DISEASE ACTIVITY AND ADHERENCE TO DISEASE MODIFYING ANTI-RHEUMATIC DRUGS AMONG RHEUMATOID ARTHRITIS PATIENTS ATTENDING THE KENYATTA NATIONAL HOSPITAL RHEUMATOLOGY CLINIC

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I thank my parents, supervisors, lecturers and colleagues for all their support in this journey.

DECLARATION

I hereby confirm that this dissertation is my own work and has not been presented for a degree at any other institution.

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ANTI CCP	Anti cyclic citrullinated peptide
CD	Cluster of Differentiation
CDAI	Clinical Disease Activity Index
CQR	Compliance Questionnaire on Rheumatology
CRP	C-reactive protein
DAS 28	Disease Activity Score 28
DMARD	Disease Modifying Antirheumatic Agents
ESR	Erythrocyte Sedimentation Rate
HAQ	Health Activity Questionnaire
HLA	Human Leukocyte Antigen
IL	Interleukin
KNH	Kenyatta National Hospital
MHC	Major Histocompatibility Antigen
RA	Rheumatoid Arthritis
ROPC	Rheumatology Outpatient Clinic
SDAI	Simplified Disease Activity Index
SPSS	Statistical Software for the Social Science
TNF	Tumour Necrosis Factor
U.S.	United States
WHO	World Health Organisation

ABSTRACT

Background

Disease activity among RA patients in Kenya has been found to be high in spite of a majority of them being on disease modifying antirheumatic drug (DMARD) treatment. Adherence to DMARDs can be challenging and multiple factors contribute to variable adherence to therapy leading to treatment goals not being met.

Objective

The aim of this study was to evaluate treatment adherence and clinical disease activity among rheumatoid arthritis patients attending the Kenyatta National Hospital Rheumatology outpatient clinic.

Methodology

A descriptive, questionnaire based, cross-sectional study was carried out at the Kenyatta National Hospital (KNH) Rheumatology Outpatient Clinic (ROPC). The sample consisted of patients over the age of 18 with a diagnosis of rheumatoid arthritis diagnosed according to the 2010 ACR criteria who had been on at least 1 DMARD for at least 3 months.

A study proforma was used to collect patient information while the validated 5 item compliance questionnaire of rheumatology (CQR-5) was administered to assess adherence. The clinical disease activity index (CDAI) was used to assess disease activity. Data was presented as measures of central tendency with means or medians with standard deviation for continuous data and as frequencies for categorical data. Bivariate analysis was carried out to detect predictors of adherence.

Results

We recruited 97 patients, of whom 84.5% were female and the mean age was 53.9 years. The overall level of adherence was 49.5%. Low disease activity was found in 5 patients (5.2%), while 85 patients (87.6%) and 7 patients (7.2%) had moderate and high disease activity, respectively. No significant correlation was found between clinical and socio-demographic factors and adherence to DMARD therapy.

Conclusion

Adherence to DMARD therapy and disease activity among RA patients attending the KNH ROPC were determined using simple and effective tools. The adherence level was lower than global averages and WHO recommendations while disease activity was high. A significant association was found between age greater than 62 years and adherence to DMARD therapy. Interventional studies are recommended to help identify suitable measures to combat non-adherence.

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1. INTRODUCTION

1.1 Rheumatoid Arthritis

Rheumatoid arthritis is a chronic systemic inflammatory disease of unknown aetiology. While it has several manifestations, it has a predilection for the joints wherein it causes a symmetrical polyarthritis which may initially be monoarticular. It is the commonest cause of chronic inflammatory arthritis and has an estimated worldwide prevalence of 0.5-1% (1,2). Prevalence of RA in the Kenyan population is unknown but projections based on studies done throughout the continent estimate the prevalence to be around 0.43% (3).

In the list of conditions ranked according to the amount of disability attributed, RA sits at number 42 with a global economic burden of 5.8 billion U.S. dollars annually. (4)

Apart from the economic impact RA has been noted to cause increased mortality mainly through cardiovascular disease. This increased risk is postulated to be due to vascular damage associated with inflammation seen in the disease. An increased risk of development of lymphomas, skin cancer and lung cancer (perhaps due to the shared risk factor of smoking) has also been noted (1).

1.2 Adherence to Treatment

A 2003 World Health Organisation, WHO, report on medication adherence observed that improving adherence to medical treatment may have a far greater impact on improving population health than any advance in specific treatments. This report estimated adherence to treatment in patients with non-communicable diseases in Africa at 50% (5).

Non-adherence to chronic therapies is rampant and costly. Estimates suggest that it costs 300 billion U.S. dollars annually and leads to the need for formulation of new therapies when existing treatments are shown to be ineffective yet the problem is not in the medication as such but rather in the adherence to treatment regimens. Aside from the economic impact, non-adherence also leads to reduced quality of life and relapses (4,6). It has been noted as well that almost a third of all hospital admission can be attributable to medication non-adherence (7).

The need for consistent therapy is highlighted by eight out of ten patients developing joint malalignment and almost half noted to have reduced work capacity within ten years of disease onset (2,8). While early diagnosis and treatment prevents disease progression in almost 90% of patients, once significant joint damage has accumulated it leads to permanent disability such that even achieving clinical disease remission

then does little by way of improving functional status. Permanent disability is caused more by cartilage than bone damage (2).

The level of adherence to RA treatment in the Kenyan population is not known. It is well known that DMARDs facilitate achievement of remission in up to 90% of patients (2). Despite an increase in utilisation of DMARDS, remission rates in Kenya have remained low as was found in a 2009 study by Oyoo and Owino. From 60 patients recruited 46.7% of patients were on DMARDs yet 88% were found to have active disease (9). Ndirangu et al, in 2016, found that while 86.5% of patients were on DMARDS 56-65% still had active disease (10). In a 2017 study at KNH Olago found that in spite of a majority of patients being on DMARDS (86%) most of the patients still had active disease with only 3% having achieved remission (3). Non-adherence may be a reason for the incongruence between DMARD therapy and disease activity seen in our setup. It is therefore important to study treatment adherence to discern the cause of this discrepancy.

1.3 Disease activity

Progression of RA has been linked to increased clinical disease activity. Sub-clinical inflammation as seen by imaging modalities such as ultrasound has not been shown to cause disease progression (1) .

Clinical assessments include joint counts (swollen and tender), global assessments of functioning (patient's and physician's) and inflammatory biomarkers (Erythrocyte Sedimentation Rate and C-reactive Protein). These are then aggregated in various permutations to form clinical indices such as the simplified disease activity index (SDAI), clinical disease activity index (CDAI), Health Activity Questionnaire and the Disease activity score 28 (DAS28), among others. These tools are indispensable in the treat-to-target strategy employed in the management of rheumatoid arthritis where the goal is disease remission.

In the Kenyan population Ndirangu et al found, in a sample of 106 patients, a median Clinical Disease Activity Index (CDAI) score of 11.0 which was indicative of moderate disease activity. They also found that only 10 percent of patients were in remission (10).

A systematic review by Li et al in 2017 looked at the correlation between adherence and disease activity. They included seven studies with a total sample size of 1963 patients and found a significant difference in erythrocyte sedimentation rate (ESR) and tender joint count, both indicators of active disease, between adherent and non-adherent patients. They concluded that RA patients with higher adherence have lower disease activity (11).

2. LITERATURE REVIEW

2.1 Epidemiology

Current prevalence in Kenya is unknown but incidence is on the rise at least in the urban population (3,9). This has been suggested by the increased sample sizes of studies conducted on patients with RA. One of, and perhaps the first study on RA in Kenya, by Bagg et al in 1969 managed to review 76 patients over a period of 18 months while Ndirangu et al, in 2015 106 patients were recruited in the same setting over only ten weeks (4,10). The median age of patients is around 50 years with a female to male ratio of 9:1 (3,9).

The global prevalence is 0.5-1% among adults with a female to male ratio of 3:1 with most cases being detected in the 5th to 6th decade suggesting a hormonal role (1). Prevalence has been noted to vary according to geographic location with a notable decrease as one moves closer to the equator. West Africa is noted to be one region with an especially low prevalence (1).

2.2 Aetiology

Genetics account for 50% of all risk with the greatest being due to HLA DRB1, which codes for the shared epitope (1). This is an amino acid sequence in the antigen presenting groove of the MHC class two proteins. This sequence facilitates presentation of critical antigens to T cells leading to initiation of the pathological process (12). Other genes implicated in the pathogenesis and are associated with increased citrullination of peptide residues of synovial tissues which are then detected as foreign antigen triggering antibody production (notably anti cyclic citrullinated polypeptide antibody, Anti CCP) thereby propagating the disease process. Presence and titres of anti-CCP are associated with increased disease severity (12).

Environmental risk factors include smoking and various bacterial and viral pathogens thought to act by inducing non-pathogen specific changes in the synovial tissues leading to autoimmunity (12).

2.3 Pathophysiology

T cell activation via antigen presentation of citrullinated peptides leads to initiation of inflammation leading to the characteristic histologic finding; lymphocytic infiltration of synovial membranes with formation of a hyperplastic , blood vessel, fibroblast and macrophage rich layer called pannus. It is this layer, via molecules such as Receptor Activator of the Nuclear factor Kappa Beta ligand (RANK-L), Prostaglandins, Tumour necrosis factor alpha, and interleukin 6, all of which lead to osteoclast activation, that is responsible for the bony and cartilaginous damage witnessed in the disease. They also account for the clinical features of the disease; pain, swelling, stiffness and tenderness (2).

2.4 Treatment

While effective non-drug therapies do exist, (1) the cornerstone of therapy remains Disease Modifying Antirheumatic Agents (DMARDS); both conventional (synthetic) and biological (1,2).

Treatment goal is usually remission or low disease activity. This can be achieved through use of combinations of DMARDS with or without glucocorticoids (1). Disease activity progression and permanent disability can be slowed down by early diagnosis and treatment in upto 9 out of 10 individuals (2). The need for achievement of low disease activity is further highlighted by the fact that patients in remission can lead relatively normal lives with normal life expectancy (2) when, otherwise, they would have an increased risk of death due to comorbidities such as cardiovascular disease (1).

DMARDS alleviate symptoms as well as retard disease progression (2). A treat to target approach is used to guide therapy. Non-Steroidal Anti-inflammatory agents only provide symptomatic relief and monotherapy with them is not recommended. DMARDs are divided into synthetic and biologic. Synthetic DMARDS are further subdivided into conventional and targeted. Conventional DMARDs' molecular targets have not been fully identified whereas targeted DMARDs have been developed with particular targets in the pathophysiological process of RA. These targets include Janus Kinases which are intracellular signalling molecules that facilitate the translation of cytokine stimulation into cellular responses (2).

The oldest DMARD which has been in use for more than 50 years is methotrexate with the commonest starting weekly dose of 7.5mg. More than 95% of all patients tolerate methotrexate. Other synthetic DMARDS commonly used include Leflunomide, Sulfasalazine and hydroxychloroquine. Targeted synthetic DMARDS that inhibit Janus associated kinases include baricitinib and tofacitinib (13).

Biologic DMARDS are grouped in two; Tumour necrosis factor (TNF) inhibitors and Non-TNF inhibitors. The former group included five approved drugs; Etanercept, Infliximab, Golimumab, Adalimumab and Certolizumab. Non-TNF inhibitors include the anti-CD20 drug Rituximab, the interleukin (IL) 1 inhibitor Anakinra, IL-6 inhibitors Tocilizumab and Sarilumab, and the T cell costimulation inhibitor Abatacept.

In 2017 Olago found among 107 RA patients attending the ROPC at KNH that 86% were on DMARDS with 60% on Methotrexate, 20% on Leflunomide, and 8% on sulfasalazine. While 46% of the patients were on a steroid only 1.9% were on steroid monotherapy. Herbal medication use was found to be 22.4% (3).

2.4 Adherence

2.4.1 Definition of Adherence

Adherence is defined as the extent to which a patient's behaviour matches recommendations from a healthcare provider to which they agreed in terms of taking their medications and instituting diet and lifestyle changes (4,5,6,14). Compliance on the other hand refers to the extent to which a patient follows medical advice regardless of their own understanding or beliefs. It is a term that has therefore fallen out of favour due to its judgemental overtones (14).

2.4.2 Components of adherence

There are three main components of adherence;

i) Initiation
ii) Maintenance/execution/implementation
iii) Interruption (4).

In terms of medication usage, not taking medication is not the only problem as adherence has been noted to range from suboptimal to overuse (6,10)

Concordance, as a concept related to adherence, identifies and values the patient's expertise and opinions about their illness and medications and recognises that it is the patient who decides whether to and when to take the medication based on the aforementioned aspects (14).

2.4.3 Non-Adherence

Non adherence can also be divided into two other categories; intentional and non-intentional (14). Intentional non-adherence revolves around the patient making a conscious decision to not take their medication due, mainly, to beliefs regarding their illness and the effectiveness and adverse effects of the medications. In short it is a risk versus benefit analysis. Therefore clinicians should not only be focussed on tackling practical and obvious barriers to adherence but must also pay keen attention to the individual patient's understanding of their disease and beliefs about the medications (14).

Unintentional non-adherence on the other hand refers to a patient not taking their medication due to issues such as forgetfulness, unavailability, or physical disability whereby they are dependent on someone else for the administration of their medications (14).

Furthermore non adherence is divided into primary; where the patient did not follow agreed upon instructions from the get-go and secondary where the patient did initiate following of the prescription but terminated before the agreed upon time (4,7).

Notably cross sectional measurement of adherence has its shortcomings as adherence is a dynamic phenomenon that is known to change over time where more often than an increase, a decrease is noted over time (15).

2.4.4 Measures of non-adherence

It is vital that adherence is measured accurately as incorrect estimates may lead to incorrect conclusions such as treatment being deemed ineffective if adherence is incorrectly thought to be adequate. This potentially has far reaching consequences such as unnecessary investigations and intensification of treatment thereby exposing the patient to increased costs and medication related risks (7).

Broadly, two groups of methods of measurement of adherence exist; subjective and objective.

2.4.4.1 Objective Methods

These are divided into direct and indirect methods.

Direct Methods

Direct methods ascertain that the medication has been ingested by the patient. There are two main direct methods;

i) Direct observation and
ii) Drug/metabolite level measurement in serum/urine (7).

Inasmuch as there is little opportunity for bias when using direct methods they have limitations which include being expensive, inaccessible, invasive and useful only in the short term. The last point is especially true given the tooth-brush effect or white coat adherence where patients would take the medication for a few

days before measurement of drug levels which would be within the reference range and one would therefore not be able to discern long-term adherence (4,7,14).

Variation between patients with regard to absorption and elimination of drugs and drug-drug interactions may also lead to incorrect conclusions regarding adherence (4,7,14).

Indirect methods

Most commonly used indirect methods include,

i) Secondary database analysis

This involves assessment of electronic prescription services and insurance claims data, assuming patient prescription refill behaviour corresponds to adherence (7).

Although this does not guarantee that the patient ingested the medication it does provide an excellent and efficient objective tool specific to identification of non-adherence (4,14).

Many studies that employ this tool to assess for adherence commonly use a derivative of the same called the medication possession ratio (M.P.R.) (14). MPR refers to the proportion of supply obtained over a certain time period.

Other drawbacks for these methods include the need for a centralised digital registry which relies on the consistency of prescribers and dispensers to input correct information. The onus of verifying that a patient remains eligible is also on the researchers as they have to ensure that treatment cessation is from non-adherence and not from patient death, change in insurance plans or verbal instructions from the healthcare provider to cease medication use (7).

ii) Electronic monitoring devices

These include the medication event monitoring systems (MEMS). These expensive systems and largely unavailable systems are by far the most beneficial in terms of detecting non-adherence. They work by compiling data on medication use by recording the number of doses taken or missed, noting any deviation from the patients' schedule (4,14).

iii) Tablet counts

Although a cheap and low-tech way of monitoring adherence, tablet counts depend on a patient's propensity to return unused medication and may therefore be insensitive in detecting non-adherence. This method also relies on ensuring that the patient receives the correct amount of medication from the get-go thereby raising a

logistical challenge. It also does not account for the patient starting off with surplus medication which may cause under-estimation of adherence (4,7,14).

2.4.4.2 Subjective Methods

This involves enquiring from the patient, in a variety of methods, whether or not they are adherent. Subjective assessment may be 100% specific when it comes to non-adherence but has an inherent risk of overestimating adherence (as patients provide inaccurate reports to avoid caregiver disapproval) and is insensitive in detecting non-adherence. There is also the fact that patients may not recall adherence beyond the last 24 hours (14).

Commonly employed subjective assessment methods include;

i) Patient diaries

This is where the patient records information about their adherence and relays the written record to the health-care worker for their assessment. The disadvantages of this method include falsification of information and failure to reproduce the diary during the clinic visit. Patients' psychological state may also affect the responses and that may lead to incorrect conclusions (7).

ii) Patient Interviews

Two forms of these exist. The traditional method involves inquiring from a patient their estimation of adherence, their knowledge about drug name, schedule and indication. This feedback is then used by the clinician to arrive at a conclusion (7).

The more modern form is a motivational interview. These combine measurement of adherence and a tailored intervention in one tool. Motivational interviews have been found to outperform traditional advice giving sessions as they address specific identifiable concerns (7).

One of the limitations of this method is the fact that a patient's knowledge of their medication regime has not been found to have a relationship with their adherence to therapy (7).

iii) Questionnaires and scales

These are meant to standardise the information obtained from patient reports. Various questionnaires have been developed for a variety of conditions and many have been validated against other objective measures.

One caveat in administering a questionnaire is that it proves difficult when it comes to assessing patients with low literacy levels (7).

Of more than the 43 validated self-report adherence scales in existence the ones that are most commonly used include;

a) *Brief Medication Questionnaire*

This scale examines a patient's medication taking behaviour as well as any hindrances to adherence they may have. consists of a five item regime screen, a two item each Belief and Recall screens. This scale is mainly used for diabetes and depression patients. One of the main limitations of this questionnaire is the need to review a patient's treatment regimen before administration of the questionnaire rendering it quite time consuming (7).

b) *Hill Bone compliance scale*

This scale which consists of three subscales that measure medication adherence, salt intake and appointment adherence also deals with a patient's medication taking behaviour and hindrances to adherence. However it is specific for use in black patients with hypertension and therefore lacks generalisability (7).

c) *Eight Item Morisky Medication Adherence Scale (MMAS-8)*

This tool was developed in 2008 with 7 yes/no questions and a five point likert like scale for the final question. Aside from measuring adherence this scale also focuses on identifying barriers to adherence. It has been validated for use in hypertension and other chronic diseases which do not include Rheumatoid Arthritis (7).

d) *Self efficacy for appropriate medication use scale (SEAMS)*

SEAMS is a 13 item 3 point Likert type scale and is reliable and consistent across all levels of responder literacy. It is employed in measuring adherence and identifying barriers to it. While it has commendable internal consistency in assessing adherence to medications in chronic conditions, one short-fall of this scale is that it takes very long to administer (7).

e) *Compliance Questionnaire for Rheumatology*

This is a 19 item questionnaire developed and validated for assessing adherence in rheumatological conditions. In a study that compared MMAS-8 to MEMS the questionnaire's performance was comparatively poor (4).

The CQR-19, on the other hand, performed well when compared to MEMS with a sensitivity of 0.98, a specificity of 0.67 and an estimated kappa coefficient of 0.78 (4,14). Abbreviated versions of the CQR-19 have been tested which draw some questions from it. These versions include CQR-5, CQR-9 and CQR-11. CQR-5 has been translated to other languages and validated in several studies (16,17,18).

Lindsay et al, in 2013, sought to reduce the respondent burden of the CQR-19 by reducing the number of questions to five. With a sample size of 225 patients who filled out the CQR_19 they found the CQR-5, after exploratory factor analysis and using Fischer's weighted regression analysis, to have good internal consistency and was successfully able to identify 69% of low-adherers to DMARD therapy (19).

The CQR-19, being the only adherence questionnaire validated for use specifically in patients with rheumatic conditions, lends itself favourably as the tool of choice when assessing medication adherence in these patients. However its lengthy nature precludes its use and we therefore opted to use the abbreviated, five item version; the CQR-5.

2.5 Factors affecting adherence

Several factors are known to play a part in determining if and to what extent a patient is adherent to their medication. As the WHO recognises them they are;

Socioeconomic factors

Demographic factors have been found to be equivocal risk factors in various studies. At times, for example, young age is seen as being favourable while other times it is older age, in fact, that is associated with better adherence (14).

Cultural factors are known to play a role as they influence beliefs about disease and medication. South Asian patients, for example, were found in one study to be more concerned about DMARD therapy than other groups (14).

It has been found that white race, younger age and cohabitation were associated with better adherence to methotrexate among patients with rheumatoid arthritis in a systematic review in 2016 (6).

Healthcare System Factors

Costs of obtaining medications and reimbursement by insurance companies play a big role in medication adherence. Also an important player is the relationship between a healthcare service provider and the patient (14).

It has been established that beginning methotrexate at a later year from diagnosis led to better adherence as did having a specific rheumatologist (6).

Disease factors

A lot of investigation has been carried out to see whether disease activity and other parameters such as morning stiffness have an effect on drug taking behaviour. No unequivocal evidence has been found for which disease factors affect adherence in rheumatoid arthritis but comorbidities and substance abuse have been found to affect adherence in other chronic diseases (4,14).

In the case of methotrexate adherence it was found that a shorter duration of disease, fewer comorbidities, higher CRP, Better patient's global assessment, no ulcers and mild liver disease led to better adherence levels (6).

Medication related factors.

These include complexity of regimen, drug load, delay in onset of action and adverse effects. It has been established that simple dosing regimens, for example methotrexate monotherapy, are associated with better adherence (4,6,14).

Patient Factors

Patients are more likely to take medication when the disease process makes sense to them and treatment seems beneficial. Also important is the patients' perceived cost-benefit implications as well as their overall mental health (4,6,14).

2.6 Prevalence Of Adherence To Medication In RA

Although adherence to medication among rheumatoid arthritis has not been studied in Kenya, various studies have been performed on the subject across the globe; from high income countries to low income countries with similar set-ups and constraints as our own.

A systematic review assessing adherence specifically to Methotrexate in 2016 discovered 13 studies that matched the inclusion criteria, 4 of those employed Medication Event Monitoring Systems, MEMS, in assessing adherence. In one of the four studies with 129 participants 58% were found to be completely adherent while 91% were more than 80% adherent to their prescriptions over the 16 week study duration. The second study had 23 patients with a mean of 107% of doses taken over the study period. The third study's population was an ethnically diverse, economically disadvantaged group of 76. Their mean percentage of correctly taken doses was 67% over two years. The final MEMS study witnessed a drop from 91.2% adherence at 3 months to 69.3% at 12 months (6).

5 studies employed claims data, with the Medication Possession Ratio, MPR, used in three. The first of these assessed adherence in commercial and Medicare enrollees in a large United States health plan with 1668 patients. 64% of these patients had an MPR>80% while in a Medicaid managed program 59% of the patients had that level of MPR. The third was a German sickness fund analysis that found an MPR of 95% for the period during which methotrexate was actively prescribed. A 10 year longitudinal study of Danish patients found a mean of 10.5 out of 12 months per year coverage of methotrexate doses. The fifth of these studies, an analysis of the United States Veterans Affairs Rheumatoid Arthritis Registry, found 84% of the patients with an MPR> 80%. It should be noted however that this population was not representative as 92% of it consisted of men (6).

A nine month prospective Danish study that used CQR at baseline and at 9 months ended up with median scores of 70.1 and 70.6 at baseline and 9 months respectively. It was noted that the 23% of patients who did not complete the 9 month evaluation had lower baseline scores. A study in Mexico utilised a standard drug registry that recorded dose timing and frequency in the prior seven days. 78% of the patients on methotrexate monotherapy were found to have more than 80% of doses correctly taken while for those on multi-drug regimens that number ranged from 14 to 49% (6).

A patient report was used to evaluate adherence at a rheumatology outpatient clinic in rural India. 92% of the patients who returned for their 3-month evaluation reported to have taken the medication as prescribed (6).

A multicentre cross sectional study in Spain that used a validated Spanish version of the Compliance Questionnaire in Rheumatology (sCQR) found an overall adherence level of 79%. This was based on an analysis done on 729 patients who had completed all 19 items on the questionnaire. No difference was noted in terms of which kind of medication the patients were using; conventional DMARDS or biologic

DMARDS. The predictors of adherence were found to be cohabitation and monotherapy. The level of adherence found was higher than the average in Rheumatoid arthritis which is around 66% (15).

A study closer to home in Egypt found a 65% level of adherence among their sample size of 73. Of note is that all the patients were on conventional DMARD therapy with no patient being on biologic DMARDS. A contributor to the relatively high level of adherence (some studies have found levels as low as 16% (7,20)) was the close follow-up of patients which was on a monthly basis. Older age and a high score on the Health assessment questionnaire disability Index (HAQ-DI) were also associated with better adherence (20).

In Brazil a 92 patient study using the Morisky scale to look at adherence in Systemic Lupus Erythematosus (SLE) and RA found strikingly low numbers of 16.4% for RA and 45.9% for S.L.E.. A duration of therapy of more than 15 years and the presence of more than 6 comorbidities were associated with the poor adherence (8).

A study involving 443 adult patients at two hospitals in Thailand that used the CQR-19 as a screening tool to assess non-compliance found a mean CQR-19 score of 80.12. They found a relatively low rate of non-compliance; 22.1%, using a cut-off score of 80 on the CQR-19. The most common reason for non-compliance was noted to be forgetfulness due to busy work schedules. In the multiple regression analysis, however, the only two factors directly linked to poor compliance were found to be older age and poor functional status as measured by the Health Activity Questionnaire (HAQ) (21).

Ragunath et al studied an Australian population at a specialist clinic investigating the level of adherence to biologic agents among 123 patients with rheumatic diseases (59% having RA) using CQR-19. An adherence level of 72% was found which, in view of the patient population being highly educated individuals with access to specialist services including a rheumatology nurse, was deemed low. Factors that favoured better adherence included male gender, young age and fewer medications. Most non-adherence was intentional in nature with reasons ranging from anxiety regarding long-term toxicity of the drugs as well as the influence of disease activity. It was found that when patients perceived a lack of difference in symptomatology before and after they started taking the drug they tended to stop for long periods (22). This study especially highlighted the need for proper patient education as the subgroup exhibiting intentional non-adherence was also the most likely to be less well informed about the disease process and the end-point of poor adherence.

A 2021 study seeking to validate a translated version of the abbreviated form of the CQR-19, the CQR-5, was conducted in Saudi Arabia. The researchers culturally adapted and translated the five item tool which has a maximum score of 20 into Arabic and administered it online. A population of 88 participants who completed the questionnaire was analysed and the overall adherence rate was found to be relatively high at 84.1%. Increasing age and the presence of other comorbidities were associated, although not significantly, with non-adherence. The high level of adherence was attributed to the specialised patient preparation in terms of counselling on adherence, medication administration and adverse effects by a pharmacist (16).

A longitudinal study in Adelaide by Wade et al investigating factors affecting adherence. The tools used include the Belief about medications disease-specific questionnaire (BMQ-specific), the Satisfaction with information about medicines scale (SIMS) and the CQR-19. The investigators found an adherence level >80% in 27.2%, 27.3% and 30.4%. These findings were in a group of 110 patients who had completed the CQR more than once with 92 of them having completed at baseline, 6 months and 12 months. Older age, rheumatoid factor and Anti Citrullinated polypeptide positivity, high sense of medication efficacy and satisfaction with information about medication were the factors associated with improved adherence (23).

In an analysis of a subset of patients enrolled in the ARCO Study (Study on Adherence of Rheumatoid Arthritis Patients to Subcutaneous and Oral Drugs), the researchers analysed 234 patients on oral medication who had completed the CQR-19 questionnaire and found a non-adherence level of 20.9%. It was shown that factors associated with non-adherence included male gender and younger age. Interestingly the investigators noted that disease activity as measured by the Disease Activity Score 28 (DAS-28) was similar among patients who were adherent and those who weren't (2.8 and 2.9 respectively) (24). This further raises the question of the role played by disease activity on medication adherence.

A study in Romania investigated the link between psychosocial factors and adherence to Rheumatoid Arthritis treatment from 2017-2019. 119 patients were enrolled and further divided into two groups of 79 and 40 patients. The patients in the first group were those on conventional DMARDS while those in the second group were those on biologic DMARDS. The tools used included the CQR-9 (a nine question variant of the CQR-19) to assess adherence and the Psychiatric Diagnostic Screening Questionnaire (PDSQ) to assess mental health. The findings of the study were a mean adherence level of 60.34 in group 1 (patients on conventional DMARDS) and 81.3 in group 2 (patients on biologic DMARDS). There was a positive association between major depressive disorder and post traumatic stress disorder with improved adherence. A similar finding was made with female gender and a higher level of education (17).

A 2016 study by Pasma et al compared 3 methods of measuring adherence; Medication Events Monitoring System (MEMS), CQR-19 and direct measurement of adherence via measurement of cellular levels of methotrexate-polyglutamates via spectrophotometry of red blood cell pellet. The sample size was 275 patients of whom 206 were included in the final analysis. The mean CQR composite score ranged from 73.0 - 73.6 over the 12 months of followup. The percentage of patients with compliance <80% was between 30.0% and 44.8%. The study found that early on electronic measurement of adherence was superior to other methods but this advantage faded as time progressed. At the 9 month assessment findings between CQR, MTX-PG levels and MEMS were comparable (25).

The first study attempting to validate the CQR-5 in Saudi Arabia was carried out at the King Fahad Hospital in Medina. The final analysis consisted of 53 patients who fulfilled the inclusion criteria and completed the questionnaire. The reliability of the questionnaire was ascertained by the test-retest method with a two week

interval. The average CQR5 scores obtained were 72.59 and 73.49 a week later. The intraclass correlation coefficient was statistically significant for reliability of the translated version of the CQR5 used. Among factors affecting the CQR5 score only the level of education was significantly found to have an association (18).

Finally, we consider a paper that attempted to use the information gained by assessment of adherence to devise an intervention with the aim of improving adherence. Researchers in France carried out a randomised pilot study with 96 patients on methotrexate with or without biologics. The intervention used was a text message reminder. Patients were divided into three groups; the control group consisting of those receiving a standard consultation, those receiving a pharmacist-led counselling session and the third group consisting of patients receiving text message reminders. CQR-19 was filled by all participants at baseline and at 6 months and scored. It was found that the change in CQR-19 score from baseline and at 6 months was significantly higher only in the text message group with a mean difference of 3.32 points (26). This study underscores the importance of measuring adherence and specifically vindicates the use of the CQR-19 for this purpose as it enables one to observe an objective change in adherence over time.

2.7 Adherence and disease activity

Commonly used measures to assess disease activity in rheumatoid arthritis patients include Disease activity score 28 (DAS-28), Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI). DAS-28 is calculated based on the total number of swollen and tender joints, patient's global assessment of functioning and the level of an acute phase reactant (Erythrocyte Sedimentation Rate or C-Reactive Protein). The SDAI entails the same components as the DAS-28 but does not involve a complex calculation rather just a straightforward summation, while the CDAI involves all the components of the SDAI without the need for invasive blood testing (2).

Contreras-Yanez et al. studied RA patients in remission in Mexico and found that incidence and risk of disease flares were increased in patients who were non-adherent to treatment as compared to those who were adherent. Non-adherence to treatment was also found to be associated with raised E.S.R. (27).

Another study from Mexico; by Salaffi et al, found from their sample of 206 patients a treatment adherence rate of 79.4%. They found that low disease activity led to non-adherence. Other factors associated with an increased risk of non-adherence were older age and a high number of comorbidities (28).

Cannon et al used medication possession ratio to assess adherence to treatment in a sample of 455 RA patients in the U.S.A.. They found an adherence rate of 81%. Markers of disease activity, DAS-28, E.S.R. and C.R.P., were lower in those with high adherence (29).

Arshad et al., studied 100 RA patients using the direct interview method involving patient recall of missed doses. An overall adherence rate of 77% was found. Non-adherence was associated with higher disease activity. Good counselling and education from healthcare providers had a positive influence on adherence to treatment (30).

Xia et al used the CQR-19 and DAS-28 to study adherence and disease activity among 122 RA patients in China. They found an adherence rate of 38%. No significant association was found between adherence and disease activity (31).

A 2018 study by Uckun et al found an adherence rate of 48.5% among 103 recruits. Clinical disease activity as measured by the Disease Activity Score-28 (DAS28) was found to be as follows; 10 patients in the non adherent group were found to be in remission compared to 36 patients in the adherent group. 43 patients in the non adherent group were found to have active disease compared to 14 patients in the adherent group (32).

2.8 Interventions to improve adherence

The goal of measuring adherence and the factors that affect it are always to formulate strategies to improve adherence and therefore treatment efficacy leading to improved patient outcomes. It has been noted that adherent patients are thrice as likely to achieve treatment goals such as improved functional capacity and quality of life (8).

It has been noted that strategies that address more than one factor have better efficacy than those that target a single cause of non-adherence.

Several interventions have been devised to lead to better adherence and among is patient education. This involves informing the patient in a detailed manner how to use the medication.

To improve formulation of interventions it has been suggested by researchers to apply measures on non-adherent patients only, difficult as their identification may be (14).

2.8 Problem statement

The level of adherence to RA treatment in the Kenyan population was unknown. Despite increase in utilisation of DMARDS, remission rates in Kenya had remained low as was found in a 2009 study by Oyoo and Owino. From 60 patients recruited 46.7% of patients were on DMARDs yet 88% were found to have active disease (9). Ndirangu et al, in 2016, found that while 86.5% of patients were on DMARDS 56-65% still had active disease (10). It is well known that DMARDs facilitate achievement of remission in up to 90% of patients (2). Non-adherence may have been a reason for the incongruence between DMARD therapy and disease activity seen in our setup.

2.9 Research Question

Is there a relationship between adherence to DMARD therapy and clinical disease activity among rheumatoid arthritis patients attending KNH ROPC?

2.10 Study Justification

The level of adherence to RA medication varies greatly from one community to another as do the factors that affect adherence. Adherence varies over time necessitating an assessment of the level of adherence to RA treatment every so often. This enables clinicians and researchers to recognise hurdles to adherence and develop measures to improve adherence thereby improving outcomes.

2.11 Objectives

Primary Objectives:

1. To determine the level of treatment adherence to DMARDS among patients with rheumatoid arthritis attending the Rheumatology Outpatient Clinic (ROPC) at Kenyatta National Hospital (KNH) using the CQR-5

2. To determine the clinical disease activity of RA patients attending the KNH ROPC using the CDAI

Secondary Objectives;

1. To determine the association between disease activity and adherence to DMARD therapy among patients with rheumatoid arthritis attending the Rheumatology Outpatient Clinic (ROPC) at Kenyatta National Hospital (KNH)

2. To document certain clinical and demographic determinants of treatment adherence among patients with Rheumatoid arthritis attending the KNH ROPC .

3. METHODOLOGY

3.1 Study Design

We carried out a questionnaire based descriptive cross sectional study.

3.2 Study Site

The study was carried out at the Kenyatta National Hospital's (KNH) Rheumatology Outpatient Clinic (ROPC) in Nairobi, Kenya. KNH is one of two national referral hospitals in the country and runs its specialised rheumatology clinic every Thursday afternoon. New patients are seen by consultant rheumatologists from KNH and the University of Nairobi while patients on follow-up are seen by University of Nairobi Internal Medicine residents in consultation with the rheumatologists.

3.3 Study Population

This consisted of patients with a diagnosis of rheumatoid arthritis based on the American College of Rheumatology attending the ROPC at KNH.

3.3.1 Patient Selection

Inclusion criteria

We screened patient records for adult male and female patients with a diagnosis of rheumatoid arthritis on file. They also had to have been on active treatment consisting of at least one DMARD and been on follow up for at least three months. Patients should have been able to fill the questionnaire in English or Kiswahili or be accompanied by an individual who could aid them in this. Qualifying patients who gave informed consent were included in the study.

Exclusion Criteria

Any patients not fulfilling any of the above criteria.

3.3.2 Sample size estimation

Given a population of 125 patients (N) with a diagnosis of Rheumatoid Arthritis attending the KNH ROPC, using an estimated adherence rate (p) of 65% as was found in an Egyptian study (19) the estimated sample size (n) was calculated using the below equation;

$$n = \frac{Nz^2pq}{E^2(N-1) + z^2pq}$$

Note,

Z= value from a standard distribution for a confidence interval of 95% which is 1.96

q= 1-p

E= desired precision = 0.05

Hence,

$n = (125 \times 1.96^2 \times 0.65 \times 0.35) / (0.05^2(125-1) + (1.96^2 \times 0.65 \times 0.35))$

n = 92

Sample size calculation for a cross sectional prevalence study. Given a population of 125 patients (N) with a diagnosis of Rheumatoid Arthritis attending the KNH ROPC, using an estimated remission rate (p) of 55% as was found by Uckun et al (33) using the following formula;

Note,

Z= value from a standard distribution for a confidence interval of 95% which is 1.96

q= 1-p

E= desired precision = 0.05

Hence,

$n = (125 \times 1.962 \times 0.55 \times 0.45) / (0.052(125-1) + (1.962 \times 0.55 \times 0.45))$

n = 95,

Therefore we required a sample size of at least 95 patients.

3.3.3 Sampling Method

We carried out consecutive enrollment of patients who fulfilled the inclusion criteria until sample size was achieved.

3.4 Clinical Methods

The principal investigator and a trained research assistant extracted relevant data from the patient file onto the study form and thereafter administered the CQR to eligible patients. Thereafter a clinical exam was conducted which entailed examining the patients peripheral joints for swelling and tenderness as well as obtaining a patient and physician global assessment of functioning. These measures were then used to fill in the clinical disease activity index part of the study form.

3.4.1 Study Instruments

The study instruments that were used include the CQR-5 which is an abbreviated form of the only questionnaire validated in assessing adherence in rheumatoid arthritis, the CQR-19. It is a 5 item tool with responses ranked on a likert scale from 1- completely agree to 4-completely disagree. It consists of questions 2,3,5,6 and 17 of the CQR-19 (appendix 1) .

The tool was translated into the Kiswahili language (Appendix 2) using the forward and back translation method by a professional translation service located in Nairobi.

We used the Clinical Disease Activity Index (CDAI) (appendix 3) which is a tool used to assess disease activity. It has 2 objective parameters consisting of the swollen and tender joint counts each out of 28 and 2 subjective parameters including the physician global assessment of function as well as the patient global assessment of function each of which is scored out of ten. The total out of a score of 76 is used to grade disease activity (appendix 3). This score is preferred to others as it is not invasive as compared to others such as the Simplified Disease Activity Index (SDAI) that require measurement of an Acute Phase reactant as they have shown to be comparable in assessing disease activity (9,33).

Additional information that was obtained from patients and their files includes demographic data and clinical characteristics which were recorded onto the study form.

3.4.2 Study Variables

Adherence level; based on the CQR score graded out of 20 with 16/20 (80%) used as the cut-off for adherence.

Disease activity- based on the CDAI score which is graded out of 76 as a composite of tender joint score, swollen joint score, patient and physician global assessment of functioning.

Demographic data;

Age - number of years from documented date of birth

Sex categorised as male/female based on patient's phenotypic characteristics

Marital Status- whether single, married (or cohabitating) or divorced

Primary residence- whether rural or urban

Level of Education= highest level of education completed (primary, secondary, tertiary)

Clinical Characteristics;

Comorbidities; number of all other documented, clinical conditions the patient has.

Seropositivity; Rheumatoid factor and anti CCP positivity according to patient records.

Number of DMARDS; Total number of DMARDs the patient is on

Class of DMARDS; whether conventional or biologic

Types of DMARDs; Specific drugs that the patient is on.

Total number of medications.

3.4.3 Case definition

Rheumatoid Arthritis; A patient with a diagnosis of Rheumatoid Arthritis documented in their file based on the ACR criteria.

3.5 Quality Assurance

Every study form (appendix 4) was carefully reviewed prior to data entry and any form with incomplete or improperly entered data excluded from the final analysis.

3.6 Ethical considerations

Patients were recruited upon giving informed consent by signing the informed consent form (appendix 4). The study was undertaken after obtaining approval from the Ethics and Research Council of the University of Nairobi and Kenyatta National Hospital.

3.7 Data Management

3.7.1 Data handling

All questionnaire and CDAI scores were recorded on paper at first with a unique patient identifier code. This data was then transcribed using an identical Google Forms form into a Google Sheets spreadsheet and exported into a Microsoft Excel 2017 spreadsheet.

3.7.2 Data Analysis

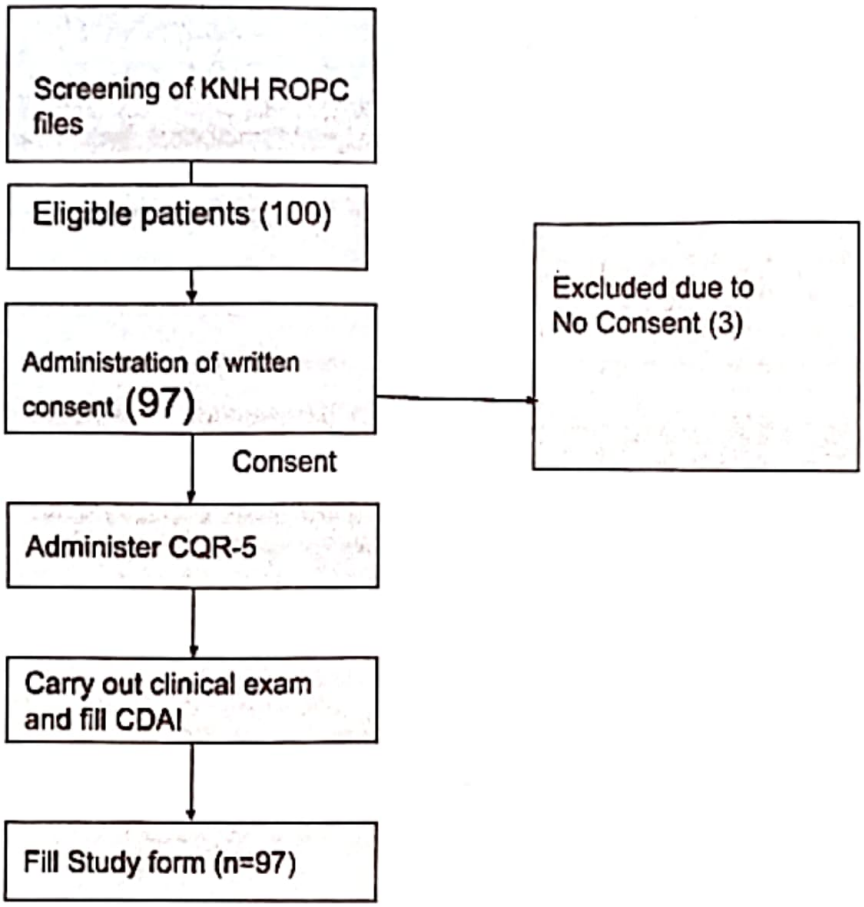
Data was checked for completeness and free of error prior to entry into Microsoft Excel 2017 spreadsheet. Thereafter it was exported to the Statistical Package for Social Sciences version 23.0. Demographic and clinical characteristics of the patients that are categorical were analysed as

frequencies and percentages, while the continuous data was analysed as means with standard deviation or median with interquartile range. The CQR5 score was calculated out of 20 with a score of 16/20 and above indicative of adherence and a score below 16 indicating non-adherence. The level of adherence to RA treatment among patients was calculated as a proportion of those adhering over the total sample size and reported as a percentage. Clinical disease activity according to CDAI score was assessed as follows; a score of 0.0 to 2.8 indicates remission, score of 2.9-10.0 indicates low disease activity, a score of 10.1 to 22 indicates moderate disease activity and a score of 22.1 to 76.0 indicates high disease activity. CDAI grades was analysed as frequencies and percentages. The link between RA adherence and clinical disease activity was analysed with the use of Chi-square test while the link difference in mean CDAI scores between adherent and non-adherent groups was assessed using the independent Student t test. The predictors of adherence were analysed with the use of Chi-square tests for categorical data, and with Independent Student t-test for continuous data, to compare between adherent and non-adherent groups.

4. RESULTS

4.1 Patient recruitment

Files of patients attending the KNH-ROPC were screened to identify patients who fit the inclusion criteria. Thereafter written informed consent was obtained from patients agreeing to participate in the study. Three patients who declined to give consent were excluded. Patients were then asked to fill in the CQR-5 and a clinical examination was then carried out to assess the tender joint count, swollen joint count, patient and physician global assessment of functioning. The study pro-forma was thereafter filled by the principal investigator or a trained research assistant using information obtained from the patient file, CQR-5 and clinical examination.



4.2 Socio-demographic Characteristics

Table 1 shows the sociodemographic characteristics of the sample population of 97 patients. The mean (SD) age was 53.9± 15.4 years with a range of 22-82 years. Majority of the patients were female; 82 (84.5%). Married patients formed 60.8% of the study population. Patients whose residence was primarily rural were 58.8% and 94.8% of patients had at least attended primary school.

Table 1. Sociodemographic characteristics

Variable	Frequency (%)
Sex	
Male	15 (15.5)
Female	82 (84.5)
Age in years	
Mean (SD)	53.9 (15.4)
Min-max	22.0-82.0
Marital Status	
Single	38 (39.2)
Married	59 (60.8)
Primary residence	
Rural	57 (58.8)
Urban	40 (41.2)
Level of education	
None	5 (5.2)
Primary	35 (36.1)
Secondary	34 (35.1)
Tertiary	23 (23.7)

4.3 Clinical characteristics

As demonstrated in table 2, comorbid conditions were present in more than 79 patients with the median number of comorbidities (IQR) being 2 (2-3). Rheumatoid factor was positive in 96.9% of patients while 52.6% were positive for Anti-CCP and 4.1% were Anti-nuclear antibody (ANA) positive. Both RF and Anti-CCP were present in 48.4% of patients. ANA was positive in 5 patients, 4 of whom were RF positive and 1 was anti-CCP positive.

Only five patients were on DMARD monotherapy, while a majority of the patients, 68, were on dual therapy. 5 patients were on biologic DMARDs with all of them taking conventional DMARDs concurrently. Methotrexate was the most commonly prescribed DMARD at 93.8%. The number of medications used by each patient ranged from 2-9 with a median of 6.

Table 2. Clinical characteristics

Variable	Frequency (%)
Number of comorbidities	
Median (IQR)	2 (2-3)
Seropositivity	
Anti-cyclic citrullinated peptide antibody (Anti-CCP)	51 (52.6)
Rheumatoid factor	94 (96.9)
Anti-nuclear factor	4 (4.1)
Class of DMARDS	
Conventional	92 (94.9)
Both	5 (5.1)
Type of DMARDS	
Methotrexate	91 (93.8)
Hydroxychloroquine	73 (75.3)
Leflunomide	33 (34.0)
Sulfasalazine	9 (9.3)
Rituximab	2 (2.1)
Tofacitinib	2 (2.1)
Adalimumab	1 (1.0)
Azathioprine	1 (1.0)
Total number of DMARDS	
Median (IQR)	2 (2-2.5)
Total number of medications	
Median (IQR)	7 (6-7)

4.4 Level of Adherence to DMARD therapy

The main objectives of the study were to determine the levels of adherence to therapy and disease activity among patients with rheumatoid arthritis attending the KNH ROPC.

Table 3 demonstrates that the overall adherence level we found; as a proportion of those patients who scored more than 16/20 on the CQR-5, was 49.5% .

Table 3: Assessment of adherence to RA drugs using CQR-5 tool

Variable	Frequency (%)
Adherence level	
Mean score (SD)	15.8 (1.7)
Min-max	13.0-20.0
Category, n (%)	
Adherent	48 (49.5)
Non-adherent	49 (50.5)

4.4 Clinical disease activity

Clinical disease activity scores as shown in table 4 demonstrate a mean (SD) CDAI score of 17.8 (4.3). Most patients were classified as having moderate disease activity (87.6%) while 5.2% and 7.2% were found to have low and high disease activity respectively. None of the patients were found to be in remission.

Table 4: CDAI

CDAI	
Mean (SD)	17.8 (4.3)
Min-max	4.0-29.0
Grade, n (%)	
Low	5 (5.2)
Moderate	85 (87.6)
High	7 (7.2)

4.5 Correlation between CDAI and adherence to DMARD therapy

Chi square test was used to analyse the correlation between CDAI grades and adherence to DMARD therapy. Odds ratios (p values) of 1.0, 0.6 (0.6) and 0.9 (0.9) were obtained for low, moderate and high disease activity respectively showing no significant difference between adherent and non-adherent groups.

However an independent student t test run to compare the mean CDAI values between adherent and non-adherent groups was found to trend toward significance with a p-value of 0.08 as shown in table 5.

Table 5: Association between disease activity and adherence to DMARDs

Variable	Adherence status		OR (95% CI)	P value
	Adherent (n=48)	Non-adherent (n=49)		
CDAI				
Mean score (SD)	17.1 (4.5)	18.6 (4.0)	-	0.082
Grade, n (%)				
Low	3 (6.3)	2 (4.1)	1.0	-
Moderate	41 (85.4)	44 (89.8)	0.6 (0.1-3.9)	0.612
High	4 (8.3)	3 (6.1)	0.9 (0.1-9.2)	0.921

4.6 Correlation between clinical and demographic factors and adherence to DMARD therapy.

We found a significant difference in adherence between patients aged less than and more than 62 years with the younger group having a higher level of adherence (OR 2.62 p 0.036). No other significant correlation was found between clinical and demographic factors between patients who were adherent to and those that were non-adherent to DMARD therapy. However, there was a tendency toward significance (p=0.11) when comparing adherence between married and married patients. This is demonstrated in table 6.

Table 6 Correlation between clinical and demographic factors and adherence to DMARD therapy

Variable	Adherence status		OR (95% CI)	P value
	Adherent (n=48)	Non-adherent (n=49)		
Sex				
Male	9 (18.8)	6 (12.2)	0.60(0.20-1.85)	0.376
Female	39 (81.3)	43 (87.8)		
Mean age in years (SD)	52.3 (13.7)	55.5 (16.8)	-	0.308
Age group				
Old (>62)	10	20	2.62	0.036
Young (<62)	38	29		
Marital status				
Single	15 (32.2)	23 (46.9)	0.51 (0.22-1.17)	0.115
Married	33 (68.8)	26 (53.1)		
Residence				
Rural	27 (56.3)	30 (61.2)	1.22(0.55-2.76)	0.619
Urban	21 (43.8)	19 (38.8)		
Level of education				
Below primary	19	21	1.14(0.51-2.57)	0.743

Above Secondary	29	28		
Comorbidities Median number (IQR)	2 (2-3)	2 (2-3)	-	0.355
DMARDS Median number (IQR)	2 (2-2.5)	2 (2-2)	-	0.861
Total medications Median number (IQR)	6 (6-7)	7 (6-7)	-	0.184

5. DISCUSSION

Rheumatoid arthritis is a chronic debilitating disease that requires long term therapy. The treatment of this condition, like other chronic conditions, is wrought with hurdles including disease factors, medication related factors and patient factors.

Previous studies in Kenya had shown a high level of disease activity among RA patients despite the majority of patients being on DMARD therapy. We therefore sought to assess the level of adherence to DMARD therapy among RA patients attending the KNH ROPC.

That the level of treatment adherence in our population is low and disease activity high were expected findings. Socio-demographic characteristics as well were found to be within expected margins while we did manage to unearth some previously undiscovered facets of the population.

Socio-demographic trends indicate that the RA population in Kenya is getting older. The average age of patients in our study is 54.9 years which is in keeping with a trend of increasing patient age from a mean of 41.4 years in the year 2007, 48.7 in 2016, 50 in 2017 and 50.7 years in 2020 (3,9,10,34). This trend can have both a positive and negative connotation. It could indicate that RA patients are living longer due to better management of their disease hence being on follow-up for a longer time. On the other hand it could indicate that there is a delay in diagnosis of patients who are then predisposed to having more severe and advanced disease at treatment initiation.

The female to male ratio of our study population; 5.4:1, this more in keeping with global trends of 3:1 compared to previous findings in Kenya which showed a much higher female to male ratio of around 9:1(3,9,10). This change could be indicative of a shift toward increased health seeking behaviour among Kenyan men leading to a higher number being diagnosed with RA.

A higher proportion of patients was found to be rural dwelling than urban; 58.8%. This demographic characteristic has not been previously studied in our population hence we are unable to make a comparison. There was no significant difference in adherence to treatment between the two groups.

There was a higher, though not significantly so, proportion of single respondents who were non-adherent than those who were married ($p=0.11$). This is in keeping with findings made in a systematic review of adherence to methotrexate therapy in RA whereby cohabitation was found to be a significant predictor of adherence (6).

A departure from previous local studies is the finding that there has been introduction of biologic DMARDs (5 patients) into the treatment repertoire with previous studies noting no usage of bDMARDs among study participants (3,9,10). This is an encouraging finding given the low remission rates our population has demonstrated. However increased numbers would be needed to assess the efficacy of these medications compared to the conventional DMARDS in attaining remission.

The level of adherence to DMARD therapy varies widely depending on many factors among them the tool used, patients' demographic and clinical characteristics. The most reliable indirect measure of adherence among patients with rheumatologic diseases remains the Compliance Questionnaire for Rheumatology-19 and we used an abbreviated and validated version of it; the CQR-5.

The total sample size obtained was 97 patients with 48 patients scoring higher than 16 out of 20 on the CQR-5 giving us an overall adherence rate of 49%. The mean CQR-5 score (SD) was 79.0%

(70.5-87.5). The mean CQR-5 score gives us an important benchmark to which future scores can be compared for a measurable assessment of improvement or reduction in the level of adherence.

Global averages for adherence are around the 66% mark (15) which puts our patient population at a much lower level of adherence. This was an expected finding given this population's historic tendency to have high disease activity (3,9,10,34). While similar studies conducted in Africa are scarce to find, one carried out in Egypt demonstrated an adherence level of 65% (20).

While the adherence level found in our population was lower than global averages of 66% many studies have found even lower adherence levels. Prudente et al found an adherence level of 16.4% in their sample of 55 Brazilian patients with rheumatoid arthritis. They found a duration of therapy longer than 15 years and the presence of more than six comorbidities to be associated negatively with adherence (8). This indirectly coincides with our finding of patients who were on more than 6 drugs having a tendency toward non-adherence (p=0.184). This perhaps could be explained by the increased cost of drug acquisition and other difficulties associated with an increased pill burden.

Wabe et al found a lower level of adherence at 27.3% among their sample of 110 patients with RA in Australia. This is much lower than that of our population (49.0%) however the median CQR score of 71-73 % was comparable to that of our population's (79.0%). The only significant socio-demographic factor found to be associated with adherence was older age (>62 years). Similarly, we found a significantly higher level of adherence among patients younger than 62 years compared to those who were older (OR 2.62, 95% CI 1.07-6.45, p=0.033). This difference could perhaps be explained by this group of patients having a higher level of education than the older group with 54 patients having attained higher than primary education in the younger age group compared to 3 patients in the older age group (23).

Many studies, however, found a higher level of adherence. A study on 96 RA patients in France using the CQR-19 found an adherence level of 59%. All patients were on methotrexate with 57% also on biologic DMARDS. This is in stark contrast to our patient population where a minority were on bDMARDS (5.1%). This difference could be explained by the fact that the Aurelian et al study population benefitted from a 15-minute counselling session led by a hospital pharmacist following the standard consultation visit (26). This amenity is not available in our setting.

A 2021 study on 88 rheumatoid arthritis patients carried out in Saudi Arabia using the CQR-5 found an adherence level of 84.1%. This study population was as well subjected to a pharmacist led counselling session which may explain the high level of adherence.

We used the CDAI to assess the level of disease activity. Studies undertaken at the same setting by Olago et al, Ndirangu et al and Jayant et al found active disease in 97.0%, 90.4% and 97.2% respectively (3,10,34). While the number of patients in remission were few in those studies no patient in our study was in remission and while a conclusive answer is beyond the scope of our study it could be postulated that due to closure of the follow-up clinics due to COVID-19 safety protocols some patients may have fallen behind in their management. This factor may also have contributed to the overall low adherence level of our patients.

While no difference in adherence to DMARD therapy was found between groups with high and low disease activity, we did encounter a trend toward significance when comparing the mean CDAI score between the adherent and non-adherent groups (p-0.08). Perhaps with a larger sample size this difference may have been significant. This finding does indicate that poor adherence may be contributing to the high disease activity in our population of RA patients.

6. RECOMMENDATIONS

Now that it is known that the level of adherence to DMARDS is low, follow-up studies with larger sample sizes may be undertaken to identify and address the causes of non-adherence.

Having noted that patients older than 62 years are significantly more likely to be non-adherent than those younger than 62 years it would be worthwhile to especially target this group with adherence enhancing interventions. It would also be prudent to specifically target single patients (as compared to married patients) with these measures as we noted them to have an increased risk of non-adherence.

Studies based on interventions such as employment of rheumatology nurses, shortened periods between follow-up visits and technological innovations such as automated text message reminders may be undertaken to assess their impact on improving adherence (20,22,26).

7. CONCLUSION

Adherence to DMARD therapy and disease activity among RA patients attending the KNH ROPC were determined using simple and effective tools. The adherence level was lower than global averages and WHO recommendations while disease activity was high. A significant association was found between age greater than 62 years and adherence to DMARD therapy. Interventional studies are recommended to help identify suitable measures to combat non-adherence.

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APPENDIX

APPENDIX 1. CQR-19

	Questions
Q1	If the rheumatologist tells me to take the medicines, I do so
Q2*	I take my anti-rheumatic medicines because I then have fewer problems
Q3*	I definitely don't dare to miss my anti-rheumatic medications
Q4	If I can help myself with alternative therapies, I prefer that to what my rheumatologist prescribes
Q5*	My medicines are always stored in the same place and that's why I don't forget them
Q6*	I take my medicines because I have complete confidence in my rheumatologist
Q7	The most important reason to take my anti-rheumatic medicines is that I can still do what I want to do
Q8	I don't like to take medicine. If I can do without them, I will
Q9	When I am on vacation, it sometimes happens that I don't take my medicines
Q10	I take my anti-rheumatic drugs, for otherwise what's the point of consulting a rheumatologist?
Q11	I don't expect miracles from my anti-rheumatic medicines
Q12	If you can't stand the medicines you might say: "throw it away, no matter what"
Q13	If I don't take my anti-rheumatic medicines regularly, the inflammation returns
Q14	If I don't take my anti-rheumatic medicines, my body warns me
Q15	My health goes above everything else and if I have to take medicines to keep well, I will
Q16	I use a dose organizer for my medications
Q17*	What the doctor tells me, I hang on to
Q18	If I don't take my anti-rheumatic medicines, I have more complaints
Q19	It happens every now and them, I go out for the weekend and then I don't take my medicines

Note: Items denoted with * have been retained in the final 5 item CQR5 questionnaire.

The above questions are answered based on a 4 point Likert like scale ranging from Strongly disagree (1 point), Disagree (2 points), Agree (3 points) and strongly agree (4 points) with a total score out of 20.

APPENDIX 2 Kiswahili Translation of the CQR-5

APPENDIX 1 CQR -19
Questions

ENGLISH TO SWAHILI TRANSLATION

English	Swahili
Q 2. I take my anti-rheumatic medicines because I then have fewer problems	Q2. Huwa ninatumia dawa zangu za baridi yabisi kwa sababu zinanipunguzia matatizo.
Q 3 I definitely don't dare to miss my anti-rheumatic medications	Q3. Bila shaka siwezi kukosa kutumia dawa zangu za baridi yabisi
Q5. My medicines are always stored in the same place and that's why I don't forget.	Q5. Muda wote huwa natunza dawa zangu sehemu moja na ndio sababu huwa sisehau.
Q6. I take my medicines because I have complete confidence in my rheumatologist	Q 6. Huwa ninatumia dawa zangu kwa sababu nina imani na ushauri wa daktari wangu wa baridi yabisi
Q 7 What the doctor tells me, I hang on to	Q 7. Kile Daktari ananiambia, ninashikilia

BACK TRANSLATION OF THE SWAHILI TRANSLATION TO ENGLISH

Swahili	English
Q 2. Huwa ninatumia dawa zangu za baridi yabisi kwa sababu zinanipunguzia matatizo.	Q 2. I take my anti-rheumatic medicines because then I have fewer problems
Q 3. Bila shaka siwezi kukosa kutumia dawa zangu za baridi yabisi	Q 3 Of course I don't dare miss using my anti-rheumatic medications
Q 5 Muda wote huwa natunza dawa zangu sehemu moja na ndio sababu huwa sisahau.	Q 5. I always keep my medication in one place and that is why I don't forget
Q 6. Huwa ninatumia dawa zangu kwa sababu nina imani na ushauri wa daktari wangu wa baridi ya bisi	Q 6. I take my medicines because I have confidence in the advice of my rheumatologist
Q 7. Kile Daktari ananiambia, ninashikilia	Q 7. What the doctor tells me, I hang on to

Certified as true translation of the original
SIGNED.....
SEAMLESS EVENTS SOLUTIONS

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COMMUNICATING THE ESSENCE
Corporate Events – Translations – Conferences

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04.12.2021

TO WHOM IY MAY CONCERN

CERTIFICATE OF TRANSLATION

We certify that Appendix 1 CQR -19

1. Question 2
2. Question 3
3. Question 5
4. Question 6
5. Question 7

– were translated by **Seamless Events Solutions** from their English version into Swahili and then back translated from Swahili into English

We further certify these are true translations of document provided by the client.

Yours Faithfully,

JAMES GACHARA NDIRITU

SEAMLESS EVENTS SOLUTIONS LIMITED
P.O. Box 75457 - 00200 NAIROBI

We work hard, deliver and love it!

APPENDIX 3. CDAI

Tender Joint score	___/28
Swollen Joint score	___/28

Patient global assessment of functioning	___/10
Physician global assessment of functioning	___/10
Total	___/76

APPENDIX 4. Data collection form

Demographic and clinical data form

*Required

Demographic data

1. Study number *

_____

2. KNH IP/OP number *

_____

3. Sex *

Mark only one oval.

- ◯ Female
- ◯ Male

4. Age *

_____

5. Marital Status *

Mark only one oval.

- ◯ Single
- ◯ Married
- ◯ Separated/Divorced/Widowed

6. Primary Residence *

Mark only one oval.

- ◯ Rural
- ◯ Urban

7. Level of Education *

Mark only one oval.

- ◯ None
- ◯ Primary
- ◯ Secondary
- ◯ Tertiary

Clinical characteristics

8. Time from initial diagnosis *

_____

Example: 4.03.32 (4 hours, 3 minutes, 32 seconds)

9. Number of comorbidities *

_____

10. Seropositivity *

Tick all that apply.

- [ ] Rheumatoid factor
- [ ] Anti-cyclic citrullinated peptide antibody (Anti-CCP)
- [ ] Anti-nuclear factor
- [ ] None
- [ ] Not available

11. Class of DMARDS

Mark only one oval.

- ◯ Conventional
- ◯ Biologic
- ◯ Both

12. Types of DMARDS *

Tick all that apply.

- [ ] Methotrexate
- [ ] Hydroxychloroquine
- [ ] Azathioprine
- [ ] Mycophenolate mofetil
- [ ] Leflunomide
- [ ] Sulfasalazine

Other: [ ] _____

13. Total number of DMARDS *

_____

14. Total number of medication *

_____

15. CDAI score *

_____

16. CQR-5 score *

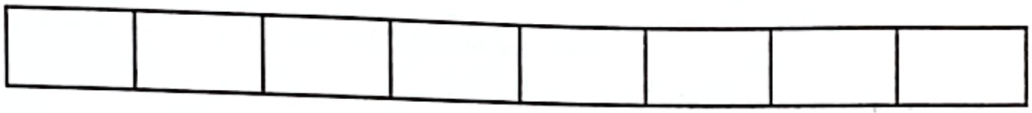
_____

TABLE 1; DEMOGRAPHIC DATA

Study #	KNH IP/OP #	Age	Sex	Marital status	Residence	Level of education

TABLE 2; CLINICAL DATA

Study #	Time From Initial Diagnosis	Comorbidities (Number)	Seropositivity (Positive, Negative Or N/A)	Number Of Dmards	Total Number Of Medications	CDAI Score	CQR-5 Score



APPENDIX 5; CONSENT FORMS

Consent Form; English

INFORMED CONSENT FOR RESEARCH STUDY TO DETERMINE THE PREVALENCE OF TREATMENT ADHERENCE AND ITS CORRELATION TO DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS PATIENTS ATTENDING THE KNH ROPC.

Institution:

Department of Clinical Medicine and Therapeutics, College of Health Sciences
University of Nairobi,
P.O BOX 30197-00400, Nairobi.

Principal Investigator:
Dr. Abdulaziz Hassanali Mithwani

P.O.BOX 52019 00200, Nairobi.
Tel : 0725866917

Lead Supervisors: Professor George Omondi Oyoo, Dr Eugene Kalman Genga.
Department of Clinical Medicine and Therapeutics (UoN).

Ethical Approval:
Kenyatta National Hospital /University of Nairobi Ethics and Research committee,
P.O. BOX 20723-00100, Nairobi.
Tel 2726300/2716450 Ext 44102

Introduction

I am Dr.Abdulaziz Mithwani, a postgraduate student pursuing a degree in Master of Medicine in Internal Medicine at The University of Nairobi. I am conducting a study on rheumatoid arthritis patients as part of my degree program.

This form will give you information you need to decide if you want to participate in the study. If you have any questions, do not hesitate to ask for clarification.

Purpose of Study

I am carrying out a study to look at the prevalence of adherence to treatment in patients with rheumatoid arthritis.

It is my aim to improve the treatment of patients with rheumatoid arthritis with the findings of this research.

Study Procedures

Once you agree to participate in the study, you will sign a consent form. Socio-demographic data will then be collected from you.

You will then be given a CQR-5 questionnaire to complete. A brief examination and some follow up questions will be asked to assess your disease condition and severity. We will also be collecting data from your file on tests already done.

Risks and costs incurred

There are minimal risks involved for participation in the study. Any information you reveal to us is strictly confidential.

Voluntariness of participation

Your participation in this research is voluntary and in the event that you refuse to participate in this study, your treatment will not be affected. If you choose to participate and not answer certain questions, you are free to do so. You are free to terminate the interview and withdraw from the study at any time. You are free to ask questions before signing the consent form.

Confidentiality

All your responses as well as your results will remain confidential. Your individual responses will be stored in a locked place under my control and will only be seen by my statistician and I.

Benefits of Participation

Your participation in the study bears no cost to yourself.

Information obtained will improve knowledge to health care givers at Kenyatta National Hospital.

Risks of participation

There are no risks of participation

Right of Withdrawal

You may at any point in time choose to withdraw from the study without any fear or risk of any damages to yourself and to your course of treatment.

Contacts

Principal Investigator

Abdulaziz H. Mithwani

Tel; 0725866917 email abdul.hassanali07@gmail.com

Primary Supervisors

Prof. George Omondi Oyoo

Tel; 0722522359

Email; geomondi@hotmail.com

Dr Eugene Genga

Tel; 0723596189

Email; eugenekalman@gmail.com

In case you need to contact me, my academic department or the Kenyatta National Hospital / University of Nairobi Ethics and Research Committee concerning this study, please feel free to use the contacts provided above.

I request you to sign the consent form attached.

CONSENT FORM – PATIENT / NEXT OF KIN

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant/ Next of kin:.....

Signature / Left thumbprint of subject:.....

Date:.....

Investigator's statement:

I, the Principal Investigator, have fully informed the research participant on the purpose and implication of this study.

Signed: ..... Date: .....

Consent form; Kiswahili

Fomu ya maelezo ya utafiti wa kiwango cha uzingatiaji wa matumizi ya madawa katika wagonjwa wenye maumivu ya viungo

Taasisi: Idhaa ya matibabu ya watu wazima, Chuo cha sayansi ya afya, Chuo kikuu cha Nairobi S.L.P. 30197-00400, Nairobi.

Mtafiti mkuu: Dkt. Abdulaziz Hassanali Mithwani, simu 0725866917, S.L.P. 5201900200, Nairobi. Idhaa ya matibabu ya watu wazima

Msimamizi mkuu: Prof. George O. Oyoo Simu 0722522359 na Dkt, Eugene K. Genga Simu 0723 596189, Idhaa ya matibabu ya watu wazima

Ridhaa:

Kenyatta National Hospital /University of Nairobi Ethics and Research committee, S.L.P. 20723-00100, Nairobi. Tel 2726300/2716450 Ext 44102

Utangulizi

Ninataraji kufanya uchunguzi kuhusu kiwango cha uzingatiaji wa matumizi ya madawa katika wagonjwa wenye maumivu ya viungo na ningependa uhusike. Utafiti huu unahitajika kama sehemu ya masomo yangu lakini matokeo yatakayopatikana yatatumiwa kutoa maelezo, ambayo ikiwa itatumika italeta manufaa katikaa matibabu na hali ya maisha ya wagonjwa wa maumivu ya viungo. Fomu hii ni ya maelezo yote utakayohitaji ukiamua kama utajiunga na utafiti huu. Unapoisoma na baada ya kusoma fomu hii, uko huru kuuliza maswali yoyote kama kuna sehemu hujaelewa vyema.

Lengo la utafiti

Ninafanya utafiti huu ili kukagua kiwango ya uzingatiaji wa matumizi ya madawa katika wagonjwa wanaougua maumivu ya viungo na kutafuta sababu za kutoweza kutimiza uzingatiaji.

Utaratibu wa utafiti:

Mara utakapokubali kuhusika kwenye utafitu huu, utatia sahihi katika fomu ya ridhaa na matakwa ya utafiti. Pia utapewa fomu itakayokuwa na maswali matano ambayo utatakikana kujibu. Itabidi ujibu maswali ya kibinafsi utakayoulizwa kisha utachunguzwa kimwili.

Hatari na gharama inayohusika

Hakuna hatari wala gharama yoyote kwako kwa kujiunganisha na utafiti huu..

Haki zako

Kujiunga na utafiti huu ni kwa hiari yako. Hutabaguliwa kimatibabu ukikataa kujiunga na utafiti huu. Ukijiunga na utafiti huu na ushindwe kujibu mojawamo au maswali mengine tutakayouliza, ni sawa. Una uhuru wa kutoka kwenye mahojiano na kujitoa kwa utafiti huu wakati wowote. Una uhuru wa kuuliza maswali yoyote uliyo nayo kabla ya kutia sahihi fomu ya makubaliano. Maelezo yako yote yatawekwa pahali pa siri. Ni mtafiti mkuu na mwanatakwimu wake pekee ambao wataangalia maelezo yako.

Manufaa ya utafiti huu

Hakuna pesa utahitajika kulipa kwa kujihusika kwa utafiti huu. Matokeo ya utafiti yatasaidia wauguzi katika hospitali ya Kenyatta.

Cheti cha ridhaa

Nimesoma, au nimesomewa maelezo yaliyopewa. Nimepata fursa ya kuuliza maswali kuhusu utafiti na maswali yote niliyouliza yamejibiwa vyema. Ninakubali kuhusika katika utafiti huu.
Jina la mhusika:.....

Sahihi/Alama ya kidole gumba cha kushoto :.....

Tarehe:.....

KAULI YA MTAFITI:

Miye, mtafiti mkuu, nimemweleza mhusika vilivyo kuhusu utafiti huu.

Sahihi: ..... Tarehe:.....

ETHICS AND RESEARCH COUNCIL APPROVAL

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Ref: KNH-ERC/A/129

29th March, 2022

Dr. Hassanali Mithwani Abdulaziz
Reg. No.H58/10883/2018
Dept. of Clinical Medicine & Therapeutics
Faculty of Health Sciences
University of Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 29 MAR 2022 KNH/UoN-ERC P.O. Box 20723 - 00202, NAIROBI

Dear Dr. Abdulaziz,

RESEARCH PROPOSAL: DISEASE ACTIVITY AND ADHERENCE TO DISEASE MODIFYING ANTI-RHEUMATIC DRUGS AMONG RHEUMATOID ARTHRITIS PATIENTS ATTENDING THE KENYATTA NATIONAL HOSPITAL RHEUMATOLOGY CLINIC (P1/01/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P1/01/2022.** The approval period is 29th March 2022 – 28th March 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 Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Chair, Dept. of Clinical Medicine and Therapeutics, UoN
Supervisors: Prof. George Omondi Oyoo, Dept. of Clinical Medicine and Therapeutics, UoN
Dr. Eugine Kalman Genga, Dept. of Clinical Medicine and Therapeutics, UoN

ANTI-PLAGIARISM REPORT

DISEASE ACTIVITY AND ADHERENCE TO DISEASE MODIFYING ANTI-RHEUMATIC DRUGS AMONG RHEUMATOID ARTHRITIS PATIENTS ATTENDING THE KENYATTA NATIONAL HOSPITAL RHEUMATOLOGY CLINIC

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