PROPORTION, PRECIPITATORS AND PROGNOSTIC MARKER OF 30-DAY HEART FAILURE READMISSION AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET,KENYA.

BY

GAMAR SALIM BAJABER

A RESEARCH THESIS SUBMITTED TO THE SCHOOL OF MEDICINE IN PARTIAL FULFILLMENT FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE IN INTERNAL MEDICINE, MOI UNIVERSITY.

DECLARATION

I declare that this is my original thesis and to the best of my knowledge it has not been presented for an award of a university degree or any academic credit in any other university or research institution.

Student Declaration

Dr. Gamar Salim Bajaber

SM/PGM/10/16

Department of Medicine

Moi University, School of Medicine

Signature ..... Date 1/9/2020

Supervisors' Declaration

We submit this proposal for marking with our approval as university supervisors.

Dr. Constantine Akwanalo

Consultant Physician/Cardiologist

Moi Teaching & Referral Hospital

Moi University,School of Medicine

Signature ..... Date 01-09-2020

Dr. Shamim M. Ali

Consultant Physician/Lecturer

Department of Medicine

Moi University, School of Medicine

Signature ..... Date 1/9/2020

HEAD DEPARTMENT OF MEDICINE
MOI UNIVERSITY SCHOOL OF MEDICINE
P. O. Box 4606, ELDORET 30100

DEDICATION

I dedicate this work to my family for their love and support. Special dedication to my late dad for his huge support through every mile of this life's journey.

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ABBREVIATION OF TERMS

AHA	American Heart Association
BNP:	Brain natriuretic peptide
CBC	Complete Blood count
CCU	Cardiac care unit
DM	Diabetes mellitus
ECG	Electrocardiogram
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HTN	Hypertension
IREC	Institutional Review and Ethics Committee
KNH	Kenyatta National Hospital
LFT	Liver function test
MI	Myocardial Infarction
MTRH	Moi Teaching and Referral Hospital
NT pro-BNP	N-Terminal pro brain natriuretic peptide
SSA	Sub Saharan Africa
UECS	Urea, electrolytes and creatinine
USA	United States of America
USD	United State Dollar

OPERATIONAL DEFINITION OF TERMS

Heart failure was defined as per the modified Framingham criteria(Mahmood & Wang, 2013) . The diagnosis of heart failure was based on 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.

Major criteria:

- Paroxysmal nocturnal dyspnea
- Neck vein distention
- Rales
- Radiographic cardiomegaly (increasing heart size on chest radiography)
- Acute pulmonary edema
- S3 gallop
- Increased central venous pressure (>16 cm H2O at right atrium)
- Hepatojugular reflux
- Weight loss >4.5 kg in 5 days in response to treatment

Minor criteria:

- Bilateral ankle edema
- Nocturnal cough
- Dyspnea on ordinary exertion
- Hepatomegaly
- Pleural effusion
- Tachycardia (heart rate>120 beats/min.)

Decompensated heart failure: presentation with sudden or gradual onset of the signs or symptoms of heart failure requiring hospitalization (Joseph, Cedars, Ewald, Geltman, & Mann, 2009)

HF Classified as :

HFrEF: Ejection fraction <40%

HFpEF: Ejection fraction>50%

NT pro BNP: Pre discharge NT-pro BNP drawn from a vein at the point of index discharge.

Outcomes: Death and readmission within 30-days post discharge

Smoking definition as per NHIS: (Ryan, Trosclair, & Gfroerer, 2012)

Nonsmoker: has not consumed 100 cigarettes in a life time

Current Smoker: participant has consumed> 100 cigarettes in a life time, and smokes every day or somedays

Former smoker: consumed >100 cigarettes in a lifetime but doesn't smoke even on somedays /everyday

Alcohol consumption as per National Institute on Alcohol abuse and alcoholism:(Halanych et al., 2010)

Never drinkers: had never drank alcohol at baseline

Former drinkers: no alcohol in previous year but had drunk in the past

Current drinkers: >14 drinks/week for men and >7 drinks/week for women

Precipitators: Factors leading to readmission in decompensated heart failure included

- **Anemia**: As per WHO, Hemoglobin of <12g/dl women and <13g/dl in men
- **Acute kidney injury:** KDIGO more than 1.5 times increase in creatinine from index discharge.
- **Pneumonia:** Defined as per infectious disease society of America/American thoracic society consensus guidelines: Presence of radiological chest infiltrates correlated with clinical findings of fever, cough, chest pain and dyspnea. This was confirmed by a study dedicated radiologist who was blinded to the precipitators
- **Arrhythmia**: Rhythms other than sinus, with rates < 60 or > 100 bpm on ECG at readmission
- **Acute coronary syndrome:** A spectrum of presentation with WHO cardiovascular risk score of >20%, typical history of angina pectoris, typical ECG changes and/or abnormal cardiac troponins.
- **Adherence to self-care behavior:** European heart failure self-care behavior scale A score of > 58,considered compliant (reliability of 0.9)
- **Uncontrolled Hypertension :** Blood pressure >140/90 despite medication

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ABSTRACT

Background: Heart failure (HF) affects 26 million people globally. It is associated with a high 30-day readmission rate due to multiple cardiovascular and non-cardiovascular precipitants. Readmissions are associated with high mortality, which may be predicted by pre-discharge N-terminal pro brain natriuretic peptide (NT-proBNP). There is no data on HF readmission rates, its precipitators and use of NT-proBNP as a prognostic marker at Moi Teaching and Referral Hospital (MTRH) in Western Kenya.

Objective: To determine the 30-day proportion of HF readmission, the precipitators of HF and the association between NT-proBNP and 30 days' readmission.

Methods: This was a six-month prospective cohort study where we carried out a census and recruited adult participants admitted with HF at Moi Teaching and Referral Hospital. At discharge from hospital, an interviewer administered questionnaire was administered and blood samples for NT-proBNP drawn. Upon readmission, precipitators for HF were identified and compliance to therapy assessed using European heart failure Self Care Behavioral Scale. Continuous variables were summarized using median and IQR, categorical variables using frequencies and percentages. Associations were determined using Chi square, Fishers exact and Wilcoxon rank test. A p-value of <0.05 was considered statistically significant.

Results: From April to November 2018, 94 participants were recruited into the study; with median age 48 years (IQR 31,70), 58 (62%) were female, 35 (38%) consumed alcohol and 25(25%) smoked. Hypertension was the commonest comorbidity 20 (21%) while cardiomyopathy was the underlying etiology for HF in 58 (63%). HF with reduced Ejection Fraction (HFrEF) was present in 76% of the participants while 24% had HF with preserved Ejection Fraction (HFpEF). Sixty percent of the participants had NT-proBNP levels of >4137 pg/ml, which implied poor prognosis. Of 17 readmitted patients, 12 participants (12.8%) were readmitted within 30 days at MTRH. Six (6.4%) participants were lost to follow up. Median time to readmission was 14 days, (IQR 7, 26). Pneumonia (55%) was the commonest precipitator of HF readmissions, followed by arrhythmias (atrial fibrillation) in 5 (42%), anemia 4 (33%), noncompliance 4 (33%), acute kidney injury 2 (16.6%) and no identified precipitator 1 (8.3%). There was no association between NT-proBNP and readmission (p =0.584) or NT-pro BNP and survival (p=0.773). Readmission was associated with a high mortality (p=0.008) with 50% of readmitted participants dying during the readmission period. The total mortality of both readmitted and non-readmitted participants was 16% at the end of the 6 months' study period.

Conclusions: In this cohort of participants with HF the proportion of 30 days readmission was high. Infections, mainly pneumonia was the commonest precipitator of readmission. Discharge NT-proBNP did not predict likelihood of 30 days' readmission. Mortality was higher among participants readmitted within 30 days.

Recommendations: Measures like pneumoccal vaccinations should be implemented to prevent pneumonia. Early appointments to cardiac clinic (less than 2 weeks post discharge) should be given to screen for precipitators and reduce HF readmissions. A follow up study to assess % change in NT pro BNP in relation to 30 days readmission.

CHAPTER ONE: INTRODUCTION

1.1 Background information

The American Heart Association (Yancy et al., 2017) defines HF as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance; and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema. European Society of cardiology defines HF as a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress (Ponikowski et al., 2016).

Decompensated heart failure refers to the onset of symptoms in heart failure that was previously controlled(Yancy *et al*., 2013). It is defined as sudden or gradual onset of the signs or symptoms of heart failure requiring unplanned office visits, emergency room visits, or hospitalization(Joseph, Cedars, Ewald, Geltman, & Mann, 2009).

Heart failure affects 26 million people worldwide and in the United States (US) and Europe ,it is associated with more than 1 million hospitalizations annually (Khan et al., 2015); however, eighty percent of the HF burden lies in low and middle income countries (LMIC) (Damasceno et al., 2012). In the developed world, the prevalence of heart failure is estimated to be 13% (Damasceno *et al.,* 2012); whereas in sub Saharan Africa (SSA) the pooled prevalence is about 39.5% (Agbor *et al.*, 2018). In Kenya, data from a hospital based study estimates prevalence at 7.5%(Kamau, 2009).

Deaths from cardiovascular diseases have risen by 14.5% between 2006-2016 (GBD 2017). In SSA, heart failure is one of the major contributors to the burden of cardiovascular diseases, with non-ischemic causes being the commonest *(*Carlson *et al.*, 2017). The attributable inhospital mortality rate for decompensated heart failure in SSA is estimated to be 8.3% (Kraus, Ogunbanjo, Sliwa, & Ntusi, 2016).

The economic burden imposed by heart failure is driven by hospitalization and mortality; for instance, the cost of treating decompensated heart failure is approximated at 12000 USD per admission in the USA. Cumulatively the economic burden is projected to amount to a total of 70 billion USD by 2030 (Hammond, Smith, Lee, Honein, & Quidley, 2016) . Despite the introduction of new medications for heart failure, post-discharge mortality and readmission rates in developed countries such as the US have not changed (Khan *et al*., 2015).In SSA the economic ramifications are even higher; for example, a study conducted in Nigeria in 2009 estimated the cost of treating heart failure at 2128 USD per patient per year (Ziaeian & Fonarow, 2016)..

Although heart failure readmissions are well documented in developed countries, there is paucity of data from resource limited settings. Worldwide, HF readmission rates within 3 to 6 months of discharge range between 27-47% (Michalsen, König, & Thimme, 1998). The THESUS-HF survey estimated a 15% sixty day readmission rate for patients with decompensated HF in sub-Saharan Africa (Damasceno *et al.*, 2012). However, readmission rates as high as 50% have been reported for patients with heart failure in Africa, with most readmissions occurring within 30 days post discharge (Hernandez et al., 2013). In SSA the limited published data that is available describes a readmission rate ranging between 13 -25 % (Agbor et al., 2018); whereas in Kenya, a KNH study found that 29.5% of HF patients were re-hospitalized once,

6.2% re-hospitalized twice and 2.3% were re-hospitalized thrice. The reported average duration from discharge to readmission was 69 days (Kamau, 2009). Similarly, in Muhimbili National Hospital in Tanzania, 50% of the cases of discharged heart failure patients were readmitted due to decompensated heart failure within 6 months of their previous discharge (Maro & Makule, 2009).

In SSA HF mortality rate was 8.3%(Callender et al., 2014) . In Kenya, a study carried out in KNH showed heart failure mortality rate at 33.5% (Kamau, 2009). A study conducted in USA Alabama by Cherinne et al.,showed that in patients readmitted within 30 days of discharge,all cause mortality was at 41% in the readmitted group and 27% in the nonreadmitted group within a 2 to 12 month follow up period.(Hazards ratio 1.89 pvalue< 0.001).This indicates that readmission increases mortality rate.(Arundel et al., 2016) .A study conducted in Taiwan by Tung et al, showed that patients readmitted within 30 days had a higher mortality rate within a 6 months follow up period when compared to patients who were not readmitted.(Tung et al., 2016)

There are several factors that predispose a patient to decompensated heart failure. These include; Cardio-Vascular (CV) causes such as treatment noncompliance (to drugs or diet), cardiac ischemia, cardiac arrhythmia, uncontrolled hypertension or worsening disease. Non-CV causes include; infections especially pneumonia, anemia, acute renal failure, and sometimes no identified factors (Fonarow et al., 2008)(Platz *et al.*, 2018) (Michalsen *et al.,* 1998). In a Berlin study, non-compliance to medication was the most common precipitator of readmission (Michalsen et al., 1998). Similarly, in a study conducted at the Muhimbili National Hospital in Tanzania, the most common predictor was also noncompliance (Maro & Makule, 2009).

The 30-day temporal threshold for assessing readmission related outcomes has important clinical significance, it is during this time bracket when HF related mortalities and future readmissions can be prevented through optimal in-hospital care of admitted cases.Thirty-day readmission is the timing of special interest because it is when, if readmitted and managed well, mortalities and future readmissions are preventable (Hernandez *et al.,* 2013).A study conducted in Alabama showed that 1 in 4 HF patients under medicare insurance cover,were readmitted within 30days,hence focus on the precipitators of readmission within the 30 day time frame will reduce the economic burden associated with HF readmissions.(Arundel et al., 2016)This study also indicated that 30 day readmission was associated with further readmissions and prolonged hospital stay upon readmission. Use of NT pro BNP in guiding treatment and prognosis can help reduce HF readmissions.

NT pro BNP,a biomarker released from the cardiac ventricles,has been used for diagnostic and prognostic purposes as well as guiding treatment in heart failure patients.As a diagnostic marker it has a 94.5% sensitivity and 90.6% specificity (Lee-Lewandrowski *et al.,* 2007). High NT-pro BNP levels are associated with an increase in all-cause mortality and readmissions (Bettencourt *et al*., 2004). Using NT-pro BNP to guide treatment can aid in reducing the HF related hospital readmissions and mortality. A study conducted in Canada showed that knowledge of NT-proBNP results reduced the duration of emergency department(ED) visits by 21% (6.3 to 5.6 hours; P=0.031), the number of patients re-hospitalized after 60 days by 35% (51 to 33; P=0.046), and direct medical costs of all ED visits, hospitalizations and subsequent outpatient services (USD 6129 to USD 5180 per patient; P=0.023) (Moe, Howlett, Januzzi, Zowall, & Canadian Multicenter Improved Management of Patients With Congestive Heart Failure (IMPROVE-CHF) Study Investigators, 2007).

Bettencourt and colleagues showed that an NT-proBNP of more than 6779 pg/mL at presentation predicted a trend towards hazard for readmission or mortality, but the discharge NT-proBNP value of 4137 pg/mL was a much stronger predictor of hazard, with an 8% increase in the likelihood for death or readmission over 6 months per 1000 pg/mL of NT-proBNP over this threshold (P<.0001)(Januzzi, Maisel, Silver, Xue, & DeFilippi, 2012). Variations during hospitalization and pre discharge NT-pro BNP levels are predictors of hospital readmission and death within 6 months of discharge from hospital. Fifty percent reduction change in NT pro BNP (from admission and at discharge) was associated with less readmissions and mortality (Bettencourt *et al.,* 2004). A 30 day heart failure readmission risk score in South East Asia used discharge NT-pro -BNP as one of the 7 independent predictors of 30 days heart failure readmission (Leong *et al.*, 2017).

To this end, this study aimed at determining the precipitators of heart failure, frequency of readmission and utility of pre discharge NT-pro BNP in predicting the propensity for readmission during the care of heart failure patients in our setting.

1.2 Problem statement

Heart failure is associated with a high 30-day readmission rate. In Sub Saharan Africa readmission rates for heart failure have been documented to be ranging between 15% and 50%. HF readmissions are not only associated with a high morbidity & mortality but also increased cost of care. The cost implications have been reported as USD 2128 per patient per year in SSA. However; despite all this, data on frequency, precipitators and prognostic markers of HF readmissions haven't been appropriately described in our setting and remains unknown at MTRH as well as the rest of Kenya.

1.3 Justification of the study

Heart failure is a common diagnosis in our set up with observed high readmission rates, but no documentation to this effect. Readmission in heart failure is associated with increased morbidity and mortality, and increased cost of treatment. Additionally, there is limited data on the precipitators and frequency of readmission rates among patients with heart failure. Furthermore, use of dicharge NT-pro BNP levels, a simple test that can be performed by the patient's bedside, in predicting heart failure readmissions is unknown in our setting. This study will yield knowledge on proportion, precipitators and the association of discharge NT pro BNP as a prognostic marker of HF readmissions which may help during the development of strategies aimed at reducing HF associated readmissions, mortality and morbidity.

1.4 Research Questions

1. At MTRH, what proportion of heart failure patients get readmitted within 30 days of discharge from hospital?
2. At MTRH, what are the precipitators of 30-day readmission among heart failure patients?
3. What is the association between discharge NT pro BNP levels and 30-day heart failure readmission at MTRH?

1.5 Objectives

1.5.1 Broad Objective

To determine the frequency and precipitators of 30-day heart failure readmission at Moi Teaching and Referral Hospital (MTRH), and explore the association thereof between discharge NT pro BNP and 30-day heart failure readmission at MTRH, Eldoret

1.5.2 Specific Objectives

1. To determine the proportion of heart failure readmissions within 30 days of discharge at MTRH.
2. To determine the precipitators of 30-day HF readmission at MTRH
3. To explore the association between discharge NT-pro BNP levels and 30-day HF readmission at MTRH.

CHAPTER TWO: LITERATURE REVIEW

2.1 Burden of heart failure

Heart failure has been noted in the 20th century to increase the burden of cardiovascular disease especially due to urbanization There are approximately 5.7 million American adults with a diagnosis of heart failure (HF), with an estimated 1 million hospitalizations annually for HF exacerbations. (Ziaeian & Fonarow, 2016). HF admissions are about 9.4-42.5% of all medical admissions in SSA(Nyaga *et al.*, 2018). Heart failure has a prevalence of about 5.7% in sub-Saharan Africa and 13%in Europe and USA. The rate of 60 days readmission from the THESUS-HF survey was 15% in sub-Saharan Africa (Damasceno et al., 2012). Inpatient cost of treatment of heart failure in SSA is about 2128 US dollars per year (Agbor *et al.*, 2018). This has led to a greater burden in the economy which was initially due to communicable diseases, but now is due to both communicable and non-communicable disease (Damasceno et al., 2012). In Africa, non-communicable diseases are on the rise, diverting from the previous trend of a burden of communicable diseases. Cardiac diseases are second to communicable diseases in the mortality list (Damasceno *et al.*, 2012) In Kenya, in-hospital research studies carried out at KNH by Barasa *et al* in 2008 and Kamau et al in 2009, found a prevalence of HF in that study period to be 5.7-7.5% (Kamau, 2009) while another study showed a pooled prevalence in SSA as 39.5% (Agbor *et al.*, 2018).

The rate of hospitalization has not changed significantly since the beginning of the decade, with up to 50% of patients readmitted within 6 months (Hammond et al., 2016). In Muhimbili National Hospital in Tanzania , 50% of the cases of discharged heart failure patients were readmitted due to decompensated heart failure within 6 months of their previous discharge (Maro & Makule, 2009). In Nairobi Kenya, in a

study conducted at KNH on outcomes of heart failure after discharge, 29.5% of the patients studied were re hospitalized once, 6.2% were re-hospitalized twice and 2.3% were re-hospitalized thrice. Average duration from discharge to readmission was 69 days (Kamau, 2009). Little is known about acute and chronic HF in sub-Saharan Africa (Damasceno *et al.*, 2012). Precise data on precipitators of readmission are not available in Kenya.

2.2 Precipitators of readmission

Some of the clinical precipitators of decompensated heart failure that were found in different studies include; noncompliance to drugs or diet, cardiac ischemia, inadequate preadmission treatment, cardiac arrhythmia, miscellaneous factors (pneumonia, hyperthyroidism, acute renal failure). Noncompliance was the most common cause of decompensation in a study conducted in Berlin teaching hospital leading to a conclusion that 54% of cases of HF decompensation could be prevented (Michalsen et al., 1998). Some of the clinical predictors of decompensated heart failure that were found in the CHARM study included the following cardiovascular precipitators; noncompliance to drugs or diet 10%, cardiac ischemia 8%, cardiac arrhythmia 15%, worsening HF 7% and uncontrolled hypertension at 2%. Non CV precipitators included; respiratory infections 10%, renal failure 4%, anemia 2%, unidentified factors at 14% (Platz et al., 2018). In Muhimbili National Hospital, the causes were poor compliance and patients not being empowered about their condition together with failure of clinical reviews after discharge (Maro & Makule, 2009).

A study conducted at KNH to assess treatment of heart failure, adverse drug reactions and determinants of adherence, revealed that only 63.9% of patients were adherent to their medication. Only 17% of the patients in this study had received tertiary education (Kimani, Karimi, Opanga, & Bosire, 2016).

2.3 NT pro BNP

Brain natriuretic peptide (BNP) is a hormone, released from the ventricles in the heart but was discovered in the brain. Cleavage of the prohormone proBNP produces biologically active 32 amino acid BNP as well as biologically inert 76 amino acid N-terminal pro-BNP (NT-pro BNP). NT-pro BNP has a longer plasma half-life than BNP, 120 minutes in the former and 20 minutes in the latter. Natriuretic peptides have a diuretic, natriuretic and hypotensive effect. They also inhibit the renin-angiotensin system, endothelin secretion, systemic and renal sympathetic activity. Among patients with HF, increased secretion of ANP and BNP may partially counteract the effects of norepinephrine, endothelin, and angiotensin II, limiting the degree of vasoconstriction and sodium retention (wilson s colucci & horng H chen md, 2017)

In normal subjects, the plasma concentrations of BNP and NT-pro BNP are similar (approximately 10 pmol/L). NT-pro BNP has been found to be useful in the evaluation of a patient presenting with dyspnea in the acute setting.

2.4 NT-pro BNP Uses

NT-pro BNP aids in facilitating cost effectiveness. In the IMPROVE-CHF study of 500 patients presenting to emergency departments with dyspnea were randomly assigned to usual care alone or with inclusion of guidance by NT-pro BNP. This study showed that adding NT-pro BNP to clinical judgment enhanced the accuracy of diagnosis, reduced the duration of the emergency department visits (5.6 versus 6.3 hours), the number of patients re-hospitalized within 60 days (13 versus 20 percent), and direct medical costs of all emergency department visits, hospitalizations, and subsequent outpatient services(USD 5180 versus USD 6129 per patient) (Moe et al., 2007).The AHA 2017 HF guideline has supported the use of NT-PRO BNP in the

diagnosis of heart failure, though still more research is needed to inform guidelines on its use as a prognostic marker.(Yancy et al., 2017).NT-pro BNP can be used in the diagnosis of heart failure in the primary care setting and the accuracy of diagnosis of heart failure improved from 49 to 71% when NT-pro BNP was used in comparison to other diagnostic modalities for heart failure (wilson s colucci & horng H chen md, 2017). NT-pro BNP also aids in determining prognosis. In the COPERNICUS study, median NT-pro BNP level was 1767pg/ml. Patients who had levels above this median had higher all-cause mortalities and hospitalizations with heart failure.(Hartmann *et al., 2004)*.

Bettencourt and colleagues showed that an NT-pro BNP level of more than 6779 pg/mL at presentation predicted a trend towards hazard for readmission or death, but the post-treatment NT-pro BNP value of 4137 pg/mL was a much stronger predictor of hazard, with an 8% increase in the likelihood for death or readmission over 6 months per 1000 pg/mL of NT-pro BNP over this threshold (P<.0001). Also NT-pro BNP has a diagnostic and prognostic role, higher NT-pro BNP levels are associated with an increase in all-cause mortality and readmissions .Variations in NT-pro BNP levels during hospitalization and pre-discharge NT-pro BNP levels are predictors of hospital readmission and death within 6 months of discharge of hospitalized HF patients.(Bettencourt *et al.,* 2004).

Additionally, post treatment NT-pro BNP provides more evidence on prognosis and readmission than the admission NT-pro BNP (Januzzi *et al.,* 2012). Based on this evidence, we used discharge NT-pro BNP in this study to assess its association to readmission.

2.5 Readmission and mortality

HF readmissions are highly associated with mortality.This is seen in the study from KNH which showed an association between re-hospitalization and increased mortality risk of 30% (Kamau, 2009) A study conducted in USA Alabama by Cherinne et al.,showed that in patients readmitted within 30 days,all-cause mortality was at 41% in the readmitted group and 27% in the nonreadmitted group within a 2 to 12 month follow up period.(Hazards ratio 1.89 pvalue< 0.001).This indicates that readmission increases mortality rate especially one year following discharge.(Arundel et al., 2016).A study in Taiwan by Tung et al showed that post 30 day readmission mortality was at 26% in the readmitted group vs 20% in the nonreadmitted group within a 6 month follow up period.(Tung et al., 2016)

CHAPTER THREE: METHODOLOGY

3.1 Study setting

This study was carried out at the medical inpatient wards (male and female) and Cardiac Care Unit (CCU) of Moi Teaching and Referral Hospital, Eldoret. MTRH is the second largest public referral hospital in Kenya with an 800-bed capacity. MTRH serves as a referral facility for western Kenya, some parts of Eastern Uganda, South Sudan and Tanzania. It has a catchment population of about 20.8 million.((2019 Kenya Population and Housing Census Volume I: Population by County and Sub-County - Kenya National Bureau of Statistics, .). The hospital also serves as a teaching facility for medical undergraduate and post-graduate students. On average, the medical wards admit approximately 11 patients and CCU admits approximately 15 patients with heart failure in a month. This was based on recorded hospital data for the month July 2017.

3.2 Study population

All adult patients discharged after management for heart failure. These patients were followed up for readmission in MTRH medical wards and CCU within 30 days from the date of discharge.

3.3 Study design

This was a prospective cohort design.

3.4 Sampling technique

Census was implemented between April and November 2018.

3.5 Sample size

The aim of the study was to determine the proportion of participants readmitted due to heart failure within 30 days of discharge at MTRH. Data from the KNH study showed

that among the patients treated and discharged due to heart failure, 29.5% were re-hospitalized once (Kamau, 2009).

To be 95% sure that we report the proportion of re-hospitalization within plus or minus 5% of the reported value at the KNH study, we determined the sample size using the following formula (Cochran, 1963).

$$Z = \left(\frac{Z_{1-\alpha/2}}{d}\right)^2 \times P \times (1-P)$$
$$= \left(\frac{1.96}{0.05}\right)^2 \times 0.295 \times (1-0.295)$$
$$= 320$$

Where Z_c is the quantile of the standard normal distribution corresponding to c x 100% percentile, c = (1-a/2), "a" is the type I error, d is the margin of error, and P is the proportion re-hospitalized due to heart failure.

Since this study had a 30 day follow up period, we anticipated that we will likely have loss to follow up participants. No study has reported this rate. Hence to protect our study from the possibility of ending up with a smaller sample size we inflate it by 10% as follows;

$$\left(\frac{n}{1-r}\right) = \left(\frac{320}{1-0.1}\right) = 356.$$

Data collection for this study was done over a period of 6 months. At MTRH, we anticipated up to 26 heart failure patients being discharged every month. This gave us approximately 156 HF patients over the period of data collection. The 156 patients included those with cor pulmonale as the hospital records pools them under heartfailure diagnosis. 156 patients were less than the calculated sample size.

For the explorative association in objective 3, there were two independent variables, mortality and readmission. Using Peduzzis formula,

n = $10 \times \frac{k}{p}$ where k is the number of indendent variables,which is 2,p is the proportion of rehospitalisation from KNH ,29.5%. n for the associations objective was 67.7, with a 10% anticipated loss to follow up, n=74.

Since both calculated sample sizes were less than 356 as per fishers formula, a census was conducted within the six months' period of April to November 2018.

3.6 Eligibility criteria

3.6.1 Inclusion Criteria

1. All Patients discharged after management for heart failure
2. All patients above 18 years of age who consented

3.6.2 Exclusion Criteria

1. Pregnant women.
2. End Stage Renal Disease
3. Underlying active malignancy / on chemotherapy
4. Immobility from stroke, fractures
5. Participants with Chronic Obstructive Pulmonary Disease and asthma, pulmonary embolism and/or Cor Pulmonale

   The above participants were excluded because End stage renal disease,Chronic obstructive pulmonary disease,Asthma Cor pulmonale and pulmonary embolism elevate NT- pro BNP levels, hence were excluded in this study to avoid confounding the results.Malignancy,and immobility has an effect on survival and also recovery of heart failure patients hence would have affected our survival data hence the exclusion.

3.7 Recruitment procedure

From the 20th of April 2018 to 20th October 2018, participants were identified on a daily basis, i.e. heart failure patients in the medical wards and CCU of MTRH; among the identified cohort of patients, I consecutively approached those who fulfilled the eligibility criteria for consenting. These were patients who had been deemed clinically fit for discharge by the primary physician. All patients who consented to be part of the study were recruited into the study at the time of discharge and assigned a unique study identification number. Study was completed at the end of November 2018 as a follow up of participants discharged in October 2018.

3.8 Study procedure

Immediately after recruitment, all participants were interviewed by the primary investigator using an interviewer administered questionnaire. This initial questionnaire which was administered at the time of recruitment was used to obtain socio-demographic, clinical, medication history, laboratory parameters, Echo findings, etiology of heart failure, NT-Pro BNP levels, discharge medications and the date of discharge.

The date of discharge and dates corresponding to day 15 and day 30 post-discharge, were also recorded in a virtual ledger. Calendar reminders corresponding to these dates were then set so as to facilitate timely follow-up of participants when assessing for readmission and mortality.

At days 15 and 30 after discharge, participants were followed up by phone to check if they got readmitted to hospital due to heart failure. These time periods were purposefully selected so as to coincide with the 2-week and 1-month cardiac clinic follow up appointment schedules routinely given to patients at the time of discharge.

In addition to follow up by phone, we also sought out for participants who were readmitted within 30 days of discharge from hospital during our daily ward and CCU surveillance.

For all the readmitted participants in decompensated HF, we administered a second questionnaire. This questionnaire assessed for presence/absence of precipitators which were not present at index discharge and led to decompensation. echocardiography, ECG, chest x-ray and laboratory findings were recorded in this questionnaire.

When seeking out for precipitators of heart failure, we only sought out for seven specific precipitators as advised by previous published research papers which included: 1) anemia, 2) acute kidney injury, 3) infections, 4) arrhythmia either new or worsening prior arrythmia if the rate is >100, 5) acute coronary syndrome and 6) adherence to self-care behavior 7) Uncontrolled hypertension

Participants who were readmitted in another facility were recorded as readmitted, but precipitators could not be obtained due to ethical limitations at other facilities which are not under MTRH/Moi University IREC catchment. The study procedure is further highlighted in Figure 1below.

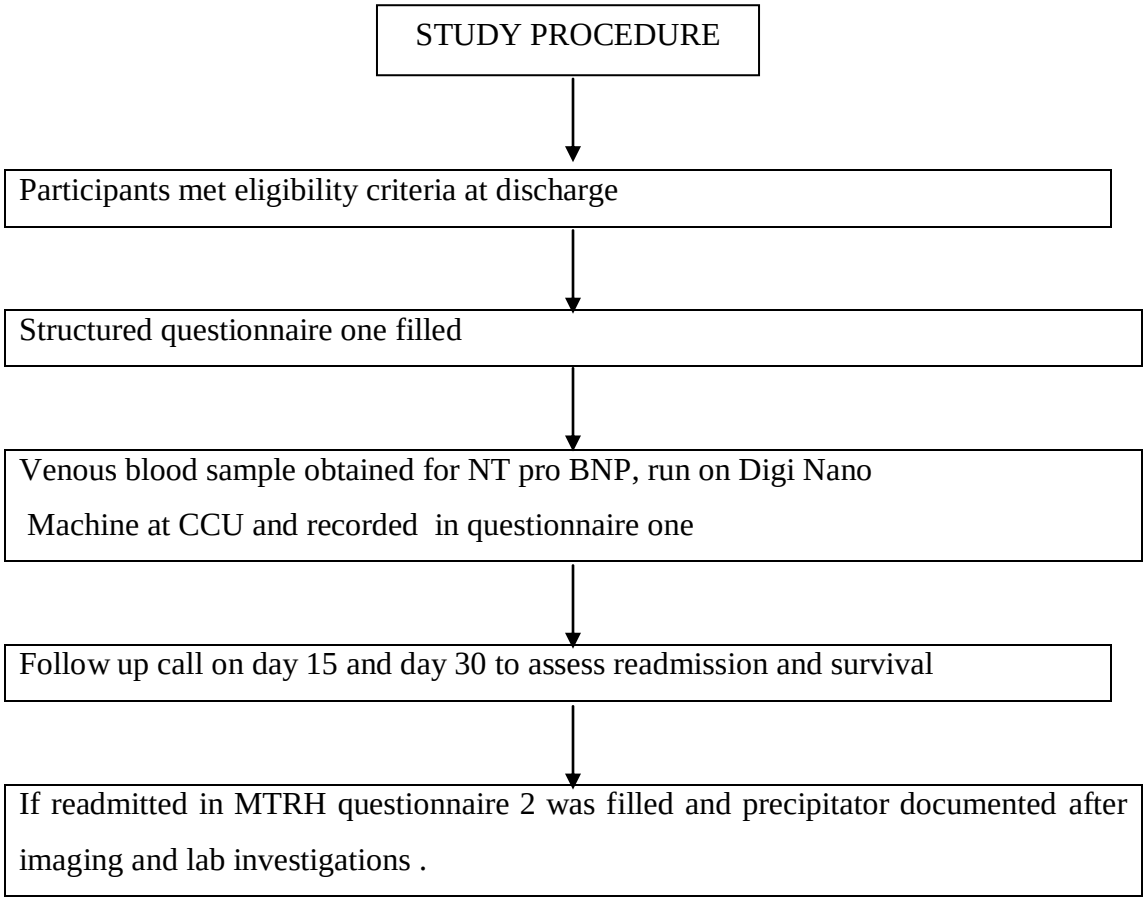

Figure 1: Study procedure

3.8.1 Measurements.

3.8.1.1 Echocardiography, ECGs and chest x-rays

Echocardiography examinations were conducted by certified MTRH sonographers using a 2D CFX 50 Echo machine. All echocardiography examinations were done at the MTRH echo lab/bedside and data recordings were reposited in a study dedicated archive. The following echocardiography parameters were collected: 1) ejection fraction which was assessed using the formula of $\frac{LVEDD-LVESD}{LVEDD} * 100 = Fraction\ of\ shortening * 2 = EF$, LVEDD is left ventricular end diastolic dimensions,LVESD is left ventricular end systolic dimensions 2) valve morphology and function assessed by color doppler,direct area measurements,planimetry,pressure half time.3) chamber morphology, dimensions measured by the echo machine 4) pulmonary pressures assessed by Bernoulli's equation, in addition to tricuspid regurgitation velocity and in addition to right atrial pressure and collapsibility of inferior venacava..

12 lead ECGs were done by certified MTRH technicians and the tests conducted at the MTRH Echo lab. All echocardiography and ECG results were re-evaluated by a board certified consultant cardiologist who was blinded to the study recruitment process.The consultant cardiologist assessed the echo messurements included LVESD, LVEDD, chamber morphology,valve morphology and area measurements,EF,TAPSE,pulmonary pressures.ECG was assessed by the cardiologist for arrhythmias and ST changes.

Posterior – anterior view Chest x-rays were conducted using an analog machine located at the MTRH radiology department. All chest x-ray imaging was done by certified technicians at the MTRH radiology department and interpreted by MTRH consultant radiologists who were also blinded to the study recruitment process.

3.8.1.2 Blood test measurements

Four millilitres of venous blood samples were obtained from a visible vein in the anterior cubital fossa and put in an EDT vacutainer bottle for discharge NT pro-BNP measurements. Discharge NT pro-BNP was assayed using a portable point of care FDA approved Digi Nano machine in CCU,details in appendix 7. The Digi Nano strips were paid for by the primary investigator. A small pipette was used to draw blood from the vacutainer and drops of blood were placed in the NT pro BNP cartridge. The cartridge was then placed in the calibrated machine. The machine was calibrated every morning using a calibration cartridge that was bought with the machine. The machine took at least 15 minutes to display the results. Further details on the machine are in appendix 7. Results were recorded in the first questionnaire. The NT pro BNP results of all participants were obtained at the time of discharge and recorded in the first questionnaire. For participants who did not have baseline workups Chest X-ray or Echo/ECG, they were paid for by the primary investigator.

3.8.1.3 Historical data obtained from patient charts.

Blood test results obtained during routine clinical care at the time of admission to hospital were recorded from the patient's files. These included urea, sodium, potassium and chloride electrolytes; liver function tests; urinalysis; complete blood count; lipid profile and cardiac troponins for patients who presented with chest pain and in whom troponins were warranted. Precipitators documented by the primary team caring for the patient were counterchecked by the primary investigator and supervisor after all lab and radiological and clinical data were obtained.

3.9 Data collection and management

Data was collected in the form of interviewer administered structured questionnaires. One at index discharge and one at readmission within 30 days' post discharge. Results of NT pro-BNP performed at primary discharge were recorded in the first questionnaire. Participants' medical records were reviewed and relevant clinical and laboratory data obtained and entered into the data collection form/structured questionnaire1 and 2. Demographics of the target population included: age, gender, weight, height, other comorbidities (hypertension, diabetes), education level, underlying documented cause of heart failure at initial admission, medication patient discharged with at initial discharge, Echo and ECG findings, laboratory results including NT pro BNP and UECS were documented on questionnaire 1/Data collection form 1.On day 15 and day 30, participants were contacted by phone to check if they were readmitted. ECG, Echocardiography, CXR, urea electrolytes and creatinine, urinalysis and complete blood count results were recorded for all patients readmitted within 30 days in Questionnaire 2/data collection form 2.Adherence ,upon readmission ,was assessed using the European heat failure selfcare and behavior scale.(Jaarsma, Arestedt, Mårtensson, Dracup, & Strömberg, 2009). Precipitators were identified and documented as per primary team and after discussion with my supervisors.

Proportion of readmission was determined by the number of patients readmitted among those discharged with heart failure at MTRH. We also determined the time between index discharge and readmission in decompensation.

The above gathered data was stripped-off of patient identifying information and entered into a developed electronic database (epidata). The database was password protected and confidentiality maintained at all levels. Back-up of the data was done

using external drives and memory sticks and kept in separate locations to cushion against data loss. Completeness and consistencies were checked regularly and/or as need arose. Once the data was completely converted into the electronic database, the questionnaires were kept in a cabinet under a lock, and access was possible to the principal investigator alone. They will be shredded after six years from the date of publication of the findings.

3.9.1Data Analysis and Interpretation

Data analysis was done using STATA version 15. NT pro-BNP levels on initial discharge was treated as an independent variable, heart failure readmissions, and mortality was treated as dependent variable. Categorical variables i.e. gender, NT pro BNP, HFrEF, HFpEF, discharge medications, were summarized using frequencies and percentages. Continuous variables i.e, age, time to readmission, duration of hospitalization, were summarized using median and IQR. Associations among dependent variables (like readmission, mortality) and independent variables like NT pro BNP was done using chi square /fishers exact/ wilcoxon rank sum test.

3.10 Ethical consideration

Approval was sought from MTRH/Moi University Institutional Research Ethics Committee (IREC) before the study commenced. Permission to conduct the study was also obtained from the management of Moi Teaching and Referral Hospital.

All the participants were notified about the purpose of the study and politely asked without any coercion to give a signed written informed consent before participating. The questions were designed to address the research objectives properly and respect the privacy and confidentiality of the participant. Data management practices that ensured adequate confidentiality were maintained and these included storing data in key locked cabinets, password coded databases and consenting in private consultation room. There was no direct financial benefit or compensation for participating in the study. Sound clinical judgement was applied in all stages and aspects of this research. No participants were denied medical care if they declined to participate in the study. Those who consented to participate were allowed to withdraw at any time they wished.

CHAPTER FOUR: RESULTS

A total of 143 participants discharged with heart failure were screened between April and October 2018 and 49 were excluded.6 participants were lost to follow up.

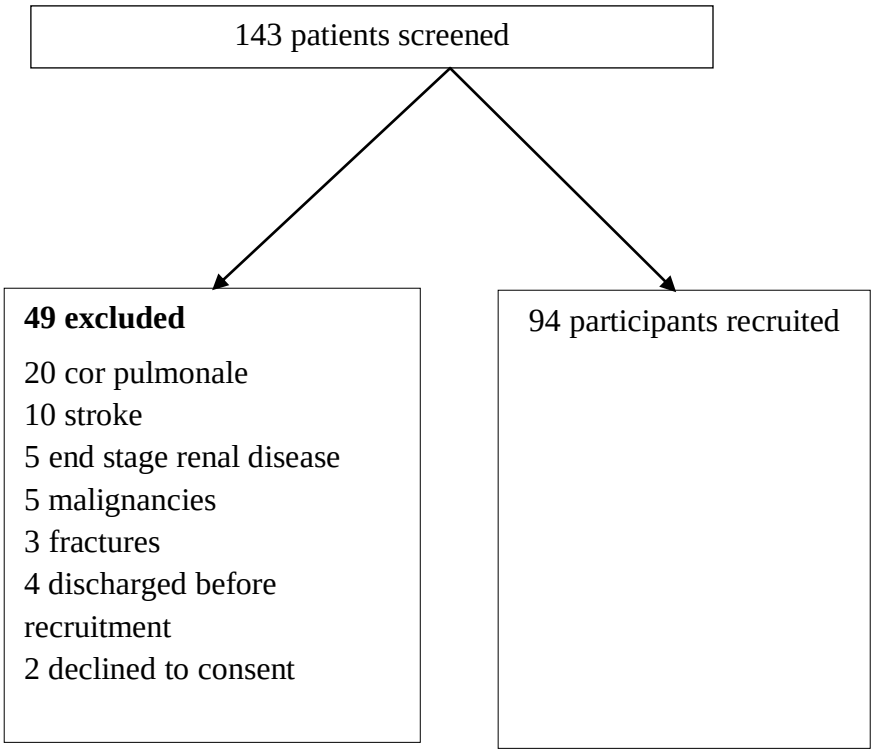

Figure 2: Subject recruitment flow chart

4.1Demographic Characteristics

Among the participants recruited, 36 (38.3%) were males with a median age of 48 (IQR 31,70). The participants level of education was mostly primary school level 44 (46.8%). Eleven (12%) were current smokers and 13 (13%) were current alcohol consumers.

4.2Clinical characteristics

Table 1: Demographic characteristics of participants discharged from MTRH with heart failure

Characteristic	Frequency n=94
Median Age, (IQR)	48 (31,70)
Female n (%)	58 (61.7)
Level of Education n (%)	
None	26 (28)
Primary	44 (47)
Secondary	20 (21)
Tertiary	4 (4)
Social History n (%)	
Alcohol	25 (38)
Smoking	24(25)
Nonsmokers/nonAlcohol consumers	45 (37)
Comorbidities n (%)	
Diabetes Mellitus	8 (9)
Hypertension	20 (21)
Dyslipidemia	2 (2)
HIV positive	5 (5)
No comorbidities	64(63)
Diagnosis of heart failure in years' n (%)	
newly diagnosed	42(44.7)
1-5	42(44.7)
5-10	3(3.2)
10 -15	5(5.3)
15-20	2(2.1)

Upon discharge (at recruitment), the mean duration of hospital stay for the participants was 11 days (IQR 6-13). The participants had a return visit to outpatient clinic scheduled within 2 weeks from date of discharge.

4.3 Etiology of Heart Failure

Among the participants, the most common documented causes of heart failure were cardiomyopathies, followed by rheumatic heart diseases as shown in graph 1 below. *cardiomyopathies include restrictive cardiomyopathy 1, pacemaker induced cardiomyopathy 1, dilated cardiomyopathy 56 and HIV related cardiomyopathy 1.The classification of etiology of HF was based on that documented by the primary physician.

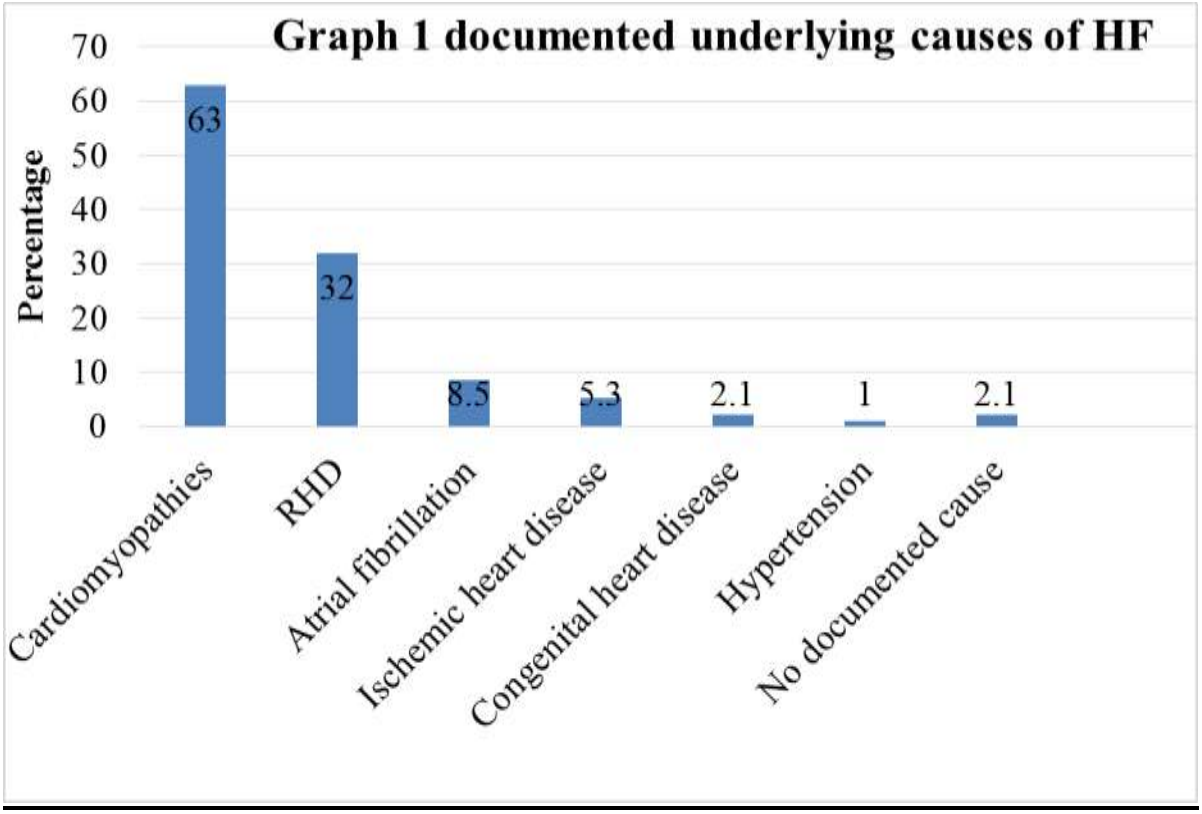

Figure 3: Graph showing documented underlying causes of HF

4.4 Laboratory Findings

Among the participants, the median creatinine level was 84 (IQR 64,103). All participants had a 2 dimensional echocardiography performed. Majority of the participants had heart failure with reduced ejection fraction (HFrEF) as shown in the table 2 below. The median pulmonary pressures were 62.5mmHg (IQR 50,76). Commonly prescribed medications at discharge were furosemide (lasix) and less frequently were beta blockers.

Table 2: Clinical characteristics of patients discharged with heart failure at MTRH

Variable	Frequency/Median
Pulmonary pressure median (IQR)	62.5 (50,76)
Ejection fraction n (%) HFpEF HFrEF	 22 (23.4%) 72 (76.6%)
NT pro BNP n (%) <20 20-15000 >15000	 10 (10.6%) 68 (72.3%) 16 (17%)
NT pro BNP (pg/ml) n (%) <4137	 35(39.7)
>4137	53 (60.2)
Creatinine Median (IQR)	84 (64,103)
Discharge Medication summary n (%) Diuretics: Lasix Metolazone	 82 (87%) 3 (0.03%)
spironolactone	49 (52%)
Beta blockers	35 (37.2%)
ACEI/ARB	59 (62.8%)
Warfarin	28 (29.8%)
Digoxin	21 (22%)

Table 3: Discharge clinical charachteristics of MTRH readmitted participants n=12

Years since diagnosis	cut off NTproBNP Pg/ml	Underlying etiology as per echo	Classification based on EF
0-5 years 9 Newly diagnosed 3	>4137 5 <4137 7	RHD 6 DCM 5 Arrythmia 1	HFrEF 9 HFpEF 3

4.5 Proportion of 30 days' readmission

Out of the 94 participants discharged with a diagnosis of heart failure, 17(18%) were readmitted within 30 days. Median time to readmission was 14 days IQR (7,26). Twelve (70.6%) of these 12 patients were readmitted at MTRH, a proportion of 12.8%,5 participants were readmitted in other facilities. We were unable to reach 6 participants on follow up.

Table 4 :Clinical findings at readmission

Variable	**Median/ Freq**	**IQR**
Systolic BP	90.5	88.5, 108
Diastolic BP	60	55, 66.5
Pulse	101.5	91,123
Spo2	93.5	91,95.5
NYHA class	**N**	**%**
2	1	8.33
3	2	16.67
4	9	75
CVS risk score	**N**	**%**
10	11	91.67
20	1	8.33
Outcome after readmission		
Died	6	50
Discharged Alive	6	50

4.6. Common precipitators of readmission

The most common precipitator of readmission among participants readmitted to hospital was infections (92%), followed by arrythmias as shown in graph 2 below. Infections encompassed 55% (6) pneumonia, pulmonary TB 27% (3), urosepsis 8.3% (1), unknown source 8.3% (1). The type of arrhythmia observed was atrial fibrillation. ACS and uncontrolled hypertension 0 participants.

Graph 2. Precipitators of readmission in heart failure at MTRH

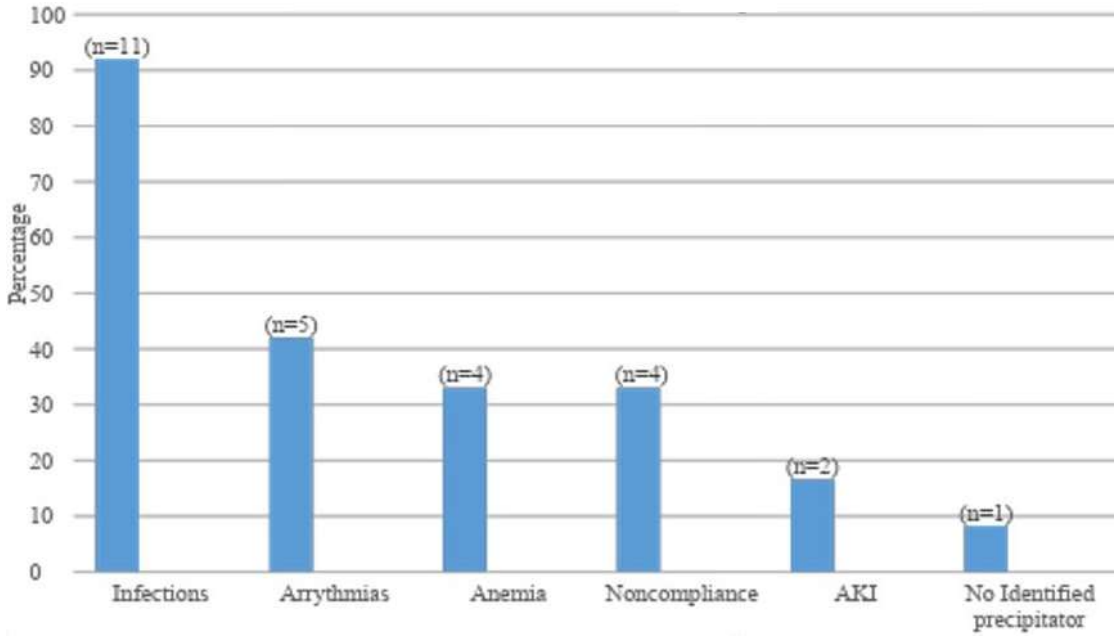

Figure 4: Precipitators of readmission in heart failure at MTRH

4.7 Association between NT-pro BNP levels and 30-day readmission at MTRH.

There was no statistically significant association between NT pro BNP and readmission (p-value 0.160) or mortality (p-value 0.728). From previous studies, a cut off NT pro BNP of 4137 has been associated with mortality and readmission. Therefore, to assess further whether there was an association, we used this NT pro BNP cut off in our analysis.

Among 55 (56%) participants with a discharge NT pro BNP of more than 4137 pg/ml, 4 (7.3%) were readmitted in MTRH. Out of the 39 participants who had NT pro BNP less than 4137, 8 (20.5%) got readmitted in MTRH within 30 days of discharge. Among the 12 patients readmitted at MTRH,4, (33.3%) had NT pro BNP more than 4137, and 8 (66.7%) had NT pro BNP less than 4137.There was also no association between NT pro BNP and duration of stay in the hospital prior to discharge (p-value 0.462), readmission or mortality as shown in Table 4 below.

Table 5: Association between discharge NT-pro BNP and readmission and mortality among patients with heart failure

NT-ProBNP (pg/ml)	**Re-admission**		**P value**
	Yes	**No**	0.584[1]
<4137	8 (22.86)	27 (77.14)	
>4137	9 (16.98)	44 (83.02)	
Survival			
	Alive	**Dead**	
<4137	30 (85.71)	5 (14.29)	0.773[1]
>4137	43 (81.13)	10 (18.87)	
Duration of stay in days	9 (6,13)	9 (6,21)	0.462[2]
Duration of stay and NT pro BNP			
	<4137	>4137	0.104 [2]
Duration of stay	9 (6,16)	5(8,13)	

*1 Fishers' exact 2 Wilcoxon rank sum test

We excluded 6 patients who were not reachable hence not possible to ascertain their readmission status.

4.8 Association between readmission and mortality

There was an association between readmission and mortality where mortality was higher among participants readmitted within 30 days (p 0.008) as shown in table 5 below.

Table 6. Association between readmission and mortality among patients readmitted with heart failure

Readmission	Outcome		Fishers' exact p-value
	Alive	Dead	
No	63 (88.73)	8 (11.27)	0.008
Yes	10 (58.82)	7 (41.18)	

4.9 Patients 30days Outcome

Out of the participants recruited, 73 (78%) were alive and 15 (16%) died by the end of30 days. Six (6%) participants were lost to follow up and thus their status was unknown. Out of the 12 participants readmitted within 30 days at MTRH, 6 (50%) died before discharge.

CHAPTER FIVE: DISCUSSION

The mean age of the participants was 51 years and was almost similar to a study in KNH (Ogeng'o, Gatonga, Olabu, & Ogeng'o, 2014). These results are in agreement with Damasceno et al's (Damasceno *et al., 2012)* findings, who reported that HF occurs 2 decades earlier in the black population than in Caucasians where it was found to occurr at a mean age of 72 years.. Similarly, Ponikowski et al also stated that in SSA, patients with heart failure are mostly below the age of 55 years (Ponikowski *et al.,* 2014).This age disparity could be due to the varied regional causes of heart failure, where ischemic heart disease is the most common etiology in the developed countries, whereas cardiomyopathies (HIV associated and peripartum) and rheumatic heart diseases which have onset occur at much younger ages, are more prevalent in Africa.(Callender et al., 2014)

The education status of our participants was low with majority having primary school education at 47% and 28% had no previous education. This is almost similar to a study conducted in Muhimbili Hospital in Tanzania which reported that 53.6% participants had primary school education and 21% had no formal education (Maro & Makule, 2009). The level of education is important as it has been documented to contribute to noncompliance among HF patients increasing their likelihood for readmission (Kimani *et al*., 2016).This could be due to the fact that patients with higher literacy level have been found to have better health seeking behavior . A study conducted in Ethiopia however, found no association between level of education and HF behavior and treatment adherence ,but rather an association between HF knowledge and adherence.(Sewagegn & Fekadu, 2015)

The most common documented cause of heart failure in this study was cardiomyopathy at 58%. Similar findings have been previously reported from studies conducted in KNH and Muhimbili hospital in Tanzania (Ogeng'o et al., 2014)Maro & Makule, 2009). In 2016, Bloomfield et al, also found cardiomyopathy to be the most common etiologic entity underlying heart failure among patients admitted in MTRH (Bloomfield et al., 2016).

Our overall 30 days' readmission rate was 18%. 12.8% of the participants were readmitted in MTRH, while others were readmitted in other hospitals. It was concluded to be a high readmission rate in comparison to THESUS-HF study(Damasceno et al., 2012) that had a 60-day readmission rate of 9.1%, vs 12.8% 30 days readmission in this study.

This was somewhat lower compared to proportions reported from other studies in the region. For instance; in a study done in KNH re-hospitalization rate was 49.2% but this was over a period of 12 weeks post-discharge as opposed to the 30 days which was assessed in this study. While the difference in proportions could be attributed to the time difference between these two studies, it could also be due to the fact that the study was conducted in 2009,currently there is improved management in terms of HF treatment (Kamau, 2009). Our readmission rate was similar to a study conducted by Michtalik et.al in John Hopkins Hospital, which was assessing changes in NT-pro BNP during hospitalization and risk of readmission and mortality in heart failure patients. The readmission rate was 13% after 30 days (Michtalik *et al.*, 2011) . A post hoc analysis of the EVEREST Trial revealed a 30-day readmission rate of 5.7% (Khan et al., 2015). However, the EVEREST trial only looked at patients with HFrEF. OPTIMIZE HF study had a readmission rate of 29.6% in the 60-90 day follow up for outcomes (Fonarow *et al.*, 2008) The difference in our rate vs OPTIMIZE-HF could

be due to pooled data from multi-facilities in OPTIMIZE-HF, and the longer follow up period. We chose to assess 30 days' readmission because several studies showed that most outcomes in heart failure occur within 30 days (Januzzi *et al.,* 2012).

In this study, the most common precipitator of readmission was infections at 92%, with pneumonia (55%) being most common. This is similar to what has been reported from Muhimbili teaching hospital in Tanzania (Maro & Makule, 2009) where out of 97 patients admitted over a 6 months period, 62.9% were readmitted due to infections (pneumonia, PTB, malaria, HIV). Similarly, the CHARM study showed that among non cv precipitants reported, respiratory infections were the commonest (Platz *et al.*, 2018). Furthermore, pneumonia was also the most common precipitator of readmission in the OPTIMIZE-HF study, albeit at much lower rates (15.3%). OPTIMIZE-HF was conducted across 259 US hospitals between years 2003 and 2004 (Fonarow *et al.,* 2008). The difference in the proportions of infection between our study and the two other studies, is that our study looked at precipitators of readmission within 30 days of discharge, while the CHARM and OPTIMIZE studies looked at precipitators retrospectively at the point of admission hence introducing the possibility of precipitator ascertainment bias. Although healthcare associated infections are defined as infections that occur 48 hours or more after hospital admission or within 30 days after discharge from hospital (Haque, Sartelli, McKimm, & Bakar, 2018) from our study we cannot deduce whether the pneumonia patients presented with at readmission was hospital /health care associated or community acquired. A systematic review done by Calvillo et al showed that community acquired pneumonia that precipitated HF readmissions was associated with social factors like low income and low education level. (Calvillo–King et al., 2013). If clinicians are aware of this, they can have closer follow up for such patients whom they will have

identified as having high-risk social factors. If it is healthcare associated, then appropriate measures by the hospital including infection prevention measures should be put in to practice to reduce the risk of hospital acquired infections.

The second precipitator for readmission was arrhythmias, mainly atrial fibrillation 5 (42%). This was similar to data yielded from the CHARM study by Elke et al, where among cardiovascular precipitants, arrhythmias were the most common precipitator of readmission. In the Muhimbili study, 15% of cases had arrhythmia as precipitating factors for readmission.(Maro & Makule, 2009). In contrast, a study conducted by Michalsen et al done in a Berlin teaching hospital in Germany had only 28.7% of cases with arrhythmias (Michalsen et al., 1998). This difference could be explained by the fact that our percentage of atrial fibrillation was from a thirty day follow up cohort of readmitted patients, while the study by Maro and Michalsen focused on patients admitted with acute decompensated heart failure and they determined the precipitators for that admission. In the OPTIMIZE-HF study, arrhythmias were 3rd listed precipitator of heart failure readmissions at13.5%(Fonarow *et al.*, 2008). The difference could be due to that in the OPTIMIZE HF study, patients were followed up for 60 to 90 days. It might be that the arrhythmias were captured and managed earlier without causing readmission/decompensation within the 90 days follow up.

Non- compliance as a precipitator was documented in 4 (33%) patients and only 1 patient had no identified precipitator. In the study by Michalsen et al 23.5% were reported to be noncompliant to medication(Michalsen et al., 1998) . The difference in results between this study and ours could be explained by the fact that the study was a cross-sectional one, while ours was a cohort which determined precipitators of readmission within 30 days of discharge for 12 readmitted patients. The Berlin study by Michalsen looked for precipitators of decompensated heart failure at the point of

admission in heart failure, while our study was a follow up for readmission within 30 days,and when readmitted,precipitators are sought. OPTIMIZE HF study showed non adherence to diet at 5.2% and to medication at 8.9%, while we assessed non-adherence of both medication and diet using one tool, the European heart failure self-care behavior score (Fonarow et al., 2008).Jaarsma et al concluded that the EHFSc-9 which is what we used in our study,as a valid international tool that can be used in research to assess factors related to HF adherence(Jaarsma, Franzé, et al., 2009). Mitchalsen determined noncompliance if a patient took >2.5 l of fluid,took meds intermittently or didn't take meds at all,or if the patient took excess sodium.There was no scoring system in that study.

NT-pro BNP was not found to have any statistically significant association to 30-day readmission (p value=0.160) or 30-day mortality (p value=0.728).This could be due to the fact that we had a small number of paticipants. Cut-off NT-proBNP of 4137 pg/ml was used to determine an association between discharge NT pro BNP and mortality (p value <0.0001). (Bettencourt et al., 2004). Although we were unable to assess percentage change in NT-pro-BNP levels in this study, our study findings show that high NT-pro-BNP levels are common in our patients upon discharge from hospital. Bettencourt et al associated readmission over 6 months to discharge and percentage changes in NTpro BNP and found an association between it and outcome i.e. death and readmission (Bettencourt et al., 2004),while our study was assessing readmission within 30 days . In comparison , a study done in Leicester showed, in multivariate analysis, that pre- discharge plasma level of NT- pro BNP (odds ratio 15.30 [95% CI: 1.4–168.9], *P*=0.026) remained independently predictive of the composite primary endpoint of readmission and death within 350 days (O'Brien, Squire, Demme, Davies, & Ng, 2003). This greatly differed from our study because the Leicester study had a

sample size of 96, and only 34 patients had both admission and discharge NT-pro BNP, and they also followed up patients for 350 days, unlike our study that was assessing readmission within 30 days.

The mortality rate at the end of the study period was 16%, which was similar to Maro et al study in Muhimbili (Maro & Makule, 2009). Similarly, a meta-analysis of HF in SSA showed a mortality rate ranging from 14.7 to 35% within 30 days of discharge (Agbor et al., 2018). An association was noted in the patients who were readmitted and mortality (p-value was 0.008). In our study, out of those participants who were readmitted, 7 died (41.2%). The study in KNH by Kamau et al proved that readmission increased mortality by 30% (Kamau, 2009).This was also similar to a study in Alabama by Arundel et al, which showed that patients readmitted within 30 days post discharge had a higher mortality risk within a year post readmission ,all-cause mortality was at 41% in the readmitted group and 27% in the nonreadmitted group within a 2 to 12 month follow up period.(Hazards ratio 1.89 pvalue< 0.001).(Arundel et al., 2016)This indicates that readmission increases mortality rate especially one year following discharge..A study in Taiwan by Tung et al showed that post 30 day readmission mortality was at 26% in the readmitted group vs 20% in the nonreadmitted group within a 6 month follow up period.(Tung et al., 2016)

The mortality rate in this study was considered to be high.THESUS-HF study had a 180 day mortality rate of 17.8% (Damasceno et al., 2012) vs our 30day mortality rate of 16%.

This study draws strength from the fact that it was a cohort study which involved following up patients for 30 days from discharge, after which readmission rates was calculated, and precipitators of HF readmission determined. 30 days readmission is a

time of interest since risk of readmissions and mortalities increases up to a year after this readmission. We also were able to assess mortality within the 30 days of discharge. In addition, we were also able to determine and evaluate Pre discharge NT pro BNP which is commonly unavailable in our settings.

5.1 Study Limitations

The study employed use of a census strategy rather than a probabilistic sampling approach; as a result, capacity to make inference on the population is limited.

CHAPTER SIX: CONCLUSION AND RECOMMENDATION

6.1 Conclusion

1. The total 30-day readmission proportion in heart failure discharges was high.
2. Infections, mainly pneumonia, was the commonest precipitator of readmission in patients with heart failure.
3. There was no association between pre-discharge NT-Pro BNP and 30 days readmission. Readmission was associated with a high 30-day mortality.

6.2 Recommendations

1. Since NT-pro BNP did not predict 30-day HF readmissions, a follow up study can be carried out to assess percentage change in NT pro BNP (difference between NT pro BNP at admission and discharge) in relation to 30 days readmission.
2. Measures e.g. pneumococcal vaccine should be given to heart failure patients to prevent pneumonia. This will help in reducing readmissions in HF.
3. Since most readmissions occurred within 2 weeks of discharge, early return clinic visits for early assessment and identification of any precipitators will help reduce readmissions and hence mortality associated with readmission.

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APPENDICES

Appendix 1: Consent (English)

You must read this greeting to the respondent and proceed with the interview only after he/she gives consent.

Good morning/afternoon, Madam/Sir. My name is Dr.Gamar Salim Bajaber. I am here today from Moi University, Eldoret to collect information and data for the study on precipitators of 30-day readmission in heart failure and NT pro BNP levels in relation to readmission in heart failure. This research has been approved by the Institutional Research and Ethics Committee (IREC) of Moi University.

I will be asking you questions on demographics and assess your clinical and laboratory information. I will do this by checking your medical charts to know the exact status of your heart failure as well as collect blood samples from a visible vein on your arm, which will be analyzed by a machine to find out your NT pro BNP levels. A sterile 10cc capacity syringe and an 18gauge needle will be used to draw sample from a cleaned and sterilized anterior cubital vein on your body. A tourniquet will be used to facilitate the collection of blood samples, and this may be associated with some feeling of pain. You may also experience some pain when your skin is punctured and blood samples are drawn; which we do not expect to last for long. Approximately 4 cc of whole blood will be drawn. I plan to sample research participants at MTRH over the period of 6 months. All information you provide will remain confidential.

Benefits

This is a research project and the findings may be used by the MTRH management and Government's policy makers and health providers to design appropriate policies and plans to provide better health services for diabetes management. Your participation will help us to gain a better understanding on the common precipitators of 30-day readmission in heart failure and an association between NT pro BNP and heart failure readmission.

Risks

I am aware of the fact that some of the questions regarding research participation are not convenient to you. Everything you will tell me will be kept confidential. Under no circumstance will we link your name to the data during analysis and dissemination of the study findings. If you choose not to participate, it will not affect you in anyway. If you feel uncomfortable in the course of the survey, you can withdraw at any time. If you agree to participate, it will take 15 minutes to complete the interview. If you have any further questions during the period and in the future, please do not hesitate to contact the primary investigator using the telephone numbers below.

May we proceed? consent:

Yes☐ Pariticipant Signature. ..... Date .....

No ☐ Pariticipant Signature …… Date ……

Thank you for your time.

Contacts of the primary investigator,

Dr. Gamar MOI UNIVERSITY, ELDORET P.O BOX 4606 -0100 Eldoret, Kenya

Phone; 0704221330; E- Mail address; gsbajaber@gmail.com

Appendix 2: Consent (Swahili)

Ni muhimu kusoma salamu hii kwa mshiriki wa utafiti, na kuendelea na mahojiano baada ya yeye kupeana ridhaa.

Habari ya leo, bibi/bwana. Jina langu ni Dr.Gamar Salim .Mimi ninatoka Chuo kikuu cha Moi, Eldoret; na leo hii nigependa kukusanya na kupata habari zaidi kuhusu utafiti unaoangalia vitabiri vya kulazwa tena hospitali katika siku thelathini badaa ya kutibiwa ugonjwa wa moyo.Pia tutapima NT pro BNP, kipimo cha damu kinachozidi wakati moyo unapokosa kupiga unavopaswa.

Nitakuuliza maswali kuhusu umri wako, makao yako, na kiwango cha ilimu ya shule uliyohitimisha; pamoja na hayo nitakusanya habari inayohusika na hali yako ya afya, na hali ya ugonjwa wako wa moyo kwa mapitio ya kina ya rekodi ya matibabu, na kufanya kipimo cha maabara. Ili kuwezesha kipimo cha maabara kuweza kutendeka, damu itatolewa kutoka kwa mshipa wa damu ambao unaonekana kwa rahisi. Mara nyingi mshipa wa damu ambao hutumika kutolea damu ni mshipa unaopatikana sehemu ya ungo wa kikukuu cha mkono. Sindano yenye ukubwa wa kipimo cha 18 ambayo ni sindano ndogo, na yenye uwezo wa kubeba damu kiwango cha 4mls ndio itakayo tumika wakati wakutoa damu kwa ajili ya vipimo vya maabara. Ninatarajia kuwa huenda ukahisi maumivu kiwango kidogo, ambayo sidhani itadumu kwa muda mrefu, pindi damu itakapotolewa kwenye mshipa wa damu. Kifaa cha kusahilisha utowaji wa damu pia kitatumika, na hii huenda itakufanya kuhisi mbano kwenye sehemu ya mwili ambayo kifaa hichi kitatumika, lakini maumivu haitaendelea kwa muda mrefu.

Mimi mpango wangu nikusajili wanaorudi kulazwa kwa moyo kutofanya kazi vyema katika utafiti huu, kwa kipindi cha miezi sita. Taarifa zote zitakazokusanywa zitawekwa kwa hali ya siri.

Faida

Huu ni mradi wa utafiti; na matokeo yanaweza kutumika na wasimamizi wa MTRH na watunga sheria serikalini kwa mipango ya kutoa huduma bora, na kubuni sera mwafaka kwa ajili ya matibabu wa ugonjwa wa moyo. Ushiriki wako itatusaidia tuelewe vizuri uhusiano kati ya NT pro BNP na kulazwa kwa siku thelathini baada ya kutibiwa moyo hospitalini mara ya kwanza.Pia itasaidia kujua vitabiri vinavyosababisha watu kulazwa siku thelathini baada ya kutibiwa kwa ugonjwa wa moyo hospitali

Hatari

Mimi nina fahamu yakuwa baadhi ya maswali kuhusu ushiriki katika utafiti huu si rahisi kwako. Kila utakachonieleza itakuwa siri. Hakuna wakati yeyote ambayo jina lako litadhihirishwa na takwimu ya utafiti , iwe ni wakati wa uchambuzi au usambazaji wa matokeo ya utafiti huu. Kama utachagua kutoshiriki katika utafiti huu, haitakuathiri wewe kwa njia yeyote. Kama utakuwa na wasiwasi katika mwendo wowote wa utafiti huu, unaweza kuondoka wakati wowote. Lau utakubali kushiriki,, itachukua dakika 15 kukamilisha mahojiano haya. Kama una maswali yoyote zaidi katika kipindi cha utafiti huu na katika siku zijazo, tafadhali usisite kuwasiliana nami kwa kutumia namba ya simu hapo chini .

Tuendelee?

Ridhaa : Ndio☐ Signature ..... Date.....

La ☐ Signature ..... Date…….

Asante kwa kushirikiana nasi.

Wasiliano na mtafiti,

Dr Gamar, MOI UNIVERSITY, ELDORET P.O BOX 4606 -0100 Eldoret, Kenya

Simu; 0704221330; Barua pepe: gsbajaber @gmail.com

Appendix 3: Data Collection Form 1

Participant no: _____ Date: _____

DEMOGRAPHICS

Age:

Gender:

Level of Education:

County of Origin:

CLINICAL CHARACTERISTICS

Weight: _____ Height: _____ BMI: _____

Social History

Alcohol:	☐ Yes	☐ No
Smoking:	☐ Yes	☐ No

Past Medical hx

Comorbidities:	Diabetes Mellitus	☐ Yes	☐ No
	Hypertension	☐ Yes	☐ No
	Dyslipidemia	☐ Yes	☐ No
	Others	☐ Yes	☐ No

HIV status:

Positive: ☐

Negative: ☐

Date of dx of heart failure:

Underlying cause of heart failure:

Underlying precipitator of decompensation:

Current admission date:

Date of discharge:

Date 15 days from current discharge:

Date 30 days from current discharge:

Duration of current hospital stay:

Discharge medications:

Investigations:

Echo Findings :

Ejection Fraction:

Pulmonary Pressure:

Valve morphology and function

Chamber morphology

Echo conclusion:

ECG Findings:

UECS:

Na:

K+ :

Creatinine:

Urea:

Ca:

Mg:

NT pro BNP (pg/ml)

Date of cardiac clinic visit:

Discharge through rehabilitation clinic: Yes/No

Mobile number of patient:

Mobile number of patients care taker:

Appendix 4: Data collection Form 2

Participant number (as per Data collection form 1)

Current weight:

Blood pressure: 1st 2nd average

Pulse

Spo2:

New York Heart failure Association CLASS :1 2 3 4

WHO CHART Cardiovascular risk score:

1.Date of readmission:

2.Days from last admission:

3.date from discharge.

4.days from discharge

5.last clinic visit

6.any medications added or removed before readmission

Lab results:

full hemogram

Urea and electrolytes calcium and magnesium

LFTS:

Glomeruli filtration rate

HBA1c if available

Urinalysis

Lipid profile

Troponins if indicated

HIV status

Radiological

Chest x-ray report

Any other done

Ecg findings

Echo results

European Heart failure Self Care behavioral scale score

APPENDIX 5: European heart failure self-care behavior scale

	I completely agree				I don't agree at all
1. I weigh my self everyday	1	2	3	4	5
2. If I get short of breathe I contact my doctor or nurse	1	2	3	4	5
3. If my feet /legs become more swollen than usual,I contact my doctor or nurse.	1	2	3	4	5
4. If I gain 2kg in 1 week, I contact my doctor or nurse	1	2	3	4	5
5. I limit the amount of fluids I drink (not more than 1.5-2l/day)	1	2	3	4	5
6. If I experience increased fatigue, I contact my doctor or nurse	1	2	3	4	5
7. I eat a low salt diet	1	2	3	4	5
8. I take my medication as prescribed	1	2	3	4	5
9. I exercise regularly	1	2	3	4	5

APPENDIX 6: Cardiovascular Risk Score Charts

WHO/ISH Risk prediction charts
for 14 WHO epidemiological sub-regions

2. Instructions on how to use WHO/ISH (World Health Organization/International Society of hypertension) risk prediction charts

The charts provide approximate estimates of cardiovascular disease (CVD) risk in people who do not have established coronary heart disease, stroke or other atherosclerotic disease. They are useful as tools to help identify those at high cardiovascular risk, and to motivate patients, particularly to change behaviour and, when appropriate, to take antihypertensive, lipid-lowering drugs and aspirin.

How do you use the charts to assess cardiovascular risk?

- First make sure that you select the appropriate charts using information in table 1
- If blood cholesterol cannot be measured due to resource limitations, use the charts that do not have total cholesterol
- Before applying the chart to estimate the 10-year cardiovascular risk of an individual, the following information is necessary
  - Presence or absence of diabetes[1]
  - Gender
  - Smoker or non-smoker
  - Age
  - Systolic blood pressure[2]
  - Total blood cholesterol (if in mg/dl divide by 38 to convert to mmol/l)

Once the above information is available proceed to estimate the 10-years cardiovascular risk as follows.

Step 1 Select the appropriate chart depending on the presence or absence of diabetes[1]

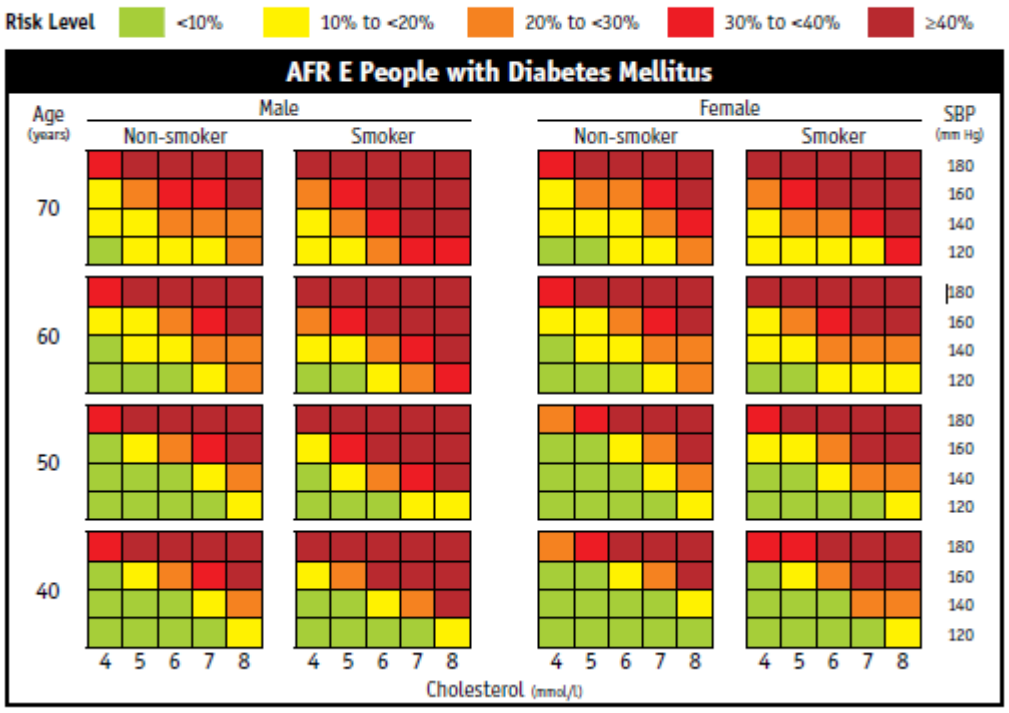
Step 2 Select male or female tables

Step 3 Select smoker or non smoker boxes[3]

Step 4 Select age group box (if age is 50-59 years select 50, if 60-69 years select 60 etc)

Step 5 Within this box find the nearest cell where the individuals systolic blood pressure (mm Hg) and total blood cholesterol level (mmol/l)[4] cross. The colour of this cell determines the 10-year cardiovascular risk.

Figure 2. WHO/ISH risk prediction chart for AFR E. 10-year risk of a fatal or non-fatal cardiovascular event by gender, age, systolic blood pressure, total blood cholesterol, smoking status and presence or absence of diabetes mellitus.



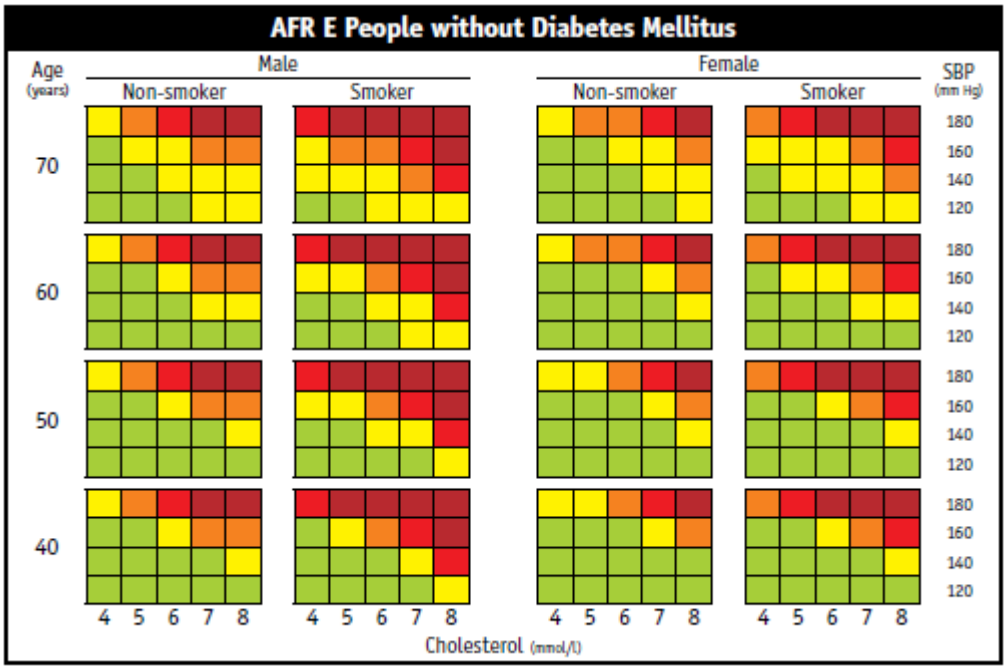


Figure 4. WHO/ISH risk prediction chart for AFR E. 10-year risk of a fatal or non-fatal cardiovascular event by gender, age, systolic blood pressure, smoking status and presence or absence of diabetes mellitus.

Appendix 7: NT pro BNP nano check machine and Strip

Product Description

1. Characteristics of Product

Nano-Checker™ 710V Reader(v1), developed by Nano-Ditech Corporation, gives you quantitative assessment by capturing and analyzing images of lateral flow immunochromatography. When the Rapid Diagnostic Test (RDT) device is inserted into the tray, an internal camera captures and saves the image, and data is automatically collected to be converted to a graphical analysis. Accurate and reliable rapid diagnosis is possible since this product provides quantitative and qualitative analysis through highly sensitive image analysis based on LED and the high quality image sensor. Convenient management of patient information is also possible by saving and transporting patient information through a USB port. And the system provides printing function using built-in thermal printer and network printer, you can print out test result through this function.
Intuitive user interface using touch pad controller with 10" color LCD makes it easy to access and use.

Main Features

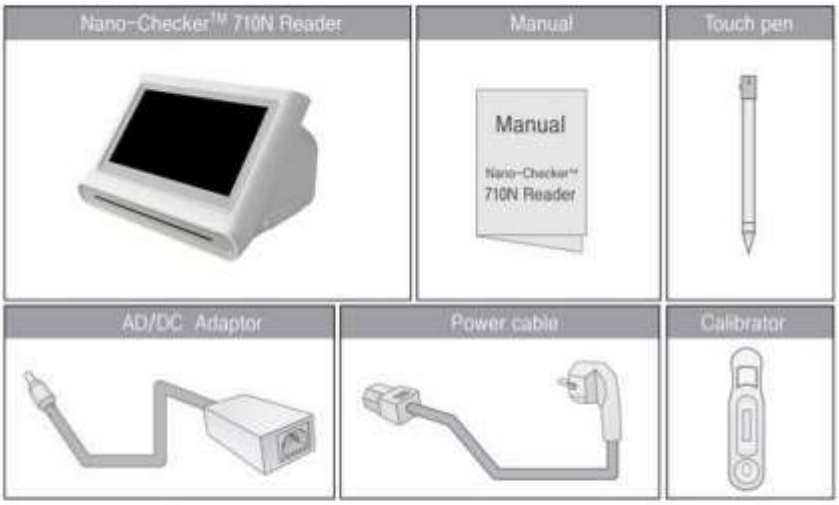
-Qualitative and quantitative analysis of various applications for POCT
-Support LIS
-Remote access for support
-Bar code & QR code

Convenient Features

-Data management
-Data printing
-User management
-Patient record management

2.1 Product Components

Components provided in the product package are as following.



Product and parts composition of ***Nano-Checker™ 710V Reader(v1)*** (Cat. No. ABA02)

- AC/DC Adapter (12V, 5A output; Cat. No. ABA061)
- Power Cable (Cat. No. ABA062)
- Touch Pen (Cat. No. ABA063)
- Calibrator: for QC purpose only (Cat. No. ABA064)

[Figure 8.] Result of Check Instrument

► When the scanning process is complete, you can see the result of measurement.

► You can see the graph and captured image of calibrator's five test lines. The graph will show intensity of each parameter measured by the ***Nano-Checker™ 710V Reader(v1)***. The x-axis stands for the relative location of each test line on the device. The y-axis stands for measured intensity value.

► Check descriptions for the 'Parameter', 'Value', 'Reference Value' and 'Result' in the Table.

Name	Description
Parameter	The parameter name matched for each parameter on the graph.
Value	Measured value
Ref. Value	The standard value. The reference value is the fixed value, which has already been set by manufacturer.

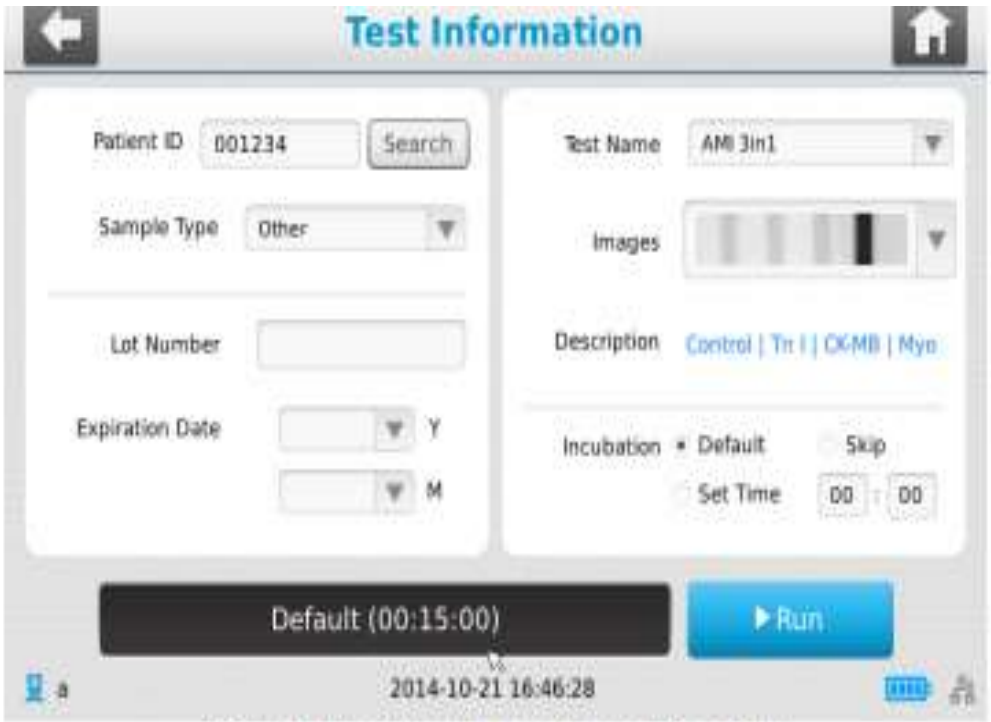
3.3 Starting New Test

[Figure 9.] Starting New Test

► Click 'New Test' button to start the test, then 'Test Information' screen [Figure 10.] will appear.

[Figure 10.] Test Information

▶ Enter patient ID. If the patient has a history of test, click the 'Search' button to search the patient. After click 'Search' button, you can see the 'Search Patients' screen as shown in [Figure 10-1.] below. ..* You can register the patient information (ID, Name, Birthday and Gender) through the 'Manager' in main menu.



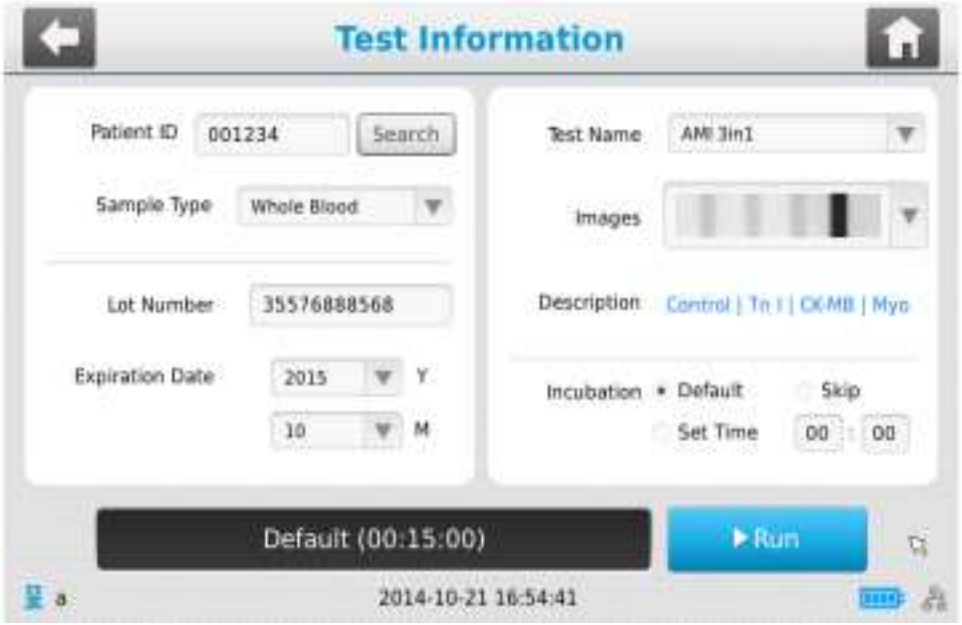
[Figure 11.] Test Information – after searching patients

▶ Select an appropriate sample type in drop down menu and enter the Lot Number, and then you can select a year and month of the test device's expiration date. The 'expiration date' is not a required input.

▶ When you select the test file from the 'Test Name', the test file's information will be shown under the selected test file name. All test file information is described in the table below.

** The test files have been preset for testing the test device.*

Name	Description
Images	Test and control lines that are captured are shown.
Description	Types of diseases that can be tested with the device.
Incubation	Total duration of the test, including the incubation time. The test can be done in a given time frame but user can also set the time for the test. ▷Select 'Default' to start measuring the test after a certain time, which is already set by each test file. ▷Select 'Skip' to start measuring the test immediately. ▷Select 'Set Time' to manually setup incubation time.



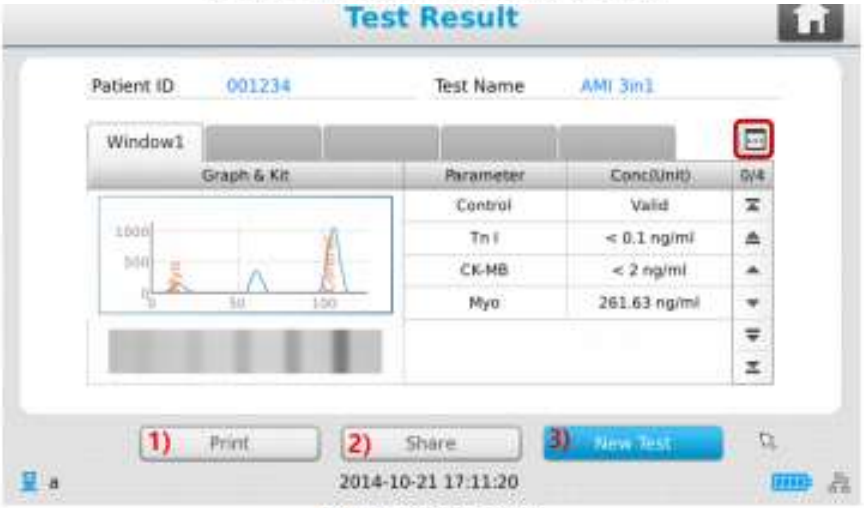
▶ Click the down arrow button next to the 'Test Name' to select the test file. After selecting 'Incubation' condition, click 'Run' button to start measurement.

[Figure 12-1.] Abort Button

▶ You can click 'Abort' button to stop the scanning process.

▶ To check the detailed information of test result. Click button.

[Figure 14.] Derailed Information of Test Result



[Figure 13.] Test Result

▶ When the scanning is successfully complete, the 'Test Result' screen appears. The test information and the measured values are presented. The left side of the image shows test and control lines of the test device, captured by the internal camera of the reader.

Nano-Check™ NT-proBNP test is used for the determination of NT-proBNP in a whole blood, serum, or plasma specimens at the cutoff concentrations of 125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older. The test is used as an aid in the diagnosis of patients suspected of having congestive heart failure (CHF).

Technology: Immunochromatography
Turn Around Time: 15 minutes
Sample Type: Whole Blood, Plasma, or Serum
Volume of Sample Required: 80 µl
Measuring Range: 30 pg/mL- 15,000 pg/mL
Storage: Room Temperature (2-30 °C)

Appendix 8:IREC

Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

25th January, 2018

Reference: IREC/2017/160
Approval Number: 0002024

Dr. Gamar Salim Bajaber,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
25 JAN 2018
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dear Dr. Gamar,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:-

"Frequency and Precipitations of Heart Failure Readmission at Moi Teaching and Referral Hospital".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 2024*** on 25th January, 2018. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 24th January, 2019. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

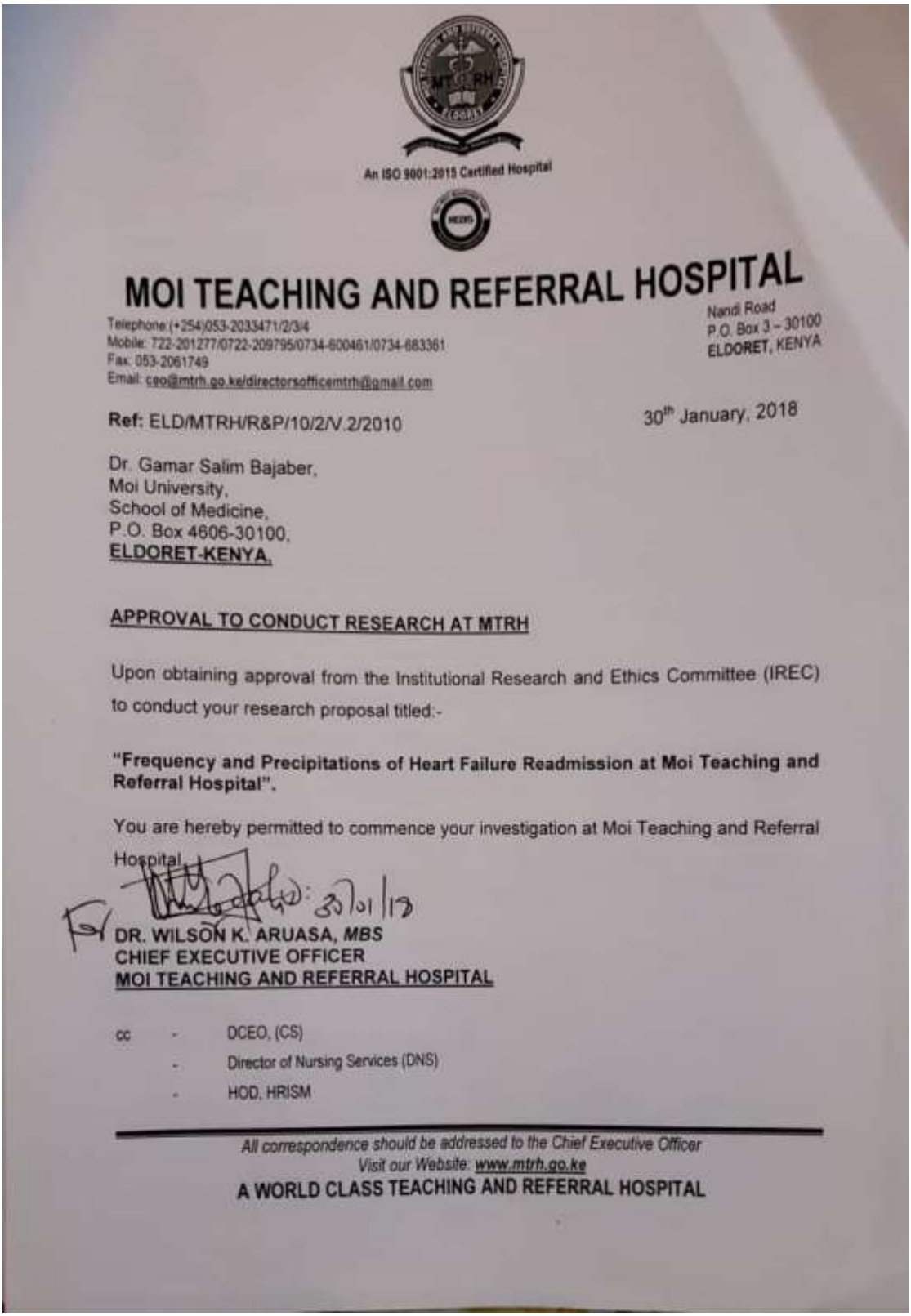
You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix 9:Hospital Approval (MTRH)



An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone:(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

30th January, 2018

Dr. Gamar Salim Bajaber,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Frequency and Precipitations of Heart Failure Readmission at Moi Teaching and Referral Hospital".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

Date: 30/01/18

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - DCEO, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM

All correspondence should be addressed to the Chief Executive Officer
Visit our Website: www.mtrh.go.ke
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