the FBG measure. These variables except for alcohol history, showed a converse positive association while using the 2-hour PPG measure, though none showed significant difference. No association between the variables of age and sex (male) and the odds of developing of PIH was observed using the FBG. Similarly, no association was observed with alcohol history using the 2-hour PPG measure. These variables which showed no associations did not indicate any statistically significant differences.

In reference to prednisone-related variables, the total daily dose, the divided daily total prednisone dose and the cycle of treatment showed positive associations in the odds of developing PIH using the fasting BGL, though these were not statistically significant (p=0.6297, p=0.6297 and p=0.3472). Negative associations were observed with the variables of duration of prednisone therapy and the dosing schedule. None of these depicted statistical significance while using the FBG measurements (p=0.1580 and p=0.6297). Similarly, analysis using the 2-hour PPG glucose levels showed positive associations in the odds of developing PIH with the prednisone-related variables of total daily dose, divided daily total prednisone dose and the cycle of treatment, none of which was significant (p=0.7330, p=0.7330 and p=0.5054). The variables of duration of use and its dosing frequency displayed a negative association. These associations were not statistically significant (p=0.1011 and p=0.1937 respectively).

4.8.2 Multivariate Logistic Regression
Backward stepwise modelling was carried out to identify the best model which explains the observed data as well as to identify the variables that are predictors in the development of PIH. Table 17 below provides the analyses outcome using the 2-hour PPG measurements:

Table 17: Stepwise Backward Logistic Regression (2-hour Postprandial Blood Glucose PIH Incidence)

Steps	Factor	B	S.E.	P-value	A.O.R	95% C.I. for A.O.R	
						Lower	Upper
Step 1[a]	Sex	-0.81	6.00	0.893	0.45	0.00	56735.70
	Age	-0.01	0.15	0.921	0.99	0.74	1.31
	BMI	0.82	0.89	0.361	2.26	0.39	13.07
	RVD status	-37.90	36784.58	0.999	0.00	0.00	
	Cycle of treatment	0.73	1.62	0.654	2.07	0.09	49.82
	Total daily dose	-2.21	31682.24	1.000	0.11	0.00	
	Duration of Prednisone therapy	-22.13	18089.00	0.999	0.00	0.00	
	Prednisone total dose divided schedule	19.33	26010.63	0.999	247186083.04	0.00	
	Prednisone dosing frequency	-1.62	2.47	0.512	0.20	0.00	24.96
	Constant	5.55	18089.02	1.000	256.26		
Step 2[a]	Sex	-0.81	6.00	0.893	0.45	0.00	56735.70
	Age	-0.01	0.15	0.921	0.99	0.74	1.31
	BMI	0.82	0.89	0.361	2.26	0.39	13.07
	RVD status	-39.73	29729.15	0.999	0.00	0.00	
	Cycle of treatment	0.73	1.62	0.654	2.07	0.09	49.82
	Duration of Prednisone therapy	-21.77	14729.62	0.999	0.00	0.00	
	Prednisone total dose divided schedule	19.31	25823.64	0.999	243644784.16	0.00	
	Prednisone dosing frequency	-1.62	2.47	0.512	0.20	0.00	24.96
	Constant	5.19	14729.65	1.000	178.94		
Step 3[a]	Sex	-0.25	2.13	0.908	0.78	0.01	51.18
	BMI	0.85	0.87	0.330	2.34	0.42	12.88
	RVD status	-39.12	30078.18	0.999	0.00	0.00	
	Cycle of treatment	0.74	1.61	0.645	2.10	0.09	49.51
	Duration of Prednisone therapy	-21.43	14816.01	0.999	0.00	0.00	
	Prednisone total dose divided schedule	18.98	26176.00	0.999	174178757.62	0.00	
	Prednisone dosing frequency	-1.73	2.26	0.445	0.18	0.00	14.88
	Constant	3.31	14816.02	1.000	27.30		
Step 4[a]	BMI	0.90	0.78	0.251	2.45	0.53	11.34
	RVD status	-38.76	29673.41	0.999	0.00	0.00	
	Cycle of treatment	0.72	1.59	0.650	2.05	0.09	46.15
	Duration of Prednisone therapy	-21.36	14659.35	0.999	0.00	0.00	
	Prednisone total dose divided schedule	18.66	25799.51	0.999	127119868.15	0.00	
	Prednisone dosing frequency	-1.87	1.92	0.330	0.15	0.00	6.62

		B	S.E.	Sig.	Exp(B)	Lower	Upper
	Constant	2.19	14659.36	1.000	8.98		
Step 5[a]	BMI	0.95	0.76	0.211	2.58	0.58	11.39
	RVD status	-38.23	29775.19	0.999	0.00	0.00	
	Duration of Prednisone therapy	-21.29	14916.36	0.999	0.00	0.00	
	Prednisone total dose divided schedule	18.42	25769.45	0.999	100317451.36	0.00	
	Prednisone dosing frequency	-1.73	1.86	0.352	0.18	0.00	6.75
	Constant	1.26	14916.37	1.000	3.53		
Step 6[a]	BMI	1.04	0.76	0.172	2.83	0.64	12.54
	RVD status	-20.54	14721.47	0.999	0.00	0.00	
	Duration of Prednisone therapy	-21.91	14721.47	0.999	0.00	0.00	
	Prednisone dosing frequency	-2.05	1.78	0.248	0.13	0.00	4.18
	Constant	0.05	14721.47	1.000	1.06		
Step 7[a]	BMI	1.13	0.73	0.123	3.10	0.74	13.05
	RVD status	-19.70	14968.34	0.999	0.00	0.00	
	Duration of Prednisone therapy	-21.95	14968.34	0.999	0.00	0.00	
	Constant	-3.15	14968.35	1.000	0.04		
Step 8[a]	BMI	1.46	0.80	0.069	4.31	0.89	20.75
	Duration of Prednisone therapy	-3.59	1.98	0.070	0.03	0.00	1.34
	Constant	-29.56	16.36	0.071	0.00		

*BMI-Body mass index, *RVD- Retroviral disease

Regression using the 2-hour postprandial blood glucose measurements showed that the model with the BMI variable was the strongest independent predictor associated with the development of PIH. The final adjusted odds ratio was 4.31, which implied that every unit increase in BMI is associated with 4.3 times the odds of developing PIH. However, there was no statistical significance (p=0.069)

Analysis using the fasting blood glucose measurements was provided in Table 18 below. This backward stepwise regression showed statistical significance between PIH and BMI (p=0.026). The A.O.R of 3.2 shows that every unit increase in BMI increases the odds of developing PIH by 3.2 times, as indicated below. All the prednisone-related variables were excluded from the model as they were not associated with the development of PIH based on the analysis.

Table 18: Stepwise Backward Logistic Regression (Fasting Blood Glucose PIH Incidence)

Steps	Factor	β	S.E.	P-value	A.O.R	95% C.I. for A.O.R	
						Lower	Upper
Step 1	Sex	-0.33	1.99	0.867	0.72	0.01	35.41
	Age years	-0.01	0.05	0.838	0.99	0.90	1.09
	BMI	1.21	0.54	**0.027**	3.34	1.15	9.72
	RVD Status	0.35	1.57	0.825	1.41	0.07	30.72
	Constant	-24.70	11.64	0.034			
Step 2	Age years	0.00	0.04	0.903	1.00	0.93	1.07
	BMI	1.20	0.54	**0.027**	3.32	1.14	9.65
	RVD Status	0.35	1.57	0.822	1.42	0.07	31.06
	Constant	-24.92	11.63	0.032			
Step 3	BMI	1.19	0.54	**0.027**	3.29	1.15	9.45
	RVD Status	0.36	1.55	0.817	1.43	0.07	30.16
	Constant	-24.98	11.61	0.031			
Step 4	BMI	1.16	0.52	**0.026**	3.20	1.15	8.90
	Constant	-24.10	10.86	0.026			

*BMI-Body mass index, *RVD- Retroviral disease

Overall results show that BMI was a strong predictor in the development of PIH using both the FBG and 2-hour PPG measurements. With the 2 glucose measuring parameters, no significant association was observed in the development of PIH and the other predictor variables of age, sex, RVD status, total daily prednisone dose, divided daily total prednisone dose, duration of prednisone therapy, prednisone total dose divided frequency and the cycle of treatment.

CHAPTER FIVE: DISCUSSION, SUMMARY, CONCLUSION AND RECOMMENDATIONS.

5.1 Introduction

This chapter highlights the findings of the research study and goes further to interpret and elaborate the basis on which the findings are founded. The next section offers a summary of the results and discussions, with a conclusion on the overall outcome of the study. Recommendations emanating from the study are offered in the last section of this chapter

5.2 Discussion

The study was successfully completed by 18 out of the 24 randomized patients. The small sample size number differed from the anticipated sample size of 56 patients due to a low patient turnout. This could have been due to the accreditation of other health facilities countrywide by the national hospital insurance fund (NHIF) to offer a standard oncology benefit package to NHIF insured patients. Most of the chemotherapy regimens for haematological malignancies except AL, can be administered on an outpatient basis, thus fewer patients needed to seek treatment at KNH due to the availability of similar subsidized oncology services offered elsewhere. Analysis of patient baseline and clinical characteristics as well as prednisone-related variables showed no statistical difference between the two groups. Participant baseline physical characteristics were also not significantly different except for body temperature and pulse rate, which were higher in the control than the treatment group (p=0.0458 and p=0.0062 respectively). This could possibly be due to differences in age and physical activity between the 2 study groups. Fortunately, these differences did not have a bearing on the outcome measure assessed.

Prednisone use in the therapeutic management of haematological cancer is focal, especially with the subclass of NHL malignancies. Various prednisone-based regimens are utilized, depending on the type of cancer involved. This study found the most common cancer in the 18 final patients to be NHL, with the subtypes of DLBCL and CLL being most prevalent. The regimen with the highest incidence was the CHOP regimen with or without Rituximab. Moreno et.al reports the use of CHOP regimen as the gold standard chemotherapy used in NHL treatment (42). Prednisone doses most encountered were in the study was total daily doses of 60mg and 100mg for a duration of either 5 days or 14 days. This tallies with the finding by Moreno et.al who noted that the

standard dose of prednisone in CHOP regimen for NHL was 100mg for 5 days (42) where 67% of the patients were using the standard dose, compared to 20.8% in the present study. The variation could be ascribed to the different study designs used.

This prospective randomized study was designed to assess the effectiveness of metformin in preventing prednisone-induced hyperglycaemia among haematological cancer patients on high-dose (≥30mg) prednisone. The findings showed no incidence of diabetes in spite of some of the study participants' blood glucose readings qualifying to be classified as prednisone-induced diabetes (fasting or 2-hour postprandial blood glucose levels greater than 7.0mmol/L and 11.1mmol/L respectively). This is because none of the patients had repeat separate clear-cut diabetic-defining blood glucose values when BGL measurements were taken at different time points. Variations in the glucose measurement results were obtained. Moreover, none of these participants presented with any symptomatic clinical criteria used in the diagnosis so they were not classified as having developed prednisone-induced diabetes.

Pre-diabetes was prevalent among the participants, particularly in the control group. A total of 10 patients developed PIH (classified as pre-diabetes), with 9 of these belonging to the control group. This represented an overall incidence of 90% of at least 1 episode of PIH from the control group and an incidence of 10% was noted from the treatment group. The general observed PIH incidence of 90% from the control group correlates with that observed by Tamez *et.al* who noted that more than half the patients on high-dose steroids will develop an incidence of 86% of at least one hyperglycaemic episode(7). Comparison determinations using FBG and 2-hour PPG measures across the 2 groups found the control group to have an incidence of PIH of 72.7% (8/11) and 54.5% (6/11) respectively. The incidence of 72.7% and 54.5% observed in the control group using FBG and 2-hour PPG compares to that of a similar study at KNH which provided a PIH incidence of 61.5%, with 25% of these arising from prednisone use in malignancies (15).

The actual BGL readings of patients in the control group showed FBG hyperglycaemia values ranging from 8.3-12.5 mmol/L, while the 2-hour PPG hyperglycaemic values ranged from 10.1-19.3mmol/L. The observed blood glucose levels and ranges provided in the present study can be related to those provided in other studies, with some existence of slight deviations of the margins. Tamez *et.al* commented on 48% of patients presenting with a mean BGL of >7.78mmol/L(7). Similarly, Rowbottom *et.al* demonstrated an incidence of 15% of non-diabetic patients having

random glucose levels ranging from 15.0-27.8mmol/L in a retrospective study carried out in 30 genitourinary (GU) cancer patients treated using continuous oral steroid use. Likewise, a review of 349 non-Hodgkin lymphoma patients (n=162) treated with a steroid-based chemotherapy regimen by Brunello *et.al* observed dysglycemia in 70% of these patients over the treatment course(83). The overall outcome from Brunello's study of NHL and prostate cancer patients was the detection of hyperglycaemia in 58.9% of patients (53 of 90), with 18.9% of patients (17 of 90) had DM- range hyperglycaemia(14). This draws a parallel to the incidence noted in the present study.

The observed incidence of PIH reported in the present study is higher than that seen by other similar studies, which reported incidences of 34.3%, 44% and 67.1% of patients with haematological malignancies (6,27,62). Gonzalez *et.al* comments on an incidence of fasting hyperglycaemia of 68.7% and an incidence of postprandial hyperglycaemia of 15.6% among ALL and NHL patients evaluated after 8 weeks on prednisone therapy (62). Forty-four per cent of patients receiving intermittent high-dose steroids developed SIH or SIDM while using short courses of treatments for lymphoproliferative diseases as reported by Vidler *et.al* (6). The differences can be attributed to the different study designs (observational versus interventional), different sample sizes (greater than 30 patients) as well different monitoring of glycaemic parameters (HbA1C measurements as well as different cut off points for random blood glucose levels). This differs from other studies which evaluated the incidence of SIH in different patient populations. These have reported an incidence of SIH in the range of 30-40% (61,65). A meta-analysis conducted demonstrated the rates of SIH and SIDM at 32.3% and 18.6% respectively (123).

In the study, PIH was observed with both the test measures of fasting and 2-hour postprandial glucose. The FBG readings indicated a proportion of PIH of 72.7% and 14.3% in the control and treatment groups respectively. The proportion was slightly lower while using the 2-hour PPG, in which 54.5% of participants in the control group developed PIH while none developed PIH in the treatment group. The results showed a greater percentage of participants with PIH using the FBG than the 2-hour PPG glucose readings. This finding draws a parallel to that seen by Vidler *et.al*, who reported fasting glycaemia as a more sensitive identifier of DM than postprandial determinations (62). Similarly, Darjani *et.al* observed pre-treatment FBG as the factor that would

increase the likelihood of glucocorticoid-induced diabetes mellitus. He observed no difference between oral and pulse PDN therapy and reported a 22.22% incidence of hyperglycaemia characterized as impaired fasting glucose (65). Pre-treatment FBG was shown to be a strong predictor in his study, with 42.2% of patients with pre-treatment FBG of 5.6-7mmol/L developing diabetes, contrasting with 17.2% of patients with normal pre-treatment FBG (65). The CTCAE uses FPG for the grading of hyperglycaemic events (124).

The above findings using FBG glucose levels to diagnose PIH reflect the opposite of what most studies have established. Majority of the other studies agree that the current practice of using FBG readings could lead to loss of some patients based on a lack of sensitivity of FBG to SIH (7,30,46,61,63). This is because the greatest diagnostic sensitivity for PIH occurs while using the postprandial glycaemic levels. Studies have demonstrated the occurrence of PIH predominantly in the afternoon and evening, suggesting that this serves as the most appropriate screening and treatment intervention time (61). Uzu *et.al* mentioned on the development of SIDM in 40.5% of patients using postprandial hyperglycaemia (24).

Despite the incidence of PIH with FBG being higher than that of the 2-hour PPG, the choice of reporting PIH using the 2-hour PPG over the FBG measure was selected. This is based on the former being the preferred test for detecting SIH or SIDM (11,13,38,46,63). A study of primary renal disease non-diabetic patients treated with a prednisolone daily dose of 0.75mg/kg reported diagnosing all 17 patients with SIDM using 2-hour postprandial glucose values which exceeded 11.1mmol/L. However, all these patients had normal fasting blood glucose values (24). Therefore, in agreement with the consensus of using the 2-hour PPG as the true diagnostic measure, the effectiveness of metformin as a preventative measure displayed clear significance. This finding further augments observations made on how the current diagnostic tests of PIH may be inaccurate as the FBG measure could undervalue the true incidence of PIH. No study participant in the treatment group developed any episode of PIH using this measure compared to the 54.5% (6/11) in the control group. Even while using the FBG measure, the overall incidence of PIH was 14.3% (1/7) in the treatment group versus 81.8% (9/11) in the control group. This supports the hypothesis of the effectiveness of metformin in preventing PIH among haematological cancer patients.

Furthermore, the mean differences in blood glucose readings between the 2 groups using this test ranged from 1.2-2.6 mmol/L. Participants in the treatment arm had the lowest and highest 2-hour

PPG glucose levels as 5.0±0.9mmol/L and 5.8±0.7 mmol/L respectively. This represents the highest mean increase from mean random baseline BGL to be at 26.1%. The control group, on the other hand, had the lowest and highest 2-hour PPG glucose levels as 6.6±1.1mmol/L and 8.0±3.0mmol/L. The highest mean increase from the mean random baseline BGL using the 2-hour PPG was 45.5%. The higher increase observed with the control group is in tandem with that reported by Tamez *et.al*, who demonstrated increases of up to 68% in glucose levels when compared to baseline glucose levels (7). The measures of association found the odds of developing PIH in the control group to be 16 (95% CI 1.3-194.6) times more than the odds of developing PIH in the treatment group.

The comparison of the effectiveness of single versus double 850mg metformin dosing using FBG and 2-hour PPG was done. There was no incidence of PIH using the 1700mg twice daily metformin dosing while one incidence of PIH was observed with the 850mg daily metformin dosing. The mean difference in BGL with single versus double dosing using the FBG was 0.06±0.5mmol/L. The mean difference in BGL using the 2-hour PPG was 0.5±0.9mmol/L. Compared to the random baseline glucose of 4.6±0.8mmol/L, the FBG glucose measure showed an increase from baseline of 4.3% using the single once-daily dosing and 2.2% using the double daily metformin dosing. This contrasts with 19.5% and 8.7% increase from baseline using the single versus double daily metformin dosing with 2-hour PPG glucose measure. This indicates that the double daily dosing was more effective in preventing PIH since the increase from baseline with both the FBG and 2-hour PPG was most minimal at 2.2% and 8.7%. This is supported by Garber *et.al* who commented that a daily dose of metformin 1500mg contributes to 80-85% glucose lowering effects (119).

The study findings on the effectiveness of metformin in preventing PIH correspond to those by Seelig *et.al* which demonstrated preventive metformin treatment to be superior to placebo. The analysis was done on patients newly initiated on PDN treatment of ≥7.5 mg or equivalent glucocorticoid for at least 4 weeks. This was with respect to glycaemic control as indicated by 2-hour glucose AUC, homeostatic model assessment (HOMA) index, fasting glucose and fasting insulin (17). The results indicated the prevention of an increase of 2-hour glucose AUC with metformin, signifying glucose tolerance preservation. No changes in baseline and after 4 weeks metformin treatment was seen with the 2-hour glucose AUC (p = 0.83), whereas this parameter increased in the placebo group (p= 0.01). This difference in the outcome of change in 2-hour

glucose AUC within four weeks was significant (p = 0.005), unlike in the present study which found no statistical significance using FBG and 2-hour PPG respectively (p=1.0000 and p=0.4531). Additionally, single therapy with metformin regulated blood glucose levels in 12 out of 17 patients in a study by Bostrom *et.al* in ALL patients treated with a median dose of 1000mg (500-2000mg) metformin for a median of 6 days (16). Blood glucose levels never exceeded 11.1mmol/L in 8 of the 12 patients. Another related study showed that patients assigned to rigorous blood glucose control with metformin had a 32% lower risk for any diabetes-related end point (p=0.002). They also had a 36% lower risk for death associated with any other cause and a 42% reduction in diabetes-related death (p= 0.021 and p=0.11 respectively) (108).

It was observed in that same study that the fasting glucose levels decreased in the metformin group, while they increased in the placebo group during the study period (17). This observation was also made in the present study where the FBG decreased in some but not all the patients in the control group. This observation was true even in the control group, a contrast to the finding. Adjustment for confounders like gender, total steroid dose and HbA1C still gave that treatment group a strong association with 2-h AUC glucose (dose adjustment: treatment group, p= 0.003; HbA1C adjustment: treatment group, p = 0.002) (17). This observation tallies with our study which found that multivariate regression analysis with predictor variables like baseline random BGL, age, sex, RVD status, total administered dose and alcohol history still showed treatment with metformin to have a significant association in the development of PIH. However, BMI was found to be a strong predictor variable in the development of PIH in the present study, with statistically significant association observed with the fasting blood glucose measure (p=0.0269). This contrasts the finding by Zeng *et.al* who denoted the steroid dose and older age to be predictors of SIDM (71). Related studies agreed on the major predictive factors in SIH development to be the total dose and the steroid type (43,44,70).

The only adverse effect encountered among the study participants was mild diarrhoea in a single patient in the treatment arm. This occurred when the dose of metformin was titrated upwards from 850mg to 1700mg per day. This was observed for a period of 2 days, with spontaneous resolution. This corresponds to other similar studies which found that the most common adverse effect of metformin treatment were gatro-intestinal related (108). It has been observed that diarrhoea, nausea, vomiting, abdominal bloating, cramping or pain, flatulence, and anorexia are the most

common symptoms associated with metformin therapy (114). These occur in 20% to 30% of patients on metformin treatment. However, this occurrence differed from the present study which found an incidence of 14.3% (1/7) in the patients treated with metformin. Discontinuation of the drug is usually warranted in less than 5% of patients (108).

Changes in baseline laboratory tests were not significantly different in the 2 groups, with the exception of serum creatinine levels whose difference was statistically significant (p=0.0400). There was a 2-directional increase in creatinine levels, with the treatment group having higher values than the control group. This occurrence could be attributed to other factors that may independently contribute to increased serum creatinine observed like increased muscle mass from the entirely male treatment group. The side effect of lactic acidosis was observed in 6 participants, occurring in the ratio of 1:1 in both groups. The mean serum lactate levels in the treatment group was 2.14 ± 0.78umol/L while that in the control group was 1.92 ± 0.47umol/L. This observation indicates that the risk of developing high serum lactate levels was not significantly associated with metformin use (p=0.4586). This correlates with a study by Salpeter *et.al* who found no variation in the mean lactate levels measured during metformin treatment compared to placebo or other medications used in diabetes treatment (114). Similarly, no cases of lactic acidosis were observed in the UKPDS with metformin therapy (125).

5.3 Study Limitations

The study was limited by the small sample size involved based on a lengthy recruitment process due to repeated patient visits to the hospital and a short period of study duration. It could also be attributed to the administration of some chemotherapy regimens on an outpatient basis which may have made it difficult to access patients and also to ensure adequate patient follow up as outlined in the protocol. Nonetheless, the expected effect size of the intervention was still adequately demonstrated in spite of the small sample size, based on the significant results obtained. Secondly, loss to follow up in the treatment arm left only male patients in the group. Luckily, this proportion was similar to that in the control group, allowing for generalizability of the results. Thirdly, inconsistent daily monitoring of blood glucose levels was a challenge, which prohibited analysis of the course of development of prednisone-induced hyperglycaemia. Fourthly, lack of use of a suitable placebo in the control group prohibited complete and effective blinding of study participants. Nevertheless, the objective measure used in determining the outcomes ensured no bias in the results verification. Lastly, the variations in prescribed high-dose prednisone amongst

the participant could have played a role in the outcome determination. However, the observed difference mirrors the general practice of treatment which truly demonstrates the effect if metformin as an intervention.

5.4 Summary of Results

Efforts to minimize SIH in exposed patients are crucial, in spite of no current consensus of the drugs effective in reducing its incidence and associated complications(30). It is imperative to seek possible interventions that could prevent the incidence of PIH among haematological cancer patients, and metformin has proven to be efficacious. No participant in the treatment group in this study developed PIH using the preferred test of 2-hour postprandial glucose while 54.5% of participants in the control group on standard care of treatment developed PIH. Even with the current diagnostic test of fasting blood glucose, 14.3% of the treatment group, equivalent to 1 patient in the treatment arm developed only one episode of PIH. The use of double dose 850mg metformin tablets (1700mg) offered a lesser increment from baseline blood glucose levels, in spite of differences in the variables of the cycle of treatment, total daily dose, prednisone total dose divided schedule and frequency. This showed that higher metformin doses are more effective as a preventative measure than lower doses. No significant adverse effects were observed with metformin treatment.

5.4 Conclusions

More than half the patients in the control group developed at least one episode of prednisone-induced hyperglycaemia characterized as pre-diabetes using both the 2-hour postprandial and fasting blood glucose levels (54.5% and 72.7% respectively). In comparison, no episode of pre-diabetes was observed with the treatment group using the preferred diagnostic test of 2-hour postprandial glucose, while only a single participant developed pre-diabetes using fasting glucose levels (14.3%). In spite of this occurrence, blood glucose control was clinically and significantly better in the treatment than the control group throughout the study period. The single incident observed was while the treatment group were using single dose daily metformin. No such incident was reported when the metformin dose was titrated upwards to 1700mg, indicating the effectiveness of metformin in preventing the increase in blood glucose among susceptible haematological cancer patients.

5.5 Recommendations

Prescribers managing patients with conditions necessitating high-dose steroids should be encouraged to frequently monitor glycaemia. This practise will enable prompt diagnosis and intervention in the onset of steroid-induced hyperglycaemia and diabetes. Metformin preventative use in high-risk patients may be beneficial in reducing the incidence of prednisone-induced hyperglycaemia.

Future studies could investigate the course of prednisone-induced hyperglycaemia and the degree of effectiveness of metformin intervention in larger susceptible populations over a prolonged study period.

Further research on the effectiveness of metformin on the population of teenagers aged 12-18 years can be conducted in resource limited settings to determine potential beneficial effects against prednisone-induced hyperglycemia.

7.0 REFERENCES

1. Ministry of Health,Kenya. National Cancer Control Strategy [Internet]2017–2022; (2):10-11.

2. Gopal S, Wood WA, Lee SJ, Shea TC, Naresh KN, Kazembe PN, et al. Meeting the challenge of hematologic malignancies in sub-Saharan Africa. 2016;119(22):5078–88.

3. Agwata B. A ten year retrospective study on therapeutic management and clinical outcomes of acute lymphoblastic leukemia among children at Kenyatta National Hospital, Kenya. 2012 Oct;46.

4. Kabera B, Riyat M, Macharia WM, Pamnani R. Acute leukemias immunophenotypes at Agakhan University Hospital, Nairobi. East Afr Med J. 2013;90(2):45–51.

5. Roberts A, James J, Dhatariya K. Management of Hyperglycaemia and Steroid (Glucocorticoid) Therapy. Jt Br Diabetes Soc. 2014;32(1):126–30.

6. Vidler J, Rogers C, Yallop D, Devereux S, Wellving E, Stewart O, et al. Outpatient management of steroid-induced hyperglycaemia and steroid-induced diabetes in people with lymphoproliferative disorders treated with intermittent high dose steroids. J Clin Transl Endocrinol [Internet]. 2017;9:18–20.

7. Tamez-pérez HE, Quintanilla-flores DL, Rodríguez-gutiérrez R, González- JG, Tamez-peña AL, Tamez-pérez HE, et al. Steroid hyperglycemia : Prevalence , early detection and therapeutic recommendations : A narrative review. 2015;6(8):1073–81.

8. Hwng JL, Weiss RE. Steroid-induced diabetes: A clinical and molecular approach to understanding and treatment. Diabetes Metab Res Rev. 2014 Feb;30(2):96–102.

9. Fathallah N, Slim R, Larif S, Hmouda H, Ben Salem C. Drug-Induced Hyperglycaemia and Diabetes. Drug Saf [Internet]. 2015;38(12):1153–68.

10. Gulliford MC, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. Diabetes Care. 2006;29(12):2728–9.

11. Fong AC, Cheung NW. The high incidence of steroid-induced hyperglycaemia in hospital. Diabetes Res Clin Pract [Internet]. 2018 Jan 22;99(3):277–80.

12. Mills E, Devendra S. Steroid-induced hyperglycaemia in primary care. London J Prim Care (Abingdon). 2015;7(5):103–6.

13. Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and Predictors of Corticosteroid-Related Hyperglycemia in Hospitalized Patients. Endocr Pract [Internet]. 2006 Jul 1;12(4):358–62.

14. Harris D, Barts A, Connors J, Dahl M, Elliott T, Kong J, et al. Glucocorticoid-induced hyperglycemia is prevalent and unpredictable for patients undergoing cancer therapy: An observational cohort study. Curr Oncol. 2013;20(6):532–8.

15. Cecilia G. Prevalence of hyperglycemia in coticosteroid therapy at the kenyatta national hospital. 2012 Jun:24-27.

16. Bostrom B, Uppal P, Chu J, Messinger Y, Gandrud L, McEvoy R. Safety and efficacy of metformin for therapy-induced hyperglycemia in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2013;35(7):504–8.

17. Seelig E, Meyer S, Timper K, Nigro N, Bally M, Pernicova I, et al. Metformin prevents metabolic side effects during systemic glucocorticoid treatment. Eur J Endocrinol. 2017 Mar;176(3):349–58.

18. Vu K, Busaidy N, Cabanillas ME, Konopleva M, Ensor J, Escalante C, et al. NIH Public Access. 2014;12(5):355–62.

19. Libby G, Donnelly LA, Donnan PT EA. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care. 2009;32(9):1620–5.

20. Ruiter R, Visser LE, Van Herk-Sukel MPP, Coebergh JWW, Haak HR, Geelhoed-Duijvestijn PH, et al. Lower risk of cancer in patients on metformin in comparison with those on sulfonylurea derivatives: Results from a large population-based follow-up study. Diabetes Care. 2012;35(1):119–24.

21. Evans JMM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ [Internet]. 2005 Jun 2;330(7503):1304-1305.

22. Currie CJ, Poole CD, Gale EAM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia. 2009;52(9):1766–77.

23. DeCensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, et al. Metformin and cancer risk in diabetic patients: A systematic review and meta-analysis. Cancer Prev Res. 2010;3(11):1451–61.

24. Uzu T, Harada T, Sakaguchi M, Kanasaki M, Isshiki K, Araki S, et al. Glucocorticoid-Induced Diabetes Mellitus: Prevalence and Risk Factors in Primary Renal Diseases. Nephron Clin Pract [Internet]. 2007;105(2):c54–7.

25. Fennell RS, Van Deusen J, Riley WJ. Steroid-induced diabetes in pediatric renal transplant recipients. Int J Pediatr Nephrol. 1983 Jun;4(2):103–7.

26. Pui CH, Burghen GA, Bowman WP, Aur RJ. Risk factors for hyperglycemia in children with leukemia receiving L-asparaginase and prednisone. J Pediatr. 1981 Jul;99(1):46–50.

27. Weiser MA, Cabanillas ME, Konopleva M, et al. Relation between the duration of remission and hyperglycemia during induction chemotherapy for acute lymphocytic leukemia with a hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate–cytarabine regimen.Cancer. 2004 Feb;100(6):1179–85.

28. Koltin D, Sung L, Naqvi A, Urbach SL. Medication induced diabetes during induction in pediatric acute lymphoblastic leukemia: prevalence, risk factors and characteristics. Support care cancer Off J Multinatl Assoc Support Care Cancer. 2012 Sep;20(9):2009–15.

29. Rowbottom L, Stinson J, McDonald R, Emmenegger U, Cheng S, Lowe J, et al. Retrospective review of the incidence of monitoring blood glucose levels in patients receiving corticosteroids with systemic anticancer therapy. Ann Palliat Med [Internet]. 2015;4(2):70–7.

30. Suh S, Park MK. Glucocorticoid-Induced Diabetes Mellitus : An Important but Overlooked Problem. Endocrinol Metab 2017;32:180-189 .

31. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006;49(2):289–97.

32. Shi WY, Xiao D, Wang L, Dong LH, Yan ZX, Shen ZX, et al. Therapeutic metformin/AMPK activation blocked lymphoma cell growth via inhibition of mTOR pathway and induction of autophagy. Cell Death Dis [Internet]. 2012;3(3):275-9.

33. Teachey DT, Grupp SA, Brown VI. Mammalian target of rapamycin inhibitors and their potential role in therapy in leukaemia and other haematological malignancies. Br J Haematol. 2009;145(5):569–80.

34. Ashour AE, Sayed-Ahmed MM, Abd-Allah AR, Korashy HM, Maayah ZH, Alkhalidi H, et al. Metformin rescues the myocardium from doxorubicin-induced energy starvation and mitochondrial damage in rats. Oxid Med Cell Longev. 2012; Article ID 434195:13.

35. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in Globocan 2012. Int J Cancer. 2015;136(5):E359–86.

36. Mostert S, Njuguna F, Kemps L, Strother M, Aluoch L, Buziba G, et al. Epidemiology of diagnosed childhood cancer in western kenya. Arch Dis Child [Internet]. 2012 Apr;97(6)

37. Saigí I, Pérez A. [Management of glucocorticoid induced hyperglycemia]. Rev Clin Esp [Internet]. 2010 Sep;210(8):397—403.

38. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy, Asthma Clin Immunol [Internet]. 2013;9(1):1.

39. Inaba H, Pui C-H. Glucocorticoid use in acute lymphoblastic leukemia: comparison of prednisone and dexamethasone. Lancet Oncol. 2012;11(11):1096–106.

40. Mwanda.W.O. Kasili's Synopsis of the Management of Paediatric Cancers in Kenya. 2012;20–145.

41. Palumbo A, Falco P, Corradini P, Falcone A, Di Raimondo F, Giuliani N, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: A report from the GIMEMA - Italian Multiple Myeloma Network. J Clin Oncol. 2007;25(28):4459–65.

42. Moreno A, Colon-Otero G, Solberg LA. The Prednisone Dosage in the CHOP Chemotherapy Regimen for Non-Hodgkin's Lymphomas (NHL): Is There a Standard? Oncologist [Internet]. 2000;5(3):238–49.

43. Geer E, Islam J, Buettner C. Mechanism of Glucocorticoid-Induced Insulin Resistance: Focus on adipose tissue function and lipid metabolism. Endocrinol Metab Clin North Am. 2015;43(1):1–27.

44. Van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: Towards expansion of therapeutic options? Eur J Clin Invest. 2009;39(2):81–93.

45. Schneiter P, Tappy L. Kinetics of dexamethasone-induced alterations of glucose metabolism in healthy humans. Am J Physiol. 1998 Nov;275(5 Pt 1):E806-13.

46. Clore J, Thurby-Hay L. Glucocorticoid-Induced Hyperglycemia. Endocr Pract [Internet]. 2009 May 6;15(5):469–74.

47. Yasuda K, Hines E 3rd, Kitabchi AE. Hypercortisolism and insulin resistance: comparative effects of prednisone, hydrocortisone, and dexamethasone on insulin binding of human erythrocytes. J Clin Endocrinol Metab. 1982 Nov;55(5):910–5.

48. AL-Jurayyan NAM, AL- Jurayyan AN., Al Issa SDA. Steroid- Induced Hyperglycemia: A Review. Int J Med Res Prof [Internet]. 2016;2(6):2–5.

49. Hoes JN, Van Der Goes MC, Van Raalte DH, Van Der Zijl NJ, Den Uyl D, Lems WF, et al. Glucose tolerance, insulin sensitivity and β-cell function in patients with rheumatoid arthritis treated with or without low-to-medium dose glucocorticoids. Ann Rheum Dis. 2011;70(11):1887–94.

50. Pagano G, Cavallo-Perin P, Cassader M, Bruno A, Ozzello A, Masciola P, et al. An in vivo and in vitro study of the mechanism of prednisone-induced insulin resistance in healthy subjects. J Clin Invest [Internet]. 1983;72(5):1814–20.

51. Dessein PH, Joffe BI, Stanwix AE, Christian BF, Veller M. Glucocorticoids and insulin sensitivity in rheumatoid arthritis. J Rheumatol. 2004 May;31(5):867–74.

52. Larsson H, Ahren B. Insulin resistant subjects lack islet adaptation to short-term dexamethasone-induced reduction in insulin sensitivity. Diabetologia. 1999 Aug;42(8):936–43.

53. Raalte H Van, Nofrate V, Bunck MC, Iersel T Van, Schaap JE. Acute and 2-week exposure to prednisolone impair different aspects of b -cell function in healthy men. European Journal of Endocrinology. 2010;162:729–735.

54. Van Raalte DH, Kwa KA, Van Genugten RE, Tushuizen ME, Holst JJ, Deacon CF, et al. Islet-cell dysfunction induced by glucocorticoid treatment: potential role for altered sympathovagal balance? Metabolism. 2013 Apr;62(4):568–77.

55. Van Raalte DH, Brands M, Van Der Zijl NJ, Muskiet MH, Pouwels PJW, Ackermans MT, et al. Low-dose glucocorticoid treatment affects multiple aspects of intermediary metabolism in healthy humans: A randomised controlled trial. Diabetologia. 2011;54(8):2103–12.

56. Nicod N, Giusti V, Besse C, Tappy L. Metabolic adaptations to dexamethasone-induced insulin resistance in healthy volunteers. Obes Res. 2003;11(5):625–31.

57. Binnert C, Ruchat S, Nicod N, Tappy L. Dexamethasone-induced insulin resistance shows no gender difference in healthy humans. Diabetes Metab [Internet]. 2018 Feb 20;30(4):321–6.

58. Pasieka AM, Rafacho A. Impact of glucocorticoid excess on glucose tolerance: Clinical and preclinical evidence. Metabolites. 2016 Aug;6(3).

59. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature [Internet]. 2006 Dec 13;444:840.

60. Trence DL. Management of patients on chronic glucocorticoid therapy : an endocrine perspective. Prim Care. 2003 Sep;30(3):593–605.

61. Burt MG, Roberts GW, Aguilar-Loza NR, Frith P, Stranks SN. Continuous monitoring of

circadian glycemic patterns in patients receiving prednisolone for COPD. J Clin Endocrinol Metab. 2011 Jun;96(6):1789–96.

62.   Gonzalez-Gonzalez JG, Mireles-Zavala LG, Rodriguez-Gutierrez R, Gomez-Almaguer D, Lavalle-Gonzalez FJ, Tamez-Perez HE, et al. Cv. Diabetol Metab Syndr [Internet]. 2013;5(1):18.

63.   Kwon S, Hermayer KL, Hermayer K. Glucocorticoid-Induced Hyperglycemia. Am J Med Sci [Internet]. 2013 Apr ;345(4):274–7.

64.   Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther. 2002 Oct;96(1):23–43.

65.   Darjani A, Nickhah N, Hassan M, Emami H, Alizadeh N, Rafiei R, et al. Assessment of the Prevalence and Risk Factors Associated With Glucocorticoid- Induced Diabetes Mellitus in Pemphigus Vulgaris Patients. 2017;2–7.

66.   Black CT, Hennessey PJ, Andrassy RJ. Short-term hyperglycemia depresses immunity through nonenzymatic glycosylation of circulating immunoglobulin. J Trauma [Internet]. 1990 Jul;30(7):830—2; discussion 832—3.

67.   Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. Diabet Med. 1997 Jan;14(1):29–34.

68.   Bjornholt J, Erikssen G, Aaser E, Sandvik L, Nitter-Hauge S, Jervell J, et al. Fasting Blood Glucose: An Underestimated Risk Factor for Cardiovascular Death. Diabetes Care. 1999;22(1):45–9.

69.   Luo J, Chen Y-J, Chang L-J. Fasting blood glucose level and prognosis in non-small cell lung cancer (NSCLC) patients. Lung Cancer. 2012 May;76(2):242–7.

70.   Gurwitz JH,Bohn RL,Glynn RJ, Monane M, Mogun H, Avorn J. Glucocorticoids and the risk for initiation of hypoglycemic therapy. Arch Intern Med [Internet]. 1994 Jan 10;154(1):97–101.

71.   Zeng Y-J, Zeng F-Q, Dai L, Yang C, Lin B-Z, Zheng D-H, et al. Characteristics and risk factors for hyperglycemia in Chinese female patients with systemic lupus erythematosus. Lupus.

2010 Oct;19(11):1344–50.

72. Howard SC, Pui C-H. Endocrine complications in pediatric patients with acute lymphoblastic leukemia. Blood Rev. 2002 Dec;16(4):225–43.

73. Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(1):16–38.

74. American Diabetes Association. Diabetes care in the hospital. Diabetes Care. 2017 Jan;40(Suppl 1):120–7.

75. Petersons C, Mangelsdorf B, Jenkins A, et al. Effects of Low-Dose Prednisolone on hepatic and Peripheral Insulin Sensitivity, Insulin Secretion, and Abdominal Adiposity in PatientsWith Inflammatory Rheumatologic Disease. Diabetes Care. 2013 Sep;36(13):2822-9

76. Duan W, Shen X, Lei J, Xu Q, Yu Y, Li R, et al. Hyperglycemia, a neglected factor during cancer progression. Biomed Res Int. 2014;2014.

77. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Abnormal glucose tolerance and the risk of cancer death in the United States. Am J Epidemiol. 2003;157(12):1092–100.

78. Ali NA, O'Brien JM, Blum W, Byrd JC, Klisovic RB, Marcucci G, et al. Hyperglycemia in patients with acute myeloid leukemia is associated with increased hospital mortality. Cancer. 2007;110(1):96–102.

79. Sonabend RY, McKay SV, Okcu MF, Yan J, Haymond MW, Margolin JF. Hyperglycemia during induction therapy is associated with poorer survival in children with acute lymphocytic leukemia. J Pediatr. 2009 Jul;155(1):73–8.

80. Lowas SR, Marks D, Malempati S. Prevalence of transient hyperglycemia during induction chemotherapy for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer. 2009 Jul;52(7):814–8.

81. Spinola-Castro AM, Siviero-Miachon AA, Andreoni S, Tosta-Hernandez PDC, Macedo CRPD, Lee ML de M. Transient hyperglycemia during childhood acute lymphocytic

leukemia chemotherapy: an old event revisited. Clin Adv Hematol Oncol. 2009 Jul;7(7):465–72.

82. Matias C do N, Lima V, Teixeira HM, Souto FR, Magalhães V. Hyperglycemia increases the complicated infection and mortality rates during induction therapy in adult acute leukemia patients. Rev Bras Hematol Hemoter [Internet]. 2013;35(1):39–43. 83.

83. Brunello A, Kapoor R, Extermann M. Hyperglycemia During Chemotherapy for Hematologic and Solid Tumors Is Correlated With Increased Toxicity. Am J Clin Oncol [Internet]. 2011;34(3).

84. Cheng AY. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction. Can J diabetes. 2013 Apr;37 Suppl 1:S1-3.

85. Kim SY, Yoo C, Lee CT, Chung HS, Shim Y, Yim J. Incidence and Risk Factors of Steroid-induced Diabetes in Patients with Respiratory Disease. 2011;264–7.

86. Najla MA, Maha MA. Steroid Induced Diabetes. Diabetes Obes Int J. 2017 Sep;2(4):1–6.

87. Jeong Y, Han HS, Lee HD, Yang J, Jeong J, Choi MK, et al. A pilot study evaluating steroid-induced diabetes after antiemetic dexamethasone therapy in chemotherapy-treated cancer patients. Cancer Res Treat. 2016;48(4):1429–37.

88. Moore MA, Park CB, Tsuda H. Implications of the hyperinsulinaemia-diabetes-cancer link for preventive efforts. Eur J Cancer Prev. 1998 Apr;7(2):89–107.

89. Pisani P. Hyper-insulinaemia and cancer, meta-analyses of epidemiological studies. Arch Physiol Biochem. 2008 Feb;114(1):63–70.

90. Shukla A, Grisouard J, Ehemann V, Hermani A, Enzmann H, Mayer D. Analysis of signaling pathways related to cell proliferation stimulated by insulin analogs in human mammary epithelial cell lines. Endocr Relat Cancer. 2009;16(2):429–41.

91. Belfiore A, Frasca F, Pandini G, Sciacca L, Vigneri R. Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. Endocr Rev. 2009 Oct;30(6):586–623.

92. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B. Diabetes mellitus and breast cancer. Lancet Oncol. 2005 Feb;6(2):103–11.

93. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J Clin Nutr. 2007 Sep;86(3):s836-42.

94. Cusi K, Consoli A, DeFronzo RA. Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1996 Nov;81(11):4059–67.

95. Stumvoll M, Nurjahan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. NEnglJMed. 1995;333:550–4.

96. DeFronzo RA, Barzilai N, Simonson DC. Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. J Clin Endocrinol Metab. 1991 Dec;73(6):1294–301.

97. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. 2001;108(8):1167–74.

98. Kahn BB, Alquier T, Carling D, Hardie DG. AMP-activated protein kinase : Ancient energy gauge provides clues to modern understanding of metabolism. 2005;1(January):15–25.

99. Inoki K, Guan K-L. Complexity of the TOR signaling network. Trends Cell Biol. 2006 Apr;16(4):206–12.

100. Christ-crain M, Kola B, Lolli F, Fekete C, Seboek D, Feltrin D, et al. AMP-activated protein kinase mediates glucocorticoid- induced metabolic changes : a novel mechanism in Cushing's syndrome. 22(6):1672–83.

101. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Review Metformin : From Mechanisms of Action to Therapies. Cell Metab [Internet]. 2014;20(6):953–66.

102. Nader N, Sin S, Ng M, Lambrou GI, Pervanidou P, Wang Y, et al. AMPK Regulates Metabolic Actions of Glucocorticoids by Phosphorylating the Glucocorticoid Receptor through p38 AMPK. 2018;24(September 2010):1748–64.

103. Knowler WC, Barret-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al.

Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. N Engl J Med [Internet]. 2002;346(6):393–403.

104. National Diabetes Information Clearinghouse. Diabetes Prevention Program.Diabetes Care. 2002 Dec;25(12):2165-2171

105. Salpeter SR, Buckley NS, Kahn JA, Salpeter EE. Meta-analysis: Metformin Treatment in Persons at Risk for Diabetes Mellitus. Am J Med [Internet]. 2008 Feb 10;121(2):149–157.

106. Richard M. Metformin. About diabetes [www.diabatesnet.com]. 2010 Nov.

107. Klip A, Leiter LA. Cellular Mechanism of Action of Metformin. 1990;13(6):696–704.

108. Defronzo RA. Pharmacologic Therapy for Type 2 Diabetes Mellitus. 1999;281–303.

109. Garber MD AJ, PhD, Duncan MD TG, Goodman MD AM, Mills RN DJ, BSN, et al. Efficacy of Metformin in Type II Diabetes. Am J Med [Internet]. 2018 Feb 6;103(6):491–7.

110. Zakikhani M, Dowling R, Fantus IG, Sonenberg N, Pollak M. Metformin is an AMP kinase-dependent growth inhibitor for breast cancer cells. Cancer Res. 2006;66(21):10269–73.

111. Matteo M, Claudia C, Daniela B, et al. Metformin and Cancer Occurrence in Insulin-Treated Type 2 Diabetic Patients. Diabetes Care . 2011 Jan;34(1):2–4.

112. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet [Internet]. 2018 Feb 6;352(9131):854–65.

113. Aguilar C, Reza A, Garcia JE, Rull JA. Biguanide related lactic acidosis: incidence and risk factors. Arch Med Res. 1992;23(1):19–24.

114. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010 Jan;(4):222-230.

115. Spiller HA, Quadrani DA. Toxic effects from metformin exposure. Ann Pharmacother. 2004 May;38(5):776–80.

116. Beniet M, Bi Y. Evaluation of Intravenous Preloading Magnesium Supplementation As a Preventive Measure of Cisplatin Induced. 2015 Nov.

117. Buttgereit F, Da Silva JPA, Boers M, Burmester GR, Cutolo M, Jacobs J, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: Current questions and tentative answers in rheumatology. Ann Rheum Dis. 2002;61(8):718–22.

118. Chan YH. Randomised controlled trials (RCTS) - Sample size: The magic number? Singapore Med J. 2003;44(4):172–4.

119. Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. Am J Med. 1997 Dec;103(6):491–7.

120. Food & Drug Administration. Metformin hydrochloride tablets. Fda [Internet]. 2002;1–16.

121. Core C, Teams D. Clinical Data Acquisition Standards Harmonization (CDASH). Rep No Cdash_Std-10, Austin, TX [Internet]. 2008;(January):1–95.

122. American Diabetes Association . Classification and Diagnosis of Diabetes. Diabetes Care 2015 Jan;38(Suppl. 1):8–16.

123. Liu X, Zhu X, Miao Q, Ye H, Zhang Z, Li Y. Hyperglycemia Induced by Glucocorticoids in Nondiabetic Patients: A Meta-Analysis. Ann Nutr Metab [Internet]. 2014;65(4):324–32.

124. NIH. Common terminology criteria for adverse events v5.0. UpToDate [Internet]. 2015;0–71.

125. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34).. Lancet (London). 1998 Sep;352(9131):854–65.

APPENDICES
Appendix 1: Ethical 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
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
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/203

June 8, 2018

Lucy Akinyi Ochola
Reg. No.U56/87314/2016
Dept.of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Lucy

RESEARCH PROPOSAL – AN ASSESSMENT OF THE EFFECTIVENESS OF METFORMIN IN PREVENTING PREDNISONE-INDUCED HYPERGLYCEMIA AMONG HEMATOLOGICAL CANCER PATIENTS AT KENYATTA NATIONAL HOSPITAL (P143/03/2018)

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 8th June 2018 – 7th June 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) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f) 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*).
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.

Protect to discover

87

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 Chair, Dept. of Pharmaceutics and Pharmacy Practice, UoN
         Supervisors: Dr. David Nyamu, Dr. Eric Guantai, Dr. Irene Weru

Protect to discover

88

Appendix 2A: Participant Information Statement

Research Study Title:

ASSESMENT OF THE EFFECTIVENESS OF METFORMIN IN PREVENTING PREDNISONE-INDUCED HYPERGLYCEMIA AMONG HEMATOLOGICAL CANCER PATIENTS AT KENYATTA NATIONAL HOSPITAL.

I am Dr. Lucy Ochola, a Masters' student in Clinical Pharmacy at the University of Nairobi. I am carrying out a study in KNH. This is a type of research study called a clinical trial. Your clinic doctor and the investigator will explain the details of the study to you. Clinical trials are studies that only include people who willingly decide and choose to take part. Please take your time to make your decision about taking part in it. You are free to discuss your decision with your friends and family and with your doctor.

You are being asked to take part in this study because you have been diagnosed with cancer and part of your management will require you to receive treatment using the drug prednisone.

Reason for the study

The purpose of this study is to assess the how metformin, an antidiabetic drug, helps in lowering blood sugar levels. Blood sugar levels tend to increase during blood cancer treatment when prednisone is used.

This study is being done to find out if giving metformin to cancer patients on prednisone management will help reduce the increase in blood sugar levels. This is important when using high-dose prednisone. In this study, in addition to you cancer treatment, you will get either the standard care or metformin. You will not get both.

Number of people in the study

About 56 people will take part in this study

Who is carrying out the study?

The study is being done by Dr. Lucy Ochola, B.Pharm, Masters' student in Clinical Pharmacy at the Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi, P.O BOX 30197-0400 Nairobi. **Contact details**: 0789233372 or 0724778550, Email:lucyochola@gmail.com

Supervisors:

Dr. David G. Nyamu: Clinical Pharmacist and Lecturer, Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy

Dr. Eric Guantai: Lecturer, Department of Pharmacology and Pharmacognosy, School of Pharmacy

Dr. Irene Weru: Deputy Chief Pharmacist, Kenyatta National Hospital.

Ethical approval: The study will seek approval from the Ethics and Research Committee of Kenyatta National Hospital/University of Nairobi P.O BOX 20723-00100, Nairobi. Tel.no. 2726300/2716450.Ext 44102.

What will happen if I take part in this research study?

Before you begin the study, you will need to have an initial physical exam and tests to find out if you can be in the study. The physical exam will be done by the research nurse. These exams and tests are part of regular cancer care and are done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be decided by your study doctor. The exams and tests will include:

1. History and physical exam and an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself)

2. Blood tests to measure the function of bone marrow, kidney and liver.

3. You will be asked to give information about any other medications that you may be taking.

During the study:

If the exams and tests show that you can be in the study, and you willingly choose to take part, you will be randomly assigned into one of two study groups. Random assignment means that you will have an equal chance of being placed in either of the groups. Neither you nor your study doctor will be able choose the group you will be in.

The patients in one of the two study groups will receive Metformin tablets while the other group will receive the standard care. The treatments that both groups will receive are described in detail below.

After randomization:

The intervention group, group 1;

You will first receive a finger prick blood glucose test to record the starting baseline glucose levels. You will then receive your respective high-dose prednisone-based chemotherapy regimen as prescribed. You will be given 14 tablets of Metformin 850mg for a duration of 2 weeks. Afterwards, you will then be advised to take the Metformin 850 mg once a day, with the afternoon meal by a specified time. You will take this tablet once a day at the same time for a period of two weeks. During the 2 weeks, your blood sugar levels will be tested once in a week. This will be done on day 1 of the study and every 7 days after (on day 8 and day 15), using the glucometer kit

provided. The weekly tests will involve a prick on the finger to find out your blood glucose levels. The tests will be done by a qualified research nurse.

After the 2 weeks, you will be recalled back for another physical assessment, to check if the treatment is working correctly and there are no health issues arising that will prevent you from continuing with the study for another 2 weeks. Once you have been cleared for continuation based on the physical exam and interviews done by the nurse and the investigator, your blood glucose reading will be taken using the finger prick test and recorded. You will be given 28 tablets of Metformin 850mg for another duration of 2 weeks. You will be advised to take the Metformin 850 mg two times a day, with breakfast and evening meal, at a specified time. You will take this tablets two for a period of two weeks. During the 2 weeks, your blood sugar levels will be tested once in a week. This will be done on day 1 of the refill and every 7 days after (day 22 and day 29), using the glucometer kit provided. The weekly tests will involve a prick on the finger to find out your blood glucose levels. The tests will be done by a qualified research nurse.

The control group, group 2;

You will receive the standard care given to patients receiving high-dose prednisone at KNH. This will include the required chemotherapy treatment as well as any other the treatment provided during this duration. This may include which includes anti-ulcer drugs like omeprazole and calcium tablet supplements.

After the start of treatment, you will need to be checked on day 1, day 8, day 15, day 22 and day 29. This will include checking of blood sugar level tests using the finger prick method, vital signs monitoring like temperature, heart rate, respiratory rate and pulse as well as questions on your physical status. On day 22 of the study, blood tests to measure creatinine and lactate levels to check kidney and liver function will be done. Approximately 3-5 milliliters of blood will be drawn from you on day 22.

You will be asked to give information about any medications that you may be taking. You will also be asked about any side effects that you may be experiencing

Duration of the study

The treatment will be administered over 28 days for both groups. The study nurse and study cancer pharmacist will ask you to visit the office for follow-up examination and to collect the blood sugar readings at day 1, day 8, day 15, day 22 and day 29 after the start of treatment.

Can I stop being in the study?

Yes. You can decide to stop at any given time. Tell the study nurse and study cancer pharmacist if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

The clinic doctor and research team may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Research has shown that side effects may be mild. Your health care team may give you medicines to help lessen side effects. Metformin side effects rarely occur at the dose given to patients. It has a well-established and proven safety profile, with minimal side effects experienced.

Risks and side effects related to metformin tablets may include common and minor effects like diarrhoea, nausea ,flatulence, vomiting. Rare but serious side effects may include myalgia (muscle pain), malaise (feeling of uneasiness or discomfort), difficulty in breathing, increased sleepiness, hypotension (abnormally low blood pressure), and chills. For more information about risks and side effects, ask your study doctor.

Benefits of the study

Taking part in this study may or may not make your health better. There is proof though that metformin tablets can prevent the increase in blood glucose levels associated high-dose prednisone but strong evidence in our setting over its effect is not available yet. We do know that the information from this study will help researchers learn more about Metformin as a preventive treatment of high blood glucose level in patient undergoing prednisone-based chemotherapy for cancer. This information could help the doctor and the wider healthcare specialty to prevent high blood glucose and its complications in non-diabetic patients.

What other choices do I have if I do not take part in this study?

Your other choice will be to get or continue with your treatment for cancer without being in the study. Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Information will be kept in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. Your personal information may be given out only if required and authorized by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON-ERC). If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

What are the costs of taking part in this study?

You will not need to pay for any additional cost in this study, other than the usual cost involved in treating your cancer. The research will supply the metformin tablets and perform the additional laboratory test at no charge while you take part in this study. You will not be paid for taking part in this study but transport and lunch reimbursement will be considered for follow up session at Days 8, 15, 22 and 29.

Participant rights in the study

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You will still get your medical care from our institution. A copy of the signed Informed Consent form will be given to you

Complaints or concerns

Any concerns or complaints about the conduct of this study should be directed to:

Secretary, KNH/UoN

University of Nairobi, School of Pharmacy

P.O BOX 20723-00100, Nairobi.

Tel.no. 2726300/2716450.Ext 44102

Email: uonknh-erc@uonbi.ca.ke.

Any complaint will be investigated promptly and you will be informed of the outcome

This information sheet is for you to keep

Appendix 3A: Participant Consent form
Research Study Title

ASSESMENT OF THE EFFECTIVENESS OF METFORMIN IN PREVENTING PREDNISONE-INDUCED HYPERGLYCEMIA AMONG HEMATOLOGICAL CANCER PATIENTS AT KENYATTA NATIONAL HOSPITAL.

KNH/UoN-ERC Approval Number: P143/03/2018

Researcher's Name: Dr. Lucy Ochola

Researcher's Relationship to UoN/KNH: Postgraduate Student in Clinical Pharmacy, University of Nairobi.

Participant Consent

I have read the above consent form and understood it. The nature of the study has been explained to me. I voluntarily agree to participate in the study.

_____   _____   _____ / _____ / ____

Signature of Participant   Name (First name and Surname)   Year   Month   Day

Address: _____ Telephone: _____

Witness: _____

Investigator's statement

I, the undersigned, have explained to the participant the procedures to be followed in the study and the risks and benefits involved.

_____   _____   _____ / _____ / ____

Signature of Person Conducting   Name (First name and Surname)   Year   Month   Day

Consent Discussion

_____   _____   _____ / _____ / ____

Signature of Investigator   Name (First name and Surname)   Year   Month   Day

Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi. P.O BOX 30197-0400 Nairobi. Tel: 0789233372 or 0724778550; email: lucyochola@gmail.com

_____   _____   _____ / _____ / ____

Signature of Witness   Name (First name and Surname)   Year   Month   Day

Relationship   of   Witness   to   Research   Participant/investigator: _____

Appendix 2B (UTANGULIZI): Taarifa ya Mshiriki Utafiti
Mada Wa Utafiti

TATHMINI YA UFANISI WA DAWA YA METFORMIN KATIKA KUZUIA UPANZI WA KIWANGO CHA SUKARI UNAOHUHUSISHWA NA DAWA YA PREDNISONE KATIKA MATIBABU YA SARATANI YA DAMU KWA WAGONJWA WA KENYATTA.

Jina langu ni Dkt. Lucy Ochola, mwanafunzi wa uzamifu katika matibabu katika Chuo Kikuu Cha Nairobi. Napangia kufanya uchunguzi katika hospitali kuu ya Kenyatta. Hili ni jaribio la kikliniki na aina ya uchunguzi wa kiutafiti. Daktari wako atakueleza kuhusu jaribio la kikliniki. Jaribio hili hujumuisha tu wale watu wanaochagua kushiriki. Tafadhali tafakari kuhusu kushiriki kwako katika utafiti. Waweza kujadili na marafiki, familia yako au na daktari wako wa kibinafsi kuhusu uamuzi wako. Unaombwa kushiriki utafiti kwa maana unaugua saratani ya damu, na kama mojawapo ya matibabu yako, utapewa tiba ya saratani yaani kemotherapia iliyo na dawa iitwayo prednisone.

KWA NINI UTAFITI UNAFANYWA?

Madhumuni ya utafiti ni kutathmini ufanisi inayotokana na dawa ya metformin ya kupunguza kiwango cha sukari mwilini. Kiwango cha sukari mwilini huwa hupanda wakati dawa ya prednisone hutumika kwa matibabu ya saratani ya damu.

Utafiti huu unafanywa kutathmini kama dawa ya metformin ina ufanisi wa kuzuia upanzi wa kiwango cha sukari mwilini. Hili ni jambo la muhimu wakati kipimo cha juu cha dawa ya prednisone inatumika. Katika utafiti huu, utapata pamoja na kemotherapia, utaratibu wa matibabu ya dawa ya metformin au kiwango cha huduma cha kawaida inayopeanwa. Hutapata yote mawili.

NI WATU WANGAPI WATASHIRIKI UTAFITI?

Takriban watu hamsini na wasita watashiriki katika utafiti huu.

NANI ANAENDESHA UTAFITI?

Mtafiti: Dkt Lucy Akinyi Ochola, B.Pharm , Mwanafunzi wa Uzamifu katika Matibabu katika Idara ya Famasia na Mazoezi ya Ufamasia, Kitivo cha Ufamasia, Chuo Kikuu Cha Nairobi S.L.P 30197-0400 Nairobi. **Simu**: 0789233372/0724778550; Barua Pepe:lucyochola@gmail.com

Wasimamizi:

Dkt. David G. Nyamu: Mhadhiri, Idara Ya Famasia Na Mazoezi Ya Ufamasia. Kitivo Cha Ufamasia

Dkt. Eric M. Guantai: Idara Ya Famakolojia Na Ufamaknosia , Kitivo Cha Ufamasia

Dkt. Ireneweru: Naibu Chifu Mfamasia, Hospitali Kuu Ya Kenyatta

IDHINISHO LA MAADILI:

Utafiti utaidhinishwa na Kamati ya Maadili na Utafiti ya Hospitali Kuu ya Kenyatta pamoja na Chuo Kikuu cha Nairobi.S.L.P 20723-00100, Nairobi. Simu: 2726300/2716450.Ext 44102.

MATUKIO NI YEPI IWAPO NITASHIRIKI UTAFITI?

Kabla ya utafiti, unahitaji kufanyiwa uchunguzi na taratibu ya awali wa mtihani wa kimwili ili kujua iwapo unafaa kushiriki utafiti. Uchunguzi na taratibu hizi ni huduma za kawaida za saratani na huweza zikafanywa hata kama hutajiunga kushiriki katika utafiti. Iwapo umekuwa na huduma hizi hivi karibuni basi si lazima zirudiwe. Hili litategemea na ujuzi wa muuguzi wa utafiti. Uchunguzi na taratibu hizi zitahusisha:

1. Historia na uchunguzi wa kimwili, na tathmini ya uwezo wako kushiriki shughuli za kila siku (maswala kama; iwapo unaweza kujilisha, kuoga na kuvaa nguo).

2. Uchunguzi wa damu ili kupima nguvu kazi ya ini, figo na ombwe la mifupa.

3. Utaulizwa kutoa habari kuhusu matibabu yoyote uliyo nayo kwa sasa.

WAKATI WA UTAFITI

Kama uchunguzi,majaribio na taratibu utaonyesha kwamba una ari ya kushiriki na uamue kuhusika, basi utanasibishwa katika mojawapo ya makundi mawili. Kunasibishwa ina maana kuwa utawekwa katika aidha kundi kupitia bahati nasibu kwa nafasi sawa. Sio wewe wala daktari mtakao aamua kundi ambalo utakalonasibishwa. Wagonjwa katika mojawapo ya makundi mawili watapokea dawa ya metformin na wale katika kundi lengine watapokea kiwango cha huduma cha kawaida inayopeanwa. Matibabu yatakayopokewa na makundi yote mawili yatafafanuliwa kwa undani panapofuata hapa chini.

UKIWA KUNDI LA KWANZA (KUNDI ZUIZI):

Utaanza kwa kupokea kipimo cha sukari kwa chomo cha kidole ili kutathmini kiwango cha sukari unayoaanzia nayo. Kisha utapokea kiwango cha juu cha dawa ya prednisone ya kutibu saratani kama ipasaavyo. Utapewa tembe kumi na nne za dawa ya metformin chenye kipimo cha nguvu cha mia nane na hamsini kwa muda wa wiki mbili. Katika wiki hizi mbili, utatarajiwa kupimwa kiwango cha sukari mara moja kwa wiki. Hii itafanywa siku ya kwanza na baada ya kila siku saba kwa kutumia mashine ya sukari itakayotolewa (siku ya 8 na 15). Taratibu za wiki zitafanywa kupitia chomo kwenye kidole ili kutathmini kiwango cha sukari mwilini. Taratibu hii itafanywa na mtafiti muuguzi mwenye sifa ifaayo.

Baada ya wiki mbili, utafuatiliwa tena kufanya uchunguzi wa kimwili kuangalia iwapo matibabu yanaendelea ipasavyo na kwamba hakuna mambo yoyote ya kiafya yanayotokana yatakayokuzuia kuendelea kushiriki katika utafiti huu kwa muda wa wiki mbili zifautazo. Utakapopewa kibali cha

kuendelea na daktari wa utafiti, kipimo chako cha sukari kitachukuliwa kwa chomo kwenye kidole na kurekodiwa. Utapewa tembe ishirini na nane za dawa ya metformin chenye kipimo cha nguvu cha mia nane na hamsini kwa muda mwengine wa wiki mbili. Katika wiki hizi mbili, utatarajiwa kupimwa kiwango cha sukari mara moja kwa wiki. Hii itafanywa siku ya kwanza na baada ya kila siku saba (siku ya 22 na 29) kwa kutumia mashine ya sukari itakayotolewa. Taratibu za wiki zitafanywa kupitia chomo kwenye kidole ili kutathmini kiwango cha sukari mwilini. Taratibu hii itafanywa na mtafiti muuguzi mwenye sifa ifaayo.

UKIWA KUNDI LA PILI (KUNDI DHIBITI)

Utapokea matibabu ya kiwango cha huduma cha kawaida inayopeanwa hospitalini. Hii itahusisha upeanaji wa matibabu ya kawaida ya chemotherapia ya saratani yako pamoja na matibabu yoyote yanayopeanwa kwa muda huu. Hii inaweza kuhusisha dawa za kuzuia vidonda vya tumbo pamoja na virutubisho vya madini vya calcium.

Baada ya mwanzo wa matibabu, utahitajika utimiziwe majaribio na taratibu zifuatazo siku ya 1, siku ya 8, siku ya 15, siku ya 22 na siku ya 29 kufuatana: Kupimwa kiwango cha sukari kwa kutumia chomo kwenye kidole, kuangaliliwa dalili za mapigo ya moyo, nyuzi joto mwilini, mkimbio wa damu na kiwango cha kupumua zitaangaliwa kutambua ubatilifu wowote. Katika siku ya 22, uchunguzi wa damu kupima kiwango cha sumu itokayo kwa misuli (creatinine) ili kutathmini uwezo wa figo na wa kuchunguza ufanyaji kazi wa ini utatimizwa. Takriban kiwango kidogo cha millilita 3-5 ya damu itachukuliwa na muuguzi kwa ajili ya uchunguzi hizi za siku ya 22.

NI KWA MUDA UPI NITASHIRIKI UTAFITI?

Matibabu yatachukua siku ishirini na nane kwa makundi yote mawili. Wakati na baada ya matibabu ya kundi la 1 na la 2, daktari wa utafiti atakuuliza kutembelea ofisi kwa minajili ya ufuatilizi pamoja na kuchukua rekodi ya kiwango cha sukari siku ya 1, siku ya 8, siku ya 15, siku ya 22 na siku ya 29 kufuatana. Utatimiziwa uchunguzi wa damu siku ya 22 baada ya kuanza matibabu.

NAWEZA KUJIONDOA NA KUTOKA UTAFITI?

Naam, waweza kuamua kujionda wakati wowote. Mwambie daktari wa utafiti ikiwa una fikra za kujiondoa au kuacha utafiti. Atakueleza jinsi ya kujiondoa kwa usalama.

Daktari wa utafiti ana uweza wa kukusimamisha dhidi ya kushiriki wakati wowote iwapo anaamini ni kwa minajili ya manufaa yako, ikiwa huzingatii sharia au ikiwa utafiti umesimamishwa.

NI ATHARI UPANDE AU HATARI ZIPI NITARAJIE NIKISHIRIKI UTAFITI?

Waweza kupata madhara ukishiriki utafiti huu. Kila mmoja anayeshiriki ataangaliwa kwa makini iwapo kutatukia madhara yoyote. Hata hivyo watafiti hawafahamu aina zote za madhara zinazoweza kuibuka. Utafiti unaonyesha ya kwamba madhara zinaweza kuwa vya ukali kiasi.

Wahudumu wako wa afya wanaweza kupa madawa ili kupunguza madhara yoyote. Hata hivyo madhara ya dawa ya metformin ikipewa katika kiwango cha nguvu iliyopeanwa hutukia kwa nadra sana. Dawa ya metformin una uzuri wa kuimarishwa pamoja na wasifu bora wa usalama na madhara chache pekee yakishuhudiwa.

Hatari na madhara zinazohusiana na dawa ya metformin ni kama madhara ya kawaida na madogo ya kuharisha, kichefuchefu, gesi tumboni na kutapika. Madhara ya nadra lakini makubwa huwa maumivu ya misuli, kuhisi usumbufu, kupata shida ya kupumua, kuhisi usingizi zaidi ya kawaida, kupata kiwango cha chini cha shinikizo la damu na kuhisi baridi.

Kwa habari zaidi kuhusu hatari na athari upande, uliza daktari wako wa utafiti huu.

JE KUNA FAIDA ZA KUSHIRIKI UTAFITI?

Kushiriki kwako kwaweza kuboresha au kutoboresha hali yako ya afya. Thibitisho lipo kwamba dawa ya metformin lina uwezo wa kuzuia upanzi wa kiwango cha sukari yanayotukia wakati matibabu ya kiwango cha juu cha dawa ya prednisone inatumika lakini ushahidi dhibiti haupo katika mfumo wetu bado. Inajulikana lakini habari itakayo tokana na huu utafiti utawezesha watafiti kujua mengi kuhusu matibabu ya dawa ya metformin kwa kuzuia upanzi wa kiwango cha sukari yanayotukia wakati matibabu ya kiwango cha juu cha dawa ya prednisone kwa saratani ya damu. Matukio haya yataweza kusaidia daktari pamoja na huduma ya afya kijumla kueza kuzuia upanzi wa kiwango cha sukari na matatizo yake kwa wagonjwa wasio na sukari.

NI CHAGUO LIPI LINGINE NINALO KWA KUSHIRIKI UTAFITI?

Uteuzi wako mwingine ni kupata tiba ama huduma za saratani pasi na kushiriki zoezi la utafiti. Ongea na daktari wa utafiti kuhusu hiari zako kabla ya uamuzi wa kushiriki zoezi la utafiti.

JE TAARIFA KUHUSU AFYA YANGU ITAHIFADHIWA KWA SIRI?

Ujumbe huu utahifadhiwa katika hifadhi data iliyo na nambari ya siri(nywila). Tutahakikisha taarifa ya kibinafsi katika rekodi zako za matibabu imewekwa kwa kisiri. Hata hivyo hatuna hakikisho la siri kamilifu maana ujumbe wako wa kibinafsi waweza kuhitajika na Kamati ya Maadili na Utafiti ya Hospitali au Chuo Kikuu cha Nairobi. Iwapo taarifa ya utafiti huu imechapishwa au kuwasilishwa mbele ya makongamano ya kisayansi basi jina lako na ujumbe mwingine wa kibinafsi havitatumika.

GHARAMA NI ZIPI KATIKA UTAFITI?

Hutagharamia chochote ili uweze kushiriki katika utafiti huu ila malipo ya kawaida ya kibinafsi ya kemotherapia yako. Mwenye kufanya utafiti atagharamia dawa ya metformin katika utafiti huu pamoja na taratibu yoyote ya ziada wakati wote utakuwa skishiriki katik utafiti huu. Aidha hutalipwa kwa kushiriki uatafiti huu bali utafidiwa malipo ya usafiri ya siku za 8, 15, 22 na 29 au siku yoyote nyengine ya kufuatiliwa na daktari wa utafiti

HAKI ZANGU NI ZIPI IKIWA NITASHIRIKI KWA UTAFITI?

Kushiriki utafiti ni chaguo lako. Una uamuzi wa kushiriki au kutoshiriki katika utafiti. Ukiamua kushiriki pia waweza kujiondoa wakati wowote. Mbali na uamuzi unaochukua, hakutakuwa na adhabu yoyote kwako na hutapoteza mojawapo ya faida zozote za kawaida ya matibabu. Kujiondoa katika utafiti hautaathiri huduma zako za kimatibabu. Utaendelea kupokea huduma yako ya kimatibabu katika kituo chetu.

NITAFANYA NINI IKIWA NINA MALALAMISHI?

Malalamishi yoyote kuhusu mfumo wa utafiti huu yaelekezwe kupitia anwani ifuatayo:

Katibu, KNH/UoN-ERC

Chuo kikuu cha Nairobi, Kitivo cha Famasia

S.L.P 20723-00100, Nairobi.

Simu: 2726300/2716450.Ext 44102

Barua pepe: uonknh-erc@uonbi.ca.ke.

Lalamishi lolote litachunguzwa kwa haraka na utaarifiwa kuhusu uamuzi.

Kartasi hii ya taarifa ni yako kuihifadhi/kuiweka.

Appendix 3B (UTANGULIZI): Fomu ya Idhini ya Mshiriki
Mada ya Utafiti

TATHMINI YA UFANISI WA DAWA YA METFORMIN KATIKA KUZUIA UPANZI WA KIWANGO CHA SUKARI UNAOHUHUSISHWA NA DAWA YA PREDNISONE KATIKA MATIBABU YA SARATANI YA DAMU KWA WAGONJWA WA KENYATTA

Nambari ya Idhinisho: KNH/UoN-ERC: P143/03/2018

Jina la mtafiti : Daktari Lucy Akinyi Ochola

Uhusiano wa mtafiti na Chuo kikuu cha Nairobi au Hospitali kuu ya Kenyatta:

Mwanafunzi wa Uzamifu katika kozi ya Matibabu ya Famasia. Chuo kikuu cha Nairobi.

IDHINI YA MSHIRIKI UTAFITI.

Nimesoma na kuelewa fomu ya idhini iliopo hapo juu. Mfumo na sura ya utafiti imeelezwa kwangu ipasavyo. Kwa hivyo nakubali kujitolea na kushiriki utafiti kwa hiari bila kushurutishwa.

_____ _____ _____ / _____ / ____

Sahihi ya mshiriki utafiti   Jina (la kwanza na la familia) mwaka   mwezi   siku

Anwani: _____ Simu: _____

TAARIFA YA MCHUNGUZI

Mimi mwenye sahihi hapo chini, nimemweleza mshiriki katika utafiti kuhusu mbinu ambazo zitafuatwa katika uchunguzi na hata athari na manufaa husika.

_____ _____ _____ / ____ / ___

Sahihi ya msimamizi wa utafiti   Jina (la kwanza na la familia)   mwaka mwezi siku

MAZUNGUMZO YA IDHINI.

_____ _____ _____ / ____/ ___

Sahihi ya Mchunguzi   Jina (la kwanza na la familia)   mwaka mwezi siku

Idara ya Famasia na Mazoezi ya Ufamasia, Kitivo Cha Famasia, Chuo Kikuu Cha Nairobi.

S.L.P 30197-0400 Nairobi. Simu: 0789233372/0724778550; Barua Pepe: lucyochola@gmail.com

_____ _____ _____ / _____/_____

Sahihi Ya Shahidi   Jina(la kwanza na la familia)   mwaka mwezi   siku

Uhusiano wa shahidi na mshiriki utafiti au mchunguzi: _____

Appendix 4: Patient Information Card

Patient Code: _____

Research Study Title   **ASSESMENT OF THE EFFECTIVENESS OF METFORMIN IN PREVENTING PREDNISONE-INDUCED HYPERGLYCEMIA AMONG HEMATOLOGICAL CANCER PATIENTS AT KENYATTA NATIONAL HOSPITAL.**

KNH/UoN ERC Approval Number : P143/03/2018

Researcher's Name **:** **Dr.Lucy Akinyi Ochola**

Today, you received high-dose prednisone chemotherapy. You will be given necessary treatment during this study period. Indicate in the patient information card the details of any form of treatment you received during this period. You may provide further details of any effect experienced in the section provided. Please note that this recordings are very important in carrying out the study properly.

Day of Study	Name of drug given	Dose and strength of drug given	Time the drug was taken	Any effect experienced	Name of any drug taken that was not issued at the hospital	Dose of drug taken that was not issued at the hospital
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						

Call Your Nurse or Doctor if you:

- Myalgia (muscle pain),
- Malaise (feeling of uneasiness or discomfort),
- Difficulty in breathing,
- Hypotension (abnormally low blood pressure),
- Chills
- Increased thirst
- Headaches
- Fatigue (feeling tired or weak)
- Frequent urination
- Blurred vision (difficulty in seeing normally)
- Have any unexpected, or unexplained problems.
- Have any questions or concerns.

Contact details: Dr. Lucy Akinyi Ochola

0789233372 / 0724778550

The information on this card is selective and does not cover all possible side effects; others may occur. Please report any problems to the investigator.

Appendix 5: Eligibility Assessment Form

Study Name:	**Assessment of The Effectiveness of Metformin in Preventing Prednisone-Induced Hyperglycaemia among Haematological Cancer Patients at KNH**
KNH Medical Record Number:	
KNH-UoN ERC number:	
Date:	
Principal Investigator:	Dr. Lucy Akinyi Ochola

Complete this table with all inclusion/exclusion criteria listed in the provided study protocol

SUBJECT # _____				
INCLUSION CRITERIA *Must be "yes"*	**Yes**	**No**	**Location of supporting source documentation**	**Notes**
1. Patient is currently on or is being initiated on high dose steroid based chemotherapy (>30mg/day)	☐	☐		
2. Patient has a haematological cancer(ALL, NHL, HL and MM)	☐	☐		
3. Patients is aged 18 years and above	☐	☐		
4. Patient has adequate renal function (serum creatinine levels of <150umol/L and/or estimated glomerular filtration rate (eGFR) of >30mL/min per 1.73m²)	☐	☐		
5. Patient has adequate electrolyte balance (serum lactate levels <5 mmol/L)	☐	☐		
6. Patient has sufficient normal haemoglobin values	☐	☐		

7. Patient is willing to comply with the study protocol and has signed informed consent	☐	☐		
EXCLUSION CRITERIA *Must be "no"*	**Yes**	**No**	**Location of supporting source documentation**	**Notes**
1. Patient is on prednisone treatment for any other indication other than haematological cancers	☐	☐		
2. Patient has pre-existing diagnosed diabetes mellitus	☐	☐		
3. Patients has had recent exposure (less than 3 months) to metformin	☐	☐		
4. Patients has more than one cancer where the additional cancer is non-haematological	☐	☐		
5. Patient is on medication that may contribute to hyperglycaemia	☐	☐		
6. Patient has any significant electrolyte disturbances	☐	☐		
7. Patient has tissue hypoxia like cardiac or respiratory insufficiencies	☐	☐		
8. Patient consumes three or more alcoholic drinks per day	☐	☐		
9. Patient has any concurrent severe illness	☐	☐		
10. Patient is currently on any other antidiabetic therapy	☐	☐		
11. Patient has been recently exposed (6 months)or awaiting radiocontrast procedures	☐	☐		

Appendix 6: Drug Reporting Form

This form is provided to you, the research oncology pharmacist, to monitor and record the administration of metformin to the intervention group of this study. Please tick if the patient has received the intended number of drugs for the treatment and the time the dispensed drug was taken. Also, assess the patients' compliance by indicating in the table provided below.

Please note that this information is private and confidential and only **<u>YOU</u>** are allowed to have access to this form.

Patients Code Number	Day of the study	Number of tablets issued	Dose of metformin administered	Time metformin was taken	Participants' adherence	
					Yes	No
	1					
	7					
	15					
	22					
	29					

Appendix 7: Case Report Form

Participant's Initials	☐☐☐	Subject ID	☐☐☐☐☐☐☐	Date	☐☐ ☐☐ ☐☐

Day   Month Year

PARTICIPANT DEMOGRAPHICS

Subject KNH Medical Record Number ☐☐☐☐☐☐☐

Birthdate ☐☐ ☐☐ ☐☐

Date Month Year

First Name:
Middle Name (or initial):
Last Name:

Gender: (check one)

☐ Male
☐ Female
☐ Unknown or Not Reported

Ethnicity: (check one)

☐ Known
☐ Unknown

[_____] (Write)

Anthropometric

Height (cm): [____]

Weight (kg): [____]

Contact Information:

Address:	
City:	Country :
Phone Number: [____] ☐ Home ☐ Work ☐ Cell ☐ Other	Alternate Phone Number: [____] ☐ Home ☐ Work ☐ Cell ☐ Other	Email address:
Preferred method of contact:	

Form Completed By: _____ Date: _____

Checked By: _____ Date: _____

106

Participant's Initials				Subject ID								Date						

Day   Month Year

PARTICIPANT DEMOGRAPHICS

Emergency contact:

Name:		
Address:		
City:	Country:	
Phone Number: ☐ Home ☐ Work ☐ Cell ☐ Other	**Alternate Phone Number:** ☐ Home ☐ Work ☐ Cell ☐ Other	**Email address:**
Preferred method of contact:		

Marital status: (check one)

☐ **Single**   ☐ **Widowed**

☐ **Married**   ☐ **Separated**

☐ **Divorce**   ☐ **Partner**

Occupation: (check one)

☐ **Work outside the home**   ☐ **Homemaker**

☐ **Retired**

☐ **Other**   ☐ **Disable**

If you work outside the home, what is your occupation? _____

Form Completed By: _____ **Date:** _____

         Checked By: _____ **Date**: _____

Participant's Initials ☐☐☐ **Subject ID** ☐☐☐☐☐☐☐ **Date** ☐☐ ☐☐ ☐☐

Day   Month Year

PHYSICAL ASSESSMENT

Was any physical examination test done? ☐Yes   ☐No

Vital Signs	Temperature(Č)	Blood Pressure(mmHg)	Respiratory rate(beats/min)	Pulse(beats/min)	Date
Day 1					
Day 15					
Day 29					

Please comment on the findings during the participants' physical assessment

Day 1

Temperature _____

Blood pressure _____

Respiratory rate _____

Pulse _____

Describe the participants' general health status

_____

_____

Is the participant fit to start/continue with the study? ☐Yes   ☐No

If No, specify below: _____

_____

Form Completed By: _____ **Date:** _____

Checked By: _____ **Date**: _____

Participant's Initials [ ][ ][ ] **Subject ID** [ ][ ][ ][ ][ ][ ][ ] **Date** [ ][ ] [ ][ ] [ ][ ]

Day   Month Year

PHYSICAL ASSESSMENT

Please comment on the findings during the participants' physical assessment

| Day 15 |

Temperature _____

Blood pressure _____

Respiratory rate _____

Pulse _____

Describe the participants' general health status

_____

_____

Is the participant fit to start/continue with the study? ☐Yes ☐No

If No, specify below: _____

_____

Form Completed By: _____ **Date:** _____

Checked By: _____ **Date**: _____

Participant's Initials ☐☐☐ **Subject ID** ☐☐☐☐☐☐☐ **Date** ☐☐ ☐☐ ☐☐

Day Month Year

PHYSICAL ASSESSMENT

Please comment on the findings during the participants' physical assessment

Day 29

Temperature _____

Blood pressure _____

Respiratory rate _____

Pulse _____

Describe the participants' general health status

_____

_____

Is the participant fit to start/continue with the study? ☐Yes   ☐No

If No, specify below:

_____

_____

Form Completed By: _____ **Date:** _____

Checked By: _____ **Date**: _____

Participant's Initials	☐☐☐	**Subject ID**	☐☐☐☐☐☐☐	**Date**	☐☐	☐☐	☐☐
					Day	Month	Year

MEDICAL HISTORY

Please provide the following information regarding your medical history:

Past Medical History

Condition	Present			
Diabetes, if yes, please specify child or adult onset	☐ Yes	☐	☐ Child	☐ Adult
High Blood Pressure	☐ Yes	☐		
Seizures/Epilepsy	☐ Yes	☐ No		
Blood Transfusions	☐ Yes	☐ No		
Cancer: if yes, what type?	☐ Yes	☐ No		
Heart Disease: **if yes**, what type?	☐ Yes	☐ No	_____	
Lung Disease: **if yes**, what type?	☐ Yes	☐ No	_____	
Kidney Disease: **if yes**, what type?	☐ Yes	☐ No	_____	
Thyroid Disease: **if yes**, what type?	☐ Yes	☐ No	_____	
Liver Disease: **if yes**, what type?	☐ Yes	☐ No	_____	
Emotional Problems/Depression: **if yes**, please explain?	☐ Yes	☐ No	_____	
Weight Loss: **if yes**, please specify weight loss in pounds?	☐ Yes	☐ No	_____	
Weight Gain: **if yes**, please specify weight gain in pounds?	☐ Yes	☐ No	_____	

For Women Only:

Currently having any monthly periods? ☐ Yes ☐ No ☐ Postmenopausal Date of last menstrual period
Are you pregnant? ☐ Yes ☐ No   If yes, what is your due date?
Are you breastfeeding? ☐ Yes ☐ No

Form Completed By:_____**Date:**_____

Checked By: _____ **Date**:_____

Participant's Initials ☐☐☐   **Subject ID** ☐☐☐☐☐☐☐   **Date** ☐☐ ☐☐ ☐☐

<div style="text-align:right">Day   Month Year</div>

MEDICAL HISTORY

Allergies:

Do you have any Allergies to Medicine(s)?   Yes ☐   (If "Yes", please describe below)   No ☐

Medication	Reaction

Form Completed By: _____ **Date:** _____

Checked By: _____ **Date**: _____

Participant's Initials	☐ ☐ ☐	Subject ID	☐ ☐ ☐ ☐ ☐ ☐	Date	☐ ☐	☐ ☐	☐ ☐
					Day	Month	Year

SOCIAL HISTORY

Tobacco Use:

Do you use Tobacco?   ☐ Yes   ☐ No

Cigarettes?   ☐ Current   ☐ Past   Year Quit? _____

Number of cigarettes per day?

Chewing Tobacco?   ☐ Current   ☐ Past   Year Quit? _____

Number of times used per day? _____

Drug Use:

Have you used any IV drugs / "street" drugs (cocaine, marijuana)?   ☐ Yes   ☐ No

If "Yes", When? _____   If "Yes", What drug(s)? _____

Do you currently use it?   ☐ Yes   ☐ No

How often?   ☐ Daily   ☐ Weekly   ☐ Monthly   ☐ Occasionally

Alcohol Use:

How many drinks do you usually have a week? _____		
Have you ever felt that you should cut down on your drinking?	☐ Yes	☐ No
Have people annoyed you by criticizing your drinking?	☐ Yes	☐ No
Have you ever felt bad or guilty about drinking?	☐ Yes	☐ No
Have you ever taken a drink the first thing in the morning to steady your nerves or to get rid of a hangover?	☐ Yes	☐ No

Form Completed By: _____ **Date:** _____

Checked By: _____ **Date**: _____

Participant's Initials				Subject ID								Date						

Day   Month Year

FAMILY HISTORY

Please provide the information below regarding your family:

Do you have any medical condition that runs in your family? ☐ Yes   ☐ No

Condition	Relationship to family member (mother, father, brother, sister, child etc.)

Family Cancer History

Has any of you family members suffered from any type of cancer?   ☐ Yes   ☐ No

If yes, please provide details below:

Relationship to family member   _____   _____

The name of the cancer   _____   _____

The duration of cancer (months/years)   _____   _____

Treatment status   _____   _____

    _____   _____

Treatment outcome (resolved/stopped/   _____   _____

continuing)

Any adverse event experienced?   ☐ Yes   ☐ No   ☐ Yes   ☐ No

Form Completed By:_____**Date:**_____

Checked By: _____ **Date**:_____

Participant's Initials ☐☐☐ **Subject ID** ☐☐☐☐☐☐☐ **Date** ☐☐ ☐☐ ☐☐

Day   Month Year

MEDICATION HISTORY

Current Medication

Medication	Indication	Route	Frequency	Drug Dose		Date		
				Dose	(unit dose)	Day	Mon	Year

Form Completed By: _____ **Date:** _____

Checked By: _____ **Date**: _____

Participant's Initials			Subject ID								Date						

Day   Month Year

MEDICATION HISTORY

Previous Medication History

Medication	Indication	Dosage Schedule				Duration	Start Date		
		Route	Frequency	Dose	Unit Dose		Day	Mon	Year

Herbal and Supplement Medication History

Type of Herb/Supplement	Indication	Dosage Schedule				Duration
		Route	Frequency	Dose	Unit Dose	

Form Completed By: _____ **Date:** _____

Checked By: _____ **Date**: _____

116

Participant's Initials ☐☐☐ **Subject ID** ☐☐☐☐☐☐☐ **Date** ☐☐ ☐☐ ☐☐

Day Month Year

LABORATORY ASSESSMENT

Please provide information on the following laboratory tests

Were any laboratory tests done on the participant? ☐ Yes ☐ No

Lab Parameter	Serum Creatinine(umol/L)	Serum Lactate (mmol/L)	Liver function tests		Vitamin B12 levels(pg/ml)
			AST(Units/mL)	ALT(Units/mL)	
Day 1					
Day 15					
Day 29					

Please comment on the laboratory results obtained

_____

_____

_____

_____

Were the laboratory test results normal? ☐ Yes ☐ No

If No, provide the details below:

_____

_____

Form Completed By:_____ **Date:**_____

Checked By: _____ **Date**:_____

Participant's Initials ☐☐☐   **Subject ID** ☐☐☐☐☐☐☐   **Date** ☐☐ ☐☐ ☐☐

Day Month Year

HYPERGLYCEMIA ASSESSMENT

Please provide the information on capillary blood glucose measurements required:

Date			Day	Metformin Dose (mg)	Capillary Blood Glucometer Reading(mmol/L)	
Day	Mon	Year			Fasting blood sugar	2hour Post prandial blood sugar
			1			
			8			
			15			
			22			
			29			

Please comment on the capillary blood glucose results obtained

_____

_____

_____

Were the capillary blood glucose readings obtained normal? ☐Yes ☐No

If No, pleases comment below: _____

_____

_____

Form Completed By: _____ **Date:** _____

Checked By: _____ **Date**: _____

118

Participant's Initials ☐☐☐   **Subject ID** ☐☐☐☐☐☐   **Date** ☐☐ ☐☐ ☐☐

Day　Month Year

ADVERSE EVENTS

Please provide details of any adverse event experienced by the participant below:

Occurrence of adverse outcome? ☐ Yes ☐ No

If yes, specify below _____

_____

_____

General comment on adverse event(s)

_____

_____

Action taken in regard to the specific adverse event

_____

_____

_____

_____

Participant status

_____

_____

Plausibility of metformin as the causative agent? ☐ Yes ☐ No

If yes, provide reasons _____

_____

Form Completed By: _____ **Date:** _____

Checked By: _____ **Date**: _____