DRUG RELATED PROBLEMS AMONG PATIENTS WITH RHEUMATIC DISEASES AND CONNECTIVE TISSUE DISORDERS IN KENYATTA NATIONAL HOSPITAL.

MANANI JOSEPH STATE
M.PHARM CLINICAL PHARMACY
U56/11762/2018

A RESEARCH DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE MASTER OF PHARMACY IN CLINICAL PHARMACY OF THE UNIVERSITY OF NAIROBI.

DEC 2020.

DECLARATION OF ORIGINALITY

Students Declaration

Name of Student:	Manani Joseph State
Registration Number:	U56/11762/2018
College:	College of Health Sciences
School:	School of Pharmacy
Course Name:	Masters of Pharmacy in Clinical Pharmacy
Department:	Department of Pharmaceutics and Pharmacy Practice

Title of work**: Drug related problems among patients with rheumatic diseases and connective tissue disorders in Kenyatta National Hospital.**

1. I understand what Plagiarism entails and Informed of the university guidelines regarding the same.
2. I confirm that this dissertation is my work and has not been submitted elsewhere for examination, the award of a degree or publication and where other people's work or my work has been used, this has properly been acknowledged and referenced as per the University requirements.
3. I have not used the services of any professional or agencies to come up with this work.
4. I have not permitted, and shall not permit anyone to copy my work with the intention of submitting it as his or her work.
5. I understand that any untrue claim with regards of this work shall result in disciplinary action, as per the University Plagiarism Policy

Signature_____ **Date**_03.12.2020__

APPROVAL BY SUPERVISORS

This proposal has been submitted for review with our approval as University supervisors.

1. Signature  Date 05.12.2020

   Dr. Sylvia Opanga

   Department of Pharmaceutics and Pharmacy Practice,

   The University of Nairobi.

2. Signature  Date 06.12.2020

   Dr. Charles Githinji

   Department of Physiology chiromo School of Medicine,

   The University of Nairobi.

DEDICATION

I dedicate this dissertation to my friends, family and lecturers for their support and prayers.

ACKNOWLEDGEMENT

I would wish to thank the almighty lord for the strength and commitment for carry out this research.

I wish to extend my gratitude to my supervisors Dr. Sylvia Opanga and Dr.Stephen Githinji for their immense contribution in formulation of the proposal, data analysis, and dissertation writing.

I am grateful to the university of Nairobi school of pharmacy department of pharmaceutics and pharmacy practice and the Kenyatta National hospital for providing me with the training and environment to conduct the study successfully.

I also wish to thank my research assistant Gibson Maina for coordinating the patients during my data collection.

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS.

DRPs – Drug related problems

DMARDS- Disease modifying anti-rheumatic drugs

KNH-UoN ERC- Kenyatta National Hospital –University of Nairobi ethics and research committee.

NSAIDs – Non steroidal anti-inflammatory drugs

OTC- Over the counter

PCNE- Pharmaceutical care network Europe.

POM- Prescription only medicine

RA-Rheumatoid arthritis

SLE- Systemic lupus erythromatosus

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background information: Patients with rheumatic diseases are often on multiple long term medications predisposing them to drug therapy problems which can occur at any point of therapy. DRPs hinder the achievement of the desired treatment outcomes and can prolong the hospital stay, allow disease progression and cause poor quality of life for these patients. There is inadequate available literature on DRPs amid these patients in Africa.

Objective: The purpose of the study is to describe drug related problems and their associated factors among patients suffering from rheumatic diseases attending the rheumatology clinic at Kenyatta National Hospital.

The significance of this study is that it will provide a basis for understanding the various drug therapy challenges patients with rheumatic disease undergo that impact negatively on the intended goals of treatment and the various factors linked to the problems and therefore provide grounds to minimize the therapy problems for both the patients and the care providers.

Methodology: A cross-sectional survey was carried on patients with rheumatic conditions including psoriasis, rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis and ankylosing spondylitis attending the rheumatology clinic at KNH. Universal sampling was employed to get participants for the study as patients with this condition are scarce. The patients were screened for eligibility using a predesigned form and the ones found eligible were taken through the consenting process and if they accepted to take part in the study willingly signed a consent declaration form. Participants data such as socio demographic data, laboratory findings and current treatment was collected using a predesigned data collection tool from the patients' files. The participants were then taken through a structured questionnaire by the principal investigator to assess for drug related problems through systemic review and patient interviews. Relevance of therapy, effectiveness and safety was also assessed as per the treatment guidelines and interactions checked by use of Medscape and Epocrites drug interaction checker. The data collected was checked for completeness and then keyed into Microsoft excel and processed using STATA version 13.0. Binary, descriptive and multi-variable logistic analysis was utilized to define the population and establish the relationship between the independent and the dependent variables with a p value of 0.05 and below being statistically significant and therefore need to investigate the relationship between the independent and dependent variable. Drug related

problems were expected to have a high prevalence among patients ailing from rheumatic conditions with the prevalence considerably related to the number of drugs the patient is on, the number of comorbidities, socioeconomic status age and duration of disease.

Results:

The data of 88 patients was reviewed, the data summarized as frequencies and percentages, and the results presented in Table 1. The mean age was 44.48±15.89 years. Most participants were female (89.8%), married (77.3%), college/university educated (51.1%), and were self-employed (60.2%).the monthly income of a majority was <5000 (42.5%), while Christians formed the majority (97.7%) of the patients studied. Most never smoke (94.3%) nor drunk alcohol (90.8%) and received care mostly from their spouses (35.6%) and children (31.0%).Comorbidities were found in 68.2%.diabetes and chronic kidney disease were found in 10% and 10% of patients. A majority (93.3%) had other comorbidities. On review of systems, Pain (69.3%) and malaise (48.9%) were reported in a majority of patients with general system problems. Occasional impaired vision (18.2%) was the commonest eye problem, while 2.3% and 3.4% had ear problems such as loss of hearing and ringing ears. Sneezing and congested nose were reported in 3.4 % and 2.3%, while only 2.3% had throat problems. Digestive problems were at 44.3%, with abdominal pain and heartburn being the commonest at 35.4% and 29.5%. Joint pain (63.6%) and backache (53.4%) were the commonest musculoskeletal problems, while itchiness (17.0%) was the commonest integumentary system problem in the population studied.A majority had a normal blood pressure (71.6%) and hemoglobin level (56.8%), but the data for ESR reading, x-rays results, and rheumatoid factor was missing for a majority. Antinuclear antibodies were mostly negative (45.5%).The hospital was the source of medication for a majority (88.6%) with the commonest class for a majority found to be conventional DMARDS (83.0%). Around 61.4% required steroids, while 26.1%, 1.1%, and 1.1% required NSAIDS, Glucosamine, and anti-cancer medication respectively. No patient was on antibiotics. When queried about their understanding of drug therapies, a majority (54.5%) did not know the dosage of medication. The frequency of medication was known by 89.8%, but only 47.7% understood the duration of medication, even though 98.9% expected medication to cure their existing condition. A minority were concerned about side effects (15.9%), medication (17.0%), and pill burden (10.2%) with a majority choosing to refill their prescription (81.8%) and take medication voluntarily (93.2%). A majority

would not stop taking medication even when the condition was in control (76.1%). On Status of Rheumatic Disease, Patients had suffered from rheumatic disease for a mean duration of 63.45±42.78 months, with a majority (51.1%) having a partially improved condition. The prevalence of DTPs was 48.9%. The prevalence of the need for additional therapy was 14.8%, mostly due to untreated conditions (53.8%) and synergistic/potentiating effect of medication (46.2%). The prevalence of ADR was 14.8% due to undesirable effects (84.6%) and unsafe drugs (15.4%), while the prevalence of non-compliance was 17.0% due to their inability to afford drugs (86.6%), forgetting to take products (6.7%), and unavailability of product (6.7%). Low dosage and high dosage were the least common DTPs with a prevalence of 1.1% and 1.1%. Common drug related problems. A majority (68.2%) liked taking medication, while only 1.1% thought drugs did not work. Four patients (4.5%) thought drugs cause more problems, while 27.3% and 20.5% were concerned about the high cost of drugs and the availability of drugs. Factors associated with DTPS. Several demographic and reproductive characteristics were associated with DTP after multivariable analysis. With each year increase in age, the odds having a DTP reduced by a factor of 0.078. With each year increase in the length of rheumatic disease, the adjusted odds of having a DTP increased by a factor of 0.028. The adjusted odds of having a DTP was 0.0 fold (95% CI=0.00-0.012) and 0.013 fold (95% CI=0.001-0.242) fold statistically significantly lower among patients with an improved and partially improved status of rheumatic disease compared to those with unimproved status ($P<0.05$). Steroid use was associated with 0.122 fold (95% CI=0.016-0.912) statistically significant reduction in the adjusted odds of developing a DTP (P=0.040), while use of NSAIDS was associated with a 6.641 fold (95% CI=1.241-35.540) statistically significantly higher increase in the adjusted odds of developing a DTP (P=0.027). Age, gender, marital status, religion, smoking status, preferred beverage, alcohol intake status, education level, employment status, income category, blood pressure, hemoglobin levels, ESR reading, X-ray results, rheumatoid factor, Antinuclear antibodies, and presence of other comorbidities were not associated with the adjusted odds of DTPs statistically significantly.

Conclusion

Rheumatic conditions were more prevalent in females at Kenyatta National Hospital. Most participants had a partial improvement of rheumatic disease after treatment. Overall, the

prevalence of DTPs was high with the high cost and unavailability of drugs indicated found to be the commonest drug problems in the population studied. Moreover, age, length of rheumatic disease, status of rheumatic disease and the type of medication (steroids and NSAIDs) were associated with the DTPs statistically.

Recommendations

Patient need to be educated on the advantages of taking a medical cover as a significant percentage are concerned about the cost of medication.

Frequent evaluation of patients for DRPs should be conducted and measures to resolve DRPs instituted.

The use of NSAIDs in rheumatic patients needs to be reevaluated and further investigated as it has shown to increase the odds of developing DRPs.

CHAPTER ONE: INTRODUCTION

1.1 Background of the study

Rheumatic diseases also referred to as musculoskeletal diseases are conditions that involve the cartilage, joints, tendons, muscles, ligaments and internal organs in some cases(1).Rheumatic diseases are majorly chronic, inflammatory and autoimmune in nature and are characterized by pain, redness, warmth, swelling and resultant decrease in range of motion and functionality of the musculoskeletal area affected.

Africa is the second most densely inhabited region on earth with an estimated 1.2 billion people by 2016 but has little to no rheumatology services in most regions in sub-Saharan Africa leaving the rheumatic patients in most regions in the hands of care providers who have limited knowledge and training on management.(2)

There are over 200 different forms of rheumatic diseases with different etiologies ranging from several kinds of arthritis to systemic connective tissue diseases and osteoporosis(1).Some aspects for example cigarette smoking, genetic factors, excessive weight, occupations which lead to damage and misuse of joints and advanced age have been shown to predispose patients to rheumatic diseases(3)(1). Cigarette smoking has been implicated for increasing the risk of rheumatic diseases by being pro-inflammatory, causing immune suppression, initiation of programmed cell death, and DNA destruction leading to formation of anti-DNA antibodies against the damaged DNA.(3)

Drug-related problems are drug therapy happenings or circumstances that potentially or truly have an influence on desired treatment outcome(4). The prevalence of drug related problems among rheumatoid arthritis patients is high.(5). This is probably occasioned by multiple treatment regimens to manage the disease. Numerous aspects may contribute to drug related problems. For example, renal or liver impairment may lead to DRP via the change of drug metabolism(6). The ageing patients are more predisposed to DRPs as a result of co-morbidities, polypharmacy and poor medication adherence.

Treatment of most rheumatic conditions involves the use of corticosteroids to modulate immune reactions and decrease inflammation, analgesics to manage pain and in this case NSAIDs are preferred, disease modifying anti rheumatic agents to halt disease progression and in some cases achieve remission and physiotherapy to assist in rehabilitation of affected joints, improve joint movement and functionality.(7)(8)

1.2 Problem statement

Most rheumatic conditions being chronic, autoimmune and often presenting with systemic complications lead to the patients being on long term treatment with multiple agents to control the disease, prevent progression and in some condition achieve remission. The multiple agents and combinations for management pose a myriad of drug related problems ranging from inadequate pain control that can be due to either inappropriate analgesic selection or suboptimal doses or dosing frequency(9).Frequent disease flare or disease progression due to inappropriate DMARD selection or insensitivity to the treatment regimen requiring a change or an additional agent for synergistic activity, drug interactions that can lead to enhanced toxicity or decreased pharmacological activity. Insufficient knowledge on the ever evolving treatment and introduction of newer molecules pose a regimen switching problem as some patient are declared failed on a regimen and switched to other regimens before optimization of a current regimen. Various molecules used in management of rheumatic conditions are known to have an array of adverse effects. Non-adherence to treatment due to barriers such as the direct and indirect economic implications of rheumatic conditions all compound to the drug related problems the rheumatic patients are exposed to(10). Pharmacological management of rheumatic diseases has been show to improve the patient's physical, social and emotional function(11) but drug related problems impact negatively on pharmaceutical care impeding achievement of desired outcomes and therefore prolonging hospital stay, having inadequate pain control, loss of function, loss of working hours, diminished quality of life and emotional and financial burden to the patient and family.(10)

Even though drug related problems are prevalent amid rheumatic patients, limited research has been done to find out the common DRPs and the associated and causative factors so as to attempt to limit and prevent their occurrence and improve rheumatic patient's treatment outcomes.

1.3 Study justification

Patients with rheumatic diseases are predisposed to drug related problems due to the chronic nature of the disease, polypharmacy, economic implication of treatment and age as studies have shown a higher prevalence of rheumatic diseases among the elderly who are also more prone to comorbidities and having reduced metabolic functions compared to the young(12) . DRPs impact on the patient's treatment outcome but few studies have been done to identify the drug related problems among rheumatic patients and their associated factors and therefore put measures to either prevent, limit or resolve the DRPs and improve treatment outcomes among rheumatic patients. This study therefore aims to identify the DRPs, their associated factors and come up with recommendations on correcting the DRPs to improve patient outcomes by improving pain control which is a noxious and debilitating stimuli that impacts negatively on the quality of life, limiting number and duration of hospital admissions for the patients, minimizing adverse drug reactions that can be life threatening and can lead to hospitalization and minimization of drugs used which decreases the pill load and financial burden. The finding will also give guidance to the practitioners on what are the common DRPs and therefore enable them to anticipate them and tackle them in advance to optimize care, the findings will also provide explanations as per to why treatment targets are not being meet in some patients.

1.4. Objectives

1.4.1. Main objectives

To determine the prevalence, the types and associated factors of drug related problems among patients with rheumatic diseases and connective tissue disorders at Kenyatta National Hospital.

1.4.2. Specific objectives

1.To determine the prevalence of DRPs among patients with rheumatic diseases and connective tissue disorders in Kenyatta National Hospital.

2.To establish the common drug related problems among patients with rheumatic and connective tissue disorders in Kenyatta National Hospital.

3.To Identify factors associated with the various DRPs.

1.5 Research questions

1.What is the prevalence of DRPs among patient with rheumatic diseases and connective tissue disorders in Kenyatta National Hospital?

2.What are the common drug related problems among patients with rheumatic a connective tissue disorders in Kenyatta National Hospital?

3.What factors are associated with the occurrence of drug related problems among these patients?

1.6 Conceptual Framework

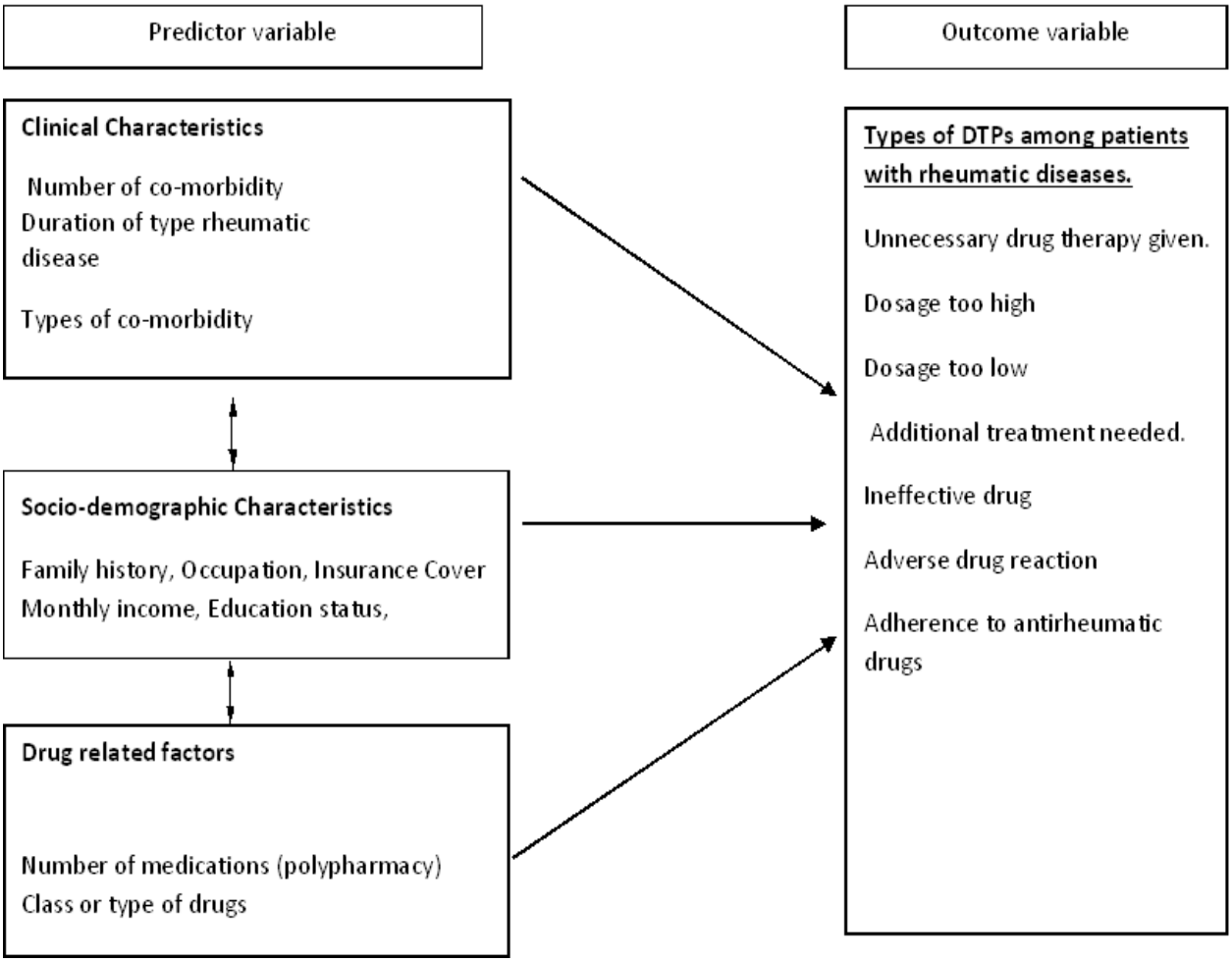


Figure 1: Conceptual framework illustrates the relationship between predictor and dependent variable. (Author: Manani Joseph,2020)

CHAPTER TWO: LITERATURE REVIEW

2.1 Rheumatic diseases

Rheumatology is a specialty that focuses on the care of patients and management complications associated with rheumatic diseases. Epidemiological studies have indicated that although the prevalence of musculoskeletal disorders in the third world is similar to that in the industrialized world, the burden is higher(13). The major rheumatic illnesses are rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, osteoarthritis, polymyalgia rheumatic, systemic lupus erythematosus, gout, ankylosing spondylitis and Sjögren's syndrome. Among the rheumatic diseases osteoarthritis is the most prevalent with prevalence varying from 5.1 % to 20.8% with the common site of involvement being the knee joints, the lumber spine and cervical spine (14).Results from a meta-analysis of prevalence studies from Africa showed osteoarthritis to be the most prevalent form of arthritis in urban settings. (15)

2.1.1 Rheumatoid arthritis

In majority of patients, rheumatoid arthritis has slow beginning. It might start with systemic symptoms such as fever, arthralgias, malaise and lethergy before the onset of obvious joint swelling. A minor fraction (about 10%) of patients with this illness have a rapid start with the severe progress of synovitis and extra-articular symptoms. Natural reduction in symptoms is rare, particularly after the initial 3-6 months.

The key presentation of rheumatoid arthritis is obstinate bilateral polyarthritis that touches majorly the feet and hands, though any joint with a synovial membrane can be affected. The extent of RA varies from time to time, but prolonged RA regularly results in the progressive damage of joints, malformation, and a considerable reduction in functionality. Involvement of other body organs such as the integumentary system, cardiovascular, eyes and lungs, can also be substantial (16).

Ideal management of rheumatoid arthritis patients is critical and requires a wholesome approach including both non-pharmacologic therapy and pharmacological therapy. several non-drug

therapies are accessible for this condition, including massage, exercise, counseling, diet, surgery and physical therapy. Active involvement of the patient and the care provider in the treatment options has also been shown to enhance compliance.

Drug-based therapies have numerous classes of drugs, including NSAIDs, biologic and non-biologic (DMARDs), immune-modulators, and corticosteroids. Timely initiation of DMARDs therapy is preferred because it slows down progression of disease preventing permanent joint damage and can achieve remission(17).

Most of the medications ranging from the NSAIDS to the immune suppressants have a number of drug related problems including cytopenia for some immune suppressants and gastrointestinal disturbances for NSAIDS among others. Psychiatric problems have been identified in SLE patients on high dose corticosteroids(18).

2.1.2 Ankylosing spondylitis

Ankylosing spondylitis is an inflammatory rheumatic condition that involves the spinal skeleton, resulting in back pain due to inflammation, which can cause functional and structural impairments and a reduction in the ability to enjoy life. Physiotherapy and NSAIDS remains an important treatment option for life long treatment of patients suffering from ankylosing spondylitis. The recent management alternatives using tumor necrosis factor inhibitors seems to provide better treatment outcomes for ankylosing spondylitis patients refractory to conventional treatment compared to psoriatic arthritis patients and rheumatoid arthritis (19)(20).

2.1.3 Psoriatic arthritis

Psoriasis is a chronic inflammatory skin disease with multi systemic involvement presenting with scaly erythematous plaques most commonly affecting extensor surfaces of the knee and elbows, and at times the umbilical and intergluteal area(21). East Africa has recorded higher rates of psoriasis than west Africa consistent with low data available from west Africa(22). psoriasis has a 2-4% prevalence in Western adults, of which 20–30% of patients will progress to psoriatic arthritis(21)

Psoriatic arthritis is a musculoskeletal disease presenting with inflammation and is related to cutaneous psoriasis. It has almost equal distribution between men and women aged between 40

and 50 years. The involved organ systems include axial and peripheral joints, nails, connective tissues and skin. Psoriatic arthritis is linked to comorbidities such as cardiovascular diseases, osteoporosis, subclinical bowel inflammation and uveitis (23).

Psoriatic arthritis disease response to immune-modulators is a show that the immune system has major role to play in the pathophysiology of disease. Conventional synthetic DMARDs such as leflunomide, cyclosporine and sulfasalazine have shown symptomatic relief with little evidence for methotrexate. Conventional DMARDS have not shown halting of disease progression by slowing radiographic progression, reduction of spinal symptoms, or relieve dactylitis and uveitis. But when used can manage peripheral arthritis.

Tumor necrosis factor inhibitors (TNFi) etanercept, infliximab, golimumab and adalimumab, have been shown to be effective in handling several fields of the illness, including enthesitis, axial and peripheral arthritis, skin psoriasis, dactylitis and nail disease, and decreasing radiographic advancement(24).

2.1.4 Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune condition presenting with antibodies to cytoplasmic antigens and the nucleus, protean clinical manifestations, multisystem inflammation, and a reverting and remitting sequence. Greater than 90% of SLE cases occur in women.

SLE may present with constitutional signs that is fatigue, fever, arthralgia and weight changes or

musculoskeletal signs like arthralgia, myalgia, arthropathy and avascular necrosis.it can also present with

dermatologic signs like photosensitivity, malar rash, discoid lupus and other systemic signs including renal failure, pulmonary hypertension, gastrointestinal disturbances, myocarditis and hematologic conditions like leukopenia, anemia, thrombocytopenia and cytopenia.

Management of SLE is by use of various classes of drugs including corticosteroids. NSAIDS, conventional DMARDS and biological DMARDS(25)

2.1.5 Osteoarthritis.

Osteoarthritis is among the most common cause of discomfort and loss of joint function among the elderly above 75years of age. The joint pathology is diverse and includes focal injury and loss of articular cartilage, abnormal remodeling and erosion of subarticular bone, osteophytes, ligamentous laxity, weakening of periarticular muscles, and in some instances synovial swelling and inflammation.

The joints most commonly affected by osteoarthritis are the knee, hand, hip, spine and

foot, while the wrists, shoulders and ankles are less frequently affected(26).

Of the various interventions investigated lifestyle modifications show the greatest benefit. Maintenance of an ideal weight and regular exercise are cost-effective and also reduces mortality.

In patients with joint damage pharmacological and surgical intervention can be the best strategy.

There is little information on the prevalence of drug related problems among these rheumatic patients in Kenya who are at a high risk.

2.2 Classification of DRPs.

Drug related problems are defined as ‘an occurrence or event involving drug use that truly or possibly interferes with desired treatment outcomes’, in agreement with Pharmaceutical Care Network Europe (PCNE)(4). Drug related problems are further classified as need for drug interaction additional drug, nonoptimal drug, nonoptimal dose, unnecessary drug, need for monitoring (that is laboratory tests, blood pressure measurements), no further need for the drug, therapy discussion (for example why a drug is favored for the patient as opposed to the other), medical chart error (for example no description of the strength of the drug to be used), need for patient education (to avoid nonadherence), adverse drug reactions, adherence problems and others. Drug related problems can occur when at different levels of management ranging from prescribing, dispensing or use of drugs. Drug use problems caused by the patient are perhaps the most common but are not frequently noted.(27)

Earlier studies have mostly addressed DRPs as a reason of hospital admission(28)

2.2.1 Inappropriate drug use

Management of rheumatic diseases calls for a balance between aggressive management of acute disease which exposes the patients to adverse effects of the drugs due to high doses and multiple agents and conservative management of mild disease. The balancing act therefore exposes these patients to a number of inappropriate drugs(29). The number of drugs the patient is using on admission was noted to be a risk factor for having an avoidable drug use problem(28). Polypharmacy in chronic conditions can lead to continued refill of drugs that ought to have been stopped for example a rheumatic patient with controlled disease on DMARDs and not in pain but still on NSAIDs.

2.1.2 Suboptimal drug or suboptimal dose.

Dose related problems have been shown to be the most frequent drug related problem ranging from the need for dosing frequency adjustment to weight dependent dose adjustment(28). Suboptimal dose DRP arises

if a drug dose is not customized for a specific patient, taking into account all of the appropriate disease, drug, and patient-specific information. Suboptimal dose can also be deemed to have occurred if a target serum drug concentration is correctly calculated and sampling done appropriately but concentrations are not achieved (coupled with all the relevant clinical signs/symptoms)(24).

Some other parameters would lead to suboptimal therapeutics if not taken into account. That includes a patient receiving an inappropriate dosing interval, or a regimen not being continued long enough. Switching of route of administration or drug formulation without taking into account the pharmacokinetic properties can also lead to suboptimal dose(15).

2.2.3 Need for additional drug

This is a situation where the patient is being managed for the primary condition but a secondary condition is not being managed or a patient would benefit from synergy of dual or triple therapy or benefit from prophylaxis for side effects that could arise from medication use(30).

Rheumatic patients have been shown to be prone to the DRP of additional drug needed compared with patients in other clinics due to the nature of the disease that more often is better controlled

with a combination of drugs like methotrexate with a biological has better control of rheumatic disease than methotrexate alone(31) (32).

2.2.4 Need for monitoring

Some drugs for example methotrexate and biologicals have a narrow therapeutic window needing close laboratory or and clinical monitoring that is complete blood count to monitor for cytopenia and anaemia that can be due to chronic disease or use of methotrexate, leflunomide and sulfasalazine. Monitoring is often not done to watch out for toxic levels and adverse effects. Inflammatory markers for example anti-cyclic citrullinated peptide antibody and c-reactive protein are markers of disease progression and prognosis(31).

2.2.5 Wrong drug being used

This is a situation where there is a more effective drug in the market than the one the patient is using, or equally effective drug but more cost effective, or the patient is using a drug that he is allergic to or that is contraindicate for their condition, or at times the patient receiving a drug not indicated for their condition(30). For example a patient with psoriatic arthritis on methotrexate will benefit more when it comes to several spheres of the ailment including enthesitis, peripheral and spinal involvement, skin psoriasis and reducing radiographic progression and dactilities from tumor necrosis factor inhibitors like etanercept and infliximab(21).

2.2.6 Adverse drug reaction

These are unwanted outcomes that occur due to drug use at the correct dose range. They are classified into type A which are the expected, occur within the normal pharmacological action of the drug and are more common while type B are the idiosyncratic and allergic ones that are not dose dependent and are unpredictable(33). DMARDs being majorly immunosuppressants have adverse effects that need monitoring and can lead to discontinuation of therapy with the leading cause of discontinuation being infections followed by cancer then gastrointestinal adverse effects with the biological DMARDs having the highest incident ratio compared to conventional DMARDs. The antimalarial showed the lowest incident ratio of adverse drug reactions leading to discontinuation of therapy(34).

2.2.7 Drug-food, drug-drug or drug laboratory interactions

Some food may interact with drugs either increasing or reducing the drug availability, some drugs are also enzyme inducers or enzyme inhibitors altering the half-life of other co-administered drugs while drugs can also interfere with laboratory investigations and therefore cause misinterpretation of the laboratory findings. Methotrexate being structurally similar to penicillins can have competitive inhibition leading to increase in methotrexate half-life and an increase in the serum concentrations of its active metabolite, potentiating its adverse effects, such as leukopenia, anemia, liver toxicity, thrombocytopenia, nephrotoxicity, and mucosal ulcerations(35). Drugs can also interact with food for example grape fruit juice is a cytochrome enzyme inhibitor which metabolizes calcineurin inhibitors like cyclosporine and tacrolimus and can lead to elevated plasma concentration of the drug increasing toxicity if co-administered(36).

2.2.8 patient not receiving the prescribed drug

This may be due to patient factors like forgetting to take drug or avoiding to take due to adverse effects like nausea, vomiting, glossitis,anorexia and diarrhea due to methotrexate or mental conditions or it can be due to factors that are beyond the patient control like the care giver not being able to administer the drug to pediatric patients, mentally incapacitated patients or unconscious patients. The external factors that can lead to the patient not receiving the drug may also include financial constraints limiting patient's ability to obtain the drug for example the biological DMARDs are quiet expensive and out of reach of most patients in developing countries without medical cover(37). Drug formulation can also limit drug availability after administration.

A study in Norway including 827 participants from medical wards and two rheumatology clinics revealed that 81% of the participants had drug related problems with clinical/pharmacological risk elements and number of medicines being independent risk features. Multivariate analysis also showed higher risk of DRPs in rheumatology than cardiology and geriatrics(28). Some DRPs can be detected via home visits especially the ones that cannot be identified via systemic reviews at the clinic. They included various pill storage areas, nondisclosure of over the counter drugs, nondisclosure of prescription medication obtained without a prescription, misunderstanding of standard and trade names, wrong drug use routine, obsolete medication

issued on repeat prescriptions, therapeutic duplication, expired medications, concomitant co-intervention with herbal products, and storage of different people's drugs in a house hold at a common location(38).

One drug can cause multiple DRPs that can be dependent or independent of each other. For example it can have dose issues and still have adverse effects unrelated to dose(39).

Barriers to treatment adherence have been shown to be similar for various rheumatic diseases including fear of side effects, financial constraints, complicated public health system, and perceived treatment inefficacy. Barriers to keeping appointment include difficulties in scheduling, financial implication, transportation, and functional impairment hindering ability to attend clinics(10).

There are little documented studies showing the prevalence and possible associated factors for DRPs among rheumatic and connective tissue disorders patients and this study aims to provide understanding of the DRPs prevalence and associated factors and therefore assist practitioners anticipate and tackle the problems to improve patient outcomes.

CHAPTER THREE: METHODOLOGY

3.1 Introduction

This chapter elaborates how the objectives were meet, the data collected, the process of collecting the data and processing of the collected data. It gives a description of research design, location of study, study population, sampling method, research tools, pre testing, quality assurance measures, data collection tools, data organization, logistical and ethical considerations.

3.2 Research design

A cross sectional survey of patients above 18 years of age with a clinical diagnosis of rheumatic disease attending the medical outpatient rheumatology clinic or admitted at the medical wards in Kenyatta National Hospital was done. Study design was appropriate as it provided a snapshot of both analytic and descriptive data of a population phenomenon at a given time. It was also cost effective and could be achieved within a limited time period. The dependent variable was the DRPs while the independent variable included adverse drug reactions, number of drugs the patient was on, patient related factors, age, types of drugs, level of care where the patient was being managed.

3.3 Location of study

The study was carried out at Kenyatta National Hospital which is a tertiary care hospital located in upperhill area in Nairobi which is Kenya's capital city. The facility is the largest referral hospital in east and central Africa and lies on a 45 acres piece of land. The hospital has over 6000 staff, a bed capacity of 1800 and 22 specialised clinics. The hospital serves as a teaching hospital for both university of Nairobi and Kenya medical training college. The study was carried out over a duration of 6 weeks in the medical outpatient rheumatology clinic held on Thursday every week and had an average of 26 rheumatic patients weekly giving a total of about 104 patients a month and the medical wards where the critically ill rheumatic patients are

admitted. Kenyatta National Hospital was a good site for the study as it receives referral patients from all over the country as most regions in Kenya lack rheumatologists.

3.4 Study population

The study population included adult patients 18 years and over admitted at Kenyatta National Hospital or visiting the rheumatology clinic with a clinical diagnosis of rheumatic disease including SLE, osteoarthritis, psoriasis, rheumatoid arthritis and ankylosing spondylitis.

3.4.1 Inclusion criteria

The participants included in the study had to be;

Over 18 years

Having a positive clinical diagnosis of rheumatic disease including patients diagnosed clinically and or by laboratory findings to have systemic lupus erythematosus, psoriasis, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

Gave voluntary informed consent.

3.4.2 Exclusion criteria

Patients with rheumatic diseases including SLE, psoriasis, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. but not on treatment either due to physician preference, patient choice not to be on medication after proper counselling or when the risks outweigh the benefits for example multiple organ failure where the drugs could cause more harm to the patient than the potential benefits(40).

Patients who declined to sign consent.

Rheumatic patients with systemic lupus erythematosus, psoriasis, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis but had cognitive impairment, unconscious or mentally unstable.

3.5 Sampling

3.5.1 Sampling technique

Universal sampling was used to select study participants who had meet the inclusion criteria and were willing to give signed consent either at the rheumatology clinic or the medical ward using

the patient file number to identify the patients and avoid repeated interview in case the patient was seen at the clinic and later admitted.

3.5.2 Sample size determination

The prevalence of DRPs among rheumatic patients was not known in Kenya and neighboring countries but the prevalence of rheumatoid arthritis is estimated to be 1% globally(41). Now that the prevalence was not known it was assumed to be 50% and then the sample size calculated using fisher's formula and a reduction formula applied as follows:

$$n=\frac{Z^2 pq}{d^2}$$

where:

n is the minimum sample size

p is the prevalence of DRPs among rheumatic patients which will be assumed to be 50%.

Q is (1-p)

Z is the standard normal deviate at 95% confidence interval corresponding to 1.96.

d is the degree of accuracy usually set at 0.05

$$n = \frac{1.96^2(0.5)(0.5)}{0.05^2}$$

$$= \frac{3.8416\times0.25}{0.0025}$$

=384 participants

The average clinic attendance is 104 rheumatic patients per month.

Using the reduction formula

$$nf = n/1+(n)/(N)$$

where

nf =desired sample size when study population is less than 10000.

n =desired sample size when the study population is greater than 10000

N =estimation of population size

Then

$$= \frac{384\times104}{384+104}$$

$$=74$$

Adjusting for 15% non-response

$$74\times1.15$$

Minimum sample size should be 85 patients.

On average the rheumatology clinic in Kenyatta national hospital attends to about 26 rheumatic patients weekly translating to a total of 156 patients in six weeks as per the patient's weekly clinic bookings records obtained from the rheumatology clinic and therefore the minimum sample size should be 85 patients for the study due to time restrictions but if time allows the target sample size is 384.

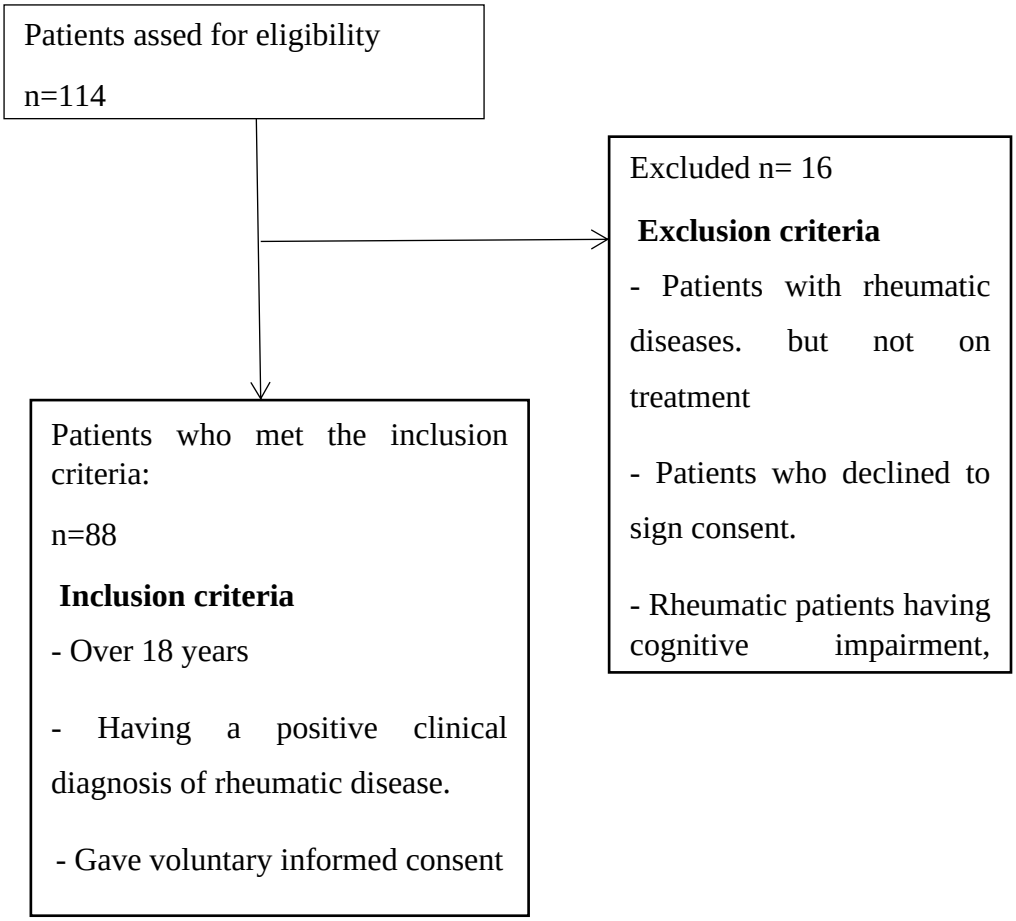
3.5.3 Participant recruitment

The principal investigator screened the patients files retrieved for the rheumatology clinic a day prior to the clinic day using the eligibility criteria form. The identified eligible patients were informed of the study during the clinic day as they awaited to be attend to by the clinicians and thereafter the ones willing to participate were taken through the consenting process and given the consent forms to sign. The principle investigator and research assistants then administered the questionnaires after the patient has been seen by the clinician at a room where the patient felt

comfortable to answer questions. The questionnaire was administered in a systematic logical manner and clarification given when the patient wasn't understanding the question and in the event that the patient wasn't understanding English or Kiswahili then a translator was used. The process was repeated every clinic day until the anticipated sample size was attained.

To evade duplication of sampled patients the already interviewed patients' files were tagged using colored stick notes at the inner back of the file and returned to the records registry.

Figure 2:participant recruitment



3.6 Research instruments

3.6.1 An eligibility screening form

A screening form for eligibility (Appendix 1) depending on inclusion criteria was used to guide on patient selection in the morning before the clinic day and the patients meeting the eligibility criteria the files were labeled with a unique random number and a list of the files made for ease of retrieval once the clinic begun.

3.6.2 An informed consent form

An informed consent form was used to obtain informed consent from the patients to participate in the study (Appendix 2) as they awaited to be seen at the rheumatology clinic and the ones who consented informed of the study after they were done with the clinician.

3.6.3 A data collection tool

A modified structured pharmacotherapy workup notes data collection sheet (Adapted from Cipolle, Strand, Morley 2012) was used to obtain patient characteristics, disease characteristics and the current treatment from the patients file (Appendix 3) for patients who had signed the consent form (Appendix 2). structured interviews were then administered using structured questionnaire consisting of the pharmacotherapy workup notes to assess whether all patients drug related needs have been met, whether all drug therapies are most appropriate, whether the drug therapies are the most effective and safest available and whether the patient is adhering to the proper use including dose, frequency, time of use and duration.

Information on medication such as potential interaction, recommended dosages, dosing frequency, and side-effects, was based on Medscape and the British National Formulary.

3.7 Pre testing

The data collection tools was tested on the first 15 participants to determine their relevance completeness and ease of use. The testing was carried by screening the patient's files for eligibility using the eligibility screening form (Appendix 1) and then listing the eligible patients file numbers. Once the clinic started the eligible patients were then informed of the study and the ones who consented had their files tagged with a unique number and the physicians attending requested to direct the patients with the tagged files to the principal investigator once they were done with them. The patients were then taken through the structured questionnaire in a room where the patient was comfortable answering questions (Appendix 3) after signing the consent form (Appendix 2) the same was done for the subsequent rheumatology clinic days for the first 15 patients and then the tool was assessed for completeness and relevance and adjustments made if need be then resubmitted to the UoN-KNH ERC for review and approval before use.

3.8 Validity

The validity of the study was sustained by ensuring the questionnaire was laid out in a clear, simple, concise and logical manner to enable completeness of data collection and avoid ambiguity. The study assistants were chosen from experienced staff and trained on the objectives of the study. The study site being a referral hospital gave validity as the study participants will be representative of the general population as Kenyatta National Hospital rheumatology clinic receives referral patients from all over the country.

3.9 Reliability

Data collection tools were pre-tested for reproducibility in the initial 15 participants and adjustments made to guarantee reliability.

3.10 Data collection technique

Data collection was done by use of modified pharmacotherapy workup notes (Appendix 3) in two phases. Phase one being structured questionnaire to obtain information on disease characteristics, patient characteristics, current treatment, medication related needs, appropriateness of therapy, effectiveness and safety of therapy in accordance to reference materials and treatment guidelines. While in phase two the investigator checked the patient's files for drugs, drug monitoring parameters and laboratory findings.

3.11 Definition of variables

3.11.1 Case definitions

Drug related problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes, it occurs when a drug related need is not met.

3.11.2 Outcome status

The outcome status statements describe the clinical outcomes resulting from drug use and encompass both the decision and action taken by the care provider and the patient. The outcome terms also describe the improvement or lack of improvement and the action to be taken towards the patients drug therapy.

3.11.3 Variables

The independent variables the age, gender, disease condition, number of drugs per prescription, type of medication dose and diagnosis while the dependent variables are the DRPs.

3.12 Data management

The data was collected using the standardized forms and checked for completeness after filling of the forms and any missing information filled or clarification sought from the participant. The data was then entered and stored on a Microsoft excel password protected file. Frequent backup

of data was done by use of a flash drive. Confidentiality was assured by use of unique identifiers for the forms used to retrieve information from patient files and interviews after they had given informed consent. All documents connecting the patient to the collected data were stored under lock and key with limited access. Categorical data collected was coded, cleaned, processed and stored in a way that allowed accurate reporting and verification then exported to STATA version 13.0.

3.13. Study limitations

The study being crossectional and being done at the outpatient clinic had a higher risk of incomplete data from the patients as some of them could not recall all the questions asked. This was mitigated by obtaining consent to retrieve information from the patient file to assure completeness of data.

Also the study being conducted at the national referral hospital, patients are expected from all over the country from different ethnic groups and some of them not conversant with the national language posing a language barrier. This was mitigated by obtaining a translator where possible and where not possible excluding the patient from the study.

Due to the limited time of the study the required sample size was not meet and therefore the minimum sample size that has been adjusted to cater for the anticipated lost to follow up was used. This therefore reduced the power of the study and limited extrapolation of its findings to the national level.

3.14 Data analysis and dissemination

The data entered into Microsoft excel was analyzed using STATA version 13.0. Descriptive statistics like range, means and standard deviation were generated for categorical and continuous variables. Also graphs and frequency tables were used to represent categorical variables. Binary and multivariable logistic analysis was used to control for confounders and predictors of DRPs such as age, gender, comorbidities and polypharmacy. Chi square test was used to check for association between the DRPs and the patient characteristics with the p value of less than 0.05 being considered statistically significant to study the association between the predictor factors and the drug related problem.

The study dissertation will be submitted to the university of Nairobi school of pharmacy as it is part of the requirements for the completion of a master of pharmacy in clinical pharmacy. The findings will also be shared with the Kenyatta national hospital as the site of study so that the findings can assist in policy making and betterment of service delivery. The findings will also be shared with the thee ministry of health department of non-communicable diseases to assist in policy design to improve patient outcomes and finally the findings will be published to enable wider access to scholars, practitioners and also provide a basis for further research.

3.15 Ethical and logistical considerations

3.15.1 Ethical approval

Ethical approval was sought from the KNH/UON research and ethics committee and authorization to conduct the study was sought from KNH administration and head of rheumatology department before the study was conducted. Voluntary informed consent was sought from the study participants before enrolling them into the study.

3.15.2 Informed consent

Patients were informed that the study is voluntary and were informed of the nature of the study and what it entailed by being taken through Appendix 2A before signing the consent declaration form (Appendix 2B). The patients were also informed that they are free to ask any questions and are free to leave the study at any point without any repercussions. And in case of any concerns regarding their rights as patients they are free to contact KNH-UoN-ERC.

3.15.3 Risks and benefits

The study being descriptive did not expose the patient to any risk as there will be no invasive procedures or administration of drugs but was beneficial as any concerns regarding their management was addressed and in case intervention was required the matter discussed with the physician before the intervention was made and documented in the patients' file for better patient outcomes.

In view of the corona virus pandemic and given that most rheumatic patients are immunosuppressed and therefore at a higher risk of contracting the corona virus the patients were interviewed in a well-ventilated room and sanitized their hands and had a mask on during the interview.

3.15.4 Confidentiality

Patient confidentiality was assured by use of serial numbers coded for the study for identification instead of names and outpatient file numbers. The data collected was password protected and the hard copy data was stored under lock and key with limited access to the principal investigator. Quality assurance was guaranteed by pretesting the research tools to ensure reliability and completeness.

3.15.5 Ethical considerations to avert the spread of corona virus during data collection

The investigator followed the laid out guidelines by the ministry of health on infection prevention to avert the spread of corona virus by ensuring the investigator and participant have a mask on, performing hand hygiene by use of alcohol based sanitizers before and after the interview, maintaining a more than one meter social distance between the investigator and the patient, advising the patient to cover mouth and nose when sneezing or coughing and also sanitizing your hands before and after touching a patient.

CHAPTER 5: RESULTS

Demographic information

Among the 114 rheumatic patients that visited the rheumatology clinic during the study period 88 patients met the inclusion criteria as per figure 2. The data of the 88 patients was reviewed, the data summarized as frequencies and percentages, and the results presented in Table 1. The mean age was 44.48±15.89 years. Most participants were female (89.8%), married (77.3%), college/university educated (51.1%), and were self-employed (60.2%).the monthly income of a majority was <5000 (42.5%), while Christians formed the majority (97.7%) of the patients studied. Most never smoke (94.3%) nor drunk alcohol (90.8%) and received care mostly from their spouses (35.6%) and children (31.0%).

Table 1: Demographic information of patients with rheumatic disease at Kenyatta National Hospital

		N (n=88)	Percent
Age (years)	Mean±SD	44.48±15.89	
Gender	Male	9	10.2
	Female	79	89.8
Marital status	Single	20	22.7
	Married	68	77.3
Education level	Primary	4	4.5
	Secondary	13	14.8
	College/university	45	51.1
	None	26	29.5
Employment status	Formally employed	4	4.5
	Not employed	31	35.2
	Self employed	53	60.2
Income category	<5000	37	42.5

	5000-10000	1	1.1
	10,001-30,000	25	28.7
	>30,000	24	27.6
	Missing	1	
Religion	Christian	86	97.7
	Muslim	2	2.3
Pregnancy status	No	87	98.9
	Yes	1	1.1
Smoking status	Previous smoker	5	5.7
	Never smoked	82	94.3
	Missing	1	
Preferred beverage	Tea	85	97.7
	Coffee	1	1.1
	Drinking chocolate	1	1.1
	Missing	1	
Number of cups	Two-three	25	28.7
	Four-five	62	71.3
Alcohol intake status	Previously drinking	8	9.2
	Never drunk	79	90.8
	Missing	1	
Care provider	Parents	15	17.2
	Extended relatives	2	2.3
	Siblings	4	4.6
	Spouse	31	35.6
	Children	27	31.0
	Grand children	3	3.4
	None	5	5.7
	Missing	1	

Clinical characteristics

a) Comorbidities

Comorbidities were found in 68.2%. As shown in Table 2, diabetes and chronic kidney disease were found in 10% and 10% of patients. A majority (93.3%) had other comorbidities.

Table 2: Comorbidities of patients with rheumatic disease at Kenyatta National Hospital

	Frequency (N=88)	Percent
Comorbidity	60	68.2
Diabetes	6	10.0
Heart failure	2	3.3
Anemia	6	10.0
Chronic Kidney Disease	4	6.7
Cancer	2	3.3
Other comorbidities	56	93.3

b) Review of systems

Pain (69.3%) and malaise (48.9%) were reported in a majority of patients with general system problems. Occasional impaired vision (18.2%) was the commonest eye problem, while 2.3% and 3.4% had ear problems such as loss of hearing and ringing ears. Sneezing and congested nose were reported in 3.4 % and 2.3%, while only 2.3% had throat problems. Digestive problems were at 44.3%, with abdominal pain and heartburn being the commonest at 35.4% and 29.5%. Joint pain (63.6%) and backache (53.4%) were the commonest musculoskeletal problems, while itchiness (17.0%) was the commonest integumentary system problem in the population studied.

Table 3. Review of systems of patients with rheumatic disease at Kenyatta National Hospital

	Frequency (N=88)	Percent
General system		
Fever	7	8.0
Malaise	43	48.9

Pain	61	69.3
Weight change	16	18.2
Eyes		
Any problem with the eyes	16	18.2
Occasional impaired vision	14	15.9
Pain in the eyes	8	9.1
Itching	7	8.0
Swelling	2	2.3
Ears		
Any problem with ears	3	3.4
Loss of hearing	2	2.3
Ringing in ears	2	2.3
Loss of balance	1	1.1
Nose		
Any problem with nose	3	3.4
Congested nose	2	2.3
Sneezing	3	3.4
Throat		
Any problem with throat	2	2.3
Pain while swallowing	2	2.3
Respiratory		
Any respiratory system problem	27	30.7
Chest pain	25	28.4
Shortness of breath	19	21.6
Wheezing	8	9.1
Coughing	7	8.0
Digestive		
Any digestive problem	39	44.3
Abdominal pain	31	35.2
Poor appetite	13	14.8
Heartburn	26	29.5

Difficulty swallowing	1	1.1
Diarrhea	10	11.4
Hard stool	3	3.4
Nausea	16	18.2
Genitourinary		
Any genitourinary system problem	6	6.8
Pain when urinating	4	4.5
Decreased sexual drive	1	1.1
Increased frequency of urination	3	3.4
Neurological		
Any neurological problem	24	27.3
Dizziness	18	20.5
Drowsiness	18	20.5
Memory loss	3	3.4
Numbness or tingling in extremities	3	3.4
Lack of sleep	7	8.0
Headache	19	21.6
Musculoskeletal		
Musculoskeletal system problem	60	68.2
Backache	47	53.4
Muscle pain	18	20.5
Joint pain	56	63.6
Joint stiffness	30	34.1
Difficulty walking	27	30.7
Swelling of joints	22	25.0
Integumentary system		
Any problem with skin	16	18.2
Itchiness	15	17.0
Rashes	13	14.8

c) Vital signs and laboratory tests

A majority had a normal blood pressure (71.6%) and hemoglobin level (56.8%), but the data for ESR reading, x-rays results, and rheumatoid factor was missing for a majority. Antinuclear antibodies were mostly negative (45.5%) (Table 4).

Table 4. Vital signs and laboratory tests of patients with rheumatic disease at Kenyatta National Hospital

		Frequency (N=88)	Percent
Blood pressure	Normal	63	71.6
	High	24	27.3
	Low	1	1.1
Hemoglobin levels	Normal	50	56.8
	High	1	1.1
	Low	24	27.3
	Not available	13	14.8
ESR reading	Normal	9	10.3
	Elevated	19	21.8
	Not available	59	67.8
	Missing	1	
X-ray	Normal joints	2	2.3
	Not available	86	97.7
Rheumatoid factor	Elevated	2	2.3
	Normal	6	6.8
	Not available	80	90.9
Antinuclear antibodies	Positive	17	19.3
	Negative	40	45.5
	Not available	31	35.2

d) Medication

The hospital was the source of medication for a majority (88.6%) with the commonest class for a majority found to be conventional DMARDS (83.0%). Around 61.4% required steroids, while 26.1%, 1.1%, and 1.1% required NSAIDS, Glucosamine, and anti-cancer medication respectively. No patient was on antibiotics (Table 5). When queried about their understanding of drug therapies, a majority (54.5%) did not know the dosage of medication. The frequency of medication was known by 89.8%, buy only 47.7% understood the duration of medication, even

though 98.9% expected medication to cure their existing condition. A minority were concerned about side effects (15.9%), medication (17.0%), and pill burden (10.2%) with a majority choosing to refill their prescription (81.8%) and take medication voluntarily (93.2%). A majority would not stop taking medication even when the condition was in control (76.1%).

Table 5: Medication

		Frequency (N=88)	Percent
Source of medication	Hospital	78	88.6
	Private clinic	1	1.1
	Private pharmacy	8	9.1
	Others	1	1.1
Classes of current medication			
	No	15	17.0
Conventional DMARDS	Yes	73	83.0
Steroids	Yes	54	61.4
	No	34	38.6
NSAIDS	Yes	23	26.1
	No	65	73.9
Glucosamine	Yes	1	1.1
	No	87	98.9
Anticancer	Yes	1	1.1
	No	87	98.9
Antibiotics	No	87	98.9
Understanding of drug therapy			
Know the doses of medication	Incorrect	48	54.5
	Correct	40	45.5
Know the frequency of medication	Incorrect	9	10.2
	Correct	79	89.8
Know the duration of medication	Incorrect	46	52.3

	Correct	42	47.7
Medication with regard to food	With food	2	2.3
	Before food	1	1.1
	After food	36	40.9
	Without regard to food	38	43.2
	I don't know	11	12.5
Expectations from medication	Cure	87	98.9
	Relief but no cure	1	1.1
Any concerns about medication	Yes	15	17.0
	No	73	83.0
High pill burden	Yes	9	10.2
	No	79	89.8
Concern on number of times taken	Yes	3	3.4
	No	85	96.6
Concerns on side effects	Yes	14	15.9
	No	74	84.1
Currently have side effects	Yes	21	23.9
	No	67	76.1
Take medication voluntarily	Yes	82	93.2
	No	6	6.8
Choose to refill prescription	Yes	72	81.8
	No	16	18.2
Stop taking when condition is under control	Yes	21	23.9
	No	67	76.1

e) Status of Rheumatic Disease

Patients had suffered from rheumatic disease for a mean duration of 63.45±42.78 months, with a majority (51.1%) having a partially improved condition.

Table 6: Status of rheumatic disease

		N (88)	Percent
Length of rheumatic disease	Mean±SD	63.45±42.78	
Status of rheumatic disease	Stable	5	5.7
	Improved	23	26.1
	Partially improved	45	51.1
	Unimproved	15	17.0

f) Prevalence of DTPs

The prevalence of DTPs was 48.9% (n =43). The prevalence of the need for additional therapy was 14.8% (n=13), mostly due to untreated conditions 53.8% (n=7) and synergistic/potentiating effect of medication 46.2% (n=6). The prevalence of ADR was 14.8% (n=13) due to undesirable effects 84.6% (n=11)and unsafe drugs 15.4% (n=2), while the prevalence of non-compliance was 17.0% (n=15) due to their inability to afford drugs 86.6% (n=13), forgetting to take products 6.7% (n=1), and unavailability of product 6.7% (n=1). Low dosage and high dosage were the least common DTPs with a prevalence of 1.1% and 1.1%.

Table 7: Prevalence of DTPs

		Frequency (N=88)	Percent
DTPs detected	Yes	43	48.9
	No	45	51.1
Unnecessary drug therapy		1	1.1
	No valid medical indication	1	100
	Not available	87	98.9
Needs additional		13	14.8

therapy			
	Untreated condition	7	53.8
	Synergistic/potentiating	6	46.2
	Not available	75	85.2
Different drug needed		2	2.2
	More effective drug available	2	100
	Not available	86	97.7
Dosage too low		1	1.1
	Frequency inappropriate	1	100
	Not available	87	98.9
ADR		13	14.8
	Undesirable effect	11	84.6
	Unsafe drug for patient	2	15.4
	Not available	75	85.2
Dosage too high		1	1.1
	Not available	87	98.9
Non compliance		15	17.0
	Cannot afford drug product	13	86.6
	Patient forgets to take	1	6.7
	Drug product not available	1	6.7
	Not available	73	83.0

g) Common drug related problems

A majority (68.2%) liked taking medication, while only 1.1% thought drugs did not work. Four patients (4.5%) thought drugs cause more problems, while 27.3% and 20.5% were concerned about the high cost of drugs and the availability of drugs.

Table 8: Common drug related problems

		Frequency	Percent
Do you like taking medication	Yes	60	68.2
	No	28	31.8
Drugs don't work	Yes	1	1.1
	No	87	98.9
Drugs cause more problems	Yes	4	4.5
	No	84	95.5
High cost of drugs	Yes	24	27.3
	No	64	72.7
Availability of drugs	Yes	18	20.5
	No	70	79.5

h) Factors associated with DTPS

Several demographic and reproductive characteristics were associated with DTP after multivariable analysis (Table 6). With each year increase in age, the odds having a DTP reduced by a factor of 0.078. With each year increase in the length of rheumatic disease, the adjusted odds of having a DTP increased by a factor of 0.028. The adjusted odds of having a DTP was 0.0 fold (95% CI=0.00-0.012) and 0.013 fold (95% CI=0.001-0.242) fold statistically significantly lower among patients with an improved and partially improved status of rheumatic disease compared to those with unimproved status ($P<0.05$). Steroid use was associated with 0.122 fold (95% CI=0.016-0.912) statistically significant reduction in the adjusted odds of developing a DTP (P=0.040), while use of NSAIDS was associated with a 6.641 fold (95% CI= 1.241-35.540) statistically significantly higher increase in the adjusted odds of developing a DTP (P=0.027). Age, gender, marital status, religion, smoking status, preferred beverage, alcohol intake status, education level, employment status, income category, blood pressure, hemoglobin levels, ESR

reading, X-ray results, rheumatoid factor, Antinuclear antibodies, and presence of other comorbidities were not associated with the adjusted odds of DTPs statistically significantly.

Table 9: Factors associated with DTPS

			95% CI		
	B	AOR	Low	High	P value
Age	-.078	0.925	0.864	0.990	**0.025**
Females	-2.30	0.100	0.010	1.004	0.050
Length of rheumatic disease	0.028	1.029	1.005	**1.053**	**0.018**
Current status of rheumatic disease					**0.002**
(reference = unimproved)					
Stable	13.659	8.5^{5}	0.000	.	0.999
Improved	-8.967	0.000	0.000	0.012	**0.000**
Partially improved	-4.359	0.013	0.001	0.242	**0.004**
Steroids use	-2.104	0.122	0.016	0.912	**0.040**
NSAIDS use	1.893	6.641	1.241	35.540	**0.027**

Variable(s) entered: Age, Gender, Marital status, Religion, Smoking status, Preferred beverage, Alcohol intake status, Education level, Employment status, Income category, Length of rheumatic disease, Blood pressure, Hemoglobin levels, ESR reading, X-ray results, Rheumatoid factor, Antinuclear antibodies, Current status of rheumatic disease, Conventional DMARDS use, Steroid use, NSAIDS use, Anticancer drugs use, Antibiotics use, Presence of other comorbidities

CHAPTER 5: DISCUSSION,CONCLUSION AND RECOMMENDATIONS

5.1. Discussion

Most participants were in their fourth decade of life with a low socio-economic status. Comorbidities such as diabetes were found in close to half of the patients, while general system (malaise and pain); respiratory, digestive, and musculoskeletal problems were diverse during clinical examination. Vital signs were mostly normal even though the large percentage of missing data might have impeded the analysis. The mean duration with rheumatic disease was 63 months. Most participants had a partial improvement of rheumatic disease after treatment. Overall, the prevalence of DTPs was high with the high cost and unavailability of drugs indicated found to be the commonest drug problems in the population studied. Moreover, age, length of rheumatic disease, status of rheumatic disease and the type of medication (steroids and NSAIDs) were associated with the DTPs significantly.

From the data, the prevalence of DTPs was common, with 48.9% of studied patients reporting at least one of the seven DTPs evaluated (unnecessary drug therapy, need for additional drug therapy, need for additional drugs, low dosage, high dosage, ADR, and non-compliance). Noncompliance was the commonest DTP type at 17%, mostly due to the high cost of drugs at 86% even though adverse drug reactions and the need for additional therapy were also common. The data was consistent with the findings of Ma et al. (2019) (5) in a retrospective study of 289 Malaysian patients with Rheumatoid arthritis where the prevalence of DTPs was high (78.5%). Like in this study, drug interactions, drug choice problems, and adverse drug reactions were the commonest contributors to the high prevalence of DTPs, necessitating immediate action. In Saudi Arabia, Al Malaq et al. (42) reported DTPs in 32.8% of patients with Rheumatoid arthritis, which was consistent with our findings, while 926 DTP were reported among patients with Rheumatoid arthritis in Iowa over a 12 month period, with adverse drug reactions contributing the most to poor self-reported mental and physical scores (43).

From these findings, DTPs seem to be common among patients with rheumatic disease than previously thought. Product substitution to lower adverse reactions and routine monitoring of the drug needs for patients can lower its occurrence(44).

From the data, most patients preferred to take medication because of their efficacy, safety, and potential to cure rheumatoid disease. However, the lack of drugs in hospitals and chemists and the high cost of drugs were a concern for more than a quarter of the population studied. This leads to non-adherence to treatment leading to digestive, respiratory, and musculoskeletal problem and psychological deficits such as anxiety. Al Heifny et al (45) had similar findings in Egypt in 2012 where the cost of medicines and non-availability of medicines were the main concerns for patients with rheumatoid arthritis. In Iran, close to half of patients evaluated by Khabbazi et al.(46) were concerned about the lack of medication, as it led to the suspension of medication. From the finding, patients with rheumatic disease should be supported financially through public programs such as the National Hospital Insurance Fund (NHIF). While NHIF covers diagnostic services such as X-ray, MRI, and CT scans and beds for inpatients(47), patients bear the majority of treatment costs, estimated to exceed 6500 Kenyan shillings per day (48).

This is concerning as patients with other chronic conditions such as cancer and chronic kidney disease (including renal dialysis and kidney transplants) have a special consideration by the NHIF. Institution factors such as improving patient-doctor relationship, patient education on drug and finance options, and simplifying the drug prescription process can also help (45,49).

After multivariable analysis, the data showed that the age, length/status of rheumatic disease, steroid use, and NSAID use were associated with the development of DTPs. In terms of age, younger patients experience DTPs at a higher rate than elderly patients, a common finding. In a study by Al Malaq et al. in Saudi Arabia, a majority of rheumatic arthritis patients with DTPs were younger than those who did not. However, Trehrane et al. (50) found deviant results in the UK in 2002 where the odds of DTP were higher among elderly patients, but was dependent on the higher prevalence of comorbidities among the elderly. In this study, comorbidities were controlled in the multivariable analysis, which might have contributed to the difference. The

differences in demographics (developed versus third world) and variances in methodologies (Trehane interpreted the 28-joint Disease Activity Score (DAS28), which we did not) might be at play. Our data also contradicted the findings of Huri and Wee (51) in 2013 that age was not a risk factor for DTPs in patients with Rheumatic disease. From this finding, age might be negatively correlated with the development of DTPs but might be dependent on health indicators such as comorbidities and differences in population characteristics.

The length of rheumatic disease predisposed patients DTPs. From the data, patients who had suffered from rheumatic disease for long were more likely to have DTPs than those who had suffered for a short time. Moreover, patients who had a partial improvement in rheumatic disease were less likely to have DTPs from the findings. This is consistent with the findings of Treharme et al (50) in the UK in 2007 where the length of rheumatic disease was statistically significantly associated with the development of DTPs. To prevent adverse outcomes, regular monitoring for DTPs should be instituted, especially among patients who have had the condition for long.

Steroid use was a protective factor for DTPs. This finding may be associated with the ability of corticosteroids to reduce disease flares and it rapid onset of symptomatic relief (8) However, patients who received NSAIDS for rheumatoid disease were more likely to develop DTPs in the population studied. This was consistent with the findings of Zhang et al (52) in 2016 and Laba et al (44) in 2013 where the use of NSAIDs were associated with a significantly higher odds of adverse events such as DTPs. While the clinical benefits of NSAIDs are diverse, particularly among the elderly, patients on NASIDs should be monitored routinely and treatment stopped when the probability of having an adverse reaction far outweighs its benefits. Product substitution with comparable steroid based drugs should be considered, as steroids seemed to lower the adjusted odds of developing a DTP.

5.2. Study strengths and weaknesses

The participants were very cooperative in giving information and thus enabling collection of most of the required information within a short time and the missing information was retrieved from the patients files enabling completeness of data. The study had a challenge of low sample size impacting negatively on the power of study that was occasioned by the low numbers of patients at the clinic due to the covid-19 pandemic. Even though, being the first in the region it provides a basis for a larger study with higher power.

5.3Conclusion

Overall, the prevalence of DTPs was high (48.6%) with the high cost and unavailability of drugs indicated found to be the commonest drug problems in the population studied.

Rheumatic conditions were more prevalent in females at Kenyatta National Hospital. Most participants had a partial improvement of rheumatic disease after treatment.. Moreover, age, length of rheumatic disease, status of rheumatic disease and the type of medication (steroids and NSAIDs) were associated with the DTPs significantly.

5.4. Recommendations

5.4.1. Recommendatons for policy and practice

Patient need to be educated on the advantages of taking a medical cover as a significant percentage are concerned about the cost of medication (86%) though not statistically significant probably due to the sample size.

The hospitals and pharmacy and poisons board should have measures in place to ensure sustained supply of DMARDS to safeguard the rheumatic patients who are experiencing stock outs and prices hikes especially during the corona virus pandemic where there where myths of some DMARDS being a cure for the virus.

A drug therapy assessment form should be introduced and regular review of the rheumatic patients by clinical pharmacists to identify and resolve drug related problems as a number patients do have unresolved or partially improved disease states yet the cause of the unresolved states is unidentified.

Drug research should also be prioritized to offer diverse and effective products for this neglected group to improve outcomes and sensitization campaigns developed to educate victims and the community.

5.4.2. Recommendations for research

A randomized control study on the impact on disease status of addressing drug related problems among rheumatic patients should be done.

A larger study on the use of NSAIDs in rheumatic patients needs to be conducted as this study has shown an increase in the odds of developing DRPs.

REFERENCES

1. EULAR Secretariat. 0 things you should know about rheumatic diseases.
2. Mody GM. Rheumatology in Africa-challenges and opportunities. Vol. 19, Arthritis Research and Therapy. BioMed Central Ltd.; 2017.
3. Harel-Meir M, Sherer Y, Shoenfeld Y. Tobacco smoking and autoimmune rheumatic diseases. Vol. 3, Nature Clinical Practice Rheumatology. 2007. p. 707–15.
4. Westerlund, J.W.Foppe van Mil, Nejc Horvat T, Zuidlaren. PCNE Classification for Drug

related problems. 2003.

5. Ma SN, Huri HZ, Yahya F. Drug-related problems in patients with rheumatoid arthritis. Ther Clin Risk Manag. 2019;15:505–24.

6. Zaman Huri H, Chai Ling L. Drug-related problems in type 2 diabetes mellitus patients with dyslipidemia. BMC Public Health [Internet]. 2013 Dec 17;13(1):1192. Available from: http://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-13-1192

7. Levels 4-6-Hospitals [Internet]. [cited 2019 Nov 25]. Available from: http://www.health.go.ke

8. Buttgereit F, Straub RH, Wehling M, Burmester G-R. Glucocorticoids in the treatment of rheumatic diseases: An update on the mechanisms of action. Arthritis Rheum [Internet]. 2004 Nov [cited 2019 Nov 25];50(11):3408–17. Available from: http://doi.wiley.com/10.1002/art.20583

9. Evaluation of Pain Management Among Patients With Rheumatoid Arthritis at Kenyatta National Hospital [Internet]. [cited 2019 Nov 25]. Available from: http://41.204.161.209/handle/11295/106130

10. Garcia Popa-Lisseanu MG, Greisinger A, Richardson M, O'Malley KJ, Janssen NM, Marcus DM, et al. Determinants of treatment adherence in ethnically diverse, economically disadvantaged patients with rheumatic disease. Vol. 32, Journal of Rheumatology. 2005. p. 913–9.

11. Tugwell P. Methotrexate in Rheumatoid Arthritis. Arch Intern Med [Internet]. 1990 Jan 1 [cited 2019 Nov 26];150(1):59. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.1990.00390130073009

12. Drug-related pulmonary problems in patients with rheumatoid arthritis | Rheumatology | Oxford Academic [Internet]. [cited 2019 Nov 20]. Available from: https://academic.oup.com/rheumatology/article/45/7/787/1788784

13. Chopra A, Abdel-Nasser A. Epidemiology of rheumatic musculoskeletal disorders in the

developing world. Vol. 22, Best Practice and Research: Clinical Rheumatology. 2008. p. 583–604.

14. Zeng QY, Chen R, Darmawan J, Xiao ZY, Chen SB, Wigley R, et al. Rheumatic diseases in China. Arthritis Res Ther. 2008 Jan 31;10(1).

15. Usenbo A, Kramer V, Young T, Musekiwa A. Prevalence of arthritis in Africa: A systematic review and meta-analysis. PLoS One. 2015 Aug 4;10(8).

16. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Vol. 62, Arthritis and Rheumatism. John Wiley and Sons Inc.; 2010. p. 2569–81.

17. Rheumatoid Arthritis Clinical Presentation: History, Physical Examination, Stiffness, Tenderness, and Pain on Motion [Internet]. [cited 2019 Dec 5]. Available from: https://emedicine.medscape.com/article/331715-clinical#

18. Denburg SD, Carbotte RM, Denburg JA. Corticosteroids and neuropsychological functioning in patients with systemic lupus erythematosus. Arthritis Rheum. 1994;37(9):1311–20.

19. Braun J, Sieper J. Ankylosing spondylitis. Vol. 369, Lancet. 2007. p. 1379–90.

20. Heiberg MS, Koldingsnes W, Mikkelsen K, Rødevand E, Kaufmann C, Mowinckel P, et al. The comparative one-year performance of anti–tumor necrosis factor α drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: Results from a longitudinal, observational, multicenter study. Arthritis Rheum [Internet]. 2008 Feb 15 [cited 2019 Dec 10];59(2):234–40. Available from: http://doi.wiley.com/10.1002/art.23333

21. Gladman DD. Psoriatic arthritis. In: Moderate-to-Severe Psoriasis, Third Edition. CRC Press; 2008. p. 239–58.

22. Leder RO, Farber EM. The variable incidence of psoriasis in sub-Saharan Africa. Int J Dermatol. 1997;36(12):911–9.

23. Sukhov A, Adamopoulos IE, Maverakis E. Interactions of the Immune System with Skin and Bone Tissue in Psoriatic Arthritis: A Comprehensive Review. Vol. 51, Clinical Reviews in Allergy and Immunology. Humana Press Inc.; 2016. p. 87–99.

24. Elyoussfi S, Thomas BJ, Ciurtin C. Tailored treatment options for patients with psoriatic arthritis and psoriasis: review of established and new biologic and small molecule therapies. Vol. 36, Rheumatology International. Springer Verlag; 2016. p. 603–12.

25. Parks CG, D'Aloisio AA, Sandler DP. Early life factors associated with adult-onset systemic lupus erythematosus in women. Front Immunol. 2016 Mar 31;7(MAR).

26. Arden N, Nevitt MC. Osteoarthritis: Epidemiology. Vol. 20, Best Practice and Research: Clinical Rheumatology. 2006. p. 3–25.

27. Drug-related problems: a cornerstone for pharmaceutical care Community Pharmacist Pharmacy Practice Consultant Secretary of Pharmaceutical Care Network Europe (PCNE) [Internet]. [cited 2019 Dec 5]. Available from: http://phi.uhce.ox.ac.uk/,

28. Blix HS, Viktil KK, Reikvam Å, Moger TA, Hjemaas BJ, Pretsch P, et al. The majority of hospitalised patients have drug-related problems: Results from a prospective study in general hospitals. Vol. 60, European Journal of Clinical Pharmacology. Springer Verlag; 2004. p. 651–8.

29. van Jaarsveld CHM, Jahangier ZN, Jacobs JWG, Blaauw AAM, van Albada-Kuipers GA, ter Borg EJ, et al. Toxicity of anti-rheumatic drugs in a randomized clinical trial of early rheumatoid arthritis. Rheumatology [Internet]. 2000 Dec [cited 2020 Feb 3];39(12):1374–82. Available from: https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/39.12.1374

30. Strand LM, Morley PC, Cipolle RJ, Ramsey R, Lamsam GD. Drug-Related Problems: Their Structure and Function. DICP [Internet]. 1990 Nov 30 [cited 2020 Jan 29];24(11):1093–7. Available from: http://journals.sagepub.com/doi/10.1177/106002809002401114

31. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.

Arthritis Rheumatol. 2016 Jan 1;68(1):1–26.

32. Viktil KK, Blix HS, Reikvam A, Moger TA, Hjemaas BJ, Walseth EK, et al. Comparison of drug-related problems in different patient groups. Ann Pharmacother. 2004 Jun;38(6):942–8.

33. FitzGerald O, Gladman D, editors. Oxford Textbook of Psoriatic Arthritis [Internet]. Vol. 1. Oxford University Press; 2018 [cited 2020 Jan 23]. Available from: http://www.oxfordmedicine.com/view/10.1093/med/9780198737582.001.0001/med-9780198737582

34. Adverse Drug Reactions Due to Disease Modifying Drugs in Patients with Rheumatoid Arthritis - ACR Meeting Abstracts [Internet]. [cited 2020 Feb 4]. Available from: https://acrabstracts.org/abstract/adverse-drug-reactions-due-to-disease-modifying-drugs-in-patients-with-rheumatoid-arthritis/

35. Bagatini F, Blatt CR, Maliska G, Trespash GV, Pereira IA, Zimmermann AF, et al. Potential drug interactions in patients with rheumatoid arthritis. Rev Bras Reumatol [Internet]. [cited 2020 Feb 4];51(1):20–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21412604

36. Masuko K, Tohma S, Matsui T. Potential food-drug interactions in patients with rheumatoid arthritis. Int J Rheum Dis. 2013 Apr;16(2):122–8.

37. Rapoff MA. Assessing barriers to therapeutic regimens for young people with juvenile idiopathic arthritis. Vol. 45, Journal of Rheumatology. Journal of Rheumatology; 2018. p. 588–9.

38. Eichenberger PM, Haschke M, Lampert ML, Hersberger KE. Drug-related problems in diabetes and transplant patients: An observational study with home visits. Int J Clin Pharm. 2011 Oct;33(5):815–23.

39. Cook MJ, Bellou E, Bowes J, Sergeant JC, O'Neill TW, Barton A, et al. The prevalence of co-morbidities and their impact on physical activity in people with inflammatory rheumatic diseases compared with the general population: Results from the UK Biobank. Rheumatol (United Kingdom). 2018;57(12):2172–82.

40. Fraenkel L, Rabidou N, Dhar R. Are rheumatologists' treatment decisions influenced by patients' age? Rheumatology [Internet]. 2006 Aug 18 [cited 2020 Feb 5];45(12):1555–7. Available from: https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/kel144

41. Dowman B, Campbell RM, Zgaga L, Adeloye D, Chan KY. Estimating the burden of rheumatoid arthritis in Africa: A systematic analysis. J Glob Health. 2012;2(2).

42. Al-Malaq HM, Al-Arfaj HF, Al-Arfaj AS. Adverse drug reactions caused by methotrexate in Saudi population. Saudi Pharm J. 2012 Oct;20(4):301–5.

43. Ernst ME, Iyer SS, Doucette WR. Drug-Related Problems and Quality of Life in Arthritis and Low Back Pain Sufferers. Value Heal. 2003 Jan;6(1):51–8.

44. Laba T-L, Brien J, Fransen M, Jan S. Patient preferences for adherence to treatment for osteoarthritis: the MEdication Decisions in Osteoarthritis Study (MEDOS). BMC Musculoskelet Disord. 2013 Dec;14(1):160.

45. Alhefny AE-A, Abd El-Rahman M, Abd El-Moteleb S, Sakr H, Hassan R. Evaluation of Adherence to Drug Treatment in Patients with Rheumatoid Arthritis. Egypt J Rheumatol Clin Immunol. 2015 Dec;3(1):68–80.

46. Khabbazi A, Kavandi H, Paribanaem R, Khabbazi R, Malek Mahdavi A. Adherence to medication in patients with rheumatic diseases during COVID-19 pandemic. Ann Rheum Dis. 2020 Sep;annrheumdis-2020-218756.

47. National Hospital Insurance Fund. Strides towards universal health coverage for all Kenyans. 2020.

48. The Star. Battle with self and the high cost of treatment. Long Suffering Patients. 2020.

49. Goh H, Kwan YH, Seah Y, Low LL, Fong W, Thumboo J. A systematic review of the barriers affecting medication adherence in patients with rheumatic diseases. Rheumatol Int. 2017 Oct;37(10):1619–28.

50. Treharne GJ, Douglas KMJ, Iwaszko J, Panoulas VF, Hale ED, Mitton DL, et al. Polypharmacy among people with rheumatoid arthritis: the role of age, disease duration

and comorbidity. Musculoskeletal Care. 2007 Dec;5(4):175–90.

51. Zaman Huri H, Fun Wee H. Drug related problems in type 2 diabetes patients with hypertension: a cross-sectional retrospective study. BMC Endocr Disord. 2013 Dec;13(1):2.

52. Zhang W, Ouyang H, Dass CR, Xu J. Current research on pharmacologic and regenerative therapies for osteoarthritis. Bone Res. 2016 Dec;4(1):15040.

Appendix 1: Eligibility screening form

Kenyatta National Hospital rheumatology clinic **OPC number**_____ **Study unique number**_____	
Criteria	**Remark as YES or NO**
Adult aged more than 18 years	

On DMARDS or steroids or NSAIDS or combination of drugs.	
Capable of communication	
Given consent	

If all are **YES** then proceed to the study Questionnaire.

Appendix 2A: Participant information form

ASSESSMENT OF DRUG RELATED PROBLEMS IN ADULT PATIENTS WITH RHEUMATIC DISEASES IN KNH.

Principal Investigator

Dr. Manani Joseph State- Master of Pharmacy (Clinical Pharmacy) Second-year student at the University of Nairobi.

Supervisors: Dr Sylvia Opanga-Lecturer, University of Nairobi; Dr.Stephen Githinji – Lecturer, University of Nairobi.

Introduction

I, Manani Joseph State, a postgraduate student at the University of Nairobi, school of pharmacy, would like to inform you about a study being carried out by the above-listed researchers. The purpose of this consent form is to give you information that will enable you choose whether or not to be a participant in the study. You are free to ask any questions or seek clarification on any unclear areas about the purpose of the study, what the study entails, the possible risks and benefits, your rights as a study participant. Once we have answered all your questions, it is your choice to be in the study or not. This process is termed 'informed consent'. Once you understand and choose to be in the study, I will request you to sign your name on this form. These are the general principles which apply to participants in a medical research: i) The choice to participate is entirely voluntary ii) You are free to withdraw from the study at any time without necessarily giving a reason for your withdrawal and without any repercussions. iii) Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities. A copy of this form will be given to you for your records.

May I continue? **YES,** **NO**

This study has approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Protocol No.: _____

WHAT IS THIS STUDY ABOUT?

Most adult patients with chronic diseases are known to have challenges when it comes to management, and treatment of the diseases and complications that arise due to the conditions. They often experience drug related problems due to the severity of their conditions and multiple medications. In this study, we will ask you to state your experiences with medications and the challenges you get with using your medications. Our aim is to establish whether the medications that have been prescribed for you are alleviating the condition optimally or not, to find out whether they are safe and effective, to find out which drugs the patient is using and identify things the patient is doing or not doing that may be significantly increasing occurrences of Drug related problems. We are requesting for your consent to be part of this study.

WHAT WILL HAPPEN IF YOU CHOOSE TO PARTICIPATE IN THIS RESEARCH?

If you agree to participate in this research, you will be interviewed by a trained health care provider in a private area where you feel comfortable answering questions. Administration of the questionnaires will be at your own convenience and you are free to skip questions that you do not wish to answer. The interview will last approximately twenty minutes and will cover topics such as your medication history, biodata, comorbidities, medication experiences, and general review of the systems. The information you provide us with will be kept confidential for research purposes and any information that can link you to the information collected will be kept separately under lock and key where it can only be accesses by the principal investigator

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Psychological, emotional, social and physical factors are risks introduced by a medical research. However, a concerted effort must be put in place to mitigate the

risk. One of the risk that you may encounter is lack of privacy. Your information will be treated confidential and will use a code number to identify you in a password protected computer database with password restricted access. Signed copies of your consent participation forms will be kept in a locked office file cabinet. Only the principal investigator and assistant researcher will access the documents. Additionally this study will consume your time.

However, we promise to observe time to avoid inconveniencing you as the study participant. Furthermore, this study does not involve any invasive procedures, taking additional drugs or additional financial implications and therefore no harm to the participants.

ARE THERE ANY BENEFITS?

The study findings will help us improve health outcomes by prioritizing each drug related problem identified among adult patients with rheumatic diseases and using the statistically significant predictors to anticipate and tackle or avoid drug related problems. Additionally, the findings will help develop guidelines and protocols that will prevent drug related issues from occurring.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

The study will utilize about twenty minutes of your time and I will try as much as possible to be brief and precise to save on your time.

ARE THERE ANY REIMBURSEMENTS?

There will be no payments inform of cash, gifts or enticements for participation in the study.

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, you are free to contact the principal investigator via call or text message before, during, and after the study. For any information about your rights as a research participant you may contact the Principal Investigator on Email: mananijoseph3@gmail.com, or Telephone Number 0721956001. In addition, you may contact the Secretary, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No.: **2726300** Ext: **44102** or Email: *uonknh_erc@uonbi.ac.ke.*

Participant's Statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw anytime. I freely agree to participate in this research study. I understand that all efforts will be made to keep information regarding my personal identity confidential. By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study:	**YES**	**NO**
I agree to provide contact information for follow-up:	**YES**	**NO**

Participant printed name:

_____

Participant signature / Thumb stamp _____

Date _____

Witness_____**Date**_____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above. The participant has understood and has freely given his/her consent as signed in appendix 2A.

Researcher 's Name:_____**Signature** _____

Date: _____

Role in the study: _____

For more information, contact_____at_____from _____to _____

Appendix 3A: Maelezo kuhusu kushiriki katika utafiti Kichwa cha Uchunguzi

KUCHUGUZA MATATIZO YA DAWA ZA TIBA KWA WAGONJWA AMBAO NI WATU WAZIMA WENYE UGONJWA WA RHEUMATIZIMU.

Mchunguzi mkuu

Dkt Manani Joseph-mwanafunzi wa mwaka wa pili katika chuo kikuu cha Nairobi.

Wasimamizi: Dkt Sylvia Opanga. Mhadhiri Chuo Kikuu cha Nairobi, Dkt. Stephen Githinji, Mhadhiri, Chuo Kikuu cha Nairobi

Utangulizi

Mimi ni Manani Joseph, mwanachuo katika chuo kikuu cha Nairobi, kitengo cha shule ya pharmacia.

Nafanya uchunguzi wa matatizo ya dawa za tiba kwa wagonjwa ambao ni watu wazima waliozaidi miaka 18 wenye kusumbuliwa na magonjwa ya rheumatizimu kwenye hospitali ya kitaifa ya Kenyatta.

UMUHIMU WA MAFUNZO

Wagonjwa wengi wanajulikana kama wameathirika na magonjwa endapo wanamatatizo ya kiafya na matibabu ya magonjwa mbalimbali, pamoja na matatizo ya dawa ya tiba kutokana na hali mbaya ya kiafya. Katika mafunzo haya tutazungumzia utumiaji dawa na mambo unayopata unapotumia dawa.

Lengo letu ni kujua na kuelewa nini wagonjwa watu wazima wanaougua kutokana na magojwa ya rheumatizimu, wanatatizwa na aina gani ya DTPs

na kuchunguza yanayo sababisha matatizo haya.

Haya yatachunguzwa kwa kutumia sehemu tatu ya maswali nitakayo kuuliza.

Tutafwata utaratibu ambapo unaweza ukakubali kushiriki kwenye mafunzo. Utatakiwa kujibu dodoso mbili ambalo litachukua makadirio ya dakika 20 na usimamizi wa dodoso utakuwa wako na utakuwa huru kuruka maswali ambayo hutaki kujibu. Taarifa zote zitakusanywa na mchunguzi mkuu na mtafiti msaindizi na zitakuwa ni za siri.

USHIRIKI WA KUJITOLEA

Katika mafunzo haya, kuchagua kushiriki ni kujitolea na unaonesha uhuru wako baada ya kukubali kushiriki. Unaweza ukawa nje ya mafunzo kwa muda wote, kwa kufanya hivyo hutakosa faida ambazo utapewa.

HATARI NA MADHARA

Kisaikolojia, kihisia, kijamii na kimwili hizi ni hatari zilizo ndani ya utafiti. Vilevile juhudi halisi ziwepo kupelekea kupunguza hatari, moja wapo unayoweza kukutana nayo ni ukosefu wa usiri. Taarifa inayokusanywa itakuwa ni ya siri na italindwa kwa kutumia nywila inayolindwa na umeme wa mfumo wa taarifa ya madawa. Nakala zako zilizosahiniwa zenye mawazo yako za ushiriki wako zitafungiwa kwenye karatasi la kuhifadhi nyalaka ya kiofisi. Mchunguzi mkuu na mtafiti msaidizi pekee hao ndio watakao fanyia kazi taarifa yako. Kwa kuongezea, wakati wa ufanyaji wa dodoso, mafunzo yatachukua muda wako binafsi, tunaahidi kuangalia muda kuondoa mwingiliano ukiwa kama mshiriki wa mafunzo, zaidi mafunzo haya hayatahusisha au kutumia madawa

TAREJESHEWA PESA ZAKO?

Utafiti huu hautakugharimu pesa.

NA KAMA UTAKUWA NA MASWALI BAADAYE?

Kama una maswali zaidi au lolote ambalo hulielewi kuhusu utafiti huu, tafadhali usisite kuwasiliana nasi kupitia nambari ambazo zimeandikwa hapa chini.

Kwa maelezo zaidi kuhusu haki za mshiriki katika utafiti, wasiliana na

Mtafiti Mkuu Daktari Manani Joseph

au Kabitu/Mwenyekiti Simu.: **2726300** ongezo: **44102** Tovuti: *uonknh_erc@uonbi.ac.ke*. Utarudishiwa ada ya mazungumzo kupitia laini hizi kama mazungumzo yenyewe yanahusu utafiti huu.

Appendix 3B: Ridhaa (kukubali kushiriki)

Taarifa ya Mshiriki

Nimesoma au nimesomewa nakala hili. Nimepata kuzungumza kuhusu utafiti huu na mtafiti mwenyewe. Maswali yangu yamejibiwa kwa lugha ninayoielewa vizuri. Madhara na manufaa yameelezwa wazi. Ninaelewa kushiriki kwangu ni kwa hiari na kwamba ninao uhuru wa kutoshiriki wakati wowote. Ninakubali bila kushurutishwa kushiriki katika utafiti huu. Ninaelewa kwamba bidii itatiwa kuhakikisha habari zangu zimewekwa siri. Kwa kutia sahihi kwa daftari hili, sijapeana haki zangu za kisheria ambazo ninazo kama mshiriki katika utafiti huu.

Nimekubali kushiriki katika utafiti huu: **ndio** ☐ **la** ☐

Nimekubali kupeana nambari ya mawasilianao baadaye **ndio** ☐

Jina la Mshiriki: _____

Tarehe_____ **Taarifa ya Mtafiti**

Mimi, ninayetia sahihi hapo chini, nimeelezea maswala muhimu ya utafiti huu kwa mshiriki aliyetaja hapo juu na ninaamini ya kwamba ameyaelewa vilivyo na kwamba ameamua bila kushurutishwa kukubali kushiriki.

Jina la Mtafiti:_____**Sahihi**_____ **Tarehe**: ___

Kazi yangu kwa utafiti huu: _____

Kwa maelezo zaidi wasiliana na_____kwa_____ Saa_____hadi ___

Appendix 4: Participants questionnaire

UNIVERSITY OF NAIROBI

RESEARCH TOPIC: ASSESSMENT OF DRUG RELATED PROBLEMS IN ADULT PATIENTS WITH RHEUMATIC DISEASES IN KNH

STUDY ASSISTANT: .....

DATE: .....

OPC number_____

Study unique number_____

INSTRUCTIONS

a. Please answer the following questions and fill in these details in the spaces provided.
b. Feel at liberty to ask for clarifications whenever in need.

PART A (TO BE ANSWERED BY THE PARTICIPANTS)

i. Demographic information

1) Age: _____years
2) Sex: Male (0) Female (1)
3) Weight……kg…height……Meters…BMI……
4) Category for BMI

Category	Code
18.5 and below (underweight)	0
18.5 to 24.9 (healthy weight)	1

25 to 29.9 (over weight)	2
30 and above (obesity)	3

5) Marital Status: Single (0) Married (1)

6) Pregnancy status: Yes (1) No (0)

7) Religion: Christians (0) Muslim (1) Others (2)

8) Smoking status: current smoker (0) previous smoker (1) never smoked (2)

9) What is your preferred beverage? Tea (0)coffee (1) cocoa (2) drinking chocolate (3) others…….

10) How many cups do you take per day? (1) one (2) two-three (3) four -five

11) Alcohol intake status: currently drinking (0) previously drinking (1) never drunk (2)

12) How many glasses of alcohol do you take per week? (1) one (2) two-three (3) >four (4)

13) Level of Education: Primary (1) Secondary (2) College/University (3) none (4)

ii. Occupation

14) What is your employment status? Formally employed (0) not employed (1) self-employed (2)

15) On average, how much do you make in a month..... shillings?

16) Categories of monthly income: <5000(1) 5000-10000 (2) 10000-30000(3) >30000 (4)

iii. Living situation

17) Who lives and cares for you at home? Kindly tick

Parents	(1)
Extended Relatives	(2)
Siblings	(3)

Spouse	(4)
Children	(5)
Grandchildren	(6)
Friends	(7)
None	(8)

18) Where do you get your medication?

Hospital (0)

Private clinics (1)

Private pharmacy (2)

Others..... (3)

iv. Comorbidities

19) Do you suffer from any other disease or medical problem apart from what I am seeing the doctor has told you?

No (0) Yes (1) If yes to question (19) above, which one(s)

	Yes	**No**
20) **Diabetes**	**1**	**0**
21) **Heart failure**	**1**	**0**
22) **Anemia**	**1**	**0**
23) **CKD**	**1**	**0**
24) **CANCER**	**1**	**0**
25) **Others**	**1**	**0**

26) For how long have you had rheumatic disease_____months

v. Medication experiences

27) Do you like taking medications? No(0) Yes (1)

If No to question (27) above, what is the reason?

29) Drugs don't work? No (0) Yes (1)

30) They cause more problems? No (0) Yes (1)

31) I don't take medications? No (0) Yes (1)

32) The cost of drugs? No (0) Yes (1)

33) Availability of drugs? No (0) Yes (1)

34) What do you expect from the medications you use?

Cure (0) Relief but no cure (1)

35) Do you have any concerns regarding your medications? No (0) Yes (1)

If yes to question (35) above, what are the concerns?

36) Is the number of pills a concern? No (0) Yes (1)

37) Is the number of times you take drugs a concern? No (0) Yes (1)

38) Are the side-effects of medications a concern? No (0) Yes (1)

39) Do you currently suffer from any side effects No(0) Yes (1)

40) Do you take your medication voluntarily? No (0) Yes (1)

41) Do you choose to refill your prescription? No(0) Yes (1)

42) When you feel like your condition is under control, do you sometimes stop taking your medication? No(0) Yes (1)

vi. Patients understanding of drug therapy

Ask the patient the following questions 42-44, and fill in the table below.

43) Do you know the dose (s) of the medication (s) you are taking_____? Correct (1) Incorrect (0)

44) Are you aware how many times you should take the drug(s) in a day_____? Correct (1) Incorrect (0)

45) Do you know the duration for which you should be on your medication (s)___? Correct (1) Incorrect (0)

46) How should you take this medication with regard to food? with food (1) before food (2) after food (3) without regard to food (4) I don't know (5)

Condition	Drug name	Dose	Frequency	Duration	Taking drug with regard to food

vii. Review of systems

i. General system

47) Fever? No (0) Yes (1)

48) Malaise? No (0) Yes (1)

49) Are you experiencing pain anywhere? No (0) Yes (1)

50) Do you have weight change? No (0) Yes (1)

Special senses

i. Eyes

51) Do you have any problem with your eyes? No(0) Yes(1)

If yes above, which problem?

52) Impaired vision occasionally? No (0) Yes (1)

53) Pain in your eyes? No (0) Yes (1)

54) Itching ?	No (0)	Yes (1)
55) Swelling?	No (0)	Yes (1)

ii. Ears

56) Do you have any problem with your ears? No (0) Yes (1) If yes above, which problem?

57) Loss of hearing?	No (0)	Yes (1)
58) Ringing in the ears?	No (0)	Yes (1)
59) Loss of balance?	No (0)	Yes (1)

iii. Nose

60) Do you have any problem with your nose? No (0) Yes (1) If yes above, which problem?

61) Congested nose?	No (0)	Yes (1)
62) Sneezing?	No (0)	Yes (1)

iv. Throat

63) Do you have any problem with your throat?	No (0)	Yes (1)

If yes above, which problem?

64) Coughing bloody mucus?	No (0)	Yes (1)
65) Pain while swallowing?	No (0)	Yes (1)

iii. Respiratory system

66) Do you have any problem with your respiratory system?	No (0)	Yes (1)

If yes above, which problem?

67) Chest Pain?	No (0)	Yes (1)
68) Shortness of breath?	No (0)	Yes (1)
69) Wheezing?	No (0)	Yes (1)

70) Coughing No (0) Yes (1)

iv. Digestive system and associated systems

71) Do you have any problem with your digestive system? No (0) Yes (1) If yes above, which problem?

72) Pain in the abdomen?	No (0)	Yes (1)
73) Poor appetite?	No (0)	Yes (1)
74) Heartburn?	No (0)	Yes (1)
75) Difficult in swallowing?	No (0)	Yes (1)
76) Diarrhea?	No (0)	Yes (1)
77) Hard stool ?	No (0)	Yes (1)
78) Nausea?	No (0)	Yes (1)

v. Genito-urinary system

79) Do you have any problem with your Genitourinary system?	No (0)	Yes(1)

If yes above, which problem?

80) Pain when urinating?	No (0)	Yes(1)
81) Decreased sexual drive?	No (0)	Yes(1)
82) Increased frequency of urination?	No (0)	Yes (1)

vi. Neurological system

83) Do you have any problem with your Neurological system?	No (0)	Yes (1)

If yes above, which problem?

84) Feeling dizziness?	No (0)	Yes (1)
85) Feeling drowsiness?	No (0)	Yes (1)

86) Experiencing memory loss?	No (0)	Yes (1)
87) Experiencing numbness or tingling in extremities?	No (0)	Yes (1)
88) Lack of sleep?	No (0)	Yes (1)

89) Headache? No (0) Yes (1)

vii. Hematological system

90) Do you have any problem with bleeding? No (0) Yes (1)

If yes above, which problem?

91) Do you bruise easily? No (0) Yes (1)

92) Have you ever been told you have anemia? No (0) Yes (1)

viii. Musculoskeletal system

93) Do you have any problem with musculoskeletal system? No (0) Yes (1)

If yes above, which problem?

94) Backache? No (0) Yes (1)

95) Muscle pain? No (0) Yes (1)

96) Joint pain? No (0) Yes (1)

97) Joint stiffness? No (0) Yes (1)

98) Difficult in walking? No (0) Yes (1)

99) Swelling of joints? No (0) Yes (1)

ix. Integumentary system

100) Are you having any problems with your skin? No (0) Yes (1)

If yes above, which problem?

101) Itchiness? No (0) Yes (1)

102) Rashes? No (0) Yes (1)

PART B (TO ABSTRACT PATIENT INFORMATION FROM THE MEDICAL RECORDS)

Vital signs and laboratory tests

What are the laboratory test done in this patient?

Vital signs and labs	**Previous readings**	**Current readings**	
103) **Blood pressure**			1. Normal range <140/90mmHg 2. High 3. Low 4. Not available
104)**Full haemogram**			1. Normal 2. High 3. Low 4. Not available
105) **ESR**			1. Normal 2. Elevated 3. Not available
106) **X-Ray**			1. normal joints 2. deformed joints

107) **Rheumatoid factor**			1. elevated 2. normal
108) **Antinuclear antibodies**			1. positive 2. negative

What are the Prescription patterns and characteristics of drug therapy problems in patients?

Serial number	Condition	Drug name	Class of drug	Dosage	Lab results/signs/ symptoms	Pharmac otherapy Outcome Status	DTPs and causes
0							
1							
2							
3							
4							
5							
6							
7							

Key to above table

DTP	**CODE**	**CAUSES**	**CODE**	**REMARKS**
106) Unnecessary drug therapy	A	Not available	0	
		No valid medical indication	1	
		Duplicate therapy	2	
		Nondrug therapy indicated	3	

		Treating avoidable ADR	4	

		Addictive /recreational	5	
107) Needs additional drug therapy	B	Not available	0	
		Untreated condition	1	
		Preventive	2	
		Synergistic/potentiating	3	
108) Different drug needed	C	Not available	0	
		More effective drug available	1	
		Dosage form inappropriate	2	
		Condition refractory to the drug	3	
		Contraindication present	4	
		Drug not effective for the condition	5	
109) Dosage too low	D	Not available	0	
		Ineffective dose	1	
		Needs additional monitoring	2	
		Frequency inappropriate	3	
		Drug interaction reduces amount of active drug	4	

		Duration inappropriate	5	
110) ADR	E	Not available	0	
		Undesirable effect	1	
		Unsafe drug for patient	2	
		Dosage administered or changed too rapidly	3	
		Drug interaction causes undesirable reaction that is not dose-related	4	
		Allergic reaction	5	
		Contraindications present	6	
111) Dosage too high	F	Not available	0	
		Dose too high	1	
		Needs additional monitoring	2	
		Frequency too short	3	
		Duration too long	4	
		Drug interaction results in a toxic reaction to the drug	5	
112) Noncompliance	G	Not available	0	
		Patient does not understand instructions	1	
		Patient prefers not to take	2	

		Cannot afford drug product	3	
		Patient forgets to take	4	
		Drug product not available	5	
		Cannot swallow/administer	6	

DTPs		**Yes**	**No**
113)	Unnecessary drug therapy	1	0
114)	Needs additional drug	1	0
115)	Different drug needed	1	0
116)	Dosage too low	1	0
117)	ADR	1	0
118)	Dosage too high	1	0
119)	Noncompliance	1	0

120) Current status of rheumatic disease

Pharmacotherapy outcome status	**Code**	**Definition**
Stable	2	Goals of therapy have been achieved. The same drug therapy will be continued with no changes. Usually associated with therapy for chronic disorders
Improved	3	Adequate progress is being made toward achieving the goals of therapy at this point in time. The same drug

		will be continued with no changes.
Partially improved	4	Some measurable progress is being made toward achieving the desired goals of therapy, but adjustments in drug therapy are required to better achieve the goals. Usually, dosage changes or the addition of addictive or synergistic therapies is required.
Unimproved	5	No or only minimal progress in achieving goals of therapy can be demonstrated at this time. it is judged that more time is needed to evaluate the full response of this drug regimen. Therefore, the same drug therapy will be continued at this time.
Worsened	6	There has been a decline in the health status while receiving the current drug therapy. Some adjustments in drug regimen (product and/or dosage) are required.
Failure	7	The goals of therapy have not been achieved despite adequate dosages and adequate duration of therapy. Discontinuation of the present medication and initiation of new drug therapy are required

Classification of drugs used in management of rheumatic diseases

Class		Yes	No
122)	**Conventional DMARDS**	**1**	**0**
123)	**Biological dmards**	**1**	**0**
124)	**Steroids**	**1**	**0**
125)	**NSAIDs**	**1**	**0**

Antirheumati drugs

Drugs		Yes	No
129)	**acetylsalicylic acid**	**1**	**0**
130)	**indomethacin**	**1**	**0**
131)	**methotraxate**	**1**	**0**
132)	**sulphasalazine**	**1**	**0**
133)	**lefunomide**		
134)	**hydroxychloroquine**	**1**	**0**
135)	**infliximab**	**1**	**0**
136)	**etanercept**	**1**	**0**
137)	**Others**	**1**	**0**

Arthritis drugs

Class		Yes	No
163)	**NSAIDS**	**1**	**0**
164)	**Glucosamine**	**1**	**0**
165)	**Others**	**1**	**0**

Other drugs

Class		Yes	No
166)	**Anti-cancer**	**1**	**0**

167)	**Antibiotics**	**1**	**0**
168)	**Others**	**1**	**0**

Thanks for your participation

Appendix 5: Outcome status terminology

A summary of the outcome status terminology with standard definition is given in the table below

Pharmacotherapy outcome status	**Definition**
Resolved	Goals of therapy have been achieved, drug therapy has been completed and can now be discontinued. Usually associated with therapy for acute disorders
Stable	Goals of therapy have been achieved. The same drug therapy will be continued with no changes. Usually associated with therapy for chronic disorders
Improved	Adequate progress is being made toward achieving the goals of therapy at this point in time. The same drug will be continued with no changes.
Impartially improved	Some measurable progress is being made toward achieving the desired goals of therapy, but adjustments in drug therapy are required to better achieve the goals. Usually, dosage changes or the addition of addictive or synergistic therapies are required.
Unimproved	No or only minimal progress in achieving goals of therapy can be demonstrated at this time. it is judged that more time is needed to evaluate the full response of this drug regimen. Therefore, the same drug therapy

	will be continued at this time.
Worsened	There has been a decline in the health status while receiving the current drug therapy. Some adjustments in drug regimen (product and/or dosage) are required.

Failure	The goals of therapy have not been achieved despite adequate dosages and adequate duration of therapy. Discontinuation of the present medication and initiation of new drug therapy are required
Expired	The patient died while receiving drug therapy

Appendix 6: Work plan

Code	Activity	Dec '19	Mid Feb '20	Jun '20	Jul '20	Aug '20	Aug '20	Sep '20	Oct '20	Nov '20
01	Proposal development	■	■							
02	Proposal approval			■						
03	Tool pretest				■					
04	Data collection					■	■			
05	Data analysis							■		
06	Follow up							■		
07	Presentation of report								■	

08	Dissemination: submission & publication									

Appendix 7: Budget

Description/item	**Unit cost**	**Quantity**	**Cost**
Human resource			
Data collection, entry and analysis	60,000/-	1×60,000/-	60,000/-
Proposal			
Typing and printing	10/-	70 pages×1copy	700/-
Photocopying	2/-	70 pages×4copies	560/-
Binding	150/-	70 pages×5copies	750/-
Materials and supplies			
Pens	15/-	12pieces	180/-
Pencils	10/-	12pieces	120/-
Rubbers	50/-	2	100/-
Folders	50/-	4	200/-
Field books	100/-	4	400/-
Stapler	200/-	1	200/-
Staples	100/-	1packet	100/-

Questionnaires printing Questionnaires photocopying Consent forms printing Consent forms photocopying	10/- 2/- 10/- 2/-	10 pages×1 copy 10pages×150 copies 4 pages×1 copy 4 pages×100 copies	100/- 1500/- 40/- 800/-
Report Typing and printing Binding	 10/- 200/-	 150 pages×5copies 150pages×5copies	 7,500/- 1,000/-
Publishing fee	journal	50,000	50,000/-
Ethics approval fee	2000/=	2000	2000
Internet subscription fee	2500/-	4 months	10,000/-
Miscellaneous			20000/-
Total			**156250/-**

The budget estimate is inclusive of the anticipated cost of the study including the cost of the pilot study and will be fully funded out of pocket.