PRINCIPAL INVESTIGATOR:

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1.0 Objectives

1.1 Purpose, specific aims, and/or objectives.

This proposed study aims to develop group-based trajectory models to identify patients with similar medication filling behavior among patients with co-morbid hypertension (HTN) and diabetes (DM) using angiotensin converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARB). A motivational interviewing (MI) pharmacy student telephone intervention will then be customized by the identified trajectories and tested to demonstrate effectiveness in improving ACE/ARB adherence.

1.2 Hypothesis
It is our central hypothesis that the customized MI based pharmacy student intervention will be beneficial in improving medication adherence to ACEI/ARBs.

2.0 Background

2.1 Diabetes (DM) and hypertension (HTN) are independent risk factors for cardiovascular (CV) disease and major public health issues in the United States (US). The two conditions frequently coexist, with 70-80% of DM patients also having HTN. The combination significantly increases the risk of macrovascular and microvascular DM complications. Controlling high blood pressure (BP) can greatly reduce these complications including the CV risk which accounts for 50-80% of DM fatalities. Angiotensin converting enzyme inhibitors (ACE) and Angiotensin receptor blockers (ARB) are highly recommended for patients with DM and HTN, with a well-documented benefit in reducing DM complications.

The project will have 2 phases: Phase 1 will be a retrospective analysis of 12 month refill data to determine patient past adherence behavior patterns. Phase 2 will entail a prospective randomized design among non-adherent patients to evaluate the effectiveness of the customized intervention. The students will contact patients assigned to the intervention group and follow a protocol using the Ask-Provide-Ask approach of MI given the patient adherence pattern for a tailored education. Monthly follow-up calls for 6 months will be carried out. Adherence during the 6 and 12 months post-intervention, will be evaluated for the intervention and control groups. Findings are expected to demonstrate the effectiveness of an innovative low cost intervention in improving adherence and have a positive impact in implementing tailored interventions leading to more desirable long term health outcomes and considerable cost savings in our financially overwhelmed healthcare system.

2.2 The primary investigator has conducted prior research collaborating with Cigna Healthspring using motivational interviewing techniques over phone calls. The IRB reference of the last study is: 16410-01-(7926)

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria: Patients over the age of 18, with continuous enrollment in the Cigna Medicare Advantage health plan in Texas starting July, 2016 until January 2018 with a diagnosis of comorbid DM and HTN and having a prescription filled for an ACEI or ARB medication during the month of January, 2017. The patient identification period will be included in the study. Patients who disenroll or die before the study ends will be excluded from the study.. Exclusion criteria include having a diagnosis (identified by ICD-10 codes) for dementia, or an ACEI/ARBS contraindication like angioedema, hyperkalemia, renal artery stenosis.

3.2 Describe how potential subjects will be screened for eligibility based on these criteria: The retrospective analysis will apply these exclusion and inclusion criteria during the data analysis stage to give the final cohort of patients.

3.3 This study will not include any vulnerable population, mentioned below:

1. Adults unable to consent
2. Individuals who are not yet adults (infants, children, teenagers)
3. Pregnant women
4. Prisoners
5. Students for whom you have direct access to/influence on grades
6. Economically and/or educationally disadvantaged persons

4.0 Vulnerable Populations

4.1 **N/A**

5.0 Number of Subjects

5.1 This study will have two phases. In the restrospective analysis stage, Cigna Healthspring will provide data on patients who fulfill eligibility criteria mentioned above. It is expected that this data will have approximately 22,000 patients with DM and HTN.

5.2 In the intervention phase, 250-300 patients will be included in the intervention phase. If 1 control is used for each patient in the intervention group, the total sample of phase 2 is expected to be 500-600.

6.0 Recruitment Methods

LOCAL:

6.1 This study will start with the retrospective phase which does not involve recruitment of patients, but involves analysis of existing data. De-identified data will be obtained from Cigna-Healthspring.

6.2 The project will be implemented in collaboration with Cigna-Health Spring, a Medicare Advantage Plan in Texas. The health plan has several electronic data files available for analysis including membership file, member

summary file, institutional claims file, professional claims file, quest lab, Cigna-Health Spring's medical claims file (CCMS) and pharmacy file. Pharmacy files contain Part D pharmacy data provided by pharmacy benefits manager including patient/ drug identifying information, fill dates, days of supply, quantity dispensed and dosing for each prescription filled. The refill data will be used to determine the non-adherent patients. ICD-10 codes will be used to determine other exclusions using professional claims data.

Phase 2 will involve project intervention which will be conducted over the phone. A list of actively enrolled members, taking the medication who were a part of phase 1 will be created by Cigna HealthSpring to be used for intervention implementation at their premises. The phone call will be made by University of Houston pharmacy students who will be on rotation at Cigna-HealthSpring. The form of informed consent which will be read to the patient is attached to the IRB. If the patient consents to receive the intervention over the phone, and completes the phone call, the patient forms a part of the intervention group. Five follow-up phones will be attempted one month apart for the patient after the initial call.

7.0 Study Timelines

7.1 The duration of the total study will be 3 years. Retrospective analysis of phase 1 and intervention development will require 12 months. The retrospective analysis will use data from July2016-January 2018. July – December 2016 will be used for baseline covariate measurement. January 2017- January 2018 will include adherence measurement. However this is de-identified patient data used for retrospective analysis and does not require patient participation.

7.2 The phase 2 of the study will involve the intervention call provided in the day of consent followed by monthly follow-up calls for six months. The patient however can refuse to participate in any of the calls, even if the patient has completed the primary phone call

7.3 The number, frequency and length of study visits: One intervention call lasting 12-15 minutes on average. Monthly follow up calls to the patients who received the initial call for six months lasting on an average for 5-10 minutes.(First call + 5 follow-up calls)

7.4 The duration anticipated to enroll all study subjects: The enrollment will continue for a period of 8 months (equivalent to an 2 active semesters)

7.5 The estimated date for the investigators to complete this study: 3 years Timeline details below

	Pre-award	Study Period: 36 months																	
		1 2	3 4	5 6	7 8	9 10	11 12	13 14	15 16	17 18	19 20	21 22	23 24	25 26	27 28	29 30	31 32	33 34	35 36
IRB Approval																			
Phase 1 trajectory modeling																			
Intervention Development																			
MI training and randomization																			
Intervention implementation																			
Post intervention analysis																			
Manuscript / Final report prep																			

8.0 Study Endpoints

8.1 Develop group-based trajectory models to identify patients with similar medication filling behavior patterns among patients utilizing ACEI/ARBs with co-morbid HTN and DM enrolled in a MAP and examine predictors associated with having different trajectories.

8.2 Customize a pharmacy student telephone intervention incorporating MI by patient adherence behavior patterns identified under aim 1.

8.3 Demonstrate the benefit of the customized intervention on ACEI/ARB adherence among non-adherent patients with co-morbid HTN and DM enrolled in a MAP.

9.0 Procedures Involved

9.1 Phase 1: Retrospective data analysis

Patients that used a study medication during January 2017 will be identified and the first prescription date during this time will be considered the index data. A dummy variable will be created to indicate prevalent user vs incident user by evaluating the 6 month data prior to index date (July – December 2016). Patient adherence will be assessed during the one year following the index date. Adherence will be measured as proportion of days covered (PDC). PDC rates over the entire 360-day assessment period will be determined. PDC will also be calculated separately for each month during the one year following the index date. During each of the 12 consecutive 30-day periods of adherence assessment, a binary indicator for "full adherence" each month, defined as PDC= 0.8 vs. non-adherence will be created. The 12 binary indicators of full adherence will then be modeled during each 30-day period as a longitudinal response in a logistic group-based trajectory model. Patients will be assigned to a trajectory on the basis of these models. Several logistic regression models will then be carried out to identify predictors associated with specific trajectories for adherence.

9.2 Covariates: Demographics (age, gender, and language), physician specialty (primary care vs. specialist), health plan (low income subsidy vs.

other), prevalent vs. incident user, Centers for Medicare and Medicaid CMS Risk Score, Charlson comorbidity index (CCI) and number of distinct medications. Additionally, selected co morbidities will be identified by ICD-10 codes during the one year prior to index date including congestive heart failure, coronary artery disease, peripheral vascular disease, myocardial infarction, diabetes, stroke hypertension, end stage renal disease (ESRD), chronic obstructive pulmonary disease, asthma, and depression. To ensure appropriate risk adjustment in the models, additional covariates which will be added to the model include, regimen complexity, class of antihypertension medication used, baseline adherence measured as PDC, previous hospitalization and patient's trajectory prior to intervention.

Customization of intervention: After completion of the retrospective analysis phase and identifying the major trajectories in this patient population, the team will meet to discuss the patterns identified, the potential barriers likely to be associated with each trajectory, and strategies that can help patients within each trajectory based on their behavior pattern. The team will then develop customized education specific to each identified trajectory. For example: some patients can have high medication use in the early part of the follow up period but poor after, others may have low initial use and improved subsequent. Some may have intermittent adherence throughout the follow up time, others may simply discontinue. The expected barrier and potential solutions that should be discussed with the patient using MI strategies will vary accordingly. Patients past adherence patterns will guide the team in determining probable barriers and what can potentially help the patient. For example, patients who discontinue the medication may have side effects concerns or may view the medication as unnecessary. Patients who continue to take medication but have less than 0.8 PDC throughout may be forgetting to take the medicine and need help remembering. The team will create a code for each trajectory identified to categorize the patients. A protocol for each trajectory will be developed to summarize the education that is likely to benefit patients with the specific behavior pattern given the code. All the developed protocols will be based on the Ask-Provide-Ask approach, a pharmacist adaptation for the Elicit-Provide-Elicit approach of MI (attached)

9.3 Phase 2: intervention implementation

Patients that are still enrolled in the health plan during 2017-2018 will be included in phase 2. Patients will be categorized by their adherence trajectory identified in phase 1 and will be randomized to intervention vs. not within each category. The proposed intervention will be a telephone call by a pharmacy student participating in rotations at Cigna-Health Spring Plan and trained in MI and 6 monthly follow up calls. During implementation, students will first examine the patient adherence pattern that was identified in phase 1 which will be coded. The student will then confirm the diagnosis, medication name, and dose with the patient answering the call and will follow the outlined protocol. Using MI, students will assess readiness for change, help patients identify potential barriers in accordance with patient past pattern of use, and guide them to develop a plan to deal with these barriers

Additionally, the students will ask the 2 questions from the Patient Health Questionnaire (PHQ)-2, a validated screening tool for depression (attached).If the patient responds positively to either question, the student will suggest that the patient schedules an appointment with his/her healthcare provider to discuss these symptoms. The Supervising pharmacists will be available to assist the students in answering any medication related questions that may arise during the calls and arrange for a diabetes educator to contact the patient at a later time if needed. Follow up phone calls will be performed each month for a total of six calls. Students will be supervised by the pharmacist preceptors and managed care pharmacy residents throughout the calls and intervention implementation. The students who will be implementing the calls will attend a three day MI training facilitated by Dr. Abughosh, who is experienced in utilizing motivational interviewing to improve adherence. The students will practice calls as a part of their training. They will also complete Human Subjects Research training before their rotation at Cigna Healthspring, and the certificates will be uploaded to the IRB application. After each initial call, students will record the date and write a summary of the interaction with the patient documenting the main barrier/s identified in the conversation and the plan made with the patient. During the follow up calls, students will emphasize the information, confirm problem solved, provide further encouragement and reinforce adherence.

Control group: For every patient that received a call, a control will be randomly selected from the list of patients randomly assigned to the control group.

10.0 Setting

10.1 The retrospective data analysis will be conducted in building HSBS2 using secured computers provided by UH-College of Pharmacy. The PI and research assistant will have access to the data.

10.2 The phone calls will be made on the premises on Cigna HealthSpring under the supervision of the research team at Cigna HealthSpring. The data will be de-identified at Cigna Healthspring and shared with UH through secured servers.

10.3 A letter of support from Cigna HealthSpring is attached to the email.

11.0 Risks to Subjects

11.1 This study does not involve more than Minimal Risk for the safety of patients.

11.2 The intervention participation is completely based on the patients consent, and they are made aware of the same. They can withdraw or choose to stop the call at any point, which is also read out to them. The students making the calls are pharmacy students who have completed human subjects' research training as well as training for motivational interviewing. Additionally, the research team members closely supervise the pharmacy students to ensure the quality of the calls. Thus, it is not anticipated that the intervention can harm any patient in any way

12.0 Potential Benefits to Subjects

12.1 Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.

12.2 As mentioned in the initial sections of this IRB protocol, medication adherence is very important for patients with comorbid conditions and the lack thereof is an important problem being faced in the real world settings. This intervention uses motivational interviewing, which has successfully been used to improve patient adherence in various other chronic diseases, by helping the patients find their own internal motivation to change and find ways to address their adherence barriers. The intention of this study is to bring about a change in the behavior of patients and to improve their adherence, with a goal to improve the outcomes associated with the disease.

13.0 Withdrawal of Subjects

13.1 There is no more than minimal risk for the subjects. There are therefore, no foreseeable circumstances which require withdrawal of subjects. However, the participant can voluntarily refuse to participate in the follow up calls even if they have participated in the first call.

14.0 Costs/Payments to Subjects

N/A. No compensation to the participating patients

15.0 Confidentiality

The intervention will occur on the premises of Cigna Healthspring. No identifiable data will leave the premises. Only encrypted, de-identified data will be available to Dr. Susan Abughosh at UH. There will be no audio recording of the intervention. Only the research team operating from Cigna Healthspring will have access to identifiers.
The UH Pharmacy students who will conduct the intervention will only interact with the patients to conduct the intervention over the phone and will not be able to access any information on the patients otherwise. The students will collect notes about the phone calls to identify number of successful calls, number of attempts made to contact each patient, and barriers to adherence for the successful calls. These notes will be made in a single excel sheet which will be available only at Cigna – HealthSpring. The students will have no access to the notes otherwise. After the completion of the intervention phase, the excel sheet will be deidentified, and will contain a de-identified ID and corresponding barrier to adherence. This information will be provided to UH for understanding the success of the intervention process.

16.0 Provisions to Protect the Privacy Interests of Subjects

16.1 The retrospective data analysis will be completely de-identified. For phase two, the personnel making the phone calls will be provided the list of names and numbers to contact at the premises of the health plan for intervention

implementation. During the follow up calls, the patients would be asked if they are willing to participate in the follow up. The students are trained to conduct training using MI to promote behavioral change in a collaborative supportive manner.

16.2 After the completion of the intervention stage, post intervention data will be de-identified and the analysis completed. Data will be stored on a secured server for a period of 3 years after completion of the study. The attached script is an example of how MI has been used previously by pharmacy students at UH, in research led by the PI.

17.0 Informed Consent Process

The intervention is conducted on the phone, and therefore the consent will be obtained orally on the phone. The pharmacy student will read the consent letter (attached) to the patient, and once the patient says that he or she agrees to participate in the study, does the student proceed with the intervention. The patient can refuse, or ask the pharmacy student to call another time.

18.0 Process to Document Consent in Writing

The research involves no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. The intervention involves only a phone call to educate the patient about adherence. A waiver of obtaining consent in writing is being sought.

19.0 HIPAA

The direct identifiers will be removed before providing any information to University of Houston. All information will be analyzed and results reported in aggregated form. Thus, the protected health information of patients will not be accessed by UH, and therefore we will not be obtaining, creating, using, and/or disclosing individually identifiable health information associated with a HIPAA-covered component or entity in the course of the research.

20.0 Data Management

20.1 The data which will be provided by Cigna will contain data with encrypted patient IDs. The electronic data files for this study will be processed on a dedicated, layered-security server, which can be accessed only by Dr. Susan Abughosh and designated project staff members who are under the direct supervision of Dr. Susan Abughosh. Since the system is behind multiple firewalls, is monitored regularly, and is accessible only to key personnel, the risk of unlawful penetration is not a significant data safeguard concern. Data will be stored on the secure server for 3 years following the completion of the study. All analysis will be conducted on the desktop at UH College of Pharmacy. The data will not be accessible through any personal computers.

SAS 9.4 is the statistical software, which will be used for the analysis.

Baseline characteristics: Comparisons in baseline characteristics will be made between the 2 study groups (intervention vs. control) using t-tests for continuous variables and chi-square tests for categorical variables. The characteristics evaluated will include predisposing factors: demographics, and number of other medications used; enabling factors: health plan (LIS vs. not), prescriber specialty (specialist vs. primary care); need factors: co-morbidities (CHF, MI, CAD, stroke, ESRD, depression), previous hospitalization and CMS risk score.

Baseline PDC in the 12 months prior to intervention and patient past adherence trajectory will also be compared between 2 groups. Because of the randomization, we do not anticipate any significant differences between the two study groups on these characteristics.

Outcome analysis: Refill data during 2 time periods -- 6, and 12 months, following the initial call of the intervention will be evaluated to calculate adherence rates for both the intervention and control groups. The two periods were chosen to evaluate the intervention effect during the 6 months when the follow up calls were ongoing as well as after these calls had stopped. The adherence rate will be defined as proportion of days covered (PDC) for six and twelve month follow up period following the intervention. An intent to treat analysis will be utilized.

To examine the effect of study group (intervention vs. control) on adherence, study group PDC means for each follow up time, 6 and 12 months, post intervention will be calculated and compared using a t-test. In the event that significant differences in baseline characteristics were observed, multiple regression will be utilized to adjust for the imbalance. The outcome variable will be PDC during each follow up period, 6 and 12 months, following the intervention initial call. The primary exposure variable will be study group, and other covariables will include any baseline characteristics not equally distributed.

Dichotomization of the outcome: Patients in both groups will also be categorized as adherent vs. not during the two follow up periods based on PDC≥80% in each time period, 6 and 12 months, to create 2 categorical outcome variables. The effect of study group on adherence will be evaluated for these categorical outcomes using chi-square tests. If significant differences in baseline characteristics were observed, logistic regression models will be utilized to adjust for imbalances

21.0 Sharing of Results with Subjects

21.1 N/A. It is impossible to contact or identify any subject as all direct identifiers that might lead to identification will be omitted.

21.2 During the consent, Patients will be informed that they can check the progress and results of the study on www.ClinicalTrials.gov

22.0 Resources

22.1 The PI has successfully completed several studies using motivational interviewing based phone calls. Collaboration with Cigna healthSpring has also been successful in the past projects and the team at Cigna Healthspring is extremely experienced as well. Everyone has completed human subhects research training. The research assistant is trained to analyze data and efficiently use research design and analytical techniques at UH- Department of Pharmaceutical health Outcomes and Policy.

22.2 Infrastructure at both Cigna HealthSpring as well as University of Houston, is updated to be able to conduct the study.

22.3 **Research Team:**

1.Susan Abughosh[1] - Principal investigator
2.Michael L. Johnson[1] - Co-investigator
3.Marc L Fleming[1] - Co-investigator
4.James Essien[1] - Co-investigator
5.5. Dr. Kamalasanthi Masilamani[1] – Co-investigator
6.Dr. Omar Serna[2] - Co-investigator
7.Dr. Tara Esse[2] – Co-investigator
8.Aisha Vadhariya[1]- UH Student, research assistant
9.Rutugandha Paranjpe[1] - UH Student, research assistant

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2= Cigna HealthSpring