4. METHODOLOGY

4.1 Study Design
The present is a cross-sectional observational (to study prescribing pattern of OHAs), randomised controlled trials (RCTs) (to evaluate the services provided by pharmacists), quasiexperimental designs (to assess the factors affecting participation in and the benefits of a pharmaceutical care programme), pre-post and descriptive studies (to compare of baseline and postintervention data) carried out among T2DM subjects.

4.2 Study Site
The present study was carried out in two community pharmacies, Anna Hajare Medical Clinic and Anjali Hospital & Nursing Home, situated in a busy location at Kanpur, Uttar Pradesh, India. The intervention was provided by pharmacists. The two pharmacies were identified on the following criteria:

- More number of patients visits per day
- Situated in the residential area
- Diabetologists and Laboratory were available near to study site
- Pharmacists employed for full time
- Consented to conduct the study

4.3 Study Duration and Period
The entire study period was 24 months, conducted between October 2011 and September 2013 in T2DM subjects who visits the identified community pharmacies regularly. Data collected over a period of 3 years; 2011 (between October and
December), 2012 and 2013 (upto September). Baseline data were collected for 3 months from October to December 2011; interventions were made for 1 month, January 2012 and the post-baseline data were collected for 20 months between February 2012 and September 2013.

4.4 Selection of Pharmacists

All community pharmacists working in both the community pharmacies, registered pharmacists, identified were eligible to participate in the study. No other eligibility criteria, such as access to computerised records or provision of private counselling areas. There were two randomizations using a web-based random number generator. The first involved patients and was applied in order to inform the subject selection process. The second randomization occurred post-baseline four months later when pharmacists and their associated subjects were randomized to either a control or intervention group. The key elements of the randomizations, namely sequence generation at recruitment and post-baseline group allocation, were concealed from the participants.

The control pharmacists were requested to provide ‘usual’ pharmaceutical care that they were accustomed to providing prior to the initiation of the study. The intervention pharmacists were provided with a diabetes pharmaceutical care plan (DPCP) intervention framework to guide the ‘enhanced’ pharmaceutical care that they were requested to provide.
All the pharmacists, in the identified study site were briefed about the study, in order to get familiar with the present study and to ensure their role in recruiting patients. In order to get confident among the pharmacists an explanatory letter was provided to them (Appendix A).

4.5 Selection of Patients
Pharmacists identified, listed and numbered all their T2DM patients and provided the researcher with the number of patients. In order to minimise selection bias a web-based random number generator (http://www.randomizer.org/form.htm) was used to determine the selection sequence for potential subjects participants. A subject selection was then forwarded to each pharmacist with the request to recruit up to a maximum of 50 patients. Patients complying with the inclusion criteria were approached by their pharmacists and asked if they would be interested in participating in a research project that would examine aspects of diabetes care being provided by Indian community pharmacists. Pharmacists provided these subjects with a brief overview of the study, together with copies of a subject study information and informed consent letter.

on December 2011]. The subjects were selected based on the inclusion and exclusion criteria as in the following sections 4.4.1 and 4.4.2 respectively.

4.5.1 Inclusion Criteria

All of the following criteria are to be fulfilled for inclusion of an individual in the study. An eligible individual:

1. Should be either male or female
2. Should be >21 to 75 years of age
3. Should be diagnosed as T2DM for at least 6 months. Diagnosis of T2DM will be based on clinical criteria including:
   a. HbA\(_{1c}\) test (> 7.5 to 10%)
   b. fasting blood glucose (FBG) test
   c. an oral glucose tolerance test (OGTT)
4. Has a BMI < 27 kg/m\(^2\)
5. Has clinical laboratory test values (clinical chemistry, hematology, and urinalysis)
6. Has a physical examination and electrocardiogram (ECG) with no clinically significant abnormalities.
7. Receiving a minimum of one prescribed anti-diabetic agent regularly from a participating pharmacy.
8. Has to provide informed consent form and willingness to participate in the study.
4.5.2 Exclusion Criteria

1. Has a fasting serum triglyceride concentration >400 mg/dL at screening
2. Has hypoglycemia unawareness
3. Currently abuses drugs or alcohol.
4. Has chronic renal insufficiency with serum creatinine > 2 mg/dL
5. Has a history of weight loss (>3%) in the last 3 months
6. Is currently enrolled or plans to enroll in a diet, weight loss, or exercise program
7. Has a sitting blood pressure >160/95 mmHg (either systolic or diastolic) at screening
8. Has a clinically significant history or presence of any of the following conditions:
   o Active cardio- or cerebrovascular disease
   o Active pulmonary disease
   o Hepatic disease
   o The presence of any other co morbid disorders that would interfere with the subject's compliance of study procedures
   o Clinically significant malignancies within 5 years of screening
   o Chronic infections (e.g., HIV or TB)
9. Has had major surgery or a blood transfusion within 2 months
10. Has previously received treatment with recombinant leptin ( metreleptin or Fc leptin)
In order to explain about the study an explanatory letter was provided to each patient (Appendix B). During the study period, all prescriptions were screened for drugs which contain OHA. The selected subjects were invited to take part in the current study.

The interview was conducted by the trained pharmacists at both the study sites to the subjects who submit informed consent form and willingness to participate in the study. Interview was carried out in amicable places at the respective pharmacies. The room provided was an adequate and environment with more conducive to conduct interview and collect data. The interview questions was structured and pretested for the study, which contains seven parts (Appendix C).

Relevant to research topic and subject’s aspects were included and emphasized, like dietary measures in obese subjects. Subjects were encouraged to ask questions regarding T2DM, their medications and lifestyle issues. The duration of interview with subject was varied from 15 to 20 minutes.

4.6 Survey instrument

A survey questionnaire was developed with the help of literatures, opinion from experts and personal experience of community pharmacists. As mentioned by Hassell et al, the proposed instrument contains: health belief and socio-behavioural qualities and factors more relevant to community care such as patient biochemical and socio-economic parameters, perceptions of the role of
the pharmacist, the efficacy of self-care and accessibility of pharmacists, financial and other resource parameters. [Hassell, K et al, 2000]

The planning, execution and management of the instrument was carried out by the researcher at both the study sites. The questionnaire was tested for validity and reliability all questions by two experienced pharmacists, professional pharmacy colleagues at both the study sites and by piloting the questionnaire in a sample of 40 randomly selected T2DM subjects. The pilot study was conducted to assure the questions were clear, easily replied and was able to collect required data to carry out the study objectives.

A pilot study was conducted in July 2011. 40 subjects were randomly selected by name from those regularly visit the pharmacy. The subjects were selected on the basis of their name beginning either with the letter A or B. The researcher identified and selected prospective subjects were selected and almost one in every four subjects were declined to participate in the pilot study.

Data were initially recorded manually with paper and pen then it was transferred to MS Excel format in the computer. The pilot study established that the survey instrument was easily managed, number of questions and duration to answer the questions was acceptable, and that generally the questions were clear and easily answered. During the framing of questionnaire encountered with technical problems which needed attention. The pilot study was revealed to have a review
over the answered provided by the subjects to avoid unclear answers for questions.

4.7 Sample Size
The primary outcome measure was a reduction in HbA$_{1c}$ (intervention vs control), FBG and 2860 at the end of 30 months study period including both the study sites. A sample size calculation, based on published data on the variability (standard deviation [SD] = 2.2%) of HbA$_{1c}$ in patients with T2DM, indicated that to detect an absolute difference of more than 1% in HbA$_{1c}$, with $\alpha = 0.05$ and a power of 90%, a sample size of 1400 and 1600 patients in each of the control and intervention groups respectively was required.

4.8 Survey Process
The study protocol was approved by the Safe Search Independent Ethical Committee, Ahmedabad, India. The community pharmacists were briefed by the researcher and written communication was provided to confirm the uniformity while explaining or getting feedback from the study subjects. The identified community pharmacists were given one week of time in order to aware themselves with the survey instruments and the recording of subject data by interviewing. Data collected during the pilot study were excluded from the main study and initial sample size was decided as 3000 subjects.

Subjects were advised that their participation was voluntary and their personal details were not recorded and all data were kept under confidential. Initially data
were manually recorded on a patient data collection form and various proforma
then it was converted into softcopy and completed questionnaire was filed. In
pilot study, total of 40 subjects were participated and conducted for 7 days.
Among 40, 2 subjects were duplicated and eliminated, giving a total of 38 valid
subjects were included in the final analysis during the pilot study. A total of 140
subjects (4.67%) were declined to take part in the main study. The subjects
expressed two main reasons for not participating in the study. The reasons (i) not
interested and (ii) insufficient time.

4.9 Diabetes Pharmaceutical Care Plan (DPCP) Interventions
Practice setup varies from pharmacy to pharmacy, and both pharmacists and
patients, as individuals, are unlikely to approach adherence or any aspect of
diabetes care in a structured uniform manner. Interventions strategies were
tailored to suit individual subjects and to make similar study settings at both the
community pharmacies.

Two key aspects of the DCP intervention were the clinical and patient education
and counselling interventions. A major component of the clinical intervention was
the monitoring of clinical indicators and other variables. Intervention pharmacists
were provided with a suggested monitoring schedule, which was informed by the
IDF guidelines. The schedule plus explanatory notes, which are shown in Appendix
D, linked the forms, questionnaires, validated scales and other instruments
provided in the manual with consultations, monitoring and review activities in the
following domains: diabetes history and medication review, diabetes knowledge
and self-management, key clinical indicators, provider referral, and behavioural indicators.

During commencement of recruitment process pharmacists’ willingness was requested to attend after hours training. Pharmacists’ expressed their unwillingness to attend, due to personal relation and stress given by their owner of the pharmacies they attend the programme with less willing. Intervention pharmacists were trained and provided with DPCP was given as written material. The resource material, in the form of a written DPCP manual which is more fully described (data not attached), was designed to encourage collaboration between pharmacists and subjects in the development and application of individualized DPCP interventions. The DPCP intervention manual was forwarded to pharmacists on October 2011, which consisted of the following sections, (i) introduction, (ii) scope and need (iii) patient education and counselling (iv) clinical intervention and (v) scales and questionnaires.

4.10 Resource Materials for Intervention
The diabetes related resource materials, primarily T2DM guidelines, provided in support of the clinical intervention are shown in the below Table No. 4.1. Pharmacists were reminded to refer to “Global Guideline for Type 2 Diabetes”, published by the International Diabetes Federation, with regard to the requirements for the provision of pharmaceutical care.
Table No. 4.1: Resource material in support of the clinical intervention

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline and medicine review</td>
<td>A Desktop Guide to Type 2 Diabetes Mellitus. [European Diabetes Policy Group 1, 1999]</td>
</tr>
<tr>
<td></td>
<td>Revised Guidelines for the diagnosis and management of type 2 diabetes mellitus for primary health care in 2002. [SEMDSA, 2002]</td>
</tr>
<tr>
<td></td>
<td>Algorithm for Diabetes Mellitus Type 2, from the South African Council for Medical Schemes. [Algorithm for Diabetes Mellitus Type 2, 2004]</td>
</tr>
<tr>
<td>Diabetes education</td>
<td>Education: IDF global guidelines for type 2 diabetes. [IDF, 2005]</td>
</tr>
<tr>
<td>Self-management adherence</td>
<td>Improving adherence to diabetes self-management recommendations. [Schechter, CB and Walker, EA, 2002]</td>
</tr>
</tbody>
</table>

Pharmacists and subjects were requested to complete the forms, scales and questionnaires at baseline and post-baseline, which are given in the below Table No. 4.2 and further discussed in Appendix C.

Table No. 4.2: Forms, questionnaires and scales to be completed by patients and pharmacists

<table>
<thead>
<tr>
<th>Form/ Questionnaire/ Scale Items</th>
<th>Attributes</th>
<th>Baseline (B)/ Post-baseline (PB)</th>
<th>Information Provided by Subject or Pharmacist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Profile</td>
<td>Diabetes-related history</td>
<td>B</td>
<td>Subject</td>
</tr>
<tr>
<td>Beliefs about Medicines Questionnaire</td>
<td>Health-related beliefs</td>
<td>B &amp; PB</td>
<td>Subject</td>
</tr>
<tr>
<td>Diabetes Satisfaction Scale</td>
<td>Health-related beliefs</td>
<td>PB</td>
<td>Subject</td>
</tr>
<tr>
<td>Diabetes Empowerment Scale</td>
<td>Health-related beliefs</td>
<td>PB</td>
<td>Subject</td>
</tr>
</tbody>
</table>
4.11 Implementation Strategies of DPCP

The procedures relating to the use of these resource materials, forms, scales and questionnaires were discussed in this section and Appendix D.

Procedures relating to the DPCP intervention, including suggestions on the process to be followed, were included in the DPCP manual (Appendix D) as well as in covering letter to patients (Appendix C). Pharmacists were requested to reflect on their practice situations and to take knowledge of the individual subject’s language, cultural and ethnic preferences and psychosocial and socioeconomic status when designing, implementing and monitoring interventions. The key parameters of the DPCP intervention framework are presented in the below Table No. 4.3.
Table No. 4.3: Key Parameters of the DPCP intervention framework

- Assess patient diabetes-related problems, needs and goals in behavioural terms.
- Discuss and agree strategies and interventions required to address needs and goals.
- Specify follow-up plan and implement agreed interventions.
- Share plan with practice team.
- Monitor key clinical variables.
- Regularly review and appropriately modify the DCP.

Pharmacists were emphasized to provide special care to identify and address probable medication related problems. In particular, it was suggested that pharmacists refer to the ASHP patient education and counselling guidelines when conducting medication reviews. Pharmacists were informed to refer the indicators recorded at baseline and the IDF guidelines in order to achieve the study objectives and inform interventions. Pharmacists were encouraged to use opportunities created during patient – pharmacist encounters, especially those associated with the medication refill process and to facilitate the care process. It was further suggested that pharmacists maintain regular contact with their subjects and that they use electronic and telecommunication technologies to follow-up with subjects.

The psychosocial patient education and counselling intervention and the biomedical clinical intervention are mutually supporting parameters of the DPCP. In counselling patients, pharmacists were encouraged to use the non-judgemental method of brief Motivational Interviewing to explore patient health beliefs,
attitudes and concerns in order to identify barriers to diabetes care and concordantly agree on suitable remedial action.

Subject education, in the context of the study, referred to the appropriate communication of T2DM related knowledge from the pharmacist to the subject in order to increase initial support for diabetes self-management. Pharmacists were requested to ensure that their subjects were appropriately grounded in key facets of diabetes self-management education as summarised in the below Table No. 4.4.

**Table No. 4.4: Salient Characteristics of self-management on diabetes education**

- Basic pathophysiology of DM2.
- Complications and co-morbidities commonly associated with the disease.
- Key tests and examinations recommended by SEMDSA.
- Recommendations for glycaemic control including the relevance of SMBG and HbA\(_{1c}\) monitoring.
- The role of anthropometric measures.
- The importance of blood pressure, blood lipid, and renal function values.
- Treatment options including diet, exercise and pharmacotherapy.
- Accessing psychosocial support.

The intervention group of pharmacists was requested to implement the DPCP intervention during the period August 2012 to July 2013. During August and September 2013, 20 months post-baseline biochemical indicators and other variables were measured for both intervention and control subjects.
4.12 Collection of baseline data

Each subject was provided with study particulars pamphlets, profile, forms and questionnaires from their pharmacist containing the following baseline forms and questionnaires (Appendix B and below Table No. 4.5):

Information to be provided by the patient

- A patient profile form for recording demographic and diabetes-related data.
- Three baseline questionnaires
  - Beliefs about Medicines Questionnaire [Horne, R et al 1999]
  - Diabetes Treatment Satisfaction Questionnaire [Anderson, R et al, 1989]
  - Self-management Adherence Scale [Fitzgerald, JT, 1996]

Information to be provided by the pharmacist

- A baseline clinical data form for the pharmacist to record biochemical and clinical indicators (blood pressure and body mass index).
- Pathology request forms to be used by the pharmacist to request biochemical tests (glycated haemoglobin, lipid profile and serum creatinine).

All survey questionnaires were previously validated and were used in this study with the permission of the authors. The scales were applied at baseline to benchmark adherence-related indicators in the areas of: medication-related health beliefs, planning and monitoring, satisfaction with care received, and self-
reported adherence to self-management recommendations. During April/ May 2011 participants were requested to complete patient profile forms and provide data relating to the variables listed in the below Table No 4.5.

**Table No. 4.5: Summary of subject profile data collected at baseline**

- Demographic data.
- Duration and family history of T2DM.
- Providers of medical care and frequency of consultations.
- Diabetes education and lifestyle issues of diet, exercise, social support, alcohol and tobacco use.
- Co-morbidities, medication used for T2DM and other co-morbidities.
- The monitoring of clinical indicators as specified in the IDF guidelines

The following clinical indicators were recorded at baseline:

- HbA1c
- Total cholesterol
- HDL-cholesterol
- LDL-cholesterol
- Triglycerides
- Serum creatinine
- BMI

In order to standardise the biochemical tests and to facilitate the reporting of results, HbA1c, blood lipids and serum creatinine tests requested by pharmacists were performed in medical laboratories. The balance of the clinical variables including proteinuria, blood pressure, BMI and waist-hip ratio were measured in
the participating pharmacies either by pharmacists themselves, or under the supervision of pharmacists. The biochemical test results directly to the researcher who, in turn, made these data available to the pharmacists. Pharmacists handed over the balance of the recorded clinical data to the researcher. Patients were responsible for the costs of the biochemical tests performed and settled these accounts directly. In keeping with standard community pharmacy practice in Kanpur, Uttar Pradesh, India, pharmacists did not levy fees for the in-pharmacy tests and measurements.

4.13 Collection of Post Baseline Data

The post-baseline data were collected for 20 months between February 2012 and September 2013. During the collection of post-baseline data, pharmacists were provided with post-baseline clinical data forms and laboratory forms and asked to conduct (covering letter Appendix E and Table No. 4.2). 20 months subject data to be provided by pharmacists to the researcher.

- HbA1c
- Total cholesterol
- HDL-cholesterol
- LDL-cholesterol
- Triglycerides
- Serum creatinine
- BMI
The use of standard treatment guidelines published by IDF serves as a guide as well as an evidence-based standard for diabetes-related biochemical and other clinical indicators. Baseline subject profile data were analysed to determine patient adherence to the guideline recommendations with regard to attending examinations and having tests done. A comparative analysis of baseline and 20 months post-baseline data including key biochemical and clinical indicator values was conducted. Pharmacists were provided with the following questionnaires for their patients to complete under a covering letter (Appendix F and Table No. 4.2). 20 months subject data to be provided by patients to their pharmacists in turn it will be handed over to the researcher.

- Beliefs about Medicines Questionnaire [Horne, R et al, 1999]
- Diabetes Satisfaction Scale [Anderson, R et al, 1989]
- Self-management Adherence Scale [Fitzgerald, JT et al, 1996]
- Diabetes Empowerment Scale Short Form [Anderson, RM et al, 2003]
- Brief Diabetes Knowledge Test [Fitzgerald, J et al, 1998]
- Understanding Self-care Practices Scale [Fitzgerald, JT et al, 1996]

Pharmacists were also requested to complete two questionnaires (Table No. 4.2). The first was a Prescribed Medication and Refill Questionnaire (Appendix G) that identified OHA used by patients for hyperglycaemia and the number of prescription refilled and changes in the therapeutic regimen, especially OHAs
during the last 6 months of the study period (April to September 2013), as specified in Table No. 4.6.

**Table No. 4.6: Post-baseline adjustments to OHA therapy**

- Increase in dosage.
- Alternative agent or agents prescribed.
- Addition of an agent or agents to the existing regimen.
- Insulin added to the regimen or substituted for any of the oral agents.

Pharmacists recorded subject biochemical and prescription medication data as well as ensuring completion the questionnaires by the subjects used in the study. Other than subject data provided by the pathology laboratories, all forms, clinical data and questionnaires were forwarded to the researcher by the pharmacists. The researcher entered the data directly from the forms, laboratory reports and questionnaires. Errors during the entry of data were identified and corrected by verifying all entries prior to statistical analysis. Pharmacists were requested to return all post-baseline biochemical data forms, subject and pharmacist questionnaires to the researcher. As was the case with the collection of baseline data, numerous follow-up attempts were required before the data collection process could be completed.

**4.14 Data analysis**

Data analysis was premised on pharmacist influence on patient adherence to long-term therapy being evaluated by means of a RCT in which the differences in the primary endpoint of HbA1c and the secondary endpoints (e.g. blood lipids,
blood pressure and body mass index) for intervention and control patients served as surrogate outcomes. Independent t-test analyses involved direct comparisons of group means between the control sample and intervention sample at both baseline and post-baseline intervals separately, on all biochemical and other clinical variables, as well as in health-related beliefs and behaviours and diabetes-related variables. Dependent t-test analyses were conducted on the data from the control sample and intervention sample between baseline and post-baseline intervals to investigate differences in biochemical and other clinical variables. Chi-squared tests were used to test for significant differences between the control and intervention groups in the frequency distributions of patient demographic and diabetes-related variables.

To guard against Type I error, Bonferroni adjustment to the level of significance was applied to the biochemical and other clinical variables test comparisons according to the number of participant characteristics investigated, including control or intervention group, gender, marital status, monitoring body mass, receiving diabetes education, consulting general practitioners or specialists, smoking, following a diabetes eating plan, exercising regularly, consuming alcohol and receiving social support. Accordingly the alpha adjustment for the test comparisons, allowing for the Bonferroni adjustment to ensure that the overall level of significance does not exceed $\alpha = 0.05$, is $\alpha/k = \alpha/11 = 0.05/11 = 0.0045527$ All tests were performed using ‘SPSS version 20’, as statistical software.
4.15 References


Berger, BA. Helping patients face change. US Pharm 1999; 24(9). [Online] Available from:

Berger, BA. Motivational interviewing helps patients confront change. US Pharmacist 1999; 24: 11.


