4. METHODOLOGY

4.1. Validity and Reliability of Kannada Version of the Kidney Disease and Quality of Life (KDQoL-36) Instrument

A cross sectional study was carried out for a period of 12 months between April 2013–March 2014 at three different outpatient HD centres of teaching, government and corporate hospitals were considered in this study. The ethical approval (IEC-165/2013) was obtained from the Institutional ethics committee (IEC), Manipal prior to the initiation of the study.

4.1.1. Cross Cultural Adaptation and Translation of KDQoL-36

The KDQoL-36 is a multidimensional both generic and disease–specific QoL instrument that typically consists of subjective assessment of positive and negative features of the life.[6] The KDQoL- Short Form v.1.3, which contains the Short form-36 generic items and 43 ESRD items is developed by Hays RD et al.; at present, the KDQoL-SF v.1.3 is developed to a abridged version known as the KDQoL-36 questionnaire.[83, 84] The KDQoL-36 subscale consists of both disease–specific (24-questions) and generic-specific (12-questions) items [symptoms/problems, burden of kidney disease (BKD) and effects of kidney disease (EKD); physical component score (PCS) and mental component score (MCS)].[85] The KDQoL-36 scale is transformed into 0 to 100 point scores with higher scores reflecting better QoL. The authorization to translate the KDQoL-36 questionnaire into the local language Kannada was obtained from its working group (RAND) and authors. [83, 84]
The questionnaire was modified to necessitate the cultural appropriateness. For example, the modifications of the original KDQoL-36 for question number 2, pushing a vacuum cleaner, bowling, or playing golf was adapted to cooking, bathing, dressing, cleaning, and walking. The original question 28a read as problems with your access site, which was modified to problems with fistula site to avoid confusion among patients. Question 28b, (meant for PD patients only) problems with your access site, was excluded for obvious reasons as the questionnaire was restricted to HD patients only. Validation of a KDQoL-36 questionnaire was done in 3 steps: forward translation, backward translation, and pilot testing.

**Step 1: Forward Translation**

In this step, the KDQoL-36 questionnaires (English version) was administered for translation to Kannada by 2 independent professional translators. The translated Kannada version of KDQoL-36 was referred back for review to the committee of experts related to healthcare of Kidney conditions for example nephrologists (n=3), senior HD staff nurse (n=1) and academic pharmacist (n=1). Based on the suggestion of the expert committee a "reconciliation" version of KDQoL-36 was prepared.

**Step 2: Backward Translation**

The aim of the backward translation is to cross-check any deviations/ discrepancies existed in the translated version from the original questionnaire. The first version of the translated questionnaire of Kannada was subjected to back translation into English. The translated version was compared with the original KDQoL-36 for any deviations in meaning of the contents. Both the versions matched perfectly and it was accepted. In case of deviations, the
translation exercises were repeated till the matching version of questionnaire is framed. The reconciled back translation was then compared with the original English version.

**Step-3: Pilot-Testing**

The pilot study was conducted for 12 ESRD patients on Hemodialysis to determine the translated version in terms of the cultural suitability and acceptability (instructions, items and response choices). Further observations on questionnaire were recorded regarding simplicity, ease of reading language and ability to understand.

**4.1.2. Sampling and Psychometric Evaluation of KDQoL-36**

The field test of the Kannada version of the KDQoL-36 was conducted on 82 patients of maintenance hemodialysis. The patients were selected randomly from the out-patient hemodialysis units from all the three centres. The inclusion criterion for choosing the patients was based on hemodialysis-continuously for preceding 3 months in the age group of 18-75 years, with written informed consent.

**4.1.3. Ceiling and Floor Effects**

The KDQoL-36 Kannada version domain scores of the patients were assigned 100% for Ceiling and 0% for floor effects. In order to capture the full range of potential responses within the patients the both effects should be <20%. This trend was continuously observed through the study for any deviation and the change over time can be noticed.[86]
4.1.4. Statistical Analysis for Reliability and Validity of KDQOL-36

The test re-test was estimated with a subsample of 45 randomly selected HD patients, by two interviews 7 days apart. For assessment of internal consistency reliability, Cronbach’s-alpha coefficient was computed. The Cronbach’s-alpha 0.70 or higher values are considerably satisfactory internal consistency reliability.\cite{87} Construct validity was evaluated by comparing the correlation coefficients between the KDQoL-36 sub-scales and European Quality of Life Visual Analog Scale (EQ-VAS). The Pearson’s two-tailed tests with p < 0.05 were considered as statistically significant.
4.2. Preparation, Validation and User-Testing of Pictogram Based Patient Information Leaflets

A quasi experimental pre-post test design without control group was carried out for a period of 12 months between June 2013–May 2014 at 3 different HD centres of teaching, government and corporate hospitals considered in this study. The IEC approval was obtained prior to the initiation of the study. HD patients on pharmaceutical care group with minimum primary educational background were selected from all the 3 HD centres. The inclusion criteria for choosing the patients was based on hemodialysis- continuously for preceding 3 months in the age group of 18-75 years, with written informed consent.

The details such as age, sex, educational status, economic status, HD vintage and co-morbidities were collected from the patients. The socioeconomic status was calculated by using Kuppuswamy socioeconomic scale.[88]

4.2.1. Sample size

The sample size was calculated based on the change in patient’s KAP of user-testing scores from pre-test to post-test intervention scores by using the Formula 1.

\[
 n = \frac{\left( Z_{1-\alpha/2} + Z_{1-\beta} \right)^2 \sigma^2}{d^2} + 2 \quad \text{……. Formula 1}
\]
\[
\sigma = 10, \; Z_{1-a/2} \text{ is } 1.96 \text{ (for } \alpha = 5\%) , \\
Z_{1-\beta} \text{ is } 0.84 \text{ for } 80\% \text{ power and } d = 5 \\
\sigma \text{ is the mean of the two standard deviations} \\
d \text{ is the minimum significant difference in the two groups} \\
\]

The minimum sample required for conducting user-testing among HD patients is 40.

4.2.2. Preparation, Validation and Translation of P-PILs

The PILs were prepared by referring the tertiary (3\textsuperscript{0}), secondary (2\textsuperscript{0}) and primary (1\textsuperscript{0}) resources. The 3\textsuperscript{0} resources like text books (Nutritive Values of Indian Foods and Pharmacotherapy Text Book) and guidelines [Indian Association of Nephrology (ISN), National Kidney Disease Education Program (NKDEP), National Kidney Foundation (NKF), Kidney Disease Outcomes Quality Initiative Clinical Practice (KDOQI) and Renal Nutrition Forum (RNF)]. The 2\textsuperscript{0} resources like various databases such as UpToDate, Medline, Micromedex, WebMD and Medscape. The 1\textsuperscript{0} resources like various articles related to HD education and others.

The content of P-PILs includes fluid management, symptoms of fluid overload, managing thirst, salt management, energy and protein turnover, potassium management, phosphorus and calcium balance, anemia management vitamins and minerals supplements, medications avoided, vaccinations, month wise monitoring laboratory tests, and commonly prescribed medication information was included. The content and pictograms of the PILs were validated by the expert committee consisting of nephrologists (n=3) and academic pharmacists (n=2). The changes were made as per the expert committee instructions and the PILs was prepared after assessing the layout and design of P-PIL as per Baker Able Leaflets Design (BALD) method.\textsuperscript{[89,90]}
The validated English version of P-PILs were translated into Kannada by using 3 step processes such as forward translation, backward translation and pilot-testing

4.2.3. Readability Testing of P-PILs

Readability was assessed by the user-testing questionnaire. For this user-testing, 10 multiple choice questions based on the content of the leaflet was prepared. The questionnaire was validated and readability was checked. During the user-testing, questionnaire was served to the HD patients on pharmaceutical care group for assessing baseline knowledge followed by provision of P-PILs (English or Kannada) to the patients depends on the choice. After allowing the patients to read for 20 minutes, they were again served the same questionnaire to assess the knowledge. At the end of the study, the response was evaluated by using the Formula 2.

User-testing response assessment = (Total number of correct responses of the patient / Total number of actual responses of the patient) X 100 .............. Formula 2

After knowledge assessment, patients were asked to provide the opinion about the content, layout and design in a rating form containing 4 questions and the scores were ranged from 5-1 scale. The interpretation of the scores was as following: If the total score of content, layout and design of the P-PILs is Good = 20-14, Average = 14-9 and Poor < 9

4.2.4. Validation and Reliability of User-Testing and User-Opinion Testing Questionnaire

Validation and reliability of the user-testing and the user-opinion testing questionnaire was checked before assessing the knowledge and the user-opinion from the patients. The user testing and the user opinion questionnaire were validated by the expert committee.
Test re-test was estimated with a subsample of 24 randomly selected HD patients by 2 administrations of Kannada and English versions of user-testing and user-opinion questionnaire 7 days apart.

4.2.5. Statistical Analysis

The test–retest of user-testing and opinion questionnaire, the ICC was estimated among the randomly selected HD patients. The descriptive statistical analysis was carried out to summarize the data and the user-testing data of pre-test and post-test. The scores were analyzed by using paired student’s t-test with $p < 0.05$ was considered as statistically significant. Data was computed and analyzed using SPSS version 15 software.
4.3. Impact of Pharmaceutical Care in HRQoL, Hemoglobin levels, Interdialytic weight gain, Blood pressure, Medication adherence and Costs on HD patients

4.3.1. Study Design, Site and Criteria

Open label Randomized control trial registered under clinical trial registry of India (Ref. no. CTRI/2014/004900) was carried out for a period of 15 months between March 2014–May 2015 at 3 different HD centres of teaching, government and corporate hospitals. The ethical (Ref. no. IEC/165/2013) approval was obtained from the Institutional ethics committee, Manipal, prior to the initiation of the study. The inclusion criteria for choosing the patients was based on HD - continuously for preceding 3 months, 2 HDs per week and patients who can speak at least English or Kannada language in the age group of 18-75 years, with written informed consent. The patients who are not willing to participate due to psychiatric illness and either shifted from peritoneal dialysis or kidney transplantation to HD were excluded from the study.

4.3.2. Randomization, Sequence Generation and Sampling Method

The patients were randomized into two groups [Usual Care Group (UC) and Pharmaceutical Care Group (PC)] by the block design method with the block size of 6 at academic, 4 at the government and corporate hospitals and concealed in the opaque sealed covers. The randomization sequence was generated based on the weekly visits of HD patients to the centres by the statistic department and concealed in the opaque sealed covers. For each centre there was one UC and PC group in the study. The patients were recruited proportionally from the each centre in 1:1 ratio of UC and PC group in the study by the purposive sampling method.
4.3.3. Usual Care Group

This group received the usual care by the hospital staff like physicians, nurses and technicians.

4.3.4. Pharmaceutical Care Group

The PC group received the usual care along with pharmaceutical care delivered by a qualified registered pharmacist. The customized care plan was designed and delivered to the patients on monthly basis based on the condition and need of the patient by WHO-FIP Pharmaceutical care model.[26] The plan gets updated based on the monthly observations of the patients in the area of diet, drugs and lifestyle. The PC emphasizes the motivation and patient education which are validated protocols regarding the knowledge about the disease, medication, life style changes, nutritional information, personal interview and medication review. The nutritional advice for HD and co-morbidities, education on foodstuffs containing potassium, phosphate, protein, sodium, depending on the patients’ prerequisite and fluid constraint. The PC group was provided with a validated pictogram based on the patient information leaflets and advice on medication administration, laboratory monitoring and adherence to HD and medication issues.

4.3.5. Data Collection

Data was collected in a designed data collection form contains the sociodemographic details such as age, gender, educational status, economic status, HD vintage and co-morbidities were collected from the patients. The socioeconomic status of the patients was calculated by using Kuppuswamy socioeconomic scale.[88] Other details such as the mode of transport, the number of persons visited to the hospital, the distance traveled to the HD centre, the healthcare scheme, medication and the laboratory data were recorded.
The annual cost data related to travel for treatment, medications, HD, laboratory costs were collected from the patients, patients’ attendants and their medical bills. The detailed patients recruitment and follow-up during the study are presented in the consort flow chart (Figure 4.3.1)

4.3.6. Outcome Assessment

The primary outcome of the study is HRQoL and the secondary outcomes include Hemoglobin levels, Interdialytic weight gain, Blood pressure, Medication adherence and expenditures. The assessment was carried out at baseline, 6th and 12th months by follow-upping both the groups for a total period of 12 months.

4.3.7. Health Related Quality of Life (HRQoL) Assessment

The quality of life was assessed by using validated KDQoL-36 instrument, which is generic and disease specific instrument consisting of 12 generic questions and 24 disease specific questions. KDQoL-36 was self-administered at baseline, 6th and 12th months to assess the HRQoL scores.

4.3.8. Hemoglobin Levels, Interdialytic Weight Gain and Blood Pressure Assessment

The hemoglobin (Hb) levels were monitored at baseline, 6th and 12th months for each patient. Interdialytic weight gain (IDW) were calculated by using the Formula 3 [91, 92]

\[
\text{IDW} = (\text{Pre dialysis weight} - \text{Post dialysis weight}) \quad \text{Formula 3}
\]

For each time point the average 8 preceding readings of IDW, Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were recorded at baseline, 6th and 12th months for each patient.
4.3.9. Medication adherence assessment

Medication adherence was assessed by using validated Morisky 8-items self-reported scale at baseline, 6th and 12th months for each patient.

4.3.10. Quality adjusted life year (QALY) and Incremental cost effectiveness ratio (ICER) Assessment

The QALY was calculated by using the Formula 4 developed by Prieto L et al.\textsuperscript{[93]}

\[
QALY = \left( \frac{\sqrt{1^2 + Utility^2}}{1.4142} \right) \cdot Time \quad \text{............ Formula 4}
\]

Whereas

Time = 1 Year

Utility values were calculated by mapping the SF-12 questionnaire to EQ-5D index vales by using the below mentioned formula\textsuperscript{[94]}

\[
\text{EQ-5D index score (Utility value)} = 0.8469 + (\text{PCS}-49.9) \cdot 0.01261 + (\text{MCS}-51.5) \cdot 0.00759 - [(\text{PCS}-49.9) \cdot (\text{PCS}-49.9)] \cdot 0.00009 - [(\text{MCS}-51.5) \cdot (\text{MCS}-51.5)] \cdot 0.00015 - (\text{PCS}-49.9) \cdot (\text{MCS}-51.5) \cdot 0.00015
\]

Whereas

PCS = Physical Component Score

MCS = Mental Component Score
ICER is calculated by using the Formula 5. \(^{[69]}\)

\[
\text{ICER} = \frac{[\text{Cost of treatment (A) - Cost of treatment (B)}]}{[\text{Effectiveness of treatment (A) - Effectiveness of treatment (B)}]} \tag{5}
\]

Whereas

Cost of Treatment (A) = Annual Cost of PC group

Cost of Treatment (B) = Annual Cost of UC group

Effectiveness of treatment (A) = QALY of PC group

Effectiveness of treatment (B) = QALY of UC group

The simplified formula for ICER is

\[
\text{ICER} = \frac{[\text{Cost of PC} - \text{Cost of UC}]}{[\text{QALY of PC} - \text{QALY of UC}]} \tag{6}
\]

The annual cost incurred for the management and 12 month quality of life of the patients’ data was used to calculate the ICER per QALY.

4.3.11. Sample size

The sample size was calculated based on the primary objective and the change in quality of life scores at 0, 6 and 12 months repeated measure at 84% power and 5% level of significance by using the Formula 7.

\[
n = \frac{[2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2]}{d^2} \times \text{DE} \tag{7}
\]
Z $1-\alpha/2$ is 1.96 (for $\alpha = 5\%$), Z $1-\beta$ is 0.84

$\sigma$ is the mean of the two standard deviations ($\sigma = 14$).

Design effect (DE) = 1.2

d is the minimum significant difference in the two groups (d = 7).

The minimum sample required for the study is 76 patients per each group

Anticipating a dropout rate of 20%, the required sample size is $76/0.8 = 95$ per each group.

4.3.1.2 Statistical Analysis

Data was analyzed on the basis of per protocol method. Repeated measures analysis was performed for the analysis of change in the HRQoL scores, Hb levels, BP, IDW and medication adherence scores in the two groups. Mann–Whitney U test was performed for the analysis of economic outcomes and hospitalization rates in both the groups. The p value less than 0.05 was considered as statistically significant.
Assessed for eligibility (n = 241)

Excluded (n = 41)
- Consent withdrawn (n = 20)
- Single hemodialysis (HD) per week (n = 7)
- Age > 75 years (n = 5)
- Patients not completed 3 months of HD (n = 5)
- Psychiatric issues (n = 3)
- Shifted from PD to HD (n = 1)

Randomized by Block design (n = 200)

Usual Care Group (UC) n = 100
- Discontinued from centre (n = 9)
- Shifted to PD (n = 1)
- Shifted to Kidney Transplantation (n = 3)
- Died (n = 12)
- Number of patients alive (n = 75)

Pharmaceutical Care Group (PC) n = 100
- Discontinued from the centre (n = 11)
- Shifted to PD (n = 2)
- Died (n = 9)
- Number of patients alive (n = 78)

Final Analysis
- Number of patients Analyzed (n = 75)
- Number of patients Analyzed (n = 78)

Figure 5: Consort flow chart