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DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS

PREVALENCE OF MEDICATION NON-ADHERENCE AND ITS ASSOCIATED FACTORS IN AMBULATORY PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AT THE KENYATTA NATIONAL HOSPITAL

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Dissertation presented in partial fulfilment for the award of Master's degree of Medicine in Internal Medicine, University of Nairobi

DECLARATION

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

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DEDICATION

I dedicate this dissertation to my daughters Lisa, Anita, and Kyla.

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LIST OF ACRONYMS AND ABBREVIATIONS

ACR	American College of Rheumatology
ANA	Antinuclear Antibodies
Anti-DS DNA	Anti-Double Stranded Deoxyribonucleic Acid
Anti β2 GP1	Anti-Beta-2 Glycoprotein 1
C3	Complement 3
C4	Complement 4
CH50	Total Hemolytic Complement
COREQ	Consolidated criteria for Reporting Qualitative research
CQR	Compliance Questionnaire of Rheumatology
ESRD	End Stage Renal Disease
EULAR	European Alliance of Associations for Rheumatology
GCs	Glucocorticoids
HIV	Human Immunodeficiency Virus
HCP-VAS	Health Care Practitioner Visual Analog Scale
HCQ	Hydroxychloroquine
KNH	Kenyatta National Hospital
MASRI	Medication Adherence Self-Report Inventory Scale
MEMS	Medications Events Monitoring System
MMAS	Morisky Medication Adherence Scale
MMF	Mycophenolate Mofetil
M-SLEDAI	Modified Systemic Lupus Erythematosus Disease Activity Index
PGA	Physician Global Assessment
PI	Principal Investigator
SDI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
UON	University of Nairobi
VAS	Visual analog Scale
WHO	World Health Organisation

ABSTRACT

Background: The attainment of prolonged remission in the management of SLE has been hindered by medication non-adherence. Various factors have been shown to influence non-adherence. There is a dearth of data on SLE medication non-adherence in the developing countries. The main aim of this study was to determine the prevalence of medication non-adherence and the reasons for medication non-adherence among patients on follow-up for SLE at the Kenyatta National Hospital.

Methods: This was a mixed method cross-sectional study, carried out at the KNH Rheumatology clinic. The study included SLE patients above 18 years, with an SLE disease duration of more than six months. The Morisky Medication Adherence Scale (MMAS-8) was administered to assess adherence. Participants scored as non-adherent were invited for individual face-face in-depth interview sessions. A semi-structured interview guide was used to guide these sessions. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) was used to assess for organ damage in all the participants. The prevalence of medication non-adherence was calculated and presented as a proportion of all SLE patients studied. Comparison for the level of adherence and the accrued organ damage was made for all participants using the chi-square and interpreted at a 5% level of significance.. Qualitative data was coded both manually and by use of a coding software with resultant development of themes and sub-themes.

Results: 80 patients were recruited into the study. 97.5% were female. The prevalence of SLE medication non-adherence was 46.2%. Thematic saturation was achieved by 15 interviews. Six themes explaining the various patient perceived reasons for non-adherence were raised: access to medications, medicine-taking behaviors, perceptions about medication, use of alternative methods, lack of knowledge, and the lack of trust in the treating physician. There was no significant association between the level of adherence and the Damage Index.

Conclusion: A significant proportion of SLE patients were found to be non-adherent to their medications. Interventions aimed at addressing the various barriers to adherence raised by the patients, can be beneficial in reducing the burden of medication non-adherence in this population.

CHAPTER ONE: INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by multi-systemic inflammatory mediated changes [1]. It is most commonly seen in women with a higher prevalence in those of reproductive age (15-45 years) [2]. Its incidence differs in different regions with the highest incidence reported in North America (23.2/100000 person-years) and the lowest reported in Africa (0.3/100000 person-years) [3]. Current evidence however supports an increasing frequency of SLE cases throughout Africa [4].

The disease course of SLE is characterized by three patterns; prolonged remission, a remitting-relapsing pattern and a chronically active pattern [5]. The management of SLE is targeted towards attaining prolonged remission while avoiding drug toxicities and managing SLE associated comorbidities which together translate to reduced damage accrual. Medications used include hydroxychloroquine, glucocorticoids, immunosuppressants, calcineurin inhibitors and biologic agents [6,7]. .

The attainment of these goals of SLE management is largely dependent on the patient's ability to adhere to the recommendations of the treating physician especially on the intake of medications. Indeed, medication non-adherence has been shown to be a hinderance to the management of all chronic illnesses [8].

In SLE, medication non-adherence has been shown to result in unnecessary treatment escalation [9], increased flares with a higher SLE Disease Activity Index (SLEDAI) [10,11], increased hospitalization [12], poor renal outcome [13–15], increased cost [16] and higher damage index [11,17]. Despites this, the rate of non-adherence in SLE measured by different methods has been shown to be high; with rates of up to 76% [9]. Different factors have been noted to influence this trend with the World Health Organisation (WHO) classifying them into patient-related factors, socio-economic factors, therapy-related factors, healthcare-system related factors and condition-related factors [8].

Identifying non-adherent patients in a specified population and the factors that influence their non-adherence forms the basis of creating targeted interventions aimed at reducing non-adherence which is noted by WHO to be more beneficial than gaining advances in treatment [8].

CHAPTER TWO: LITERATURE REVIEW

2.1 Diagnosis of Systemic Lupus Erythematosus

There is no definitive SLE diagnosis tool. Classification criteria which were developed primarily for epidemiological and research purposes, have ended up forming a cornerstone for clinical diagnosis [18]. The criteria currently in use is the 'European League Against Rheumatism/ American College of Rheumatology (EULAR/ACR) classification criteria' developed in 2019 with a sensitivity of 96.1% and specificity of 93.4% in labeling a patient with SLE [19].

The classification requires that patients have presence of antinuclear antibodies (ANA) as an entry criterion; after which additional criteria (immunologic and clinical) are applied. To be classified as SLE, a patient requires at least one clinical criterion and ≥10 points.

Table 1: EULAR/ACR Classification criteria [19] (Appendix I)

Entry Criterion Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)			
Additive criteria			
Clinical domain and criteria	**Weight**	**Immunology domains and criteria**	**Weight**
Constitutional - Fever	2	**Antiphospholipid antibodies** Anti-cardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant	2
Hematologic Leukopenia Thrombocytopenia Autoimmune hemolysis	 3 4 4	**Complement Proteins** Low C3 OR Low C4 Low C3 AND Low C4	 3 4
Neuropsychiatric Delirium Psychosis Seizure	 2 3 5	**SLE-Specific antibodies** Anti-dsDNA antibody OR Anti-Smith antibody	6
Mucocutaneous Non-scarring alopecia Oral ulcers Subacute cutaneous or discoid lupus Acute cutaneous lupus	 2 2 4 6		
Serosal Pleural or pericardial effusion Acute pericarditis	 5 6		
Musculoskeletal Joint involvement	6		
Renal Proteinuria >0.5g/24h Renal biopsy Class II or V lupus nephritis Renal biopsy Class III or IV lupus nephritis	 4 8 10		

* Within each domain, only the highest weighted criterion is counted toward the total score

2.2 SLE Disease Course Patterns

In 1999, Barr et al sought to describe the patterns of SLE disease activity [5] using two instruments – a Physician Global Assessment (PGA) which assessed the clinician's judgement of the disease activity of the patient; and a modified SLE Disease Activity Index (M-SLEDAI) that excluded the two serology tests. They described three patterns of disease activity-:

a) Long quiescent/ Prolonged remission where the disease remained inactive for at least 1 year.

An international task force later in 2021 described remission as "clinical SLEDAI = 0 and PGA < 0.5 irrespective of serology and the patient may be on antimalarials, low dose glucocorticoids (prednisone≤5mg/day) and /or stable immunosuppressive drugs including biologicals" [20].

b) Remitting-relapsing pattern described by periods of disease activity alternating with periods of disease inactivity over a year.

c) Chronic active where the disease remained active throughout the year.

2.3 Management of Systemic Lupus Erythematosus

2.3.1 Pharmacological Management of SLE

Several medications are used in the management of SLE-:

a) Hydroxychloroquine (HCQ) given to all patients at doses not exceeding 5mg/kg of ideal body weight due to the risk of retinal toxicity [6].

b) Glucocorticoids (GCs) – Prednisone/ Prednisolone as oral glucocorticoids and methylprednisolone as the parenteral glucocorticoid for acute, organ-threatening disease [21]. The adverse effects are vast and lead to increased irreversible organ damage accrual [6,22]. EULAR recommends minimizing daily dose to ≤7.5mg/day for medium to long term use [6].

c) Immunosuppressants - These drugs allow for quick tapering of glucocorticoids [6,22]. They include mycophenolate mofetil (MMF), Cyclophosphamide, Methotrexate and Azathioprine.

d) Calcineurin Inhibitors - Cyclosporin and Tacrolimus [6].

e) Biologic Agents – These include Anifrolumab, Belimumab and Rituximab [6,22].

2.3.2 Non-Pharmacological Management of SLE

These measures are aimed at-:

a) Reducing risk of flares by sun protection [6,23].

b) Preventing infections [6,23] by immunization; Screening for infections and; Monitoring for increased risk of infection.

c) Minimizing cardiovascular risk [6,23] by lifestyle changes as well as monitoring of blood pressure, sugar levels, lipid levels and body mass index.

d) Reducing risk of Osteoporosis [23] by assessing for adequate vitamin D and calcium intake, regular exercising and cessation of smoking.

2.3.3 Goals of Management of SLE

The management of SLE shifted towards a target based approach in 2014 with the major goal being achievement of prolonged remission [7]. This approach was re-echoed in the 2019 EULAR recommendations for the management of SLE [6] and is summarized in the figure below.

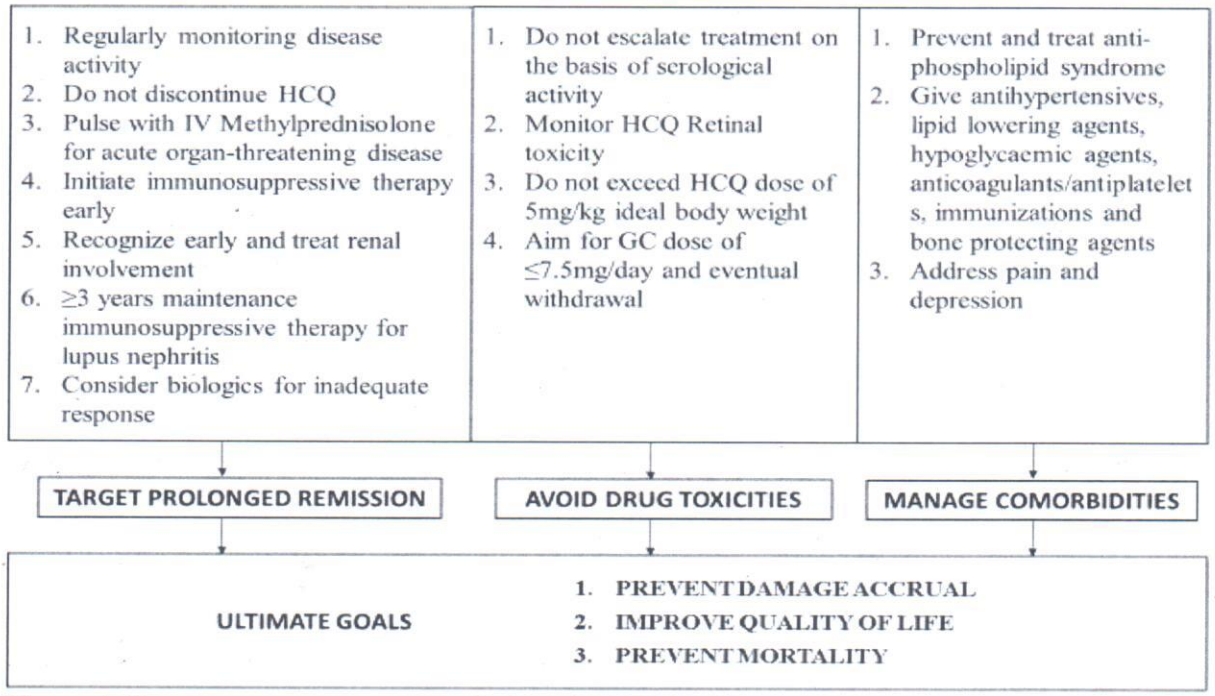


Figure 1:Treat to target recommendations in SLE [6,7]

2.3.4 Factors limiting the achievement of Prolonged Remission in SLE

Even though prolonged remission has been linked to decreased damage accrual and improved quality of life and is a major target in the management of SLE, the rates of remission have been shown to remain low.

Table 2: Rates of Remission in SLE

Author	Remission Definition	Remission Achieved
Barr et al [5] 1999, John Hopkins	Clinical SLEDAI = 0, PGA = 0 (or one PGA<1) for ≥ 1 year	16% (204 patients)
Tselios et al [24] 2019, Toronto	Clinical SLEDAI- 2K of 0 for ≥ 10 years on stable treatment	10.1% (267 patients). *Linked to decreased damage accrual*
Zen et al [25] 2014, Padova	SLEDAI-2K = 0 ≥ 5 Years on and off treatment	37.4% (224 patient). *Linked to decreased damage accrual*
Nikfar et al [26], 2020 Iran	Clinical SLEDAI 2K= 0 ≥ 5 years on and off treatment	33.2 % (193 patients). *Linked to decreased damage accrual*
Medina et al [27], 2016, London	Clinical SLEDAI 2K = 0 over 1 year on and off treatment	19.35% off medication, 33.06 % on medication
Nyambane et al [28], 2016, Kenya	Clinical SLEDAI 2K; remission =0 on therapy. Mild disease activity (0-5); Moderate (6-12); severe disease activity (>12)	12% (8 of 62 patients) achieved remission. 50% of patients had moderate to severe disease activity

Factors hindering the achievement of remission were also studied. These include-:

a) Non-adherence to medications – poor adherence was linked to a persistently active course of disease [24,26].
b) Infections [24].
c) Higher disease activity at onset [24,26].
d) Epigenetic variables [24].

2.4 Adherence to Medication in Systemic Lupus Erythematosus

2.4.1 Definition of Medication Adherence

Medication adherence was defined by the World Health Organization (WHO) in 2003 as, "the extent to which a person's behavior of taking medication, corresponds with agreed recommendations from a health care provider" [8].

Depending on the tool used to assess adherence, a person/ patient can either be termed as adherent or non-adherent. Most tools use a cutoff point of 80% in SLE adherence studies. Patients with adherence rates of ≥ 80% are interpreted as adherent and patients with adherence rates of <80% are interpreted as non-adherent.

Medication non-adherence can either be intentional or unintentional. Intentional medication non-adherence refers to non-adherence that is deliberate, whereby, a patient actively chooses not to follow treatment recommendations. In contrast, unintentional medication non-adherence is a passive process, largely caused by a lack of capacity or resources to follow the treatment recommendations [29].

2.4.2 Tools for Assessing Medication Adherence

There is no gold standard method for measuring adherence.

2.4.2.1 Direct (Objective) methods

These methods offer evidence that the medication has been taken by the patient. These include-:

a) Direct Patient Observation

This involves directly observing the patient taking the medication. This method is tedious as well as impractical for most studies [30].

b) Drug Levels in Biologic Fluids

In SLE, measurement of hydroxychloroquine (HCQ) levels in blood has taken center stage in adherence studies. This is because HCQ has been shown to be a cornerstone in the management of SLE and is recommended for all patients [6,22].

HCQ levels in blood can be quantified by use of High Performance Liquid Chromatography [9]. A threshold of 200ng/ml has been used in most SLE adherence studies with patients having levels <200ng/ml being classified as nonadherent [31].

Measurement of blood HCQ levels is currently not available in Kenya.

2.4.2.2 Indirect (Subjective) methods

These methods imply that the medication has been taken by the patient. These include-:

a) Health-care Practitioner Visual Analog Scale (HCP-VAS)

It is based on the physician's judgement of the patient's adherence. It is done on a visual analog scale (VAS) ranging from 0 (complete non-adherence) to 100 (complete adherence). Patients with a score of < 80% are termed as non-adherent. This has been shown in most studies to be an inaccurate method as clinicians tend to overestimate patient's adherence and fail to recognize patients with significant non-adherence [9].

b) Patient self-reports

Various questionnaires to assess adherence have been developed over time. Their advantage lies in the ease of use and cost (inexpensive). Their accuracy is however questioned as they tend to overestimate adherence due to their full reliance on the word of the patient [9,31,32].

Three validated questionnaires have been used in SLE patients. These are-:

Morisky Medication Adherence Scale (MMAS)

This was developed by Morisky et al in 1986; initially with 4 items [33]. Later, in 2008, four additional items were added to it, with the updated version now widely known as MMAS-8 [34]. The MMAS-8 due to its simplicity and ease of scoring has been used in >200 adherence studies [35]. It has been shown to have a sensitivity of 93% and a specificity of 53% [34].

The questionnaire contains 8 questions (Appendix IV) giving a score that ranges from 0-8. Patients with a score of <6 are interpreted as non-adherent [36].

Medication Adherence Self-Report Inventory Scale (MASRI)

This was developed by Walsh JC et al in 2001. It contains two parts [37].

The first part (Part A) is used to measure adherence by use of a visual analog scale (VAS) for the percentage of drugs taken in the month before. Part A of the MASRI is shown to have sensitivity of 87% and specificity of 86% [9].

The second part (Part B) measures the accuracy of medication timing which is an uncommon requirement in SLE [38].

Compliance Questionnaire of Rheumatology (CQR)

This was developed by de Klerk et al specifically for rheumatic diseases in 1999[39]. It contains 19 questions answered on a 4-point Likert scale. The total score is given from 0 (complete non-adherence) to 100% (complete adherence). Patients with a score of < 80% are termed as non-adherent. It has been shown to have a sensitivity of 95% and a specificity of 62% [40].

c) Pill count

This involves counting the number of pills a patient has brought back at a scheduled appointment or clinic visit. This method has been found to overestimate adherence as non-adherent patients tend to tamper with the number of pills returned [30].

d) Pharmacy Refill Approach

This involves comparing the amount of medications picked by patients at the pharmacy with that prescribed by the physician over a period of time [9]. Adherence is then calculated as (total number of medications dispensed/ total number of medications prescribed) x 100 [38]. Patients with a score of < 80% are termed as non-adherent.

Though a more accurate method of assessing adherence, the pharmacy refill approach requires a centralized pharmacy system or the ability to access pharmacy records from all the pharmacies used by the patient which may be a tedious approach [30]. In addition, adherence may be overestimated as purchase of medications does not necessarily equate to intake of the medications [9].

e) Medications Events Monitoring System (MEMS)

This involves placement of an electronic chip in the cap of a medicine bottle that keeps record of every time the cap is opened on a software platform that then calculates the patient's adherence as a percentage. Patients with a score of < 80% are termed as non-adherent [41].

MEMS offers a lower risk of deception. Due to this, MEMS is considered a gold standard in measuring adherence, coming second to direct intake observation. However the major disadvantage with this method is that it is extremely expensive [41].

2.4.3 Rates of SLE Medication Non-adherence

Management of chronic illnesses has proven to be challenging due to medication non-adherence. WHO records that adherence among patients with chronic illnesses in developed countries only averages 50% with great paucity of data in developing countries which are faced with even greater challenges [8]. In addition, adherence to chronic illnesses has been shown to decrease drastically after 6 months of treatment [9]. SLE, being a chronic illness, faces the same challenge.

It is important to note that the prevalence of SLE medication non-adherence varies widely depending on the assessment method used. The most common method used is patient self-reports. By comparing studies done using patient self-reports, developed countries record lower rates of non-adherence to SLE medication with great paucity of data especially in the least developed countries where most African countries lie including Kenya.

Table 3: SLE Medication Non-adherence rates in Developed Countries

	Study	Country	Method used	Non-adherence Rate
1.	Daleboudt et al [29]	New Zealand	MASRI	13.3%
2.	Chehab et al [42]	Germany	MMAS-4	37.3%
3.	Georgopoulou et al [43]	England	MASRI	14.1%
4.	Costedoat-Chalumeau et al [31]	France	MASRI	23.4%

5.	Mendoza-Pinto et al [44]	Mexico	CQR-19	25.5%

Table 4: SLE Medication Non-adherence rates in Developing Countries

	Study	Country	Method used	Non-adherence Rate
1.	Abdul-Sattar et al [11]	Egypt	CQR-19	47.5%
2.	Oliveira-Santos et al [45]	Brazil	MMAS-8	68.3%
3.	Chambers et al [46]	Jamaica	MASRI	44%
4.	Alsowaida et al [47]	Saudi Arabia	MMAS-4	62.1%

It is important that all the above studies noted a limitation in the use of self-reports which could have led to underestimation of the extent of SLE medication non-adherence. For example, despite the low medication adherence reported in the developed countries, similar studies done by use of medicine pill count have shown non-adherence of up to 76% [41].

2.4.4 Factors that Influence Medication non-adherence in SLE Patients

Non-adherence is influenced by multiple factors. WHO divides these factors into 5 dimensions.

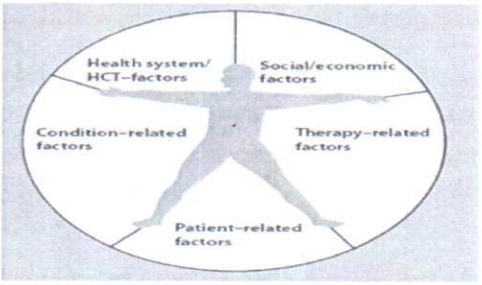


Figure 2:WHO'S 5 Dimensions of Medication Adherence [8]

Identifying patients who are non-adherent in a targeted population of SLE patients and the specific factors that hinder their ability to adhere to treatment forms the basis from which targeted interventions are implemented [8].

Studies on SLE adherence have tackled a few of these factors. Several limitations are however noted in these studies. The studies done in various populations have noted a limitation in

showing temporal relationships between these factors and non-adherence due to limited sample sizes and the cross-sectional aspect of these studies.

Patient-related Factors

Forgetfulness – most patients cite this as the reason for non-adherence to medications [32,45,48].

Illness Perception – This relates to what the patient understands about their illness as well as their emotional response to their illness. Georgopoulou et al demonstrated that patients with a clearer understanding of SLE, were more involved in making decisions pertaining their treatment which translated to better adherence [43]. In addition, patients with a positive emotional response to SLE are noted to have better adherence [42,45].

Use of alternative (herbal) medication – In some studies, use of herbal medication has been noted to occur concurrently with SLE medication [36,46]. However some patients do replace SLE medication with the use of herbal alternatives [29,46].

Patients' beliefs in medicines – In order to adhere to medications, patients must believe that they need the medications and that the medications confer to them benefit rather than harm. Such beliefs are influenced by culture, religion as well as past experiences [8]. The belief that medication is unnecessary and harmful has been shown to be an important predictor of poor adherence to medications in SLE [42,43].

Socio-economic Factors

Age – Younger patients have been shown to be non-adherent [29,42].

Literacy –low educational level has been indicated as one of the predictors of non-adherence [11,32,49,50].

Employment status –lack of employment has been linked with inability to afford medications and therefore non-adherence [11,46,49,51].

Cost of Medications – Inability to afford medications leads to non-adherence [11,46,49,51]. This is not an issue in countries where patients do not have to pay for their medications [42,43,47].

Social support – Good family support with marital status as the surrogate measure, has been shown to be associated with good adherence [45,50].

Health-care system related Factors

Availability of medications – In a qualitative study done by Chambers et al [46], patients reported that their adherence to SLE medication was affected by unavailability which necessitated them to travel in search of pharmacies that had the specified medication.

Physician-patient relationship – good, detailed and positive communication between the doctor and the patient fosters good medication adherence in SLE patients [43,49,52].

Therapy-related Factors

Side effects of drugs – a substantial number of studies have reported patients stopping their medication due to the side effects experienced [32,43,45,46,49]. In addition to this, the fear of side effects (e.g. steroid-induced weight gain or acne) has also been shown to be a great hinderance to adherence [52].

Relief of Symptoms – Some patients are noted to stop medications once they feel better. This has impacted the use of hydroxychloroquine which is maintained during remission [45,46,48,53].

Pill burden – A high pill burden is associated with medication non-adherence in most chronic illnesses including SLE [11,48,50].

Condition-related Factors - Depression

Mood and anxiety disorders are reported to be the second most common neuropsychiatric conditions in SLE [54]. The prevalence of depression in SLE patients varies from 17%-75% across various populations [55].

Depression has been shown to negatively impact medication adherence in the management of chronic illnesses [56]. This has been echoed repeatedly in SLE studies [11,32,47].

2.4.5 Consequences of SLE Medication Non-adherence

Poor medication adherence has been shown to have several negative effects in SLE. These include-:

a) Higher SLE disease activity.

Failure to adhere to a regular treatment regimen, results in poor disease control. A study by Costedoat et al, demonstrated that SLE patients who were non-adherent to HCQ, had higher scores of disease activity as well as an increased risk of recurrent flares [10]. Similar results were demonstrated by El-Azizi et al in a study done in Egypt [48].

The failure to achieve disease control in non-adherent patients leads to unnecessary treatment escalation [9].

b) Increased hospitalizations.

A study by Feldman et al demonstrated that non-adherence to HCQ and immunosuppressants was associated with higher acute care utilization in terms of emergency department visits and hospitalization [12].

c) Poor renal outcomes.

In a study done by Bruce et al, non-adherence was deemed to be the major reason for development of chronic renal insufficiency in patients with SLE [15]. Similar results have been demonstrated in 2 other similar studies [13,14].

d) Increased cost

This is due to treatment escalations, increased hospitalizations, increased need of emergency department services and poor outcomes (for example requiring dialysis for ESRD lupus patients) [9]. In USA, poor adherence to various medication regimens is reported to cost an estimated $300 billion annually [16].

e) Permanent Lupus associated Organ Damage.

Patients who are non-adherent to SLE medications have been shown to have higher accrued organ damage as compared to those who are adherent [36,48]. This may be explained by the poor disease control, recurrent flares and the treatment escalations in non-adherent patients.

2.5 Assessment of Damage in Systemic Lupus Erythematosus

Damage accrued in SLE is irreversible and can be due to the disease itself, the treatment of SLE, as well as comorbidities[57].

The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus (SLICC/ACR Damage Index) developed from 1985 to 1996 took this into account.

To differentiate damage from disease activity, the index stipulates that the change in the organ system must be present for at least six months. This is with the exception of myocardial infarction and stroke that are recorded once they occur.

All damage is recorded and scored by a physician from the time of SLE diagnosis and can only plateau or increase over time.

Nine organ systems are scored with ranges from zero as follows (Appendix IX): Ocular (0-2), Neuropsychiatric (0-6), Renal (0-3), Pulmonary (0-5), Cardiovascular (0-6), Peripheral vascular (0-5), Gastrointestinal (0-6), Musculoskeletal (0-7) and Skin (0-3). Three disease states are added; Diabetes mellitus (0-1), Premature gonadal failure (0-1) and malignancies (0-2); giving a total maximal score of 47.

Assessing damage through the SLICC/ACR Damage Index (SDI) in the clinical setup is important as it has been shown to predict several outcomes. A high SDI score is a strong predictor of mortality [58]. Rahman et al went further and demonstrated that even early damage, at the first SDI assessment within the first year of diagnosis with an SDI≥1 was predictive of mortality [59]. Higher SDI scores also predict a poorer health related quality of life [58]. Higher SDI scores are also predictive of hospitalization [59].

2.6 Conceptual Study Framework

2.6.1 Conceptual Framework Narrative

The inability to adhere to SLE medication has been shown to be a major hinderance towards achieving prolonged remission in SLE leading to treatment escalation, increased number of flares, higher SLE disease activity index, poor renal outcomes, and increased morbidity. All these translate to increased irreversible organ damage accrual. Different studies done in different regions have identified various factors that hinder patients from adhering to SLE medication. These have been classified by WHO into patient-related factors, socio-economic factors, healthcare-system related factors, condition-related factors, and therapy-related factors. The successful implementation of successful interventions to reduce non-adherence lies in identifying non-adherent patients in a specific population and the factors influencing their non-adherence.

2.6.2 Conceptual Framework Schema

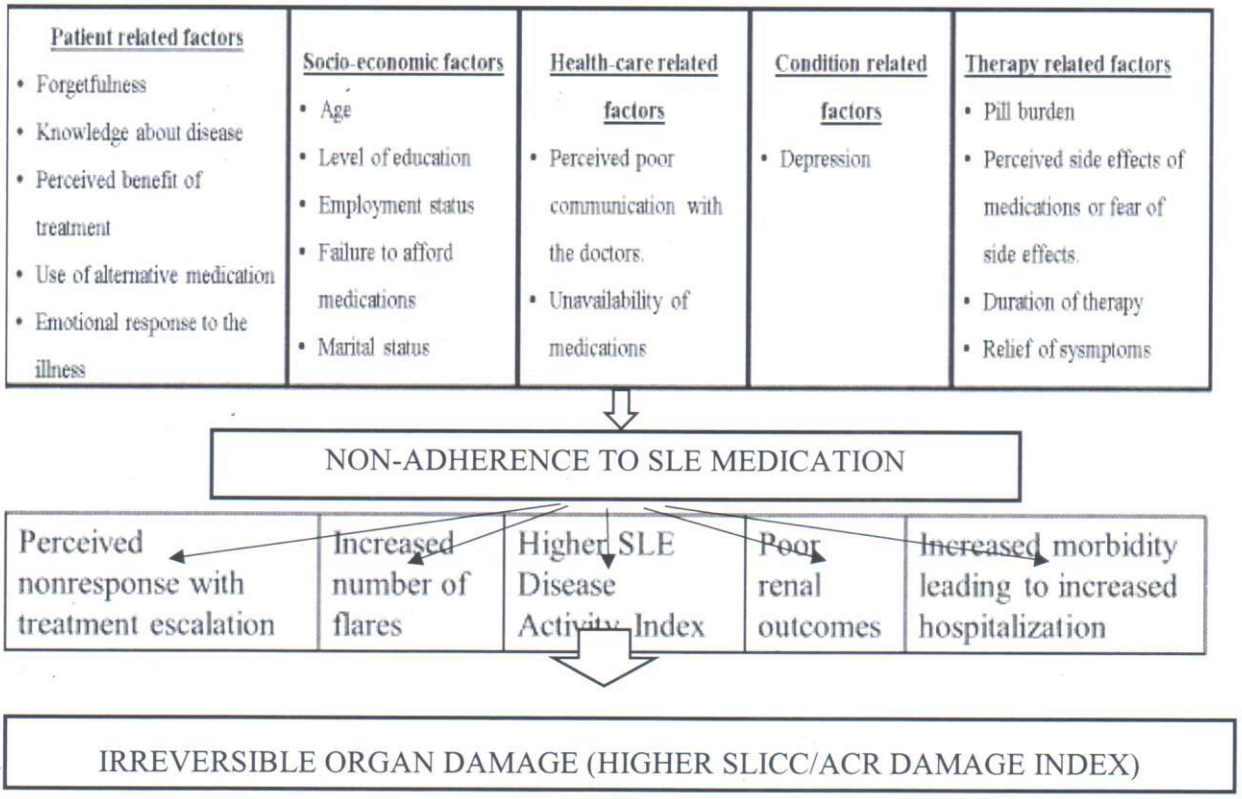


Figure 3: Conceptual framework schema

2.7 Study Justification

Management of SLE is aimed at achieving a prolonged clinical remission [6] which was defined as a one year consecutive period of no disease activity as per assessment using the modified SLEDAI (M-SLEDAI) and the Physician Global Assessment (PGA)[5]. This is associated with less organ damage accrual which is in turn linked to improved long-term patient outcomes and less mortality [48,58,59].

Despite the advantage conferred by remission, most studies show that only a small percentage of SLE patients achieve prolonged remission (Table 2). The study by Tselios et al in 2019 on the SLE disease patterns, pointed out poor medication adherence as one of the factors responsible for poor response in these patients [24].

Indeed, medication non-adherence has been demonstrated to be of significant concern in SLE patients and a major driving force towards lack of clinical remission leading to increased accrued organ damage, increased morbidity and mortality, and poor quality of life [9,17,47,48].

Few studies have been done on SLE medication adherence with most having been done in developed countries and very few in developing countries (Table 3 and 4)[11,32,46,49]. It is generally assumed that non-adherence in developing countries is worse due to inadequate health resources and poor access to healthcare. However, these assumptions fail to give a complete picture.

In Kenya, a study done by Nyambane et al in 2016, only 12% of 62 SLE patients had achieved remission as measured by the SLE Disease Activity Index (SLEDAI) with corresponding low quality of life [28]. It is therefore necessary to investigate medication non-adherence as a contributor to this poor trend.

In Kenya this was, to our knowledge, the first study on SLE medication non-adherence. It provides insight on targeted interventions that can be implemented in order to improve patient outcomes among SLE patients in KNH.

2.8 Research Question

What is the burden of medication non-adherence among Systemic Lupus Erythematosus patients?

2.8 Broad Objective

To determine the prevalence of medication non-adherence and the reasons for medication non-adherence among patients on follow-up for systemic lupus erythematosus at the Kenyatta National Hospital.

2.9 Specific Objectives

2.9.1 Primary Objectives

1. To determine the prevalence of medication non-adherence among patients with Systemic Lupus Erythematosus on follow up at the Kenyatta National Hospital using the MMAS-8.
2. To determine the patient perceived reasons for medication non-adherence among Systemic Lupus Erythematosus medication non-adherent patients on follow up at the Kenyatta National Hospital.

2.9.2 Secondary Objective

1. To determine the association between adherence to medication and the accrued organ damage as measured by the SLICC/ACR Damage Index among patients with Systemic Lupus Erythematosus on follow up at the Kenyatta National Hospital.

CHAPTER THREE: METHODOLOGY

3.1 Study Design

This was a cross-sectional study. The study incorporated the use of both quantitative and qualitative research methods.

The qualitative section utilized the principles of a constructivist grounded theory approach with the use of individual in-depth interviews for data collection.

3.2 Study site

The study was conducted at the Rheumatology Outpatient Clinic at the Kenyatta National Hospital (KNH). KNH is situated within Nairobi and serves as the national referral hospital. It also serves as the teaching hospital of various colleges including the University of Nairobi, College of Health Sciences. It runs various specialized medical outpatient clinics. The Rheumatology outpatient clinic is the only rheumatology specialized clinic in the public health sector in Kenya and follows up rheumatology patients from all over the country. It runs on Tuesdays and Thursdays and is covered by consultant rheumatologists and residents from the department of Internal Medicine, University of Nairobi. The average number of patients seen per clinic ranges from 50 – 60. SLE patient reviews are usually scheduled on Tuesdays, with a few spill overs seen on Thursday. 10-15 SLE patients are seen every week.

3.3 Study Population

The study population comprised of SLE patients who fulfilled the EULAR/ACR classification criteria for SLE (Appendix II) as documented in their medical records at the time of diagnosis. These patients were on follow up at the Rheumatology clinic at the KNH.

3.3.1 Inclusion Criteria

The patients were included in the study if:

1. They were 18 years of age and above.
2. They had an SLE disease duration of at least 6 months from the time of diagnosis.

3.3.2 Exclusion Criteria

Patients with significant cognitive impairment requiring a caregiver to administer medications were excluded from the study. We also excluded those who did not consent to participate in the study.

3.4 Sample Size Estimation

According to the 2019 health records estimates in KNH, approximately 100 SLE patients were on follow up at the rheumatology clinic. A representative sample was drawn from this finite population and the sample size was determined using the Daniel's formula [60] as follows:

$$n = \frac{NZ^2P(1-P)}{d^2(N-1) + Z^2P(1-P)}$$

Where

n' = sample size with finite population correction,

N = size of the target population = 100

Z = Z statistic for 95% level of confidence = 1.96

P = Estimated prevalence of medication nonadherence in SLE patients = 47.5% (Abdul-Sattar et al, 2015)

d = margin of error = 5%

$$n = \frac{100 \times 1.96^2 \times 0.317 \times 0.525}{0.05^2\,(100-1) + 1.96^2 \times 0.317 \times 0.525}$$

n = 79.

3.5 Sampling and Recruitment Procedure

3.5.1 Sampling Method

Consecutive sampling was utilized until the desired sample size was achieved.

For the qualitative section, non-adherent participants were consecutively invited to participate in the in-depth interviews until we achieved thematic saturation.

3.5.2 Study Recruitment Procedure

Participant recruitment was done by the Principal Investigator (PI). The PI attended the Rheumatology Clinic every Tuesday and Thursday between 11am to 5pm. The files of all clinic attendees were initially evaluated. The files with a diagnosis of SLE were then assessed for eligibility. Patients who met the eligibility criteria were then identified and approached individually. They were given a detailed explanation of the study (Appendix III Part A), after which they were required to give a written consent (Appendix III Part B). An eligibility screening form, containing the eligibility criteria for the study, was used for the recruitment of the participants (Appendix I).

Data from the recruited patients was then obtained through a PI administered questionnaire, in-depth interviews, and review of patients' medical records.

3.6 Clinical Methods

3.6.1 Data Collection Tools

1.Morisky Medication Adherence Scale (MMAS-8) Questionnaire (Appendix IV)

The MMAS-8 is a validated self-report measure that assesses medication adherence with a high sensitivity of 93% [34]. It has also been validated for use in different cultural settings for example Germany [61], China [62], Portugal [63], Nigeria [64], Uganda [65], among others. Since its development in 2008, the MMAS-8 has been used in over 200 adherence studies partly due to simplicity and ease of scoring [35]. It has also been used repeatedly in SLE adherence studies [31,45,49,66].

It contains 8 questions. The first 7 questions are scored as yes or no. The last question is answered on a 5-point Likert scale. Patients were classified as adherent if they scored ≥6 and non-adherent if the scored <6.

2. The SLICC/ACR Damage Index for SLE (SDI) (Appendix VII)

This was used to quantify organ damage accrual as documented in the patient's medical records.. This is a validated tool that contains items that represent permanent, irreversible damage in a Lupus patient. The information was extracted from the patient's medical records and included doctor's recorded assessment findings, radiological findings and laboratory findings recorded from the time of SLE diagnosis.

3. Semi-structured Interview Guide (Appendix VI)

This contained a list of open-ended questions set by the Principal Investigator that was used to guide the in-depth interviews. The use of a constructivist grounded theory approach allowed the PI to use prior literature done on the subject (factors affecting non-adherence) to develop the interview guide [67]. The interview guide was then initially piloted in two participants to refine the final guide.

3.6.2 Data Collection Procedure

Stage 1: Demographic data regarding the participants' age, sex, occupation, education level, marital status and the place of residence was obtained and recorded in the study proforma (Appendix V). A list of all their current medications and the disease duration were also recorded.

Adherence to SLE medication was then assessed using the Morisky Medication Adherence Scale (MMAS-8) Questionnaire (Appendix IV) on each of the recruited participants. The scoring of the MMAS-8 questionnaire was done real-time. The participants who score <6 were marked as non-adherent while those who scored ≥6 were marked as adherent.

Stage 2: Participants who were scored as non-adherent were then invited to participate in face-to-face individual in-depth interviews. Consecutive sampling was used to avoid bias. Every non-adherent participant was invited to participate in the interview until we reached thematic

saturation i.e., when additional data failed to identify new factors unique to those expressed in the earlier interviews.. Thematic saturation had been achieved by the 15th interview.

The interviews were conducted by the PI in the consultation rooms at the KNH outpatient clinic department. These interviews were aimed at assessing the various patient perceived reasons for medication non-adherence. One to two interviews were done per recruitment day. The sessions took 30 – 60 minutes. All the interviews were audio-recorded using a digital recorder. The participants were informed before-hand that the sessions would be recorded.

The semi-structured interview guide was used to guide the sessions. The structure of the interviews consisted of the use of initial open-ended questions for example, '*How has your lupus been over the years*?' These were followed by more focused intermediate questions for example '*What herbal remedies have you used over the years*?' The ending question was also more targeted and was aimed at bringing the interview to an end (Appendix VI).

The interviews were then transcribed verbatim by the Principal Investigator with the analysis of the data running concurrently with the data collection.

Stage 3: The medical records of all the participants were then assessed for documented evidence of organ damage based on the SLICC/ACR Damage index for SLE (Appendix VII).

3.7 Outcome Variables

1. **Level of Adherence** – scored from the MMAS-8. Participants scoring <6 were termed as non-adherent and those scoring ≥6 were termed as adherent.
2. **SLE Damage Index** – The Damage Index was scored using the SLICC/ACR Damage Index for SLE (SDI). Participants were categorized into 2 groups – those without any documented evidence of organ damage (SDI Score 0) and those with documented evidence of organ damage (SDI Score ≥1).
3. **Patient perceived factors contributing to non-adherence as assessed by the in-depth interviews**.

3.8 Data Management

3.8.1 Data Entry and Validation

Data was collected on a paper-based form and checked for accuracy and completion by the PI. The data did not bear the participants' name or any unique identifiers; a study registration number was used. The data was then entered by the PI into a password protected Microsoft Excel 2016 spreadsheet with access restricted to only the PI and the statistician.. Data cleaning was done continuously during data entry to ensure accuracy and completeness.

3.8.2 Data Handling and Storage

The data collected was made confidential and only available to the Principal Investigator, the Statistician, and the Supervisors. All digital data was stored in a password protected computer database with backup provided in two password-protected hard-drives. All written data, audio data and the backup hard drives were kept in a locked cabinet, accessible only to the Principal Investigator. All the data will be stored for 5 years and will be availed to the department of Clinical Medicine if required. After this period of 5years, all data will be destroyed by the Principal Investigator.

3.8.3 Data Analysis

3.8.3.1 Quantitative Data Analysis

Cleaned data was exported from the Microsoft Excel 2016 spreadsheet into the SPSS version 23.0 for analysis. Descriptive analysis was done by summarizing socio-demographic and clinical characteristics of the participants into percentages and means/ medians for categorical and continuous data respectively. The prevalence of medication non-adherence was calculated and presented as a proportion of all SLE patients studied with 95% CI. Comparison for the level of adherence and the accrued organ damage was made using the chi-square. All statistical tests were interpreted at 5% level of significance. Tables and charts were used to present the results.

3.8.3.2 Qualitative Data Analysis

The audio-recorded interviews were initially transcribed verbatim. This was followed by reading and re-reading the transcripts in order to completely familiarize with each participant's responses.

This allowed for the noting of recurring ideas with constant comparison between the transcripts. The end result was the development of themes and subthemes that were in line with the study objective. This was done by the Principal Investigator.

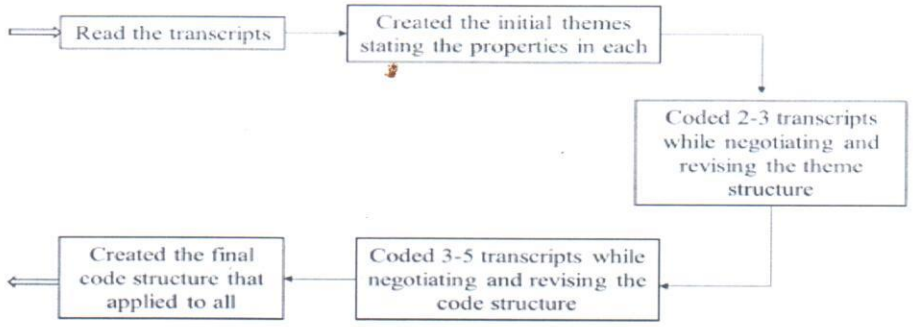


Figure 4: Manual Coding Process

To ensure efficiency, the transcripts were also integrated into a qualitative analysis software (NVivo) which also coded the data, identified emerging themes and grouped the data into themes and subthemes.

Thematic saturation was determined throughout this process.

All the analyzed data was then summarized into thematic charts using the Microsoft Excel 2016 spreadsheet. Synthesis of this data was then done to identify patterns and relationships, in keeping with the objective of this study.

3.9 Quality Assurance

Continuous monitoring and evaluation of the study was done to ensure standards of quality were met. The Principal Investigator had prior Good Clinical Practice certification as well as certification in qualitative research methods. The statistician was also well versed in both quantitative and qualitative research methods.

Three major study tools were used in this study – the MMAS-8 questionnaire, the SLICC/ACR Damage index and the semi-structured interview guide. The MMAS-8 and the SLICC/ACR Damage index are validated study tools and have been used in similar previous studies.

The semi-structured interview questions were based on a rich database from previous studies done on the factors affecting medication non-adherence in SLE patients. The questions were

open-ended to avoid bias. Two pilot interviews were done to test, adjust and perfect the interview guide. The interviews were done by the PI who is a female registrar in Internal Medicine with a special interest in SLE. She had no previous relationship with the participants.

Face to face interviews were done using a digital recorder in a quiet consulting room in the hospital. The proper functionality of the digital recorder was ensured every day and spare batteries were always carried. The interviews recorded were transferred immediately to a password protected computer database to ensure no loss of data. The coding process of the qualitative data was done by both the Principal Investigator and by the use of the software (NVivo). This ensured that the coding process was exhaustive.

3.10 Ethical Considerations

Approval to conduct the study was granted by the Department of Clinical Medicine and Therapeutics as well as the Kenyatta National Hospital-University of Nairobi (KNH/UON) Ethics and Research Committee. A license agreement was also obtained for the use of the MMAS-8 prior to data collection (Appendix VIII).

All eligible patients were required to provide a duly signed informed consent. They were approached individually and given a detailed explanation of the study. The process was voluntary and patients who declined to participate were not discriminated in any way. An option to withdraw from the study at any time without any consequences, was also given to those who consented to participate in the study.

The anonymity and confidentiality of the participants was observed at all times. Their names and hospital numbers were not revealed in the data collection including in the recorded interview, analysis, and reporting of the study findings. A study registration number was used to identify the participants. Privacy of the interview environment was also managed carefully. Transcribing of data from audio-recordings was conducted in a private room using earphones to avoid the possibility of the recordings being heard by other people. Secure storage of all written and digital data was ensured.

The participants did not incur any cost and we ensured that their usual care was not interrupted. All Covid-19 prevention measures were strictly adhered to.

CHAPTER FOUR: RESULTS

4.1 Patient Recruitment

The files of all clinic attendees were assessed on Tuesdays and Thursdays between the months of November 2022 to February 2023.102 files had a diagnosis of SLE and were assessed for eligibility. 19 were ineligible of which; 1 did not meet the EULAR/ ACR classification criteria as documented in the file during the time of diagnosis, 5 were of patients below the age of 18 years, and 13 had a disease duration of less than 6 months. As per the 83 eligible files, the 83 patients were individually approached and given a detailed explanation of the study. 1 patient was excluded as she required the constant assistance of a caregiver to administer medications; and 2 patients declined to provide consent.

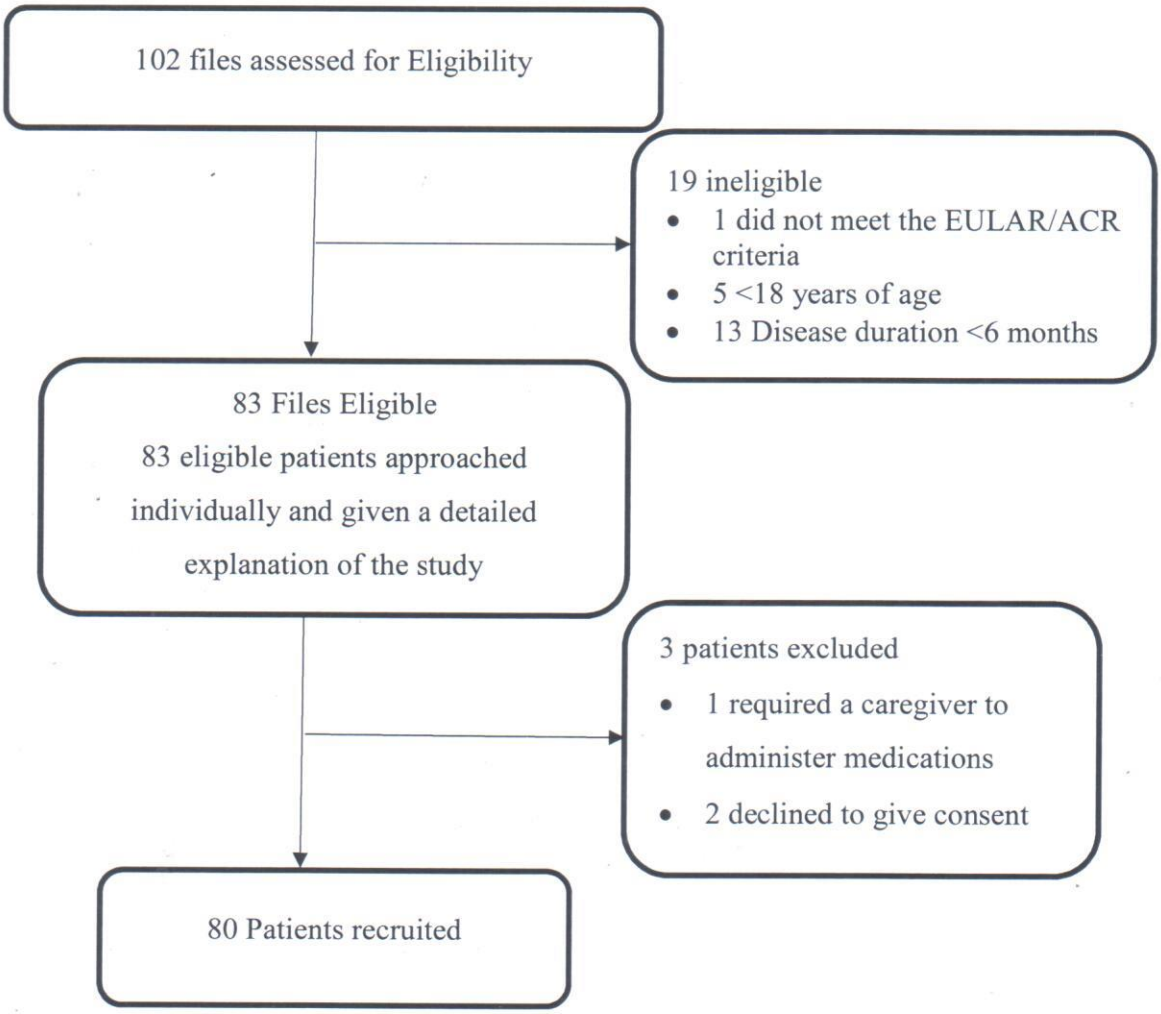


Figure 5: Recruitment flow chart

4.2 Socio-demographic characteristics of the participants

The study population was predominantly female, with 78 females (97.5%) and 2 males. The mean age of the participants was 37.9 years, where the range was 18 years to 68 years. The median age was 36.0 (IQR 26.5 – 47.5) years.

65 (81.3%) had attained a post primary education; 50 (62.5%) were urban residents; 46 (57.5%) were unemployed; and 36 (45 %) were married.

A summary of the socio-demographic variables are depicted in Table 5.

Table 5: Socio-demographic characteristics of the patients

	Frequency *(n=80)*	**Percent**
Age		
≤30	25	31.3
31 – 40	28	35.0
41 – 50	12	15.0
>50	15	18.8
Sex		
Male	2	2.5
Female	78	97.5
Marital status		
Single	30	37.5
Married	36	45.0
Separated	11	13.8
Widowed	3	3.8
Education level attained		
Primary	15	18.8
Secondary	30	37.5
Tertiary	35	43.8
Occupation		
Formal	15	18.8
Informal	19	23.8
Unemployed	46	57.5
Residence		
Urban	50	62.5
Rural	30	37.5

4.3 Clinical characteristics of the participants

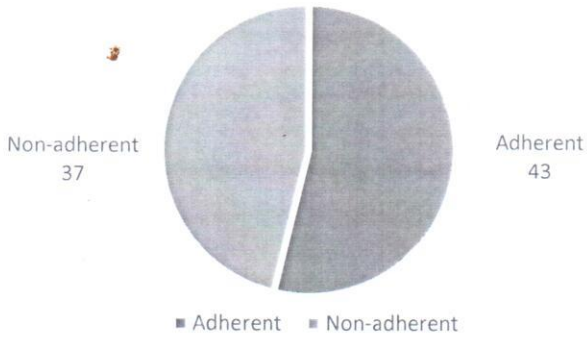
The median duration of illness was 36.0 (IQR 12.0 – 72.5) months with the range at 6 months to 24 years. Majority of the participants (42.5%) had a disease duration of between one to five years. Majority of the participants (62.5%) had a comorbidity with hypertension being the most common comorbidity at 51.3% (41 patients). 6 of the participants were on HCQ mono-therapy. The other participants were on various SLE drug combinations. The most frequently prescribed drug combination was Hydroxychloroquine, Mycophenolate mofetil and glucocorticoids. Biologics were used in 4 of the participants.

Table 6: Clinical characteristics of the participants

	Frequency *(n=80)*	**Percent**
Duration of disease		
6 months to one year	21	26.3
1.1 – 5 years	34	42.5
5.1 – 10 years	16	20.0
>10 years	9	11.3
Comorbidities		
None	30	37.5
Hypertension	41	51.3
Antiphospholipid syndrome	7	8.8
Diabetes	6	7.5
Hypothyroidism	4	5.0
Retroviral disease	2	2.5
Other connective tissue diseases	2	2.5
SLE Medications prescribed to participants		
HCQ only	6	7.5
HCQ + Glucocorticoids	8	10.0
HCQ + Azathioprine	4	5.0
HCQ + MMF	4	5.0
HCQ + Methotrexate	1	1.3
HCQ + Methotrexate + Glucocorticoids	4	5.0
HCQ + Azathioprine + Glucocorticoids	20	25.0
HCQ + MMF + Glucocorticoids	28	35.0
HCQ + Tacrolimus + Glucocorticoids	3	3.8
HCQ + Tacrolimus + MMF + Glucocorticoids	1	1.3
HCQ + Methotrexate + Leflunomide + Glucocorticoids	1	1.3
Biologics (Rituximab)	4	5.0

4.4 Prevalence of Non-adherence to SLE Medications

The prevalence of non-adherence to medication as a proportion of those participants who scored <6 in the MMAS-8, was 46.2% (95% CI, 36.9% - 58.3%).



4.5

Figure 6: Prevalence of Non-adherence to SLE medications

Characteristic presentation of the interview participants

Data saturation had been achieved by the 15th interview. All the various demographic and clinical categories were well presented in the interviews as shown in the table below.

Table 7: Characteristic presentation of the interview participants

	Total participants	Non-adherent	Interview participants
Age			
≤30	25	18	7
31 – 40	28	12	5
41 – 50	12	5	2
>50	15	2	1
Sex			
Male	2	1	1
Female	78	36	14
Marital status			
Single/separated/widowed	44	26	8
Married	36	11	7
Education level attained			
Primary	15	5	3
Secondary	30	13	5
Tertiary	35	19	7
Occupation			
Formal	15	8	4
Informal	19	11	4

Unemployed	46	18	7
Residence			
Urban	50	26	9
Rural	30	11	6
Duration of disease			
<5 years	55	26	12
5.1 - 10 years	16	9	2
> 10 years	9	2	1
SLE Medication combination			
1 – HCQ only	6	2	1
2	17	7	3
3	55	27	10
4	2	1	1

4.6 Perceived reasons for medication non-adherence

Themes and subthemes were identified. These were grouped into those contributing to unintentional medication non-adherence and those contributing to intentional medication non-adherence as shown in Table 7.

Table 8: Perceived reasons for medication non-adherence

Unintentional non-adherence	Intentional non-adherence
1. Access to medication • Failure to afford the medications • Unavailability of medications	1. Perceptions about the medications • The experience of side effects • Perceived lack of benefit
2. Medicine taking behaviors • Forgetfulness	2. Medicine taking behaviors • Apathy • Negative emotional well being • Stigma
	3. Use of alternative methods • Religious or cultural practices • Use of herbal medications • Alcohol and substance abuse
	4. Lack of knowledge about the illness and the medications
	5. Lack of trust in the treating physician

4.6.1 Access to medication

a) Failure to afford the medications

50% of participants stated that the costs of the SLE medications were beyond their financial capability and thus could not adhere to the medications as prescribed.

> *Money is the major reason I do not take my medication. I did not take my medications yesterday. Today the chemist gave me azathioprine for free. I was given a rich man's disease and yet I cannot even afford food.'* **(Participant 3)**
>
> *'Cost is a big issue. If I follow the prescription as is, I will be left with nothing. I spread out the money so that at least I have a bit of every medication.'* **(Participant 11)**

b) Unavailability of medications

The participants obtained their medications from either Kenyatta National Hospital or from pharmacies in Nairobi Central Business District, whether they lived in Nairobi County or outside Nairobi County. Unavailability of immunosuppressants and hydroxychloroquine, was repeatedly pointed out as a reason for medication non-adherence.

> *'HCQ is the only difficult one to get. We have to call a guy called X in town to assist. But there are times it is completely unavailable so you just stay without.'* **(Participant 9)**
>
> *'…….I have looked for tacrolimus for two weeks and now I have given up. Even Kenyatta does not have it, which has never happened before.'* **(Participant 11)**
>
> *I have to look for MMF in town. There are times I also fail to get it in town…….. During these times, I just go without.* **(Participant 12)**

4.6.2 Medicine taking behaviors

a) Forgetfulness

This was the most cited reason for missed medication doses.

> *'I do forget easily especially the evening doses. I will reach home and just sleep.'* **(Participant 3)**

Sometimes I forget. I think lupus affects your memory because I forget a lot. I take my medications once a day so if I leave the house, that is it, I will have forgotten the drugs until the next day.' **(Participant 10)**

b) Apathy

Many of the participants expressed a lack of motivation to adhere to the treatment regimen. Some of the participants had completely stopped taking medications while others maintained an on and off pattern.

Am only taking HCQ which I restarted a month ago. I completely stopped all the other medications for 6 months now. I was tired.' **(Participant 2)**.

'Am the kind of person who does not take medications regularly. When I take and I feel better, I stop for two days, relax, and listen to my body. Taking medications every day is boring.' **(Participant 4)**

'……there was a time I felt the medications were tiring so I was only taking HCQ on alternate days or when I feel like. I needed my body to rest.' **(Participant 11)**

c) Negative emotional well being

Negative emotional wellbeing with resultant non-adherence to medications was noted in some of the responses.

'Most times I feel depressed. I do not want to eat, I do not want to take medications, I do not want to relate with anybody. Am just there.' **(Participant 14)**

'What is the point of all this. The pain is too much. Sometimes I even dream about death. This disease has driven me to a wall.' **(Participant 9)**

'I feel like a huge burden. I look at my parents struggling with my drugs and tests and wish I could die and make it easier for them. Sometimes I just hide the prescription, especially if new drugs have been added.' **(Participant 7)**

d) Stigma

Some of the participants avoided taking medications in certain environments in order to avoid negative comments from their peers, family members or colleagues.

'I cannot talk much at home. People ask me which disease this is that does not stop. They say I have HIV and am only hiding. I cannot take my medications when I am home. The negative talk is too much.' **(Participant 3)**

'As long as my friends and relatives do not know about it, I think I will be okay socially. One time I had a cousin stay over. You should have seen his face when he saw me taking the medications. From that time, if a relative or a friend stays over, I would rather not take the medications.' **(Participant 9)**

4.6.3 Perceptions about the medications

a) The experience of side effects

Several participants had experienced unwanted side effects, which caused them to selectively discontinue some tablets.

'Do you know it is now like a week since I last took HCQ. You see, with HCQ, I get stomach ache, difficulty eating, diarrhea and my legs really swell and cramp. I doubted it from the start so I initially stopped it for three days to do my own research and imagine I was very okay.' **(Participant 1)**

'I hate taking prednisolone. The side effects put me off. Headaches and especially acne yet my skin has been okay all my life. It also gave me pneumonia at one point. I have no issues with the other drugs.' **(Participant 10)**

MMF comes from different companies. There is one I am used to. There are times I fail to get this specific one and what I am given gives me diarrhea. When this happens, I stop taking the medication and wait until the next month so that I can get the one I am used to.' **(Participant 12)**

b) Perceived lack of benefit

Participants decision on which medication to adhere to and which medications to ignore, was guided by symptom control. They labelled a medication as necessary if it conferred to them a tangible benefit.

'If I fail to take my blood pressure medication, the blood pressure goes very high. If I also do not take prednisolone, I will not be able to get out of bed. I can never stop these two. The rest of the medication (MMF and HCQ) am not so sure what they do. Nothing happens when I do not take them.' **(Participant 6)**

'Sometimes I fail to take medications because of various reasons, but I have never failed to take Keppra. I would not want to have another convulsion.' **(Participant 8)**

'For me the one I find effective is prednisolone. It stops the joint pains and swelling. The rest I doubt they have any effect. So, usually, I do not miss taking prednisolone, not ever. The rest (MMF and HCQ) I take when I feel like.' **(Participant 9)**

4.6.4 Use of alternative methods

a) Religious or cultural practices

Participants took religion as their pillar of comfort and strength. For the majority, these beliefs did not intrude on their pill taking practices. For some however, this was not the case.

'Isn't this disease demonic. Even doctors do not know the cause. The only way to fight demons is through spiritual warfare, not taking medications.' **(Participant 14)**

'My family urges me to stop medications in order to have the Quran read to me. I have been taken to Imams to pray for me severally. They tell me it is not a normal disease. It is more spiritual. I have tried everything.' **(Participant 15)**

Other participants sought after traditional practices for healing.

'I once stopped my medications because of traditional healing. They cut my joints to drain out the bad blood.' **(Participant 5)**

b) Use of herbal medications

Ten of the participants reported having used herbal medications. Four of them reported using herbal medications as an adjunct to their prescribed medications. The rest however, reported to have stopped their prescribed medications during the period of herbal medication use.

'I have tried herbal medications. Actually, they are in my house. So many. I had gone to see a herbalist and he stopped all the medications I was taking and gave me his own. Some he would press on my body; others were pills; and others I would boil in water. I stopped them. They did not help me. I became worse.' **(Participant 4)**

'Earlier on, my parents took me to Ethiopia and I was given some herbal medications. Later I was taken to Nanyuki then again to Mombasa for the same. Those drugs did not

help me; I was still in a lot of pain. I asked my mom to allow me to take the prescribed medications after which I got relief.' **(Participant 15)**

c) Alcohol and substance abuse

One of the participants pointed out to using alcohol and 'khat' as a means of relief.

'When you take alcohol, you do not feel the pain. So, I have indulged a bit and also tried out several other things. The best is muguka (khat). It has no side effects and I feel very okay with zero pain. I do not even need to take medications unless I want to.'
(Participant 9)

4.6.5 Lack of knowledge about SLE and the medications

Our participants had poor understanding of lupus and the medications prescribed to them. This was evidenced by:

a) Some participants did not know of the chronicity of SLE.

'I do not know how long this disease will last. No one has ever told me.' **(Participant 6)**

'I do not know how long it will last. I do not know what cures it. Anyway, I do not know much about the disease.' **(Participant 13)**

Others did not understand the relapsing-remitting nature of lupus and therefore the lack of symptoms (especially pain) signified the end of the disease.

'I would like to be tested again for Lupus. I do not believe I have this illness now. I think it is over.' **(Participant 3)**

'I do not think I have Lupus right now because I do not feel anything. I have even gone back to taking a bit of alcohol. I think am now cured.' **(Participant 10)**

b) The purpose of the medications was poorly understood by most participants, especially in the case of immunosuppressants and hydroxychloroquine. Glucocorticoids were generally well taken by most participants because of the benefit they offered in reducing joint pain and swelling.

'Furosemide I know it is for removing excess water. Prednisolone is for pain because when I fail to take it, I get pain. I do not know the use of Azathioprine and HCQ.'
(Participant 4)

'I do not know the uses of MMF or HCQ. I just know that Prednisolone is the one that helps me the most and the ones for blood pressure.' **(Participant 6)**

c) The participants associated Lupus with joint pains, fatigue, and skin manifestations. Most of them however, did not associate kidney involvement, neuropsychiatric manifestations, or cardiovascular manifestations with Lupus. These were either not understood or were taken as completely separate entities from Lupus.

'Ah, Lupus with the kidney, like how? I thought medications are the ones that affect the kidney. Lupus just affects my joints.' **(Participant 1** – on MMF due to proteinuria).

'...because I got two diseases at the same time. I suffer from convulsions in addition to Lupus. I fear the convulsions more, so I never miss taking Keppra. For Lupus I am able to listen to my body and know when my joints are acting up.' **(Participant 8)**

You see again it is hard to take a lot of medications. I also have a heart issue. I suffered a heart attack earlier on, so I have medications for the heart also..... I tend to prioritize the heart medications. **(Participant 13)**

4.6.6 Lack of trust in the treating physician

The participants raised concerns they felt impacted negatively on their patient-doctor relationship leading to medication non-adherence.

a) Lack of continuity of care

'The main problem is finding a new doctor every time and each doctor has to start from the beginning and sometimes give different medications. I find myself skipping the clinic appointments because of this.' **(Participant 9)**.

'I wish each doctor can be given specific patients who they follow up for consistency because our medications keep changing when we see different doctors and it is very confusing.' **(Participant 13)**

b) Dissatisfaction with the service received

'There is one doctor who dispatched me from the clinic. He asked me what proof I have that I have Lupus. I could not answer…… I stopped going to the clinic until my joints were swollen all over again. I wish I could just see the specialists.' **(Participant 13).**

'There are some doctors who brush you off when you ask questions, then at the end add medications. I do not take those medications.' **(Participant 11)**

4.7 Secondary Objective

4.7.1 Organ Damage in SLE

A few set-backs were noted in the scoring of the accrued organ damage due to poor documentation-:

i. Ophthalmology reviews were not routinely done for most patients.
ii. 8 of the patients had evidence of proteinuria by urinalysis only. Quantification of the proteinuria had not been done in these patients as required by the Damage Index. Renal damage was therefore not recorded in these patients.
iii. Despite documentation of amenorrhea or oligomenorrhea in some patients, there was no documentation of hormonal levels for these patients and therefore no patient had a confirmed diagnosis of premature gonadal failure.
iv. Screening for malignancies is not routinely done.

Despite these set-backs, 72 patients (90%), demonstrated some degree of organ damage (with a score of 1 and above). Organ involvement was highest for Renal damage (36/80; 45%) followed by, neuropsychiatric damage (32/80; 40%), peripheral vascular damage 31/80; 38.8%) and skin damage (24/80; 30%).

Table 9: Organ Involvement according to SDI

Organ Involved	Frequency *(n=80)*	Percent
Ocular	6	7.5
Cataracts	2	
Retinopathy	4	
Neuropsychiatric	32	40.0
Major Psychosis	10	
Seizures	7	
Cerebrovascular accident	7	
Peripheral neuropathy	17	
Renal	36	45.0
Proteinuria	35	
Estimated glomerular filtration <50%	8	
End stage renal disease on dialysis	2	
Pulmonary	23	28.8
Pulmonary Hypertension	9	
Pulmonary Fibrosis	13	
Pleural Fibrosis	3	
Pulmonary Infarction	3	
Cardiovascular	15	18.8
Myocardial Infarction	3	
Cardiomyopathy	8	
Pericarditis	6	
Peripheral Vascular	31	38.8
Claudication	26	
Loss of digit or limb	2	
Venous thrombosis	8	
Gastrointestinal	9	11.3
Chronic peritonitis (painless ascites)	9	
Musculoskeletal	14	17.5
Muscle weakness	7	
Deforming or erosive arthritis	7	
Skin	24	30.0
Scarring chronic alopecia	15	
Extensive scarring (other than scalp)	15	
Lupus Panniculum	4	
Lupus Profundus	1	
Skin Ulceration	6	
Diabetes	6	7.5
Malignancy	0	0
Premature Gonadal Failure	0	0

* Note – A participant can have more than one manifestation for each organ

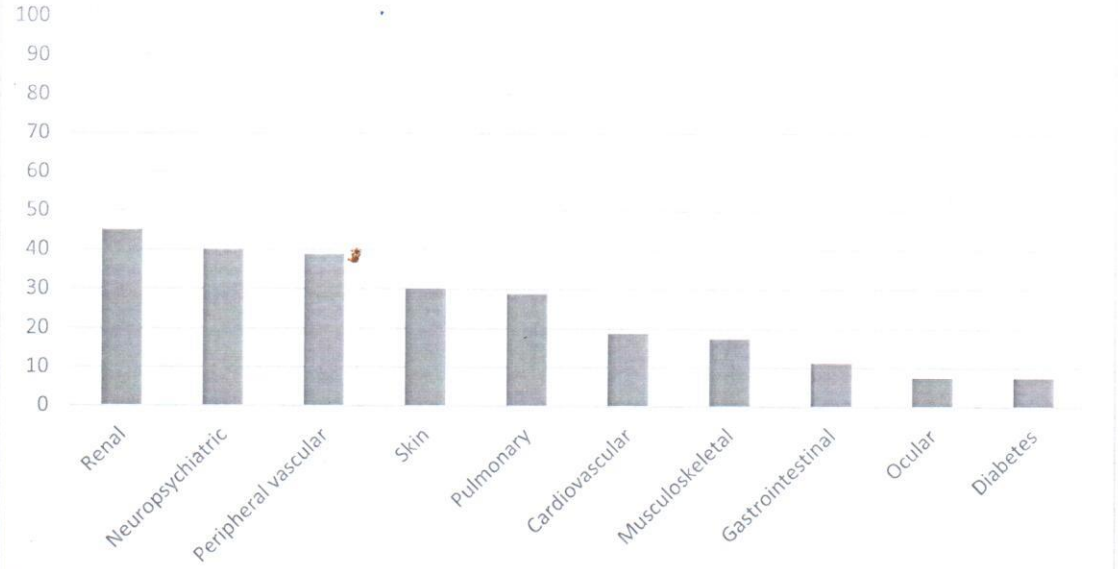


Figure 7:Frequency of organ involvement

4.7.2 Association between the level of medication adherence and the accrued organ damage

No significant association was found between the level of medication adherence and the accrued organ damage as measured by the SDI.

Table 10: Association between the level of adherence to medication and the SDI

	Non-adherence (n=38)	Adherence (n=42)	OR (95% CI)	p-value
Total damage score				
≥1	35 (92.1)	37 (88.1)	1.6 (0.4 – 7.1)	0.550
0	3 (7.9)	5 (11.9)	Reference	

CHAPTER 5: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

This study set out to determine the prevalence of medication non-adherence, and to evaluate the various patient perceived reasons for medication non-adherence, in patients on follow up for SLE at KNH.

The majority of the participants were female with a mean age of 38 years. This is in keeping with epidemiological studies that have shown SLE to be most common in women with a higher prevalence in adults aged 30 - 39 years [2,3].

The prevalence of SLE medication non-adherence was 46 %. This is comparable to the prevalence of SLE medication non-adherence reported in studies done in developing countries. A study done on 80 participants by Abdul-Sattar et al at a university hospital in Egypt reported an SLE medication non-adherence rate of 47.5% [11]. Other similar studies include one done in Jamaica by Chambers et al that reported an SLE medication non-adherence rate of 44% [46]and another done by Prudente et al in Brazil that reported an SLE medication non-adherence rate of 54.1% [68]. In studies done in developed countries, the prevalence of SLE medication non-adherence is significantly lower than the prevalence reported in this study as well as in studies done in other developing countries. A study done by Daleboudt et al in New Zealand reported a non-adherence rate of 13.3% [29]; another done by Georgopoulou et al in the United Kingdom reported a non-adherence rate of 14.1% [43]; and another done by Costedoat-Chalumeau et al in the USA reported a non-adherence rate of 23.4% [31]. This difference in non-adherence rates between the developing countries and the developed countries has been noted by the WHO and has been attributed to the scarcity of healthcare resources in developing countries [8].

Failure to afford medications was identified as a reason for unintentional non-adherence in this cohort. The National Health Insurance Fund (NHIF) is an affordable government health insurance used by many Kenyans to access healthcare especially in the public hospitals like KNH. For majority of Kenyans, NHIF covers inpatient services and radiological investigations to a certain extent, but does not cover outpatient medications. SLE patients on chronic medications, therefore have to pay for the medications or pay for additional private insurance covers. Most of them reported an inability to meet this gap. Failure to afford medications has also been reported

as a reason for medication non-adherence in countries with similar healthcare policies for example Jamaica by Chambers et al [46] and the USA [69]. Studies done in countries with fully publicly funded healthcare system for example United Kingdom and New Zealand, do not report failure to afford medications as a hinderance to SLE medication adherence.

The other reasons for unintentional medication non-adherence were unavailability of medications and forgetfulness. Unavailability of medications was also reported by patients in a qualitative study done by Chambers et al in Jamaica [46]. Forgetfulness is reported as a reason for SLE medication non-adherence in multiple studies [32,45]. In a study done by El-Azizi et at in Egypt, 66.6% of participants reported forgetfulness as the reason for SLE medication non-adherence [48].

Our participants showed multiple gaps in their knowledge about SLE and the medications prescribed to them, resulting in medication non-adherence. The lack of knowledge about SLE and the medications prescribed could explain why our participants' developed apathy and why they developed non-adherence when they perceived a medication to be of no benefit. It could also explain why some of the participants shifted their belief from prescribed medications to the belief that lupus could be controlled using alternative methods. Kobue et al in a qualitative study done in South Arica on medication adherence in Rheumatoid Arthritis patients reported similar findings. The study attributed the lack of knowledge to a number of reasons such as, limited opportunities and time for discussing the illness and treatment with the healthcare team; inability by the patients to seek clarification about the information given; and inconsistent patient education which in our study could be driven by the lack of continuity of care [70].

Various qualitative and quantitative studies done on medication adherence in SLE have shown the important role of patient education in improving medication adherence [42,43,49,71]. The study done by Georgopoulou et al noted that patients with a better understanding of their illness, showed greater participation in decision-making which translated to better adherence to their medications [43]. It is therefore crucial to develop methods of enhancing patient education in this population.

Lack of trust in the treating physician was another reason given by the participants for intentional medication non-adherence. This was mostly caused by the lack of continuity of care as participants reported being reviewed by a different doctor on every visit. The KNH

Rheumatology clinic is run by rheumatology consultants and Internal Medicine registrars. The Internal Medicine Registrars rotate in the rheumatology department on a monthly basis which may contribute to the constant change of doctors as reported by the participants. The study done by Georgopoulou et al reported that greater levels of trust in the treating physician was associated with greater medication adherence rates [43]. The same was reported by Farinha et al in a qualitative study done on SLE patients in Portugal [52]. The two studies stated that greater levels of trust in their treating doctor, made patients develop the confidence to ask questions and to also readily accept the information provided to them [43,52].

Negative emotional well-being was mentioned by our participants as a reason for intentional non-adherence. Omondi et al in a study that explored the perspectives of patients living with SLE, noted that SLE had a lot of negative impact on the lives of patients. This included loss of employment, separation from spouses and pregnancy losses. Mood disorders are also a common manifestation in SLE [55]. In other studies, negative emotional wellbeing has been studied as either an aspect of illness perception or as an aspect of depression. Georgopoulou et al noted in their study that SLE patients with a positive emotional response as a component of illness perception, had better adherence [42]. Depression has also been shown to be associated with SLE medication non-adherence [47]. Our participants were not assessed for depression.

We found stigma to be a reason for medication nonadherence in our participants. Stigma has been mentioned previously as a reality faced by SLE patients. In a local study done by Omondi et al, most participants expressed having faced stigma due to the physical changes that occurred in SLE [72]. A global survey released in May 2018 by the Lupus Foundation of America, showed a low global understanding of lupus, resulting in social stigmas toward people living with lupus [73]. Our study however, is the first to bring up stigma as a reason for medication non-adherence in SLE patients. Stigma has mostly been associated with medication non-adherence in HIV patients [74].

Experience of side effects was found to be a common reason for medication adherence in our participants. This has been reported in other studies as well, including the qualitative studies done by Chambers et al in Jamaica [46] and the United Kingdom [75].

In general, non-adherence to SLE medications was noted to be a multifactorial problem.

90% of our participants showed some degree of organ damage. This percentage may be an under-estimation, considering the set-back of poor documentation noted in the scoring of organ damage in some patients. This is despite the fact that majority (68.8%) had a disease duration of ≤ 5 years. Three major factors contribute to organ damage in SLE. These are persistently high disease activity or the inability to achieve prolonged remission, the presence of comorbidities, and SLE medications especially if given in high doses for prolonged periods [57]. A study done by Nyambane et al in KNH, demonstrated that majority of our patients had moderate to severe disease activity and only 13% had achieved remission at the time of the study. Based on our study, 62.5% of our participants had various comorbidities and 92.5% were on glucocorticoids and/ or immunosuppressive medications in addition to HCQ. All this factors could be contributing to the high prevalence of organ damage in our set-up. However, 90% prevalence of organ damage demonstrated in this study, is a substantially higher percentage than those seen in other studies (28.8% in Canada [76], 47.9% in Malaysia [77] and 49.4% in a 2023 study done in Egypt [78]). Other factors may contribute to this significant difference for example delayed lupus diagnosis as eluded by Omondi et al in a local study [72] and the lack of continuity of care as reported by our participants.

This study did not also show any statistically significant association between the level of adherence and the accrued organ damage. This was contrary to our expectations that the high prevalence of medication non-adherence, which has been shown in previous studies to contribute to higher disease activity, would have a significant contribution to the even higher prevalence of organ damage. Previous studies done by Sun K et al and El-Azizi et al, with similar prevalence of medication non-adherence to our study, demonstrated that patients who were non-adherent to SLE medication had higher accrued organ damage as indicated by their higher SDI scores [17,48]. Since organ damage is assessed from the time of diagnosis, there is a probability therefore, that organ damage in our SLE patients, is largely influenced by late diagnosis with most of our patients presenting with evidence of organ damage at the time of diagnosis [72]. The impact of non-adherence on organ damage in our set up, may therefore be better appreciated by studying the increments in organ damage from the time of diagnosis rather than the presence of organ damage.

5.2 Conclusion

Close to half of SLE patients were found to be non-adherent to their medications. Non-adherence was found to be multifactorial. Failure to afford medications, unavailability of medications, and forgetfulness were pointed out as the reasons for unintentional non-adherence. Lack of knowledge about SLE and the medications prescribed, lack of trust in the treating physician, negative emotional wellbeing, the experience of side effects and stigma formed the basis for intentional non-adherence. Interventions targeted at addressing these barriers could be useful in reducing medication non-adherence in this population. There was no association between the level of adherence and the accrued organ damage.

5.3 Study Strengths

This is the first study focusing on medication nonadherence in SLE at the Kenyatta National Hospital. The use of qualitative methods in our study allowed us to gain a better understanding of this group of patients and to generate concepts that can be used in clinical practice or in future studies.

5.4 Study Limitations

- Our data on medication nonadherence was based on self-report which could have been influenced by social desirability and recall bias leading to underestimation of the extent of nonadherence.
- The qualitative section does not also offer generalizable statistical associations.
- Our study findings were based on a public hospital set up. Therefore, our sample may not be representative of patients with SLE from other clinical settings.
- Poor documentation may have resulted in under-estimation of the extent of SLE organ damage in this population.
- The probability that patients in our set-up present with already existing end organ damage due to delays in SLE diagnosis may have limited the association of medication non-adherence and organ damage.

5.5 Recommendations

1. Advocacy for increased affordability of SLE medications.
2. Advocacy for increased availability of immunosuppressants at the Kenyatta National Hospital.
3. Increased avenues for patient education including creation of educational pamphlets, webinars as well as creating local lupus educational websites.
4. Restructuring of the KNH rheumatology clinic by increasing the number of clinic days. This will ensure that less patients are booked per clinic day, allowing for joint consultation of patients by the consultant and the Internal Medicine registrars in order to ensure continuity of care.
5. Incorporation of psychological support in the management of lupus patients through patient support groups, offering counselling services as well as, active referral of lupus patients to the mental health department for regular psychological and psychiatric evaluation.
6. A follow-up study looking at the impact of medication non-adherence and SLE disease activity and increments in accrued organ damage

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APPENDICES

Appendix I: Eligibility Screening Form

Rheumatology Outpatient Clinic

Unique Identifier Number: ☐☐

Entry Criteria: SLE Diagnosis

Did the participant fulfil the EULAR/ACR classification criteria for SLE at the time of diagnosis?

YES ☐ NO ☐

Additional Criteria:

Criteria	Remarks	
Adult aged ≥18 years	Yes ☐	No ☐
Disease duration of ≥ 6 months	Yes ☐	No ☐
Does not require caregiver to administer drugs	Yes ☐	No ☐
Consent given	Yes ☐	No ☐

If all **YES**, proceed to the Questionnaire

Appendix II: The 2019 EULAR/ACR Classification Criteria for SLE

Entry Criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more lkely explanation than SLE
Occurrence of a criterion on at least one occasion is sufficient
SLE classification requires at least one clinical criterion and ≥10 points
Criteria need not occur silmultaneously
Within each domain, only the highest weighted criterion is counted toward the total score

Clinical domain and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement Proteins	
Low C3 OR Low C4	3
Low C3 AND Low C4	4
SLE-Specific antibodies	
Anti-dsDNA antibody OR	
Anti-Smith antibody	6

Total Score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled

Definitions of SLE Classification Criteria

Criteria	Definition
Antinuclear antibodies (ANA)	ANA at a titre of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid phase ANA screening immunoassay with at least equivalent performance is highly recommended
Fever	Temperature >38.3°C
Leucopenia	White blood cell count $<4.0\times10^9$/l
Thrombocytopenia	Platelet count $<100\times10^3$/l
Autoimmune haemolysis	Evidence of haemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated lactate dehydrogenase (LDH) AND positive Coomb's (direct antiglobulin) test.
Delirium	Characterised by (1) change in consciousness or level of arousal with reduced ability to focus, (2) symptom development over hours to <2 days, (3) symptom fluctuation throughout the day, (4) either (4a) acute/subacute change in cognition (eg, memory deficit or disorientation), or (4b) change in behaviour, mood, or affect (eg, restlessness, reversal of sleep/wake cycle)
Psychosis	Characterised by (1) delusions and/or hallucinations without insight and (2) absence of delirium
Seizure	Primary generalised seizure or partial/focal seizure
Non-scarring alopecia	Non-scarring alopecia observed by a clinician
Oral ulcers	Oral ulcers observed by a clinician
Subacute cutaneous or discoid	Subacute cutaneous lupus erythematosus observed by a clinician: Annular or papulosquamous (psoriasiform) cutaneous eruption, usually lupus photodistributed Discoid lupus erythematosus observed by a clinician: Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/haematological(scalp), leading to scarring alopecia on the scalp If skin biopsy is performed, typical changes must be present. Subacute cutaneous lupus: interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Discoid lupus: interface vacuolar dermatitis consisting of a perivascular and/or periappendageal lymphohistiocytic infiltrate. In the scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition and basement membrane thickening may be noted
Acute cutaneous lupus	Malar rash or generalised maculopapular rash observed by a clinician If skin biopsy is performed, typical changes must be present: interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Perivascular neutrophilic infiltrate may be present early in the course.
Pleural or pericardial effusion	Imaging evidence (such as ultrasound, X-ray, CT scan, MRI) of pleural or pericardial effusion, or both
Acute pericarditis	≥2 of (1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), (2) pericardial rub, (3) electrocardiogram (EKG) with new widespread ST-elevation or PR depression, (4) new or worsened pericardial effusion on imaging (such as ultrasound, X-ray, CT scan, MRI)

Joint involvement	EITHER (1) synovitis involving two or more joints characterised by swelling or effusion OR (2) tenderness in two or more joints and at least 30 min of morning stiffness
Proteinuria >0.5 g/24 hours	Proteinuria >0.5 g/24 hours by 24 hours urine or equivalent spot urine protein-to-creatinine ratio
Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003	Class II: mesangial proliferative lupus nephritis: purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immune-fluorescence or electron microscopy, but not by light microscopy Class V: membranous lupus nephritis: global or segmental subepithelial immune deposits or their morphological sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
Class III or IV lupus nephritis on renal biopsy according to (ISN/RPS) 2003	Class III: focal lupus nephritis: active or inactive focal, segmental or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations Class IV: diffuse lupus nephritis: active or inactive diffuse, segmental or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Positive antiphospholipid antibodies	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titre (>40 A phospholipids (APL), GPL or MPL units, or >the 99th percentile) or positive anti-β2GP1 antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant
Low C3 OR low C4	C3 OR C4 below the lower limit of normal
Low C3 AND low C4	Both C3 AND C4 below their lower limits of normal
Anti-dsDNA antibodies OR anti-Smith (Sm) antibodies.	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥90% specificity for SLE against relevant disease controls OR anti-Sm antibodies

Appendix III: Participant Information and Consent Form

PARTICIPANT INFORMATION SHEET

Study Title: "MEDICATION ADHERENCE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS ON FOLLOW UP AT THE KENYATTA NATIONAL HOSPITAL"

Principal Investigator: **Dr Esther Nyambura Matu**
University of Nairobi
0721778496
estherirumbi@gmail.com

Supervisors:

Prof Omondi Oyoo
Professor, Department of Clinical Medicine and Therapeutics
University of Nairobi

Dr Loice Achieng
Senior Lecturer, Department of Clinical Medicine and Therapeutics
University of Nairobi

Dr Eugene Genga
Lecturer, Department of Clinical Medicine and Therapeutics
University of Nairobi

Introduction

You are being invited to participate in this study. Before you make a decision to do so, it is necessary that you understand why the study is being done and what it will involve. Please take time to carefully read and understand the information given. Feel free to ask us anything that is not clear or if you would like more information provided.

Thank you for reading this information. If you decide to take part, you will be given a copy of this information sheet and your signed consent.

What is the Purpose of this Study?

Adherence to medication has been shown to be an uphill task in many patients with chronic illnesses including Sytemic Lupus Erythematosus with eventual failure to prevent organ damage. This study aims to investigate the extent of medication nonadherence among Systemic Lupus Erythematosus patients of follow up at the Kenyatta National Hospital. We will also seek to understand the various factors that hinder or facilitate medication adherence in these patients. The findings of this study will aid in setting up targeted interventions that will aid in improving adherence in order to increase positive outcomes.

Why have you been chosen?

You have been chosen because you were diagnosed with Systemic Lupus Erythematosus and have been on medication for the same for a period of ≥6 months. There will be approximately 80 participants in this study.

Do you have to take part?

Your decision to participate in this study is voluntary. You may also withdraw from the study at any time without necessarily giving a reason for your withdrawal. Refusal to participate in the study will not affect the services you are entitled to in this facility or any other facility.

What will happen if you take part?

If you agree to participate in the study, the following events will happen:

In a private comfortable area, the interviewer will ask you questions contained in two questionnaires. Information on your personal biodata will also be obtained. This will take approximately 20 minutes.

You may then be invited to participate in an additional in-depth interview lasting approximately 40 minutes to one hour. This interview seeks to understand from the patients' perspective various factors that hinder their adherence to medication. The interview will be audio-recorded in order to allow a more engaging and effective session.

Information regarding evidence of organ damage will be obtained and verified from your medical records.

Are there any risks associated with participating in this study?

You will be required to answer questions which may be personal but this will help in strengthening the study. If there are any questions you feel uncomfortable answering, you are allowed to skip.

Are there any benefits associated with participating in this study?

The information you provide in this study will help us better understand how to aid our SLE patients (including yourself) improve their overall adherence to their medication.

Will your taking part in this project be kept confidential?

All the information that we collect about you during the course of the study will be kept strictly confidential. You will not be able to be identified in any reports or publications. We will use a code number to identify you in a password-protected computer database where we will also store any audio-recordings. Any data collected through paper work will be stored in a locked file cabinet. If your telephone number is required, it will only be used by the study team and will never be shared with others.

Will your participation cost you money?

The study will not cost you anything. All costs pertaining to the study will be borne by the principal investigator. The interview(s) will be done on your routine visit day to the hospital. If you are asked, for purposes of the study, to come back to the hospital on another day, we will reimburse your transport expenses.

Additionally, participation does not attract any monetary compensation.

Contacts for Further Information

If you have any questions, you can contact:

The Principal Investigator, Dr Esther Nyambura Matu, Tel No +254721778496 or email estherirumbi@gmail.com.

The Chairman, KNH/UON – Ethics and Research Committee, P.O. BOX 20723-00202, Nairobi or Tel No 020 2726300 ext 44355 or email uonknh_erc@uonbi.ac.ke.

A. CONSENT TO PARTICIPATE IN THE STUDY

Participant's statement

I have read and understood all the information provided or it has been read to me. I have been given the opportunity to ask questions and these too have been answered satisfactorily. I understand that my participation is voluntary and that I am free to withdraw from the study at any time, without having to give reason and without any consequences.

	Please circle your response	
I agree to take part in the study	YES □	NO□
I agree to the interview being audio-recorded	YES□	NO□
I agree to the use of anonymised quotes in the study report	YES□	NO□

Participant's name: _____

Participant's signature: _____

Date: _____

Researcher's statement

I have fully explained the details of the study to the participant and given him/her an opportunity to willingly participate in the study.

Researcher's name: _____

Researcher's signature: _____

Date: _____

Appendix III: Maelezo ya Washirika na Kibali cha Ruhusa

A. MAELEZO YA WASHIRIKA

Mada ya Utafiti: "UZINGATIAJI WA DAWA KWA WAGONJWA WA SYSTEMIC LUPUS ERYTHEMATOSUS WANAOFUATILIWA KATIKA HOSPITALI YA KITAIFA YA KENYATTA"

Mtafiti Mkuu: **Dr Esther Nyambura Matu**

Chuo Kikuu cha Nairobi

0721778496

estherirumbi@gmail.com

Wasimamizi:

Prof Omondi Oyoo

Profesa, Idara ya Elimu ya Matibabu ya Binadamu

Chuo Kikuu cha Nairobi

Dr Loice Achieng

Mhadhiri Mwandamizi, Idara ya Elimu ya Matibabu ya Binadamu

Chuo Kikuu cha Nairobi

Dr Eugene Genga

Mhadhiri, Idara ya Elimu ya Matibabu ya Binadamu

Chuo Kikuu cha Nairobi

Utangulizi

Unaalikwa kushiriki katika utafiti huu. Kabla ya kufanya uamuzi wa kufanya hivyo, inahitajika uelewe kwanini huu utafiti unafanywa na ni nini kitahusisha. Tafadhali chukua muda kusoma kwa uangalifu na kuelewa habari iliyotolewa. Jisikie huru kuuliza chochote ambacho sio wazi au ikiwa ungependa habari zaidi itolewe.

Asante kwa kusoma habari hii. Ukiamua kushiriki, utapewa nakala ya karatasi hii ya habari na idhini yako iliyosainiwa.

Ni Nini Kusudi la Utafiti huu?

Uzingatiaji wa dawa umeonyeshwa kuwa kazi ngumu kwa wagonjwa wengi walio na magonjwa sugu, ikiwamo ugonjwa wa 'Systemic Lupus Erythematosus', hatimaye kushindwa kuzuia uharibifu wa viungo. Utafiti huu unakusudia kuchunguza kiwango cha wanaokosa kuzingatia dawa kati ya wagonjwa wa Lupus wanaofuatiliwa katika Hospitali ya Kitaifa ya Kenyatta. Tutatafuta pia kuelewa sababu anuwai zinazozuia au kuwezesha uzingatiaji wa dawa kwa wagonjwa hawa. Matokeo ya utafiti huu yatasaidia katika kuanzisha hatua zinazolengwa ambazo zitasaidia katika kuboresha uzingatiaji wa dawa ili kuongeza matokeo mazuri.

Kwanini Umechaguliwa?

Umechaguliwa kwa sababu uligunduliwa na ugonjwa wa Lupus na umekuwa kwenye dawa za matibabu ya ugonjwa huu kwa kipindi cha zaidi ya miezi sita. Kutakuwa na washiriki takriban 80 katika utafiti huu.

Je! Ni lazima ushiriki?

Uamuzi wako wa kushiriki katika utafiti huu ni wa hiari. Unaweza pia kujiondoa kwenye utafiti huu wakati wowote bila kutoa sababu ya kujitoa kwako. Kukataa kushiriki katika utafiti huu hakuwezi kuathiri huduma unazostahiki katika kituo hiki au kituo kingine chochote.

Ni nini kitatokea ikiwa utashiriki?

Ikiwa unakubali kushiriki katika utafiti, matukio yafuatayo yatatokea:

Katika eneo la faragha la kibinafsi, mhojiwa atakuuliza maswali yaliyomo kwenye dodoso mbili. Habari juu ya biodata yako ya kibinafsi pia itapatikana. Hii itachukua takriban dakika 20.

Basi unaweza kualikwa kushiriki katika mahojiano ya kina ya kinasa sauti ya kudumu ya takriban dakika 40 au zaidi. Mahojiano haya yanalenga kuelewa kutokana na mtazamo wa wagonjwa, mambo mbalimbali ambayo yanazuia ufuasi wao wa dawa. Mahojiano yatarekodiwa ili kuruhusu kipindi cha kuvutia zaida na cha ufanisi.

Habari kuhusu ushahidi wa uharibifu wa viungo zitapatikana kutoka kwa rekodi zako za matibabu.

Kuna hatari zozote zinazohusiana na kushiriki katika utafiti huu?

Utahitajika kujibu maswali ambayo yanaweza kuwa ya kibinafsi lakini hii itasaidia katika kuimarisha utafiti. Ikiwa kuna maswali yoyote ambayo hujisikia kujibu, unaruhusiwa kuruka.

Je! Kuna faida yoyote inayohusishwa na kushiriki katika utafiti huu?

Habari unayotoa katika utafiti huu itatusaidia kuelewa vizuri jinsi ya kuwasaidia wagonjwa wetu wa SLE (pamoja na wewe mwenyewe) kuboresha uzingatifu wao kwa jumla kwa dawa zao.

Je! Kushiriki kwako katika mradi huu kutafanywa kuwa siri?

Habari yote tunayokusanya juu yako wakati wa utafiti itahifadhiwa kwa siri. Hutaweza kutambuliwa katika ripoti yoyote au machapisho. Tutatumia nambari ya kukutambulisha katika hifadhidata ya kompyuta inayolindwa na nywila ambapo pia tutahifadhi rekodi yoyote ya sauti. Takwimu yoyote iliyokusanywa kupitia kazi ya karatasi itahifadhiwa kwenye baraza la mawaziri la faili lililofungwa. Ikiwa nambari yako ya simu inahitajika, itatumiwa tu na timu ya utafiti na haitashirikiwa na wengine kamwe.

Je! Ushiriki wako utakugharimu?

Utafiti hautakugharimu chochote. Gharama zote zinazohusu utafiti zitachukuliwa na mchunguzi mkuu. Mahojiano yatafanywa katika siku yako ya kawaida ya kutembelea hospitali. Ukiulizwa, kwa madhumuni ya utafiti, kurudi hospitalini siku nyingine, tutakulipia gharama zako za usafiri.

Kwa kuongezea, ushiriki hauvutii fidia yoyote ya pesa.

Anwani za Habari Zaidi

Ikiwa una maswali yoyote, unaweza kuwasiliana na:

Mchunguzi Mkuu, Dr Esther Nyambura.Matu, Simu Nambari + 254721778496 au barua pepe estherirumbi@gmail.com.

Mwenyekiti, KNH / UON - Kamati ya Maadili na Utafiti, P.O. BOX 20723-00202, Nairobi au Simu Nambari 020 2726300 ugani 44355 au barua pepe uonknh_erc@uonbi.ac.ke.

B. RUHUSU YA KUSHIRIKI KATIKA UTAFITI

Taarifa ya mshiriki

Nimesoma na kuelewa habari zote zilizotolewa au nimesomewa. Nimepewa nafasi ya kuuliza maswali na haya pia yamejibiwa kwa kuridhika kwangu. Ninaelewa kuwa ushiriki wangu ni wa hiari na kwamba niko huru kujiondoa kwenye utafiti wakati wowote, bila kulazimika kutoa sababu na bila matokeo yoyote.

	Tafadhali weka alama kwenye jibu lako	
Ninakubali kushiriki katika utafiti	NDIO□	HAPANA□
Ninakubali mahojiano yakirekodiwa kwa kinasa sauti	NDIO□	HAPANA□
Ninakubali matumizi ya nukuu bila kumtaja aliyesema katika ripoti ya utafiti	NDIO□	HAPANA□

Jina la mshiriki: _____

Saini ya mshiriki: _____Tarehe: _____

Kauli ya mtafiti

Nimeelezea kabisa maelezo ya utafiti huu kwa mshiriki na kumpa nafasi ya kushiriki kwa hiari yake katika utafiti huu.

Jina la mtafiti: _____

Saini ya mtafiti: _____ Tarehe: _____

Appendix IV: The Morisky Medication Adherence Scale Questionnaire (MMAS-8)

Individuals with Lupus all over the world have identified different issues in regards to their medication-use behavior. We are interested in your experiences. There is no right or wrong answer. Please give honest answers based on your personal experience with your prescription SLE medication.

1.	Do you sometimes forget to take your medication?	YES □ (Score=0)	NO □ (Score=1)
2.	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medications?	YES □ (Score=0)	NO □ (Score=1)
3.	Have you ever cut back or stopped taking your medications without telling your doctor, because you felt worse when you took it?	YES □ (Score=0)	NO □ (Score=1)
4.	When you travel or leave home, do you sometimes forget to bring along your medications?	YES □ (Score=0)	NO □ (Score=1)
5.	Did you take your medications yesterday?	YES □ (Score=1)	NO □ (Score=0)
6.	When you feel like your health condition is under control, do you sometimes stop taking you medications?	YES □ (Score=0)	NO □ (Score=1)
7.	Taking medications every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	YES □ (Score=0)	NO □ (Score=1)

8. How often do you have difficulty remembering to take all your medications?

□4 Never/Rarely (Score=1)

□3 Once in a while (Score=0.75)

□2 Sometimes (Score=0.5)

□1 Usually (Score=0.25)

□0 All the time (Score=0)

TOTAL SCORE = _____

□ Score ≥ 6 (Adherent)

□ Score < 6 (non-adherent)

Appendix V: The Study Proforma

Study Date: _____ **Study number:** _____

Date of SLE Diagnosis: _____

Duration of therapy: _____

Age: _____ **Sex:** Male □ Female □

Occupation: Formal _____ Informal _____ Unemployed _____

Marital Status: Single □ Married □ Separated □ Widowed □

Level of Education: □ None □ Primary □ Secondary □ Tertiary

LIST OF MEDICATIONS

	Medication	Dosage

Appendix VI: The Semi-structured Interview Guide

Welcome and Introduction

Lupus

1. Tell me about your journey with lupus. How has it been for you?
   - What impact has lupus had on your life – work, finances, family, social life?
   - How does this diagnosis make you feel?
   - Where do you see yourself 10 years from now in regards to this illness?
   - Are there any beliefs – cultural or religious that affect the way you view Lupus?

2. What do you understand about this disease from your own research or from the information provided by your healthcare providers?
   - How long do you think your lupus will last?
   - What symptoms do you associate with Lupus? (Expound on their knowledge of Lupus complications)

Medications

1. What medications are you on currently?
   - What is your understanding of the reasons why the various medications have been prescribed?

2. What has been your experience with the medications?
   - How effective have these medications been for you? What do you do with the medications once you feel better?
   - Are there any medications you feel have not been effective for you? Do you still take these medications?
   - What negative effects have you experienced with your medication? What changes have you made to deal with the negative effects?
   - How often do you forget to take your medications? When are you most likely to forget to take your medications?

3. What challenges have you faced in obtaining your medication?
   - How much do your drugs cost on a monthly basis?
   - What is the source of these funds? Have you ever failed to take any of your medication as prescribed due to lack of funds?
   - Where do you purchase your lupus medications from?
   - Are the medications always available? What do you do when they are not available?

4. What do you think about herbal medications?
   - Which herbal medications have you used so far? (Probe on whether they stopped the prescribed medications in favor of the herbal remedies)

Clinic Experience
1. What is your experience with the healthcare providers at the rheumatology clinic at the Kenyatta National Hospital? • What do you think can be done to improve your experience?
Closing Question Is there any other issue as pertaining lupus or your medication that you feel you need to discuss?

Appendix VII: The SLICC/ACR Damage Index for SLE

Item	Score
Ocular (either eye by clinical assessment)	
Any cataract ever	1
Retinal change or optic atrophy	1
Neuropsychiatric	
Cognitive impairment (e.g., memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) or major psychosis.	1
Seizures requiring therapy for 6 months	1
Cerebrovascular accident ever (score 2 if > 1)	1(2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate<50%	1
Proteinuria ≥ 3.5 grams/24 hours OR	1
End stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	
Pulmonary Hypertension (right ventricular prominence or loud P2)	1
Pulmonary Fibrosis (physical and radiograph)	1
Shrinking Lung (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary Infarction (radiograph) OR resection not for malignancy	1
Cardiovascular	
Angina or coronary artery bypass	1
Myocardial infarction ever (score 2 if >1)	1(2)
Cardiomyopathy (ventricular dysfunction)	1
Vascular disease (diastolic murmur or systolic murmur >3/6)	1
Pericarditis for 6 months or pericardiectomy	1
Peripheral vascular	
Claudication for 6 months	1
Minor tissue loss (pulp space)	1
Significant tissue loss ever (loss of digit or limb) (score 2 if >1 site)	1(2)
Venous thrombosis with swelling, ulceration or venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver or gallbladder ever for any cause (score 2 if > 1 site)	1(2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture or upper gastrointestinal tract surgery ever	1

Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
Avascular necrosis (score 2 if > 1)	1(2)
Osteomyelitis	1
Skin	
Scarring chronic alopecia	1
Extensive scarring or panniculum other than scalp and pulp space	1
Skin ulceration (excluding thrombosis) for >6 months	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if >1 site	1(2)

* Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

(Gladman DD, Urowitz MB. The SLICC/ACR damage index: progress report and experience in the field)

Appendix VIII: MMAS-8 License Agreement

mmar.
MORISKY MEDICATION ADHERENCE
RESEARCH, LLC.

Certificate Number: 1218-0862-0477-7564-7888

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Assessments		101-500

Customer Information:

ESTHER NYAMBURA MATU

UNIVERSITY OF NAIROBI, SCHOOL OF MEDICINE
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www.moriskyscale.com

Appendix IX: KNH-UON Ethics and Research Committee Approval

UNIVERSITY OF NAIROBI
FACULTY 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/445

7th November, 2022

Dr. Esther Nyambura Matu
Reg. No. H58/33967/2019
Dept. of Clinical Medicine & Therapeutics
Faculty of Health Sciences
University of Nairobi

07 NOV 2022

Dear Dr. Matu,

RESEARCH PROPOSAL: ASSESSMENT OF THE PREVALENCE OF MEDICATION NON ADHERENCE AND ITS ASSOCIATION FACTORS IN AMBULATORY PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AT THE KENYATTA NATIONAL HOSPITAL (P654/07/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P654/07/2022.** The approval period is 7th November 2022 – 6th November 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected 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.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. 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.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Assistant Director, Health Information Dept., KNH
The Chairperson, KNH- UoN ERC
The Chair, Dept. of Clinical Medicine & Therapeutics, UoN
Supervisors: Prof. Omondi Oyoo, Dept. of Clinical Medicine & Therapeutics, UoN
Dr. Loice Achieg, Dept. of Clinical Medicine & Therapeutics, UoN
Dr. Eugene Genga, Dept. of Clinical Medicine & Therapeutics, UoN

PREVALENCE OF MEDICATION NON-ADHERENCE AND ITS ASSOCIATED FACTORS IN AMBULATORY PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AT THE KENYATTA NATIONAL HOSPITAL

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APPROVAL BY LEAD SUPERVISOR AND THE CHAIRMAN OF DEPARTMENT

This dissertation has been submitted with the approval of my lead supervisor and the chairman of the department of Clinical Medicine and Therapeutics.

Lead Supervisor:

Prof Omondi Oyoo

Consultant Physician and Rheumatologist

Department of Clinical Medicine and Therapeutics

The University of Nairobi.

Signed.....Date.....22/11/2023

Chairman of Department:

Prof Erastus Amayo

Consultant Physician and Neurologist

Department of Clinical Medicine and Therapeutics

The University of Nairobi

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Signed .....Date.....24/4/2023