CHAPTER 3
METHODOLOGY
3.0 METHODOLOGY:

3.1 OVERVIEW
The principle components of this research project were pain, K+ and RA. RA is a complex disease with several therapeutic targets. Though ‘pain’ was the principle clinical target, the protocol included evaluation of several measures pertaining to ‘inflammation’. The principle research intervention was K+ through dietary sources and supplementation. The research methodology was based on comprehensive literature review of each of the targets and current standards and norms of clinical trial methodology.

This project was carried out in two main parts.

Part 1 consisted of a cross-sectional pilot study. It was carried out in patients suffering from RA attending a community based rheumatology referral clinic, to study the community and patient demographics, disease attributes, suitability and feasibility of questionnaires pertaining to disease evaluation, health assessment and dietary recall (prospective and retrospective) and the process of patient enrollment and clinical data capture.

Other project activities in First Part: This included development and validation of some selected patient centric questionnaires such as RA pain score (RAPS) and diet survey and monitoring proformas/questionnaires. Laboratory related activities including standardization of some important measurements like serum cortisol and urinary K+.

Part 2 consisted of a randomized, single blind (assessor), allocation active controlled, parallel efficacy study of 4 months duration. It was designed to compare active diet based interventions in patients to an active control of routine diet in patients suffering from painful RA and on supervised stable standard of care in a rheumatology setting. Data was analyzed to study the effect of dietary K+ augmentation with or without oral K+ supplement on pain in RA and this included clinical assessments, disease activity, health status and quality of life. Interventions were carefully assessed for safety and compliance.
This chapter describes the study population, design, data collection and statistical analysis.

3.2 Conceptual frame work of the study

This study is focused on the role of a planned structured non pharmacological intervention in patients suffering from RA and treated with standard of care treatment by rheumatologists in a community referral clinic.

3.3 Scope of the study

The published literature (described in literature review) suggests that RA is a chronic disease and patients require long term care. The treatment comprises of not only drug therapy, but also dietary advice and life style modification to arrest and control the disease and cope up with the consequences of the disease which includes articular deformities, osteoporosis and several systemic co-morbidities. Treatment of pain and inflammation is an overarching therapeutic target at all times.

Based on literature review and discussion with experts and colleagues in Center for Rheumatic Diseases, Pune, a K+ enrichment diet modification based strategy for intervention groups was designed to be executed as an adjunct therapy to standard of care in patient suffering from RA. An outcome of the study methodology and intervention is shown in figure below.
Patients suffering from rheumatoid arthritis (in intervention groups)

Baseline evaluation

First follow up evaluation
(After 4 weeks)

Second follow up evaluation
(After 8 weeks)

Third follow up evaluation
(After 12 weeks)

Fourth & Final follow up evaluation
(After 16 weeks)

Received intervention (Arm A & B)

- Intervention programs will be highly interactive, focusing on building skills, practical and sharing experiences especially diet

- A short telephonic reminder related to supplement food packet and diet guidance, answered query related to program, follow up visit and evaluation timing at 4 weeks after baseline visit

- A short telephonic conversation related to follow up visit, checking the compliance and evaluation timing after every follow up visit.

- A short telephonic conversation related to follow up visit, checking the compliance and evaluation timing

Arm C was control only on routine diet; All the arms received standard of care treatment

Fig 3.1: Follow up evaluation and schedule of interaction with patients in Active intervention (Arm A & B) to ensure compliance and timely visits
The primary hypothesis was that K+ augmented diet with addition of oral K+ rich MFDS reduces pain in patients suffering from RA and on standard of care treatment. The active K+ dietary intervention was also expected to reduce disease activity (anti-inflammatory effect) and overall improve treatment outcome. This would be indicated by indicators of better health and disease outcomes in the intervention groups when compared with the control group.

3.4 Overall aim of this thesis

To study the clinical benefits with special reference to pain relief of oral potassium rich mixed food dietary supplement (MFDS) in patients suffering from painful RA on supervised standard of care treatment in a Rheumatology setting.

3.4.1 PART 1 (cross-sectional pilot study): The specific aim was to estimate dietary K and other content in patients of RA and healthy subjects.

3.4.2 PART 2: Main study

This was the main study (i.e. intervention study) for the primary objective.

3.5 Objectives

3.5.1 Primary objective:

☐ To study the effect of oral potassium rich (MFDS) on pain in patients suffering from rheumatoid arthritis.

3.5.2 Secondary objectives:

☐ To study the effect of oral potassium rich (MFDS) on standard disease activity measures and outcome in RA.

☐ To study the safety and tolerability profile of oral potassium rich MFDS

3.6 Hypothesis

Oral K+ administered as K+ rich diet with additional oral potassium rich MFDS reduces pain in RA on Standard of care treatment

3.6.1 Operational hypotheses
1. Dietary augmentation with K+ in addition to standard-of-care treatment helps in better outcome as per clinical assessment in RA.

2. Dietary augmentation with K+ in addition to standard-of-care treatment helps in better outcome as per health status assessments in RA.

3. Dietary augmentation with K+ in addition to standard-of-care treatment helps in better outcome as per quality of life assessment in RA.

3.7 Site Location: Center for Rheumatic Diseases (CRD), Pune (state of Maharashtra, west India), which runs an outpatient community referral clinic for both adults and children. CRD is recognized by University of Pune a research institute for doctorate and post – doctorate studies. There is a dynamic and dedicated team that includes rheumatologists, research doctors, pathologist, microbiologist, lab technicians, soft ware and data-base expert, statistician, pharmacist and clinical research personnel (including drug trial coordinator) and other supportive and administration staff. Patients suffering from various types of rheumatic diseases from all over the state of Maharashtra are evaluated and the daily attendance varies from 70-100 patients. Each patient is screened meticulously and systematically as per standard of care clinical approach and case record forms. Clinical and all investigations findings of all patients, both on initial and follow up examinations, are recorded and entered into a database. CRD maintains a comprehensive arthritis database which includes demographic measures, treatments and outcomes of all patients including RA since 1996. (www.rheumatologyindia.org)
3.8 Pilot study:
The study was carried out in the period June 2012 to Feb 2013. Data was collected from CRD OPD. The study was verbally explained to consenting patients. 139 patients suffering from clinical RA and 165 healthy controls were enrolled. A dietary questionnaire was prepared and translated to the local language (Marathi). The same was approved by the scientific committee of CRD. The process of data collection was carried out at CRD. Data collection process was interview based directly with patient in presence of investigator and interpreter (expert interpreter Marathi language). During the first visit investigator and interpreter introduced themselves and explained the aim and purpose of the interview. The questionnaires were completed after patient had verbally given the consent.
The place of interview was calm, and ensured privacy. Participants were made comfortable and independently answered the questionnaire.

A seven day recall food consumption questionnaire was planned which was changed to 3 days. Patients found it difficult to recall food details of a 7 day period. The diet questionnaire recorded patient answers based on a 3 days recall pertaining to demographic and socioeconomics, the information about arthritis, medication and quality of life. Diet K+ and other components were estimated using standard Indian guidelines and recommendations (daily allowance) described by the National Institute of Nutrition, Hyderabad and reference book on diet. Statistical analysis was performed using SPSS (software package for statistical analysis) v16.5 and BMDP (BioMedical Package 2007) program.

All patients and healthy controls records were analysed for diet K+ intake. Complete diet analysis (such as proteins, fat, minerals and vitamins) were performed for 20 female and 10 male records chosen randomly using simple random tables in patients and healthy controls. Important observations and results of the pilot study are attached as Appendix 2.

Cases and controls matched well for several diet components and energy except for K+. Dietary K+ was low in RA and it was lower in females as compared to males (p<0.05).

The pilot study data was used to develop and create the framework and protocol of the main interventional study.

3.9 RA Pain Score (RAPS): Development of an Indian version and validation

RAPS was developed by Anderson (2001) and found to be valid and reliable instrument in American Caucasian patients. It was composed of theoretical subscales that represent indicators of the total pain experience. The subscales include physiologic (P),

C. Gopalan, B.V.Rama Sastri and S.C.Balasubramanian, Nutritive value of Indian food, national institute of nutrition Indian council of medical research, Hyderabad - 500007
Http://icmr.nic.in/guide/Draft_RDA-2010.pdf
affective(A), sensory-discriminative(S), and cognitive(C) factors. There are 24 questions to address these subscales and each question is scored in one of the seven categories marked 0-6. Thus the total range is 0-144.

The questionnaire was translated into Marathi by a professional and pilot tested amongst 10 patients of RA in CRD. With input from patients, paramedics and treating doctors, an expert consensus was taken on the final draft version which was back translated into English language to ensure comparability with the original version. The translation was contextual rather than ad verbatim. The final version was adopted as an Indian version and pilot tested for reliability and validity in 90 consenting patients of RA with pain VAS ≥ 4 cm (10 cm scale) classified as per the American College of Rheumatology criteria 1987 with disease duration ≥6 months. All patients were receiving supervised standard of care treatment for RA for at least 12 weeks.

The Indian version of RAPS was demonstrated to be valid and reliable. It was well understood and took less than 10 minutes to complete by the patient. Patients preferred face to face interview rather than self-reporting. It had face and content validity and criterion validity was shown by a correlation matrix using several clinical measures of disease activity, function and quality of life. Results of regression and factor analysis further endorsed its unique value as a measure of the complex nature of pain in RA.

Important observations and tests of validation are shown in Appendix 3.

RAPS was included in the protocol for the main interventional study (see below)

3.10 Dietary K+ and supplement Intervention Study

Second part was a controlled three arm intervention trial study. The intervention study was conducted between Feb 2014 to Nov 2014. Time lines of intervention study were:

- Screening and Enrollment- Feb 2014 to July 2014
- Follow up to completion- July 2014 to Nov 2014

3.10.1 Study design:
The details are described in the protocol (Appendix 4). However, a summary and some other practical details on intervention assessment and monitoring are described here. (Fig 3.1)

This was a randomized, single blind, active control three arm parallel efficacy study of 16 weeks duration. It was designed to evaluate outcomes in the two intervention arms (K+ augmented diet and oral potassium MFDS in patients with standard of care treatment) compared with active control group (only standard of care). Patients were examined by rheumatologists in the rheumatology clinic of CRD. Patient centric measures of pain, function, quality of life and diet intake were completed under supervision of the current PhD student researcher (TK) and assisted by selected study nurse and paramedics. The entire trial was supervised by the current PhD guide (AC). The protocol of the study is enclosed as Appendix 4 and registered with CTRI - Clinical Trial Registry India-(REF/2015/05/008963)
Patients suffering from RA were screened for eligibility. Voluntary eligible subjects were first provided with the patient Information Brochure (available in Hindi, Marathi and English and attached as Appendix 5). The Researcher introduced the program verbally first and patients were asked to volunteer their consent to participate. All patients signed the informed consent form (Appendix 6) under audio video recording as per the recent regulatory guidelines issued by the Indian Council of Medical Research, Government of India. Patients were randomized to one of the three intervention arms (2 study intervention arms and 1 active control). All patients underwent clinic based evaluations and completed the study questionnaires as per protocol. Safety and drug/intervention
toxicity was monitored throughout the study period. Clinical assessments and laboratory measurements were carried out to assess the efficacy and safety as per the protocol. Final end point evaluation was completed at 16 weeks. All patients were treated with standard of care rheumatology treatment. The active study intervention arms were K+ rich diet and oral potassium MFDS and the active control arm was only standard of care intervention.

The intervention groups were into three arms (see figure below):

- SOC plus K+ rich diet
- SOC plus K+ rich diet plus oral K+ MFDS
- Standard of care (SOC)

Inclusion and exclusion criteria

3.10.2 Inclusion criteria:

1. Patients diagnosed RA according to ACR1987 classification criteria and the new ACR/EULAR 2010 criteria (see Appendix 1)
2. Duration of illness ≥6 months
3. Pain VAS ≥ 4 cm (10 cm scale)
4. Requiring frequent pain relieving medication for over 2 weeks or moderately severe pain interfering with daily activities of at least 2 weeks duration
5. Patient receiving supervised standard of care treatment for RA for at least 12 weeks prior to enrollment.
6. Able to understand the study and willing to give informed consent

3.10.3 Exclusion criteria:

1- Oral steroid prednisolone ≥ 10 mg daily and unstable consumption of 4 weeks prior to screening.
2- Male/female patients <18 years of age or >75 years of age
3- Patients with abnormal kidney function test as per standard laboratory criteria.
4- Serum K+ level ≥ 5.5 mEq/L
5- Patients with uncontrolled diabetes and hypertension
6- Patients on diuretics or any drug altering serum K+
7- Pregnant or breast feeding women
8- Patients who are incapacitated largely or wholly bedridden.
9- Patients on any herbal, homeopathic or ayurvedic medicine.
10- Patients with history of heart failure or unstable angina.
11- History or presence of any medical or psychiatric condition.
12- Any other concern as per the discretion of study rheumatologist

3.10.4 Withdrawal criteria:

Patients may be withdrawn from the study due to following criteria:

- Refusal of patient to continue treatment and/or procedures
- Voluntary withdrawal of informed consent.
- Need to treat the patient with any medication that is not allowed as concomitant medication during the study.
- Protocol violation, including lack of compliance
- Serious adverse event (SAE) or other adverse event (AE) that prevent patient from participating in the study as per the discretion of the study rheumatologist.
- Loss to follow-up
- Pregnancy
- Death of a patient from any cause.

3.10.5 Treatment Plan

Patients were randomized to one of the 3 treatment arms by a computer-generated code

Arm 1:

- Dietary advice of oral K+ rich diet (see App)
- Supervised standard of care treatment.
Arm 2:

- Dietary advice of oral K+ rich diet. (see Appendix 7)
- 3 tablespoonful of oral K+ MFDS twice daily (see Appendix 8)
- Supervised standard of care treatment.

Arm 3:

- Supervised standard of care treatment.
- Routine diet.

3.10.6 Study procedure:

All visits were on a-priori fixed scheduled visit dates with a permitted window period of 5 days. In case of any premature discontinuation of the trial, the patients were contacted and requested to undergo the End of Trial visit evaluation. Study clinical evaluation were recorded in standard rheumatology case record form (CRF) (Attached as Appendix 9). Clinical evaluations were carried out by a rheumatologist, who was blind to the study intervention. Other evaluations (HAQ, SF 36, RAPS) were done by the designated nurse and designated paramedic blind to the study intervention under supervision of the study researcher and details of the measures are described in Appendix 16. Laboratory evaluations were carried out in CRD laboratory as per protocol. (See Appendix 4) A 3 days retrospective daily diet survey was recorded at visit 1 and at every follow up visit by the study researcher. (See Appendix 7)

3.10.7 Pre-study procedure (Screening Visit):

Patients of RA with painful joints who met the eligibility criteria and volunteered to participate completed the following procedures during this visit prior to study entry:

(a) Evaluation by rheumatologist during routine clinical follow up visit for confirmation of diagnosis and suitability to participate and general counselling about the study. (b) The study researcher (TK) introduced the patients to the salient features of the study especially with respect to diet intervention with K+, randomization, blind nature of the study, supervised standard of care, patient safety issues and other patient logistics. (c) Patient was provided with the Patient Information
Brochure (Appendix 5) in the language best understood by the patient and mostly Marathi. Patient was given adequate time to read and understand the details of the study. Those consenting voluntarily for the study signed an informed consent form under audio video recording. A copy of the signed Informed consent was handed to the patient. Phone numbers of researcher and participants were exchanged after consent to facilitate timely reminders. (See Appendix 6)

(c) Study patient underwent a comprehensive training session wherein the researcher introduced them to the intervention program and the study schedule in detail. Importance of their role in the study process was emphasized. Patients were informed about schedule of visits for the entire study in the Screening visit itself. (e) Patients were randomized into intervention and control groups by computer generated code by the researcher and an early baseline visit scheduled (it could be the day of screening if all other eligibility criteria were met)

3.10.8 Diet Intervention:

The dietary advice was provided through face to face discussion and a comprehensive brochure on the subject was handed over to the patients in the K+ rich diet arm and Oral K+ MDFS arm on the first visit. (See Appendix 8). In the brochure, patients were provided with a simple framework of several optional common K+ rich foods classified as cereal, vegetable, pulse, fruits to choose from along with some dos and don’ts to ensure balanced diet and this was based on Indian recommendations ^^^. The principle intervention was a oral K+ MFDS containing powdered food items rich in K+ and mixed with oral rehydration salt (See Appendix 8 for preparation and composition details). Patients randomized to receive the oral K+ MFDS in addition to K+ rich diet, were instructed to take 3

252 Gopalan, Nutritional requirements and recommended dietary allowance for Indians, A report of the expert group of the Indian council of medical research, 2009
tablespoonful of food supplement powder mixed with cooked meal twice a day and taken along with a glass of water.

All details of diet intervention were carefully recorded in the study CRF at every visit by the researcher (TK).

The total K+ intake of a patient per day in the 3 study arm groups was as follows:

K+ rich diet: 3.5-4.5 gm/day

Oral K+ MFDS along with K+ diet: about 7.5-8 gm/day

Routine diet: about 2-3 gm/day (as per the findings and results of the diet survey of the pilot study conducted in CRD Pune prior to this research study and described in this report; see Appendix 2)
Table 1: Study activity schedule

The following table shows an overview of the various procedures and examinations performed on trial study patients at every study endpoint visit.

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<th>Visit no</th>
<th>Screening (-1 to -5 days)</th>
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<tr>
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### Assessment

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<th>DAS28</th>
<th>Physician assessment</th>
<th>Patient’s global assessment</th>
<th>General Health</th>
<th>Joint count</th>
<th>Swollen joint count</th>
<th>Joint count tenderness</th>
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</table>

Hemoglobin, total WBC, differential count (polymorphs, lymphocytes, Monocytes, Eosinophils, basophiles), platelet count, ESR, SGPT, BUN, Serum Creatinine, Serum Electrolyte, BSL (F).

### 3.10.9 Concomitant medication and treatment:

Patients continued standard of care treatment under supervision of rheumatologist. The majority of patients as per the local practice were expected to be treated with weekly methotrexate (15-20 mg weekly) and were monitored accordingly. Stable dose of Methotrexate was continued throughout the study and or in combination with other DMARD’s i.e Hydroxychloroquine, Salazopyrin, and Leflunomide. As per disease activity dose modification was permitted which was recorded in the CRF. Pain management was decided by rheumatologist and recorded. Patients were instructed to consume pain-relieving medicines only for severe and intolerable pain on need basis and its consumption recorded. The use of NSAIDs were discouraged and was limited to bed
time use with long acting drugs. Patients were allowed to use oral paracetamol and tramadol as rescue analgesic. A stable fixed dose of oral corticosteroids (≤10 mg/day prednisolone or equivalent) begun 4 weeks prior to the study was permitted and reduced during the study as per rheumatologist discretion. As a standard of care patients receiving corticosteroids or NSAIDs were also prescribed prophylactic treatment with a proton pump inhibitor at the recommended dose.

Patients were allowed to continue medication for co-existent illness like hypertension, diabetes, under care of their physician, and the details recorded in CRF. Any other concomitant medications (including over the counter medications, vaccines, vitamins and food supplement) and essential ongoing procedures (eg physiotherapy) were recorded. A description of the type of drug or procedure, strength, frequency, indication, duration, and the outcome of any procedure was documented in the CRF.

3.10.10 EVALUATION

Details of various procedures performed at every visit and laboratory investigations are described in the protocol attached as Appendix 4.

The important physician centric measures were physical examination, joint counts for pain/swelling and global assessment of disease activity. Safety assessments included recording of all adverse events (AE) and Serious adverse events (SAE) by the physician from the screening visit till the end of the study. The important patient centric measures were pain visual analogue scale, global assessment of disease activity, HAQ, RAPS, SF 36, general health assessment. Details of diet consumed by the patients were also recorded as per protocol.

ACR core set measures of efficacy

253, 254, 255, 128

• Joint count tenderness
• Joint count swelling
• Acute phase response (ESR or CRP)
• VAS scale for pain
• Patient's global assessment of disease status.
• Physician global assessment of disease status.
• Patients assessment of disability (HAQ)

ACR 20 index improvement response is at least 20% improvement each in joint count for pain/tenderness and joint count for swelling and 20% improvement in any 3 of the following 5 measures; pain VAS, patient global assessment, physician global assessment, HAQ and ESR.

**DAS 28: Disease activity score (DAS) 28**

- The DAS 28 is a combined index for measuring disease activity in RA, (\(5.1\) High disease activity, \(3.2-\leq 5.1\) Moderate disease activity, \(\leq 3.2\) Low disease activity, \(\leq 2.6\) Remission). The DAS score will be calculated using the following measures:
  - Swollen Joint counts (28 joints)
  - Tender Joint counts (28 joints)
  - ESR
  - General Health Assessment (0-100 mm)

The index is calculated using the following formula:

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255 Chopra A, Saluja M., Validation and usefulness of Indian version (CRD Pune) health assessment questionnaire: Drug trials, community practice and COPCORD Bhigwan population study (1994e2012), Indian Journal of Rheumatology 2012 June Volume 7, Number 2; pp. 74e82

256 [http://www.das-score.nl/dasculators.htm](http://www.das-score.nl/dasculators.htm)
• DAS28 = 0.568*√TJC + 0.28*√SJC + 0.7*ln(ESR) + 0.014*GH

Where TJC = tender joint count on 28 joints, SJC = swollen joint count on 28 joints, Ln = natural log, ESR = erythrocyte sedimentation rate (mm/hr) and GH = general health

QUALITY OF LIFE MEASURES

Health assessment questionnaire (HAQ) (See Appendix 10): The CRD Pune HAQ was used to evaluate the overall functional profile related to the musculoskeletal system. The CRD Pune HAQ is a modified version of the modified Stanford HAQ to suit the requirements of the Indian patient and has been appropriately validated for Indian use. It consists of 23 questions referring to 8 components: dressing, arising, eating, walking, hygiene, reach, grip and activities.

SF36: Used with permission (http://www.qualitymetric.com) (See Appendix 11)

RAPS (See Appendix 12)

All questionnaires related to patient centric measure of pain and function were duly validated a-priori and administered to the patient in the Marathi language or the language best understood by him/her.

The Fig 3.2 shows the patients disposition in the current trial study at baseline and each follow up visit till completion. Number of patients lost to follow up is also shown at each follow up visit.

3.10.11 Compliance:

Interactive discussions were held with patients on enrollment explaining the details of the study and dietary intervention. Brochures in regional language on K+ diet were issued to the patients of the A and B arm. Regular reminders were given by research Investigator (Fig 3) to check the compliance. Patients in B arm were instructed to get the unused packet of the MFDS at each follow up visit. The unused powder amount was
checked and consumption verified. Patients were counseled for compliance at each visit. Lab measure of serum and urine K+ were carried out to correlate with dietary K+.
Fig 3.4: Patient disposition-Sample Recruitment

Participant Entering Study n=172

- Baseline, n=57
  - LFU=1
- Month 1, n=56
  - LFU=0
- Month 2, n=56
  - Poor compliance =1
- Month 3, n=55
  - LFU=3
- Month 4, n=52
  - Withdrawal rate= 8.8%

- Baseline, n=58
  - LFU=4
- Month 1, n=54
  - LFU=0
- Month 2, n=54
  - LFU=0
- Month 3, n=54
  - Poor compliance = 3
- Month 4, n=51
  - Withdrawal rate= 12.1%

- Baseline, n=57
  - LFU=2
- Month 1, n=55
  - LFU=0
- Poor compliance = 1
- Month 2, n=54
  - LFU=0
- Month 3, n=54
  - LFU=2
- Month 4, n=52
  - Withdrawal rate= 8.8%


3.10.12 Ethical Considerations:
The research project was approved by the CRD ethics Committee, Pune. The progress of the study was updated to the Ethics Committee regularly. The patients were informed that participation is voluntary and that their future medical treatment will not be compromised by participation in the study and that they can withdraw any time. All information obtained during the conduct of the study was regarded as confidential and confidentiality of all patients maintained.

3.10.13 Sample Size calculation:
There is no data in the published literature on the clinical efficacy of food based K+ rich supplement in reducing pain in patients of RA that can be used for sample size calculation. However, assumptions were made based on opinion amongst the CRD rheumatologists, pharmacy experts, biostatistician and researcher. It was concluded that the magnitude of effect size of the intervention is likely to be modest. All other factors of feasibility and socioeconomics and patient logistics were considered. A drop out rate of 20% based on earlier experience of drug trials in CRD was taken in to account. Finally, a sample size of 171 patients was decided. The study would have 80% power with a significance p <0.05 to minimize Type I and II errors. Thus 57 subjects would be enrolled in each of the 3 arms of this intervention study.

For this study the sample size was calculated based on ‘Pain VAS’ as a primary efficacy variable. It was assumed that K+ supplement intervention will improve the pain VAS at least 10% more than that observed in the active control (standard of care)^257.  

3.10.14 Statistical plan and analysis:
This was a randomized, single blind, 3 arm study. This study was designed to test for superiority of dietary intervention with K+ rich diet and/or supplement. The primary efficacy variable was changed in pain VAS from baseline to study completion (16 weeks). Several secondary efficacy variables included (ACR core set measures, SF36,____________________)

HAQ and RAPS). The sample size was based on 80% power (type 2 errors) and a significant $p \leq 0.05$, 2 tail (type 1 error). It was calculated that 171 patients required considering a dropout rate of 20%. At least 50 patients were expected to complete the study in each treatment arm. It was an intention to treat analysis with last observation carried forward. Data were coded and entered into personal computer for analysis. After the data was checked for completeness it was locked and a copy given to the Investigator. All data was checked for normal distribution. Besides calculating p value, 95% confidence intervals was computed for all effect size and differences between study treatment arms. Data were analyzed using ANOVA or Chi-Square test, depending on the nature of the variable. For ordinal variables in addition to ANOVA, data were analyzed by equivalent of parallel non-parametric test namely Kruskal Wallis. Categorical data were analyzed by Chi-Square test. Standard statistical correction was applied for repeated measures. ANOVA testing was adjusted for baseline variation in important variable. Graphs were drawn to describe change in efficacy variable over time.

Regression analysis was carried out to determine predictors of response to reduction in pain VAS and detail analysis is attached as Appendix 17. For this purpose, both the arms with K+ rich diet were combined to compare with only standard of care.

Data on the number of subjects, number of drop-outs and reason for drop-out, demographics (i.e. gender, age, weight, height) and other baseline characteristics were summarized with the summary measure such as mean, standard deviation, median and range (minimum and maximum) when the variable of examination is continuous or summarized using counts and percentages when the variable of examination is categorical.

Standard statistical soft ware package (SPSS, USA,2007) were used for statistical analysis of the study data.