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CALCULATING AND PREDICTING MEDICATION ADHERENCE IN A CHRONICALLY ILL LOW-INCOME POPULATION

A DISSERTATION

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BY

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Table of Contents

I. ABSTRACT

BACKGROUND: Physicians and researchers have long studied the importance of medication adherence and how it relates to patient outcomes. METHODS: Medications received, client characteristics, pharmacist interviews, and baseline health information were collected from a chronically ill indigent rural population accessing a medication access program in Central Louisiana (n=3488). RESEARCH QUESTIONS: 1) Does a new self-reported adherence measure (ASR) agree with electronic pharmacy data? 2) What client characteristics predict adherence to chronic care prescription medications using logistic regression methods? 3) Does adherence predict the use of the ED or hospitalizations? The three adherence measures will be divided into adherent and non-adherent using five cut-points. RESULTS: The two electronic adherence measures, the continuous, single-interval measure of mediation availability (CSA) and the medication possession ratio (MPR), were highly correlated with each other (kappa = 0.90, $p<0.001$) but not with ASR (kappa=0.16, $p<0.001$ and 0.093, $p<0.001$, respectively). Predictors of adherence varied by the measure and cut-point examined, with age and race associated with CSA, race and primary diagnosis with MPR, and age, race, gender, self-reported current health with ASR. Refills and number of medications were significant predictors of ASR. CSA and MPR both showed an interaction where those that had ≤ 3 medications but received ≥ 30 refills were as much as 9.24 (CI: 4.46, 19.14) and 3.48 (CI: 2.29, 5.28) more adherent..While examining the relationship of adherence and utilization, CMAP patients who were non-adherent and did not utilize the ED prior to enrollment were 1.69 (CI: 1.02, 2.81) and 1.96 (CI: 1.08, 3.54) times as likely to have an ED visit after enrollment at MPR adherence cut-points of 85% and 90%. CONCLUSION: Varying the "adherent/non-adherent" cut-offs of CSA and MPR influenced the findings, and non-adherence was found to be a predictor of ED visits.

II. BACKGROUND AND SIGNIFICANCE

Introduction

Physicians and researchers have long-studied the best way of determining how well patients adhere to or comply with their drug regimens. An individual will often seek medical care in order to elicit assistance from a healthcare provider with a specific disease or condition. Often these individuals will be prescribed a medication in order to help eliminate, alleviate, or delay the signs, symptoms, or progression of the disease or condition. Ideally, patients would take medications as prescribed, following the dosing and frequency pattern recommended to them. Medications can be prescribed for short durations in the case of antibiotics, for example, where taking the medication is crucial for the quick resolution of the infection or illness. In chronic disease care when medications are often prescribed for much longer periods of time, in some cases for the rest of the patient's life, long-term medication adherence is key to continued success in treating the disease or condition.

Defining Medication Adherence

From the beginning there has been an ongoing debate and discussion as to the terminology and definitions used to describe this process. Early researchers referred to this process as "cooperation," and later "compliance," "adherence," and "persistence (1, 2, 3, 4)." Debate continues to this day as to which term to use, however for the purposes of this study the term adherence has been chosen due to its non-judgmental connotation (5). A definition of adherence has also been debated since the concept was first introduced in the 1970's. In 1976 Haynes and Sackett published the book Compliance with Therapeutic Regimens in which they put forth one of the first and most widely used definitions of adherence (which they called

compliance), "the extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice (2)." Osterberg and Blaschke recently defined adherence as "the extent to which patients take medications as prescribed by their health care providers," and the International Society for Phamacoeconomics and Outcomes Research in 2008 defined adherence as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen (6, 7). " Although these definitions may vary slightly, there is a consistent theme of the patient following the healthcare provider's advice in regards to medication taking.

Predicting Medication Adherence

Although varying definitions of medication adherence and its calculation exist, there is a consensus in the scientific literature that, in general, high medication adherence is associated with better clinical and patient outcomes (8). Scientifically, it stands to reason that patients who use their prescription medications as prescribed for optimum results will benefit the most. Therefore a large group of research and subsequent scientific literature has been devoted to optimizing medication adherence. The questions often asked is: Who is most likely to be adherent? Although a simple question, the literature varies greatly as to what patient characteristics predict adherence.

As discussed above, the utility of the adherence measure must first be determined to ensure that the adherence being predicted is as accurate as possible. Once an agreed upon adherence calculation is used, often researchers will then look at differences in the study population to see who were most likely to adhere and under what conditions. Depending on the types of statistical analysis used and the question being asked, adherence can be predicted as a continuous or dichotomous variable. Often adherence is dichotomized into those who adhere to

their medications and those who don't. In general, the cut-off is 80%: those patients whose overall adherence is 80% or greater are considered to be adherent to their medication regimen, while those below the 80% threshold are considered to be non-adherent (9). The "80% rule" is based on the general principal that if a patient consumes their medication 80% of the time, they are receiving close to the maximum pharmacological benefit (10, 11, 12, 13). A recent study in the American Heart Journal found that the cut-point for optimal adherence for individuals with heart failure was 88% based on optimal outcomes observed (14). Some studies have used anywhere from 70% (15) to 90% (16, 17) as the threshold for adherence, however since this concept of the "80% Rule" was first introduced, almost all studies which dichotomize adherence use the 80% cut-off, with few exceptions (18, 19).

Consistency as to which client characteristics are predictors of adherence, however, has been lacking (8). A review of the literature reveals very few predictors of adherence that are similar across differing study designs and populations.

Medication Adherence Predicting Outcome

A large amount of research has been devoted to measuring and predicting medication adherence. A natural question that leads from this research is: What outcomes do good (or conversely poor) medication adherence predict? Medication adherence as a concept relies on the assumption that those individuals who are more adherent will experience better outcomes. Although not always associated with positive outcomes, the evidence to date shows that medication adherence does in fact predict a better disease course for patients, and subsequently lower costs for providers (20).

Patients with high medication adherence tend to benefit in two measurable ways; better biological/physiological outcomes, and decreased use of the health care system and the subsequent cost savings. Adherent patients will often experience greater improvement in levels

of markers and indicators of illness or health than non-adherent patients. However, there is still a demand to continue to study the association between medication adherence and improved outcomes. Cleemput, Kesteloot, and DeGeest (2002) assessed eighteen published studies based on their method of measurement of adherence, measurement of cost-savings, study design, and outcomes (21). The authors found that there were no consistent methodologies used in the studies to assess the above measures, and that "there is a clear need for more and better research on the impact of noncompliance." Decker and colleagues (2009) also suggest, "More research is needed to explore if these findings are seen in larger cardiac populations...targeted to increase adherence and optimize their health status (22)."

Significance of the Study

The current study provides new insights into the determination of the best adherence measures to use in indigent rural populations by comparing accepted measures of adherence with a new instrument developed as part of a medication access program (23). Medication adherence is widely accepted in the literature as an important measure of health success. The proposed study will add to the current knowledge by determining the patient characteristics that are associated with an individual adhering to their medication-taking regimen. This study will also examine if adherence is a predictor of utilization of Emergency Departments (ED) and hospitalizations, two very expensive and burdensome forms of healthcare. Understanding the impact of adherence on ED visits and hospitalizations can help physicians in understanding the importance of measuring and tracking patient adherence, serving to reduce the burden of non-necessary and costly emergent care.

III. LITERATURE REVIEW

This chapter will provide an overview of the literature related to medication adherence, predictors of medication adherence, and the association of medication adherence with health and utilization outcomes.

History of Medication Adherence

Early studies of medication adherence were dedicated to looking at specific drugs or conditions and were based mostly on self-report (24, 25). In the early 1970's scientists began to use different methods in place of patient self-report, such as medication monitors and biological detection techniques, to determine how well someone was adhering to their prescribed regimen (26, 27, 28). In 1984, Jacqueline Dunbar presented one of the first review papers of the type of methods used to monitor medication adherence (29). Dr. Dunbar put forth one of the earliest definitions of adherence in the literature, citing the lack of a uniform definition at the time. She suggested that adherence be viewed in three parts: as both a continuous variable that could be measured and quantified; a variable that is qualitative in nature and could separate individuals into good or poor adherence; and as an index which could be summed up over different types of adherence by regimen, appointment date, medication consumption, and appointment keeping. Dr. Dunbar then classified the different methods used to determine medication adherence, including biological markers, assays, pill counts, medication monitoring, self-monitoring, and patient interview. In the context of scientific research, she theorized that the most effective method of monitoring medication adherence is through the use of pill counts, followed by the measurement of markers in the patient's biological fluids or tissue. Since Dr. Dunbar's paper, many new methods to monitor medication adherence have been used, with varying success (30).

In the mid-to-late 1980's, as computers became more widely used in medical practices and pharmacies, electronic databases containing prescription refill information were more common. These pharmacy databases allowed for easier analysis of pharmacy records, and are now the most widely used method of looking at medication adherence (31). Electronic monitors which track the date and time when a pill box is opened by a patient are often used in clinical trials as the "gold standard" of adherence measurement, but they can be costly and recently their utility have come into question (32, 33).

In 1988, the landmark paper on drug adherence was published by JF Steiner and colleagues in the journal Medical Care (34). It was in this paper that the first validated use of electronic pharmacy data to determine medication adherence was explained. Drs. Steiner and Prochazka suggested that electronic pharmacy data could be used to validate other existing more intense methods of medication adherence in order to produce a measure that was equivalent but much easier to perform. Although it was not called it at the time, this concept of Medication Possession Ratio (MPR) would change the way drug adherence was measured, allowing for its utility in both practical and research settings. The MPR, as defined by Steiner et al, is "the quantity of pills dispensed divided by the number of pills prescribed per day(34). " Although more complicated variations of this definition exist today, it is still the most widely used formula to determine drug adherence (18).

Common Methods for Measuring Medication Adherence

Today, the concept of MPR is ubiquitous. In a review article by Andrade et al in 2006 looking at the most common types of methods to calculate drug adherence, 77 of 136 studies found by the authors used MPR or a slight variation of MPR as their measure of medication adherence (18). The Medication Possession Ratio is used in both clinical and experimental

research in a variety of different populations as a simple but effective way of monitoring medication adherence. Most often MPR is used to calculate adherence to long-term chronic care medications used to treat common conditions such as hypertension (35, 36, 37, 38, 39), diabetes mellitus (40, 41, 42, 43, 44, 45, 46, 47), congestive heart failure (48, 49, 50), hyperlipidemia (10, 16, 51, 52, 53) or to look at medication adherence in patients with combinations of these health conditions (54, 55, 56, 57. 58, 59, 60). Additionally, the MPR has been used to calculate adherence in patients receiving antidepressant therapy (61, 62), antipsychotic therapy (63, 64), patients receiving glaucoma medications (65, 66), individuals being treated for anxiety disorders (67), osteoporosis prevention (68), asthma therapy (69), and anti-ADHD medications (70).

In the majority of the above-mentioned studies and publications, the MPR is a standard calculation based on Steiner's formula using electronic refill records from administrative/pharmacy databases. However, variations of the MPR formula have been used to determine adherence, including methods that take into account large gaps in refills. Recently, Hess and colleagues used several of the different available medication adherence formulas to calculate adherence using an existing research study dataset (71). The authors first conducted a review of the literature on medication adherence to compile a list of current or recently used measures of calculating adherence from administrative/pharmacy data. They identified eleven measures from their search, and then applied all eleven measures to a dataset of 283 individuals who participated in a year-long study to assess the impact of a new weight loss drug in combination with a weight management program. The authors found that six of the measures produced similar results (adherence ranged from 63.0% to 63.4%), however the other five measures had a large range in adherence percentage (84.4% to 109.7%). The authors concluded that the difference in the six similar measures and the five differing measures was due to how the

measures took into account patient attrition from the study, and when only data on a single refill exist for a patient. A limitation with this comparison, however, is that the authors were only interested in adherence for a finite study period, in this case one year. Often, however, researchers are looking at long-term medication adherence over time based on medication a patient is taking for a chronic illness, and set periods of time such as one year are not feasible. Hess found that it was the denominator in the medication adherence formula that varied the most based on the one-year expectation of adherence, and therefore adherence not limited to one year would yield different results. The final recommendation of the authors was the use of the Medication Refill Adherence (MRA) formula, which is the total days' supply divided by number of days of study participation and multiplied by 100. This formula only differs from MPR as it pertains to "study participation," which in this case was a predetermined study length of one year. Therefore the MRA is in essence the MPR for a set length of time, rather than relative to the amount of data that exists for an individual.

One component of MPR that is glaringly missing from the scientific literature is the calculation of MPR based on differing, pre-determined lengths of time and its effect on overall adherence measures. Of the above mentioned studies, only Hess et al looked at calculating a version of MPR based on varying lengths of time, but failed to make it patient specific, rather than study length specific (71). In 2007, Bryson and colleagues attempted to confront this issue of using short intervals to determine medication adherence by creating a new algorithm (72). The algorithm, which they called ReComp, was compared to two common methods of measuring medication adherence (one of which was MPR). The authors found that using regression based correlations, ReComp performed better than the other two measures. However, by the authors own admission, a limitation of the algorithm is its ability to estimate adherence effectively over

short intervals. Hudson et al also studied the differences in calculating mediation adherence using prescription databases and found that the overall adherence result was greatly influenced by the calculation method used (73).

Another method of calculating medication adherence that is seldom used is the continuous, single-interval measure of mediation availability (CSA). CSA was introduced by Steiner et al in order to calculate adherence at each interval between medication refills. These very short intervals (usually one-month in length) could then be averaged together to calculate an overall medication adherence for all prescription refills. This method is not widely used in the scientific literature, with very few studies reporting the CSA in published papers.

Comparison of Self-Reported Adherence Measures with Adherence Determined from Pharmacy Databases

Recently, Krousel-Wood et al (2008) used CSA and MPR in conjunction with a third measure to compare medication adherence with a patient-administered self-reported adherence questionnaire (74). The authors found that CSA correlated as well with the self-reported measure as MPR and the third measure. Karve and colleagues examined Medicaid data in Arkansas for diabetics and looked at the predictive value of 11 adherence calculations in predicting hospitalization episodes and total nonpharmacy costs (75). They found that MPR was one of the best predictors of hospitalizations, and that CSA was not predictive. However, the authors were looking at adherence over a defined interval of 1 year (365 days). If a patient had at least two refills but did not refill a medication again in the interval, their adherence was biased downward based on not having refilled their medication for the remainder of the year. This unique circumstance, where individual's adherence is calculated taking into account the interval even after their final refill (not taking into account attrition – either through death, moving,

change in insurance status, etc) is an artificial circumstance created for a defined study and analysis period. However, this does not reflect "real-life" circumstances where an individual should only be accountable for their adherence during the period for which they have quantifiable prescription data. This author argues, therefore, that CSA will be an effective estimate of mediation adherence if the refill data under study are not artificially truncated or expanded, and only the data available are used to calculate medication adherence.

With the expansion of use of pharmacy records to calculate medication adherence in research, the use of self-reported measures of adherence has diminished. However, in non-research settings self-reported medication adherence may be the only practical way of clinician's to determine if a patient is taking medication in the prescribed way. In the mid-1980's, Morisky, Green & Levine recognized the need for a simple straight-forward method for determining patient adherence that clinicians could apply in their practice. They developed a four-question interview (later expanded into eight questions) and validated its psychometric properties and utility by comparing it to long-term blood pressure control in an outpatient hospital setting (76). The Morisky scale is still used today, and its utility is being studied in a variety of populations and settings (77, 78, 79). Since this time, many other instruments have been developed to measure medication adherence in different populations (80, 81). However, many can be long, requiring patients to give 10 or more responses in order to complete a self-report questionnaire (82).

The agreement between self-reported measures and objective measures varies depending on the types of methods, instruments, and settings used in the comparison. In HIV settings, where adherence is often near optimal due to the nature of the outcomes of the disease, close relationships between self-reported and biological validation medication taking is high (83).

However, in other diseases and settings the agreement is much poorer. A comparison between self-report and electronic medication monitoring (via a computer chip in the cap of medication bottles) in several patients of a county health clinic found that clients over-reported medication taking by almost double (84). Correlations between pharmacy refill records and validated self-reported adherence instruments were found to be very poor (.213 - .261)in a comparison study of data from physicians' offices in rural Georgia (85). Similarly low correlations (<0.1) were found between two self-report scales when compared to electronic monitoring in a cardiovascular patient population in Switzerland (86). A common theme that emerges throughout the above mentioned studies is that patient self-report is almost always higher than the objective measures of medication adherence (87).

A 2008 review of self-reported measures of medication adherence concluded that there is still a large need for further study into the easiest and most effective instruments to use (88). The authors found that numerous self-report instruments exist, many of which vary in their focus (intentional vs. non-intentional adherence), and what they measure (beliefs, attitudes, knowledge, etc.). In the end they were only able to identify seven instruments, and they were unable to compare the instruments due to the differences in populations and settings in which each was used. A similar review by Garber et al (2004) also failed to identify any one self-reported method that correlated best with non-self-reported measures of medication adherence, suggesting the need for further study (89).

Predicting Medication Adherence Using Patient Characteristics – Inconsistency in the Literature

A review of the literature on patient characteristics used to predict adherence elucidates that there is much more work to be done. Predictors identified in the literature tend to fall in

three categories: 1) Variables that predict adherence in a consistent direction; 2) Variables that predict adherence in some studies, but are also found to be non-predictive in others; and 3) Variables that vary in direction depending on the study and population under study.

The only two variables that regularly appear in the literature as having the same directional effect on adherence are dosing pattern and race. Dosing pattern appears to be a fairly consistent predictor of adherence, with simpler dosing patterns leading to higher adherence in almost all studies where dosing pattern was examined (10, 16, 37, 59, 60, 90). Patient race is sometimes looked at as a predictive measure of adherence, and recently two studies released in 2008 by Adams et al and Dickson and Plauschinat have found that African-Americans appear to be slightly less adherent than Caucasians (6% less in both studies) (38, 91). Two other studies found that African-American patients were 4% and 8% less adherent to their prescription medications compared to Caucasian patients, however the proportion of African-American's in one the samples was 8%(39, 45). This may indicate that any perceived differences in adherence may be due to other factors (socioeconomic, demographic, etc.), and needs to be explored further. Recently, Lanouette and colleagues in a meta-analysis of the literature found that both Latino's and African-American's had consistently lower adherence than Euro-Americans, but found strong indications of socioeconomic status as a confounding factor (92). The current CMAP population affords an opportunity to examine this issue of socioeconomic status because of the racial diversity among the population under study, coupled with the relatively small variation in socioeconomic status (all participants in the CMAP are considered the "working poor" and have similar family/household incomes).

Other than dosing pattern and race, few variables have shown to be consistently predictive of adherence. Older age is often linked to better adherence, as evidenced by a variety

of studies conducted in populations of varying age. Schectman et al (2002) (58) found that increasing age correlated to better adherence in an indigent rural population taking chronic care medications, as did a study in over 8000 enrollees in a managed care plan (59), a study in a sample of 6090 newly treated working-aged adults who had employee-sponsored health insurance (47), an analysis of pharmacy data from over 40,000 veterans in the Veterans Administration (39), a meta-analysis of correlates of diabetes' patients' compliance with their prescribed medications (46), in a study of antidepressant use among patients in Iowa Medicaid Pharmaceutical Case Management program (93), and in a recent comparison of 706,032 patients with seven common chronic health conditions (54). However, other studies have found no effect of age on adherence, including studies of pharmacy records of HMO patients (16), a study of oral and inhaled asthma medications in a medical population (94), as well as in a study of community-dwelling older adults (60). Gender too has been found to be predictive of adherence in some studies, with female gender relating to lower adherence in some studies (16, 47, 59), while others found no gender differences existed (46, 54, 58, 60, 93, 95). So many of these observed differences may be attributed to a variety of factors, one of which is the study population being examined (8), and has led at least one researcher to argue that little or no demographic differences truly exist in adherence (10).

Often different studies produce patient and clinical characteristics as predictors of adherence with no consistent direction as to their relationship with adherence. The number of medications being taken has a contradictory affect on adherence depending on which study is being examined. Some studies find that as the total number of medications increases, so does adherence (39, 96). Other studies have found, however. that the fewer concomitant medications the patient was taking, the greater the adherence (59). Further adding to the confusion is the data

from Grant et al which found that adherence was unaffected by the number of medications diabetic patients were taking (97). This inconsistency in findings calls for continuing research to be conducted on the predictors of adherence in different populations.

Impact of Adherence on Outcomes

In a study of 653 patients being treated for dyslipidemia in a managed care diabetes program, Parris et al (2005) found a significant correlation (− 0.393, P <0.001).with medication possession ratio and plasma LDL cholesterol (53). Individuals with significantly higher MPRs were more likely to have achieved their LDL cholesterol target than those with lower MPRs. The authors found that those patients with MPRs greater than 80% were most successful at achieving their cholesterol goal. Similarly, researchers examined the relationship between adherence and diabetes metabolic control in a rural low-income population in rural Virginia. Schectman et al (2002) looked at the effect of adherence to oral diabetes medication on Hemoglobin A_{1c} (HBA_{1c}) levels in 810 diabetic patients. They found that with each 10% increase in drug adherence (as assessed through MPR), there was a statistically significant decrease of 0.16% in HBA_{1c} level (45). Some research has even shown that adherent patients had lower all-cause mortality than nonadherent patients, as was the case in a study of mortality among patients with diabetes and ischemic heart disease (OR 0.52; 95% CI 0.39–0.69) (98). In a review by Munger, Van Tassell and Lafluer (2007), the authors found such compelling evidence of the association of adherence with positive cardiovascular outcomes that they suggested "patient nonadherence is a universal significant risk factor for cardiovascular disease (99)." In a 2009 study, researchers found that HIV-positive patients who were non--adherent were 1.48 (CI: 1.02–2.14) times as likely to go on to treatment failure (defined as death or progression to AIDS)

(100). These examples of the association between mortality and adherence further underscore the utility of examining adherence as a risk factor for the severity of chronic conditions.

More often, research on the outcomes of medication adherence focus on the decrease or reduction in overall health care utilization and costs. Sokol and colleagues (2005) evaluated the impact of medication adherence on healthcare utilization and cost for individuals with four of the most common chronic conditions: hypertension, dyslipidemia, diabetes, and congestive heart failure (101). They examined disease-specific claims for outpatient, emergency department, or inpatient services for 137,277 patients enrolled in a medical and prescription benefit plan. The authors found that overall costs and disease-related medical costs were significantly lower for patients with a high level of adherence. They also found that patients with high medication adherence had hospitalization rates that were significantly lower. In a much smaller study of indigent rural patients being provided medical care and prescription drugs at no cost, the authors examined if adherence would be associated with overall reduction in health care charges and utilization. They found that patients were highly adherent to their medications and experienced 39.5% reductions in inpatient admissions, 64.4% reductions in outpatient visits, and led to lower overall medical costs compared to a control group (102). Hepke, Martus, & Share (2004) looked to determine whether adherence with pharmaceutical therapy affected health care utilization among 57,687 patients of a large Health Maintenance Organization (HMO) with diabetes (44). They reported that patients in the upper level of medication adherence (≥80%) were 0.88 times less likely to have an emergency department visit than those in the lower adherence groups. Finally, when evaluating medication adherence and health outcomes in a small sample of patients enrolled in a subsidized prescription program, Spiker et al (2005) observed that adherent

patients had fewer unscheduled visits to their primary care physician, another health facility, an emergency department, or hospital admissions compared to nonadherent patients (103).

Some studies have focused on the disease-specific cost-savings associated with high medication adherence. Looking at costs for patients taking antidepressant drug therapy, Katon et al (2005) found that among the 8040 patients of a managed care database those patients that were the most adherent had 14-17% lower disease-specific charges and 6.4-19.8% lower total medical charges (62). In 2004, Lau & Nau analyzed administrative claims data from 9000 enrollees in a managed care organization in Michigan (43). Defining non-adherence as an MPR <80%, the authors looked at the association between non-adherence and risk of hospitalization and found that enrollees who were non-adherent had a 2.53 (CI 1.38–4.64) times higher risk of hospitalization than those enrollees that were adherent. Also, while examining costs associated with non-adherence to first-line therapy for ulcerative colitis, Kane and Shaya (2008) examined pharmacy records of 4313 patients enrolled in a managed care program (104). They used the MPR to determine adherence, and found a two-fold difference in gastroenterology-related inpatient costs in non-adherent versus adherent patients. Non-adherent patients also incurred significantly higher costs for office visits and outpatient services. A study of over 13,000 transplant patients found that those in the highest third of adherence rates had lower risk of graft loss and lower overall medical costs compared to those in the lowest two-thirds of adherence rates (105).

For individuals on psychotropic medications, the benefit of medication adherence is striking. Valenstein and colleagues (2002) studied the risk of inpatient admission among 67,079 veterans with schizophrenia in the Veterans Administration National Psychosis Registry (64). Looking at the association of MPRs with admissions, they found that patients with MPRs near

100% had the lowest rates of admission. As MPRs decreased, rates of admissions increased, with those veteran having MPRs less than 80% being 2.4 times as likely to have a psychiatric admission than those with 80% or greater. The authors also found that those patients with lower MPRs had more hospital days once admitted. In 2009, Hassan and Lange studied the relationship between non-adherence to antipsychotic medication after hospital discharge and risk of re-hospitalization in patients who were previously hospitalized for treatment of bipolar disorder. The authors found that those patients who were adherent (adherence $\geq$ 75%) had lower risks of both all-cause and psychiatric re-hospitalizations (106).

Conversely, the savings associated with high medication adherence can also be evidenced by the increase in costs related to low medication adherence. Yee et al (2005), while examining adverse drug events and their effect on healthcare utilization among older veterans, found that 19% of drug-related emergency department visits were due to medication non-adherence (107). Medication adherence and its association with ED visits were also studied among 61 participants in a usual care group of an ongoing clinical trial of chronic heart failure (48). The researchers found that, after adjusting for demographic variables, lower medication adherence was associated with increased number of cardiovascular-related ED visits. Similar results were found in a study of cardiovascular patients taking statins in Canada, with lower adherence rates equating to increased hospitalizations and increased hospitalization costs, and in a study of individuals post acute myocardial infarction in the northeastern Unites States (13, 108). A review of published clinical trials on medication adherence and outcomes for individuals treated for ulcerative colitis showed that both increased costs and increased rates of symptomatic relapse were associated with lower medication adherence (109). Finally, overall costs for non-adherent

diabetes patients were found to be greater than for adherent diabetes patients in the latest review of the literature on the relationship of non-adherence and costs in patients with diabetes (110).

IV. RESEARCH QUESTIONS

1. To examine whether a new measure of self-reported medication adherence developed for an evaluation of a community medication access program compares to two existing methods of calculating medication adherence via pharmacy records (MPR and CSA). Pharmacists performing program-related medication reviews administered the new measure (a series of basic questions) as part of their interview with program participants, and this new measure will be assessed for its correlation and agreement with the electronic pharmacy records calculations of MPR and CSA.
2. To examine what baseline demographic and health characteristics of a rural indigent population enrolled in a medication access program predict medication adherence (calculated using the three methods in "1" above).
3. To examine whether medication adherence (calculated using the three methods in "1" above) can predict utilization of the Emergency Department (ED) or hospitalization while controlling for patient factors. Emergency department and hospital admissions in the first 6-months post-enrollment in the medication access program will be compared between those patients that were adherent to their medications ($\geq$ 80%) and those that were non-adherent to their medications (<80%), using the 6-month period prior to enrolling in the program as baseline.

V. METHODS AND MATERIALS

Setting and Population

All data has been collected as part of the evaluation of the Cenla Medication Access Program (CMAP). The CMAP is a project of The Rapides Foundation, a not-for-profit private hospital conversion foundation located in Alexandria, Louisiana. The goal of the foundation is to provide assistance to the surrounding community in the form of programs that will positively affect the community health and well-being. In early 2000, the Foundation conducted a needs assessment to determine the greatest needs of the surrounding community in order to place funding into a program to help address these needs. The largest issue revealed by the needs assessment was the need for prescription assistance to individuals living in the area who had little or no prescription coverage. Those individuals who had jobs, but did not qualify for Medicaid and who had no prescription coverage, as well as the elderly who had Medicare but no prescription coverage, were targeted as those most in need of assistance. In 2001 the Foundation initiated the CMAP in order to provide medications at little or no cost to those needing assistance. The CMAP initiative was launched in two components; the first component centered at the local state-funded hospital and began in May 2001, while the second component began in September 2001 and focused on individuals in the surrounding community who did not access the state-funded hospital. The program has been previously described in detail, and can be found in a previously published paper by Harmon et al (111). This study focuses on the second component, which will be referred to as the Card Component from here on, which provided a prescription benefits card to individuals who met the following inclusion criteria:

No private insurance that covered prescription medications:

- Income less than 200% of the Unites States Poverty Guidelines, more for larger families, and could prove this information with a pay-stub or tax filing;

  Accessed their care through private physicians and did not use the local state medical center as their primary source of medical care;

  Diagnosed with a chronic condition for which regular medication was necessary; and

  Required Medication that was on the formulary created for the Card Component.

Individuals who met the inclusion criteria were recruited into the CMAP through their private physicians and public advertising. Potential participants were required to take part in an interview with a CMAP staff member at pre-determined sites throughout the central Louisiana area. Patients were interviewed at sites located in Allen, Avoyelles, LaSalle, Natchitoches, Rapides, Vernon and Winn parishes. Information was collected during the interview on income, demographics, sources of care, and health indicators. All participants were required to sign IRB approved consent forms. Participants were also asked to list from which hospitals they accessed their emergent or long-term care, and to provide HIPAA-compliant consent for CMAP to contact these hospitals in order to collect information on hospital admissions and emergency department visits. Participants then received a prescription benefits card that entitled them to up to three medications per month at a co-pay of $8. The card could be used at any pharmacy in the central Louisiana area.

The Card Component of the CMAP ended on December 31, 2005, therefore providing a complete dataset for analysis. The sources of data are outlined below.

Table 1: Select Characteristics of Individuals Enrolled in the Central Louisiana Medication Access Program Card Component (N=3448)

Variable		
Age at Initial Interview		
mean (SD)	59.15 (17.28)	
median	59.72	
Age Group at Initial Interview	**n**	**%**
18-29	173	(5.02)
30-39	325	(9.43)
40-49	607	(17.60)
50-59	639	(18.53)
60-69	650	(18.85)
≥ 70	1054	(30.57)
Gender	**n**	**%**
Females	2391	(69.34)
Males	1057	(30.66)
Race/ethnicity	**n**	**%**
African-American	1127	(32.69)
White	2268	(65.78)
Other	52	(1.51)
Unknown	1	(0.02)
Marital Status	**n**	**%**
Married	1072	(31.09)
Single	538	(15.60)
Divorced	588	(17.05)
Separated	228	(6.61)
Widowed	1022	(29.64)
Other	0	(0.00)
Unknown	0	(0.00)
Education Level	**n**	**%**
8th Grade or Less	880	(25.52)
9th Grade	251	(7.28)
10th Grade	334	(9.69)
11th Grade	351	(10.18)
12th Grade/GED	1250	(36.25)
College or More	380	(11.02)
Unknown	2	(0.06)

Table 1 CONTINUED: Select Characteristics of Individuals Enrolled in the Central Louisiana Medication Access Program Card Component (N=3448)

Monthly Income		
mean (SD)	$613.41 (349.92)	
median	$646.00	
Primary Diagnosis		
HTN[1]	1562	(45.30)
DM[2]	457	(13.25)
Heart Disease	428	(12.41)
Depression	149	(4.32)
Asthma/	123	(3.57)
Respiratory		
Arthritis	118	(3.42)
Other	571	(16.56)
None Given	40	(1.16)
Work Status	n	%
Employed	397	(11.51)
Unemployed	699	(20.27)
Retired	1176	(34.11)
Disability	930	(26.97)
Other	220[3]	(6.38)
Unknown	26	(0.75)

[1] HTN = Hypertension
[2] DM = Diabetes Mellitus
[3] These people are listed as "never worked"

Sources of Data

Patient Information

The CMAP staff member collected several demographic variables on all participants when conducting the initial interview. In addition to collecting information on income to determine eligibility, the following data were collected: Patient Name, Social Security Number (to be used as the participant unique identifier), Date of Birth, Gender (male, female), Race (Caucasian, African-American, Other), Marital Status (Married, Single, Divorced Separated, Widowed), Educational Level (1 through 17+), Work Status (full-time, part-time, retired, disability, never worked), Primary Physician, Current Medications (both Over the Counter, and Prescription).

In addition, several self-reported health indicators were collected on all participants; Current health status (rated on a five point Likert scale), Health status compared to one year ago (rated on a five point Likert scale), Number of emergency department admission in the previous six months, Number of hospitalizations in the previous six months, General mood (five point depression scale), Brief memory test (day of the week, current president, year, current location), Number of missed prescription refills in the previous six months.

Pharmacist Medication Reviews

A significant part of the CMAP program was the opportunity for CARD participants to meet with a licensed pharmacist to review their current medications. These medication reviews were performed to help patients understand and use their medications in the safest, most effective manner. The pharmacist spent over 33 minutes, on average, meeting one-on-one with the CMAP participant, reviewing each of their prescription medications (23). The pharmacist

spent the time questioning the patient as to what each medication is used for to make sure that they understand the purpose of each medication. The pharmacist also asked about the proper dosing of each medication, making sure that the patient knows when, how often, and with what each medicine is taken. The pharmacists also asked, one medication at-a-time, if they always took each medication as prescribed. This information was used to determine the level of medication adherence for each patient by looking at their medication taking behavior.

Pharmacists encouraged patients to utilize only one pharmacy if possible to keep a complete medication profile in one system and to form a relationship with their pharmacist. They provided pill boxes, glucometers (as needed), written and oral education, as well as corresponded with patients' physician and regular/local pharmacist to inform them that their patient is on the program, to encourage assistance from them, and to notify them of any interactions or other pertinent information collected during the medication review.

The program pharmacists also utilized the pharmacy benefits manager to review prescription fill history three months after the patient initially applied to make sure they are maximizing the benefits available, as well as to check adherence. Whenever possible, one-on-one contact with local pharmacists and physicians was made to educate them about the program and to encourage referrals

A part of the pharmacy interview is for the pharmacists to complete an Assessment of Medication Review. This assessment is a way of keeping track of patient's reviews, and to ensure that the reviews are being performed thoroughly. The Assessment of Medication Review was created by the CMAP pharmacists in collaboration with the project evaluators. This Assessment was created as a way of keeping a formal record of all contacts between the

pharmacists and program participants, and as a way of tracking patient outcomes over time. The five major outcomes tracked via this Assessment were:

1. Proportion of Medications the Patient Understands the Purpose Of =

$$\frac{Total\ \#\ of\ Drugs\ Patient\ Understands\ the\ Purpose\ Of}{Total\ \#\ of\ Drugs\ Patient\ is\ Taking}$$

   This question asks if the patient understands why they are taking each medication.

2. Proportion of Medications the Patient Understands the Proper Use Of =

$$\frac{Total\ \#\ of\ Drugs\ Patient\ Understands\ the\ Proper\ Use\ Of}{Total\ \#\ of\ Drugs\ Patient\ is\ Taking}$$

   This question asks if the patient knows the correct dosing of each of their medications.

3. Proportion of Medications the Patient is Compliant/Adherent With =

$$\frac{Total\ \#\ of\ Drugs\ Patient\ Is\ Compliant\ With}{Total\ \#\ of\ Drugs\ Patient\ is\ Taking}$$

   This question asks if the patient always takes each of their medications.

4. Drug-Drug or Drug-Disease Interactions – This question asks whether the patient has experienced any drug-drug or drug-disease interactions. It is a yes/no question.

5. Adverse Drug Events/Experiences – This question asks whether the patients have experienced any adverse drug events. It is a yes/no question.

Note that the term "Compliance" was used rather than adherence on the assessment form, but it was meant to have the same definition. For the purposes of this study, number 3 above will be used to compare self-reported adherence with two validated measures of adherence based on electronic pharmacy records.

Prescription Medication Information

All prescription medication data were tracked via a pharmacy benefits manager. Every time a participant used their prescription medication card, the data were sent electronically to an online pharmacy benefits manager. The data were stored in their system, and regular reports

were provided to the CMAP staff and CMAP evaluation staff. Each time the prescription card was used the following information were collected; Patient Identification Number (Social Security Number), Patient Name, Physician Name, Drug Name, Drug NDC Code, Drug Dose, Drug Strength, Days Supply Dispensed, Date Drug Dispensed, Quantity Dispensed, Retail Cost of Medication, Processing Fee, and Pharmacy Name.

Emergency Department Use and Hospitalizations

In addition to the self-reported number of emergency department and hospitalizations, independent verification of this information was collected. As a part of the initial interview, as well as all subsequent bi-annual interviews, all participants were asked to provide the name of any and all hospitals that they has assessed for care (either emergent care or long-term care) in the previous six months. Participants were then asked to sign a HIPAA-approved consent form for each hospital reported, allowing the CMAP evaluators to contact the hospitals in order to gain access to the participants medical records of emergency care visits and hospitalizations. The CMAP evaluators contacted the hospitals, who were asked to provide the following information; type of service provided (inpatient or emergent care), date of service/admission, patient condition code (International Classification of Disease Version 9 – ICD-9), patient admission code (ICD-9), and date of discharge.

Research Question 1: Is there agreement between a self-reported measure of medication adherence assessed during an intensive interview with a licensed pharmacist and calculated medication adherence via two widely used methods of calculation – the medication possession ratio (MPR) and the measure of continuous single-interval medication availability (CSA)?

Description of Adherence Measures

Adherence to prescribed medications can be calculated in numerous ways when using pharmacy claims data. There are many methods that are used to help control for some of the problems encountered with pharmacy claims data, and these methods have been explained previously in detail (71). For the purposes of this study, the author will focus on two particular methods that are found in the literature; the medication possession ratio (MPR), and the continuous single-interval medication availability (CSA), both of which will be assessed for agreement with a self-reported measure of adherence that was created for the Cenla Medication Access Program (which will be referred to as "Adherence Self-Report" in this paper).

Adherence Calculations

Medication Possession Ration (MPR)

MPR can be defined as:

$$\frac{\Sigma \text{ \# of days of therapy dispensed on all but the last prescription interval}}{\text{\# of days in the treatment interval}}$$

The result of the calculation above is a ratio expressed as a decimal. In order to make it more interpretable, the result of the MPR is often multiplied by 100, and the resulting measure is sometimes referred to as MPR% or Medication Refill Adherence (MRA).

The above formula is a function of both how much medication is prescribed and the amount of time an individual takes to refill the prescription. An example of how MPR is calculated is given below:

Sample Data - MPR

Prescription Name	Date of Original Fill	Days Supply Dispensed	Date of Refill	Days To Refill
X	1/1/2005	30	1/31/2005	30
Y	1/1/2005	30	2/10/2005	40
Z	1/1/2005	30	3/3/2005	60

Adherence for Prescription X:

MPR %: 30/30 = 1.0 x 100 = 100%

Adherence for Prescription Y:

MPR %: 30/40 = 0.75 x100 = 75%

Adherence for Prescription Z:

MPR %: 30/60 = 0.50 x100 = 50%

Mean MPR: (100% + 75% + 50%)/3 = 75%

Continuous Single-interval Medication Availability (CSA)

CSA can be defined in very similar manner to MPR, except in CSA each refill interval is calculated separately. For example, if the above data were presented a little differently, and were presented as three distinct refill episodes for the same medications:

Sample Data - CSA

Prescription Name	Date of Fill/Refill	Days Supply Dispensed	Date of Refill	Days To Refill
X	1/1/2005	30	1/31/2005	30
X	1/31/2005	30	3/12/2005	40
X	3/12/2005	30	5/11/2005	60

Adherence for Prescription X:

CSA: 30/30 = 1.0 x 100 = 100%

CSA: 30/40 = 0.75 x100 = 75%

CSA: 30/60 = 0.50 x100 = 50%

Mean CSA: (100% + 75% + 50%) / 3 = 75%

Benefits and Limitations of using MPR and CSA

MPR and CSA are preferred over other methods for several reasons:

- The formulas can be adjusted to vary the length of time for which adherence is calculated;
- They are sensitive to the amount of time an individual takes to refill a prescription;
- The calculation allows for classes of medication to be looked at to determine adherence. Therefore, if an individual takes several different medications for the same condition, adherence can be provided for that specific condition; and
- They can be calculated by drug, or by individual.

There are several limitations to using MPR, CSA, and other similar methods to calculate adherence:

- The formulas exclude the last refill for all medications. The last refill must be excluded because it is impossible to determine the number of days in the treatment interval if there

is no date of prescription refill. Therefore individuals who only fill a medication once will not have an adherence measure for that medication;

- If no information is available on samples given to the patient by the doctor, it may appear that a patient isn't refilling their prescriptions on time. (this, however, is a caveat all for measures of prescription adherence that use pharmacy claims data);
- There is an opportunity for gaps in prescription refills to bias adherence towards an individual being non-adherent. Gaps in prescription refills can occur for various reasons:
    - Patient decides not to take the drug for a while (drug holiday);
    - Patient uses the medication other than how it is prescribed (taking only once daily when it is prescribed for twice daily);
    - Physician writes the prescription so that the patient can get a larger dose refilled but instructions don't change. For example, if a medication comes in a 100 mg tablet, the physician can write the prescription for the patient to take two 100 mg tablets per day, but the patient's dose is only 100 mg per day. Therefore a 30-day supply as written, will actually last 60 days; and
    - Patients may be taken off a certain drug and given a similar drug in the same class that treats the same condition. If the new drug is not tolerated well by the patient, the physician may switch back to the original drug. This situation could cause a gap if only individual drugs are tracked, not classes of drugs. It would appear as though the patient may have skipped several months of refills, when, in fact, they may only have been taking a different medication.

Several of the limitation listed above cannot be controlled for, as they are limitations in using pharmacy claims data to determine medication adherence. However, where possible, an attempt has been made to minimize the influence of these limitations, most specifically by taking into account gaps in medication taking through use of the CSA formula.

Adherence Self-Report

Self-reported adherence is calculated by using the results of the medication interview between the pharmacist and patient (See Appendix). The pharmacist, as part of the review asked the patient to bring all of their prescription medications with them for the interview. The pharmacist then asked the patient if they took each of the medications as prescribed all or most of the time. The pharmacist would record the answer for each medication and the results would be expressed as a percentage.

The following tables is an example of how Adherence Self-Report is calculated:

Medication Name	**Does Patient Take Medication as Prescribed All or Most of the Time?**
X	Yes
Y	No
Z	Yes

Total # of Medications: 3

Number Takes as Prescribed: 2

Adherence Self-Report: 2/3 x100 = 66.7%

Calculation of Adherence Measures

An analysis of CMAP data will begin by calculating the two main measures (MPR and CSA) for each participant. The MPR will first be calculated by prescription (or drug class in the cases where individuals switched medications within the same class), and then averaged together to calculate an overall MPR per participant. This is the most common method for calculating MPR, and the utility of it has been described elsewhere (31). CSA is generally calculated for each interval where one-month of medication has been dispensed, and then is averaged over all of the intervals to calculate an overall CSA per drug. The CSA's are then averaged together to calculate the overall CSA per participant. The interval used to calculate the MPR will be the length of the prescription. It will be calculated by using the formula from the date of first fill to the last date of refill for any prescription. This will serve as an "overall adherence" for each prescription medication, and will also serve as a basis of comparison for the Adherence Self-Report measure.

As medication adherence is a measure of not just any one medication, but a measure of an individual's overall medication taking behavior, the MPR and CSA for each medication (or class of medications) will be calculated separately for each individual and then averaged together. Generally, the overall MPR and CSA are based on the adherence per medication, where each medication contributes equally to the overall average calculated adherence. However, as participants in this study often take multiple medications for varying lengths of time, it would be unfair to calculate an overall adherence measure per participant without taking into account how many times each medication was refilled. For example, an individual who is highly adherent to one medication with 10 refills for example, shouldn't have their overall adherence biased downward based on another medication with low adherence that may have

only 3 refills. Therefore the overall MPR and CSA per participant will be calculated by using weights. Each medication will be weighted by the number of days of therapy dispensed. See below for an example of how weighting will be used:

CSA for Client A:

Drug	Unweighted CSA	Days Dispensed
X	0.935	90
Y	0.885	90
Z	0.415	30
Total	**0.745**	**210**

To calculate the weighted CSA for Client A, we would first multiply each of the drug's unweighted CSA's with the total number of days dispensed for that drug:

Drug X: 0.935 x 90 = 84.15
Drug Y: 0.885 x 90 = 79.65
Drug Z: 0.415 x 30 = 12.45

Then:

Weighted CSA = (84.15 + 79.65 + 12.45)/210 = 0.840.

Therefore, the weighting process has reduced the amount of influence the low adherence for Drug Z had on the Client A's total adherence. This is appropriate as only 30 of the total 210 days of therapy received were for Drug Z. This process of calculating weights will be repeated with MPR. Weighting makes no judgment as to the importance of each medication. Therefore if an individual is highly adherent to an arthritis medication and less adherent to a diabetes medication, although one could argue that the diabetes medication is more important in terms of adherence, the overall MPR and CSA will not take this into account. Individuals that have one-month or fewer prescription data (due to drop-out of the program or censure due to the end of the CMAP program) will not be included in the analysis.

The procedure in Microsoft Access to calculate CSA's and MPR's will be as follows:

- First the dataset of prescriptions received by CMAP clients will be cleaned to remove any missing or repeated data, as well as to remove any CMAP clients who have only one refill;

- The data will be separated by CMAP participant and their medications received. Each individual prescription is coded with an Rx number to identify the original refill of the prescription and the same number is used for each refill;

- The intervals will then be defined for each prescription as follows:

    - For each prescription, Access will be used calculate the number of days from the date of first refill to the date of the next refill using queries. This will be considered a one-month interval, because it is the time it takes to refill one month's worth of medication;

    - The number of days of medication dispensed in the first prescription is stored in the database and will used as the numerator to calculate the CSA for the monthly interval;

    - The monthly CSA will be calculated using an Access query which will specify that the days of therapy dispensed should be divided by the number of days in the monthly interval. This ratio will then be multiplied by 100 to calculate the CSA % for that medication for that month;

    - This method will then be repeated for each prescription from the date of the second fill (first refill) to the date of the third fill (second refill) in order to calculate the CSA for each month for each medication:

- Once monthly medication adherence has been calculated for all prescriptions, the data will be separated by client based on unique client identifiers embedded within the data;

- For each client, CSA's for each prescription will be averaged monthly to calculate the CSA for each medication;

- The overall CSA for each medication will be assigned a weight based on the number of days the medication was dispensed; and

- The overall CSA per patient will be calculated by averaging the weighted CSA's for each medication in order to calculate an overall CSA per patient based on monthly intervals. This will be referred to as the CSA one-month.

- The overall MPR will be calculated per medication by taking the total number of days of therapy dispensed and dividing it by the total number of days in the interval from the first fill to the final refill;

- The overall MPR for each medication will be assigned a weight based on the number of days the medication was dispensed; and

- The overall MPR per participant will be calculated by averaging together the weighted medication MPR's.

The procedure in Microsoft Access to calculate Adherence Self-Report will be as follows:

- As each participant will have one or more medication reviews, each medication review will be taken separately;

- Data for all medication reviews are stored in an MS Access database by client ID and date of medication review;

- The number of medications the participant is adherent with (via self-report) will be divided by the total number of prescription medications the participant is taking. This will be the Adherence Self-Report measure for that medication interview;

- The overall Adherence Self-Report will be the mean of all the Adherence Self-Report measures from each of the medication interviews (if the participant has more than one medication interview); and

- Much like the MPR and CSA, a weight will be assigned to each individual Adherence Self-Report measure to adjust for the number of medications the participant is receiving at each review. This will help take into account the number of medications that contribute to each Adherence Self-Report measure.

Example of how CSA will differ from MPR

In order to illustrate how the overall CSA will from MPR, two examples are provided The first example shows the case of one large gap in refills for a client that has fairly equal refill lengths for the remaining fills, while the second example shows the difference in overall CSA if the client has varying lengths of time to refill.

Example 1

Client A, Drug X:

Days Dispensed	30	30	30	30	30	30
Time to Refill	32	32	72	33	36	35

Overall MPR = (30+30+30+30+30+30) / (32+32+72+33+36+35) = 180/240 = 0.75 x 100 = 75.0%

Single Interval CSA:

Days Dispensed	Days to Refill	Interval CSA
30	32	0.9375
30	32	0.9375
30	72	0.416667
30	33	0.909091
30	36	0.833333
30	35	0.857143
Overall CSA		0.815206

Overall CSA = .815206 x 100 = 81.5%

Therefore Client A would be considered non-adherent based on the "80% rule" of adherence (75.0%) if only overall MPR were calculated, whereas if monthly CSA's are averaged together to calculate the overall CSA, the client would be considered adherent (81.5%).

This elucidates how varying the interval in which overall adherence is calculated can and will change the overall adherence measure for an individual. In the above example, the reason for the large difference in overall and monthly CMA is due to the one large gap in refills in the middle of the collected data (after refill 3). However, even without such a single large gap in refills, the CSA can differ from the MPR. See Example 2 below:

Example 2

Client A, Drug X:

Days Dispensed	30	30	30	30	30	30
Time to Refill	42 |	32 |	45 |	25 |	44 |	39 |

Overall MPR = (30+30+30+30+30+30) / (42+32+45+25+44+39) = 180/227 = 0.7930 x 100 = 79.3%

Single Interval CSA:

Days Dispensed	Days to Refill	Interval CSA
30	42	0.714286

30	32	0.9375
30	45	0.666667
30	25	1.2
30	44	0.681818
30	39	0.769231
Overall CSA		0.82825

Overall CSA = .82825 x 100 = 82.8%

So in Example 2, even without any large obvious gap in time to refill, the adherence measure would vary enough to change the determination as to whether or not an individual was adherent to their medications (although one could argue that 79.3% would approximate 80% for some analyses, this is only an example to illustrate how varying the interval for calculation will affect the overall measure).

Cut-Points of Adherent/Non-Adherent

Each of the continuous calculated adherence measures will dichotomized in order to classify CMAP patients as "adherent" and "non-adherent." Traditionally, the "80% rule" is used as the cut-point to make this adherence determination, and will be the main focus of analysis here. However, in order to determine if 80% is the optimal cut-point, additional cut-points above and below 80% will be used; 70%, 75%, 85%, 90%. Varying the cut-point has been done previously by Wetzel and colleagues, who argued that it was necessary since the true level of optimal compliance is unknown and varies by population (32). Further justification for dichotomizing the continuous adherence measures will be presented through normality diagnostics of the continuous measures using graphing techniques (histograms, Stem & Leaf, P-P, Q-Q, and Boxplot) and Kolmogrov-Smirnoff and Shapiro-Wilk tests.

Analysis Questions

Once overall adherence has been calculated for each individual based on the three methods (MPR, CSA, Adherence Self-Report), a comparison will be made between MPR and Adherence Self-Report and CSA and Adherence Self-Report. There will be two main questions being asked while making these comparisons:

1. Is there a significant difference in the proportions of participants that are characterized as non-adherent and adherent based on the 3 calculations of adherence? To calculate whether a significant number of clients switched adherence groups, McNemar's Test for Binomial Proportions for Matched-Pair Data will be used (112). This will be performed by comparing the proportions of patients who are adherent between MPR and Adherence Self-Report and CSA and Adherence Self-Report.

2. Is there agreement between the MPR and Adherence Self-Report and/or CSA and Adherence Self-Report? In order to determine whether the self-reported measure can estimate calculated adherence based on pharmacy records, we will need to look for agreement in the overall methods. Although it could be argued that measures of correlation (the correlation coefficient or "*r*") would alone be appropriate to determine if each of the measures based on pharmacy data would be correlated with the self-reported measure, we want to know not only the strength of the relation between the different measures, but also the agreement between them as well.

Test of Proportions: McNemar's Test

McNemar's Test for Binomial Proportions for Matched-Pair Data is a test of differences between treatments, or in this case, adherence measures. In this analysis we are only interested in discordant pairs, rather than concordant pairs because we are looking to see if there is a

difference in overall adherence based on the adherence measures. The normal-theory test will be used to test for significant differences in adherence proportions as the sum of the discordant pairs in all comparisons is greater than 20. The table below is an example of how the data is organized for McNemar's Test comparing MPR to Adherence Self-Report:

Data are placed in a 2 x 2 table of matched pairs:

		MPR	
		<80%	≥80%
Adherence Self-Report	<80%	a	b
	≥80%	c	d

Where:

a, d = concordant pairs (not of interest in this analysis)

c = discordant pair where the "Adherence Self-Report" member is adherent and the "MPR" member is not

b = discordant pair where the "MPR" is adherent and the "Adherence Self-Report" is not

In order to test whether there is a significance difference we will use the Normal-Theory Test (preliminary data analyses indicate that the number of discordant pairs will be greater than or equal to 20):

Hypothesis:

$H_o: p = \frac{1}{2}$ vs. $H_a: p \neq \frac{1}{2}$

Test Statistic:

$$X^2 = \frac{(|n_A - n_B| - 1)^2}{(n_A + n_B)}$$

Decision:

If $X^2 > X^2_{1,1-\alpha}$ then reject H_o

This test will be repeated to look for differences in proportions between CSA and Adherence Self-Report. Depending on the outcomes of the tests, we will be able to determine if the proportions of individuals who are non-adherent and adherent differ by the method used to calculate adherence. The test will be repeated at each of the four additional cut-points of adherence to look for changes in the magnitude and significance of the relationships.

Correlation and Agreement

Although McNemar's Test in the preceding section will help to show whether there is a difference in the proportion of CMAP participants that are considered adherent based on the different adherence measures, it becomes important to discuss whether the each of the two pharmacy data methods agree with Adherence Self-Report. First, it is important to investigate whether there is a relationship between each of the pharmacy adherence methods and Adherence Self-Report using the sample (Spearman's) correlation coefficient (r_s). We want to know if MPR and CSA are linearly correlated with Adherence Self-Report. First, we will plot the mean adherence produced by each method of calculation and visually look for correlation between self-report and each of the calculated measures, and then calculate r between each of the measures, testing the hypothesis that each of the calculated measures is not correlated with the self-reported measure.

Calculating Spearman's Correlation Coefficient (r_s)

In a series of n measurements of X and Y written as x_i and y_i where $i = 1, 2, ..., n$, then the Pearson product-moment correlation coefficient can be used to estimate the correlation of X and

Y. However, a requirement of using Pearson's Correlation Coefficient is that both X and Y must be normally distributed, which can not be the case with the measures of adherence. Therefore the nonparametric analogue, Spearman's Rank Correlation, will be used. This can be calculated by:

$$r_s = \frac{L_{xy}}{\sqrt{L_{xx} \times L_{yy}}}$$

Where:

X = MPR (or CSA)

Y = Adherence Self-Report

L_{xx} = ranks of MPR (or CSA)

L_{yy} = ranks of Adherence Self-Report

In order to test the hypothesis that MPR or CSA is not correlated with Adherence Self-Report we would use the following procedure (112):

Hypothesis:
$H_o: \rho = 0$ vs. $H_1: \rho \neq 0$
Test Statistic:

$$t_s = r_s \frac{\sqrt{n-2}}{\sqrt{1-r_s^2}}$$

Decision:

If $t > t_{n-2,1-\frac{\alpha}{2}}$ or $t < -t_{n-2,1-\frac{\alpha}{2}}$ then reject H_o

Rejecting H_o reveals that the self-reported measure is found to be linearly correlated with one of the calculated measures, however this does not determine the magnitude of the correlation

between the measures. Unfortunately, there are not set "cut-offs" to determine a strong correlation and a weak correlation, but it is accepted that the closer a value is to 0, the worse the correlation (113). The use of the correlation coefficient has several limitations, including: 1) correlation only measures the strength of the relationship between two variables, not the agreement between them; and 2) if the range of true quantity of the data is wide, the correlation will be greater than more narrow ranges (in the current samples, the range of adherence is wide); and 3) the test of significance only shows that two methods are related, but does not make any conclusions as to the level of agreement between the measures (114). Therefore beyond hypothesis testing to decide whether or not the self-reported measure is linearly correlated with one of the other two measures, it is reasonable to then explore the level of agreement. Therefore the Kappa statistic will be used to quantify the degree of association between Adherence Self-Report and both MPR and CSA. Kappa is particularly useful as it serves to provide a quantifiable measure of reproducibility between the adherence measures comparing the observed concordance rate (p_o) with the expected concordance rate (p_e) The Kappa statistic will be calculated by:

$$\kappa = \frac{p_o - p_e}{1 \quad p_e}$$

$$se(\kappa) = \sqrt{\frac{1}{n(1-p_e)^2} x \left\{ p_e + p_e^2 - \sum_{i=1}^{c} \left[a_i b_i (a_i + b_i) \right] \right\}}$$

And hypothesis testing will be performed:

H_o: $\kappa = 0$ vs. H_1: $\kappa > 0$

Test Statistic:

$$z = \frac{\kappa_e}{se(\kappa)}$$

Decision:

Reject H_o at level α if $z > z_{1-\alpha}$ and accept H_o otherwise.

Rosner provides guidelines for the evaluation of Kappa (112):

$\kappa > .75$ denotes excellent reproducibility
$.4 \leq \kappa \geq .75$ denotes good reproducibility
$.0 \leq \kappa < .4$ denotes marginal reproducibility

This will be repeated to compare CSA with Adherence Self-Report. Depending on the strength of the correlations and levels of agreement between each of the pharmacy refill data adherence measures and the self-reported adherence measure, a final determination will be made as to the utility of the self-reported measure. The data analysis for this paper was generated using SAS software 9.2 and PASW software version18 (formerly SPSS) using a significance level cut-off value of p=0.05, unless otherwise noted (115, 116).

Research Question 2: What baseline demographic and health characteristics of a rural indigent population enrolled in a medication access program predict medication adherence (using the three methods in "1" above).

Potential Predictors

Once agreement between Adherence Self-Report and MPR and CSA has been calculated, the next step is to look for differences in the study population to see who were most likely to adhere and under what conditions. The methods of calculating adherence used in Research Question 1 will then be used as the dependent variables when attempting to determine what patient factors predict adherence using logistic regression. Logistic regression is the preferred method of analysis to look for predictors of adherence in this study for two main reasons; 1) the dependent variable (adherence) is not normally distributed, therefore violating one of the requirements of linear regression, and 2) adherence is often dichotomized into adherent (greater than or equal to 80%) and non-adherent (less than 80%). Although transformation methods can be used to assist in making a non-normally distributed variable approximate the normal distribution, the dichotomized dependent variable is preferred in this analysis because the outcome is most commonly analyzed this way in the literature and it is ideal for predicting adherent vs. non-adherent rather than on a continuum (18).

In order to examine what patient characteristics predict adherence in the CMAP sample it is important to look at what factors have previously shown to be predictive in other studies and populations. As highlighted in the Background section, there appears to be very few patient

characteristics that are consistently associated with adherence in the scientific literature. Therefore all available baseline demographic and medication-related variables will be studied to determine each variable's association with the adherence measure chosen in Paper 1 including:

Independent Variable	Type
Age	Continuous
Race	Categorical
Gender	Categorical
Marital Status	Categorical
Education	Continuous
Monthly Income	Continuous
Primary Diagnosis	Categorical
Work Status	Categorical
Current Health Status	Continuous
Health Status Compared to One Year Ago	Continuous
Total # of Medications Received	Continuous
Total # of Refills Received	Continuous
Total Number of Days Patient Received Medications	Continuous

In the initial stage of the analysis, unadjusted means and proportions of baseline characteristics and the outcome measures (adherence from Paper 1) will be compared. Further, multiple logistical regression analyses will employed to examine the effect of significant baseline characteristics on medication adherence.

Unadjusted Comparisons

Descriptive statistics will be used to observe the differences in the proportion of adherent subjects (<80% vs. ≥80, <70% vs. ≥70, etc.) observed in different demographic and clinical groups. Simple logistic regression methods will be used to compare each of the continuous and categorical independent variables separately to the adherence measures. Any unadjusted comparisons showing marginal significance ($p<0.25$) will be considered a possible predictor and will be entered into the larger multiple logistical regression model. The cut-point of $p<0.25$ was

chosen based on previous work by Mickey and Greenland suggesting that using a lower cut-point often does not identify related independent variables that should be included in the multivariate analysis (117). In order to determine if possible collinearity exists, Pearson correlation coefficients will be calculated between variables where there are suspected strong correlations.

Multiple Logistic Regression

Multiple Logistic Regression will relate adherence to the independent variables using a step-wise model building process. The following process will be followed.

- First, a log odds model will be fit that contains only the intercept:

$$\log\left(\frac{p}{1-p}\right) = \beta_0, \text{ where } p = \Pr(\text{Adherence=Yes}).$$

This intercept-only model will provide a basic log-likelihood for which to compare the models in the next step.

- Secondly, each of the independent variables will be fit against adherence using a univariate logistical model to obtain each of the log-likelihoods:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X_j$$

Where X_j represents the variable with the strongest unadjusted association that has been added to the model.

- Third, the comparison of the log-likelihoods of each dependent variable in the univariate analysis will be made to the intercept-only model using the likelihood ratio test. The first

variable to be entered into the multivariate logistic regression model will be the one with the smallest p-value as determined by the likelihood ratio test.

- Fourth, this process will continue as the next most significant variable (based on p-value in our univariate analysis) will be entered into the model. The likelihood ratio test will be used to determine if the next variable entered into the model provides a better fit than the first variable entered alone. This will be

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X_j + \beta_2 X_k$$

Where X_j represents the first variable entered into the model and X_k represents the second most significant independent variable entered into the model.

At this point it is appropriate to look at whether the addition of *k* affects the relationship *j* has with adherence. In order to do that, we will examine the p-values from the likelihood ratio test to see if the addition of *k* has significantly altered the relationship, or if shows improvement on the model with only the intercept and *j*. This process will continue, adding the next most significant variable that leads to the most improvement. If none of these relationships are significant, no more variables will be added to the model.

Interactions

At the conclusion of the above step-wise model selection procedure, a set of variables have been identified that appear to be statistically significant. It will then be important to identify potential interactions between the chosen covariates. This will be performed using a similar step-wise model building process, with the exception that the first step will be to fit the

model with all of the identified variables in the initial step-wise selection process. Interaction terms will then be built into the model, with improvement tests helping to determine which are significant and should be added to the final model. The final model will include the main effects and the interaction terms.

Goodness of Fit

In order to assess whether the final model with main effects and interaction terms effectively describes the outcome variable (adherence), several goodness-of-fit tests will be employed. Deviance of the fitted model will be examined comparing the log-likelihood of the fitted model to the log-likelihood of a model with n parameters that fits the n observations perfectly (118). For continuous predictors, the Hosmer-Lemeshow Goodness of Fit test will be used, while for ordinal predictors the contingency table approach will be used. These methods will help to determine if the final model containing the main effects and interaction terms is the correct one to use.

Interpretation of the Final Model

Once the fit of the final model is determined acceptable, the model will be used to answer the question: In what direction do the chosen main effects and interaction terms determine adherence? First odds ratio estimates and confidence intervals for all the dichotomous and polychotomous covariates, including any significant relevant interaction terms will be determined (118). Cut-offs for the continuous variables will be defined in order to assess odds ratio relationships of the categorical variables to the outcome.

Research Question 3: To examine if medication adherence (using the three methods above) predict utilization of the Emergency Department (ED) or hospitalization while taking into account pre-enrollment utilization and controlling for patient factors

A key question when examining adherence data is whether adherence is a predictor of emergent healthcare utilization – mainly Emergency Department (ED) visits and overnight hospitalizations. Previous studies have shown that individuals who are more adherent to their chronic care medications are less likely to utilize the ED for routine care and are less likely to be hospitalized (43, 44, 48, 101). However, a flaw found in many of these studies is that they only take into account emergent care utilization after a patient has been filling their prescription medications. For example, Hepke and colleagues examined ED utilization in a cohort of diabetic patients in a non managed-care setting. They compared adherence to utilization for the cohort at a single point in time, determining that those patients in the highest category of adherence (80%-99%) were 0.88 times as likely to have an ED visit. However, they did not take into account utilization prior to the period being measured (44). In the CMAP sample, data is available on utilization both before and after clients enrolled in the program. This scenario gives the unique advantage of being able to determine if adherence has an effect on change in utilization. Therefore the data will be analyzed looking at both ED visits and hospitalization in separate models. Contingency tables and McNemar's Test of Binomial Proportions will be used to examine if evidence exists that there is a change in utilization from the 6-month period before to the 6-month period after enrollment. Poisson regression methods will be used to model the affect of adherence on the count of ED visits and hospitalizations.

Contingency Tables

In order to obtain the count data, contingency tables will be created for both ED visits and hospitalizations comparing the pre and post number of visits/hospitalizations. This allows for an initial visual check if there is indeed a difference in the number of visits/hospitalizations in the 6-month period prior to 6-months post CMAP enrollment. An example of the contingency table set-up is below:

Example Contingency Tables

Emergency Department Visits

	ER Post					
ER Pre	0	1	2	3	>=4	N
0						
1						
2						
3						
>=4						
N						

Hospitalizations

	Hosp Post				
Hosp Pre	0	1	2	>=3	N
0					
1					
2					
>=3					
N					

McNemar's Test of Binomial Proportions

McNemar's Test for Binomial Proportions for Matched-Pair Data is a test of differences between treatments, or in this case, ED and hospitalizations pre and post CMAP enrollment. In this analysis only discordant pairs are of interest, rather than concordant pairs because a

difference (change) in utilization, not equal utilization pre and post is important. This is an important question to ask, because if there is no reduction in utilization from pre to post-enrollment then further exploration of the effect of adherence will be unnecessary. The table below is an example of how the data is organized for McNemar's Test comparing pre to post ED visits:

Data are placed in a 2 x 2 table of matched pairs:

		Pre	
		Ye s	No
Post	Yes	A	b
	No	C	d

Where:

a, d = concordant pairs (not of interest in this analysis)

c = discordant pair where the "pre" member has a visit and the "post" member does not

b = discordant pair where the "post" member has a visit and the "pre" member does not

In order to test whether there is a significance difference we will use the Normal-Theory Test (preliminary data analyses indicate that the number of discordant pairs will be greater than or equal to 20):

Hypothesis:

$H_o: p = \frac{1}{2}$ vs. $H_a: p \neq \frac{1}{2}$

Test Statistic:

$$X^2 = \frac{(|n_A - n_B| - 1)^2}{(n_A + n_B)}$$

Decision:

If $X^2 > \chi^2_{1,1-\alpha}$ then reject H_o

Once it has been shown that there has been indeed an overall reduction in utilization from pre to post then we will proceed to the next step which is to use Poisson Regression to model whether those CMAP patients that are adherent are more likely to see a reduction in utilization.

Poisson Regression Analysis

Outcome Measure

The main dependent (outcome) measure for both Poisson regression models will be the utilization in the 6-month period prior after enrollment into the CMAP In order to examine the effect of adherence while taking into account utilization pre-enrollment, the main independent variable will be the interaction between adherence (at varying cut-points of the three adherence measures) and the count of ED visits prior to enrollment. Therefore modeling the interaction between adherence and the number of ED visits and hospitalizations pre-enrollment provides the advantage determining if access to low-cost medications serves to reduce utilization taking into account prior utilization. This is a fundamentally different question than asked in other studies, which is whether adherence predicts utilization. In order to answer the research question, count data on utilization for each participant must be obtained. For each model, the count of ED visits/hospitalizations both in the 6-months prior to 6-months post-enrollment into the CMAP will be compared to adherence while adjusting for various covariates.

Statistical Analysis

Poisson regression will be used to relate the number of visits (ED visits and hospitalizations) for the 6-month post-enrollment to measures of adherence, adjusting for the number of visits pre-enrollment. Counts are all positive integers and for rare events the Poisson distribution (rather than the Normal) is more appropriate since the Poisson mean > 0 (119).

Therefore Poisson regression is a multivariable method of analyzing count data while adjusting for covariates. The Poisson Regression equation will take the form of:

$$(E(Y)) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 \ldots$$

where E(Y) is the expected utilization count per six month interval post-enrollment, and Y follows a Poisson distribution. The analyses will be done using SAS Proc Genmod, specifying a Poisson link, allowing for the calculation of odds ratios to determine if associations exist. As most CMAP patients will not have had an ED visit or hospitalization, the large number of zeroes in the data will be reduced by collapsing the groups into covariate patterns, categorizing previously continuous variables.

To account for the collapsing of groups, the dependent variable will be the count of ED visits (model 1) or the count of hospitalizations (model 2) post-enrollment divided by the number of person days in each covariate pattern. The Poisson models will contain independent variables; the interaction between adherence (each of the three adherence measures at five cut-points) and count of visits/hospitalizations pre-enrollment, age (categorized into <40, ≥ 40 and <60, and ≥ 60), gender, race, education (categorized into $\leq 11^{th}$ Grade and $\geq 12^{th}$ Grade/GED), and primary diagnosis (categorized into hypertension, diabetes, and other). Significant interaction in the main variable of interest, the interaction of adherence and pre-enrollment count, implies the effect of adherence on the number of visits post-enrollment depends on the pre-enrollment visit count. The above covariates are included because they are known to affect adherence (from our analysis in Paper 2), and also are associated with ED visits and hospitalizations in the literature cited above. Two separate models will be built – one each for ED visits and hospitalizations, including the same covariates for each of the five cut-points of CSA, MPR, and ASR. To

determine model fit, the Pearson Chi-Square deviance statistic will be used. A potential problem with count data is the potential for overdispersion, when the data's observed variance is larger than the predicted variance (119). A model with the absence of overdispersion will have dispersion parameters close 1. Should any models display overdispersion with a Pearson Chi-Square deviance statistic greater than 3, it will be corrected for with the use of a dispersion parameter (120).

Interpretation of the Final Models

After the relevant models have been built and analyzed it will be important to obtain odds ratio's to determine the association of the adherence measures and the included covariates on utilization. If the interaction between the adherence measures and the count of ED visits/hospitalizations pre-enrollment is significant and less than 1, it will indicate that individuals with higher adherence were less likely to have an ED visit or hospitalization taking into account the previous 6-months visits/hospitalizations. The odds ratios of the other covariates will be examined to determine if significant relationships exist with the outcome variable. Any covariate trends observed will be compared with similar studies in the Discussion section.

VII: RESULTS

RESEARCH QUESTION 1

Electronic pharmacy Records

The initial electronic pharmacy records database contained a total of 79,898 records for 3181 patients. However, in order to calculate MPR or CSA a patient must have at least one refill in the database, which eliminated 325 patients and 529 records. The final dataset of electronic pharmacy records contained a total of 79,369 records for 2,856 patients.

Pharmacist Interview Data

A total of 3585 patients had 9948 interviews in the initial pharmacy interview database.

Study Sample

A single dataset was created to compute the three adherence methods, MPR, CSA, and ASR. In order to ensure a complete dataset, patient identification numbers were crossed-referenced between the electronic pharmacy records and the pharmacist interview data. After crossing the two datasets, there were a total of 2417 patients with 73,363 fill/refill records and 8251 pharmacy interviews. A demographic and health breakdown of the 2417 can be found in Table 2. The mean age of the study sample was 61.4 years, with 54.8% aged sixty or older. The majority of the patients were female (70.7%) and Caucasian (68.1%), with 54.3% not receiving a high school diploma or equivalency. Patients were most likely to report poor or fair health (67.0%) at initial interview, and 79.7% reported that their health was the about the same or worse compared to one year ago. The most common self-reported primary diagnosis is hypertension (63.8%), followed by diabetes (10.6%) and heart disease (9.6%).

Table 2: Demographic and health characteristics of the CMAP sample with complete adherence data (n=2417)

Variable	Mean (SD)	
Mean Age (SD)	61.4 (16.0)	
Mean Education (SD)	10.2 (2.9)	
Mean Income per Month (SD)	$503.07 ($382.20)	
Mean # of Refills per Patient (SD)	30.4 (27.5)	
Mean # of Medications Received	4.1 (2.5)	
Mean # of Days Enrolled in CMAP	584.2 (409.9)	
Variable	**N**	**%**
Age Groups		
18-29	80	3.3
30-39	150	6.2
40-49	388	16.1
50-59	474	19.6
60-69	510	21.1
70-79	500	20.7
≥80	315	13.0
Gender		
Male	708	29.3
Female	1709	70.7
Race/Ethnicity		
Black or African-American	771	31.9
White	1646	68.1
Education		
8th Grade or Less	640	26.5
Some High School	670	27.7
High School Diploma or GED	867	35.9
Beyond High School	240	9.9

Table 2 CONTINUED: Demographic and health characteristics of the CMAP sample with complete adherence data (n=2417)

Variable	N	%
Employment		
Unemployed	437	18.1
Employed (Full or Part Time)	214	9.3
Disability	626	25.9
Retired	947	39.2
Never Worked	159	6.6
Self-Reported Health		
Poor	542	22.4
Fair	1078	44.6
Good	475	19.7
Very Good	132	5.5
Excellent	28	1.2
Missing	162	6.6
Self-Reported Health Now		
Much Worse	203	8.4
Somewhat Worse	565	23.4
About the Same	1157	47.9
Somewhat Better	223	9.2
Much Better	108	4.5
Missing	162	6.6
Primary Diagnosis		
Hypertension	1543	63.8
Diabetes/Blood Sugar	256	10.6
Heart Disease	232	9.6
Depression	71	2.9
Asthma/Respiratory	52	2.2
Other*	263	10.9
Secondary Diagnosis		
Diabetes/Blood Sugar	447	18.5
None	385	15.9
Heart Disease	314	13.0
High Blood	293	12.1
High Cholesterol	287	11.9
Other*	691	28.6

*Please see Appendix for full list of diseases/conditions

Comparison of CMAP Patients

T-tests and chi-square procedures were used to compare whether the 2417 CMAP patients with complete adherence data differ from those CMAP patients missing adherence data. The comparison group of CMAP participants with no adherence data consisted of 1168 patients with no electronic pharmacy data and 439 patients with no Adherence Self-Report data for a total of 1607 patients. Usable demographic and health data were available for 1550 of the 1607 patients (96.5%). Table 3 contains the comparison of the 2417 CMAP patients with adherence data to the 1550 with no adherence data. The samples appear to significantly differ in mean age, at 61.4 years for the sample with adherence data and 52.6 years for the sample without ($p=0.022$). The adherence sample also had significantly less education (10.2 years vs. 11.0 years; $p<0.001$) and lower average monthly income ($503 vs. $735; $p<0.001$). The two samples also differed in gender ($p<0.001$), and race ($p<0.001$), with more men and fewer African-Americans with missing data. Patients in the adherence sample were more likely to be widowed (32.7% vs. 17.0%), while patients in the sample with missing adherence data were more likely to be married (38.2% vs. 29.7%) or single (20.2% vs. 13.2%). Current employment varies between the two samples as well, with "retired" and "disability" the two most common for the adherence sample (39.2% and 25.9%, respectively) while "unemployed" and "employed" are the most common for the sample with missing adherence data (28.6% and 24.4%, respectively). The two samples also appear to diverge in health-related indicators such as self-reported health, self-reported health compared to one year ago and primary diagnosis (all $p<0.001$), however a fairly large amount of observations for the sample with no adherence data are missing (23.7% to 42.0%). A discussion of the potential reasons for the differences between the samples with and without adherence data is provided in the discussion section.

Table 3: Comparison of CMAP Patients With and Without Complete Adherence Data

Variable	With Complete Adherence Data (n=2417)	Without Complete Adherence Data (n=1550)	p-value*
Mean Age (SD)	61.4 (16.0)	52.6 (16.1)	**.022**
Education (SD)	10.2 (2.9)	11.0 (2.8)	**<.001**
Total Income (SD)	$503.07 (382.2)	$735.63 (635.0)	**<.001**
Gender (n, %)			**<.001**
Male	708 (29.3)	544 (35.1)	
Female	1709 (70.7)	1006 (64.9)	
Race/Ethnicity (n, %)			**<.001**
Black or African-American	771 (31.9)	444 (28.6)	
Caucasian	1646 (68.1)	1070 (69.0)	
Other	0 (0.0)	36 (2.3)	
Marital Status (n,%)			**<.001**
Single	319 (13.2)	313 (20.2)	
Married	717 (29.7)	592 (38.2)	
Divorced	426 (17.6)	269 (17.4)	
Separated	163 (6.7)	113 (7.3)	
Widow	790 (32.7)	263 (17.0)	
Other/Missing	2 (0.1)	0 (0.0)	
Employment (n, %)			**<.001**
Unemployed	437 (18.1)	44 (28.6)	
Employed (Full or Part Time)	224 (9.3)	377 (24.4)	
Disability	626 (25.9)	336 (21.7)	
Retired	947 (39.2)	299 (19.3)	
Never Worked	159 (6.6)	81 (5.2)	
Other/Missing	24 (1.0)	13 (0.8)	
Self-Reported Health (n, %)			**<.001**
Poor	542 (22.4)	239 (19.7)	
Fair	1078 (44.6)	370 (23.9)	
Good	475 (19.7)	214 (13.8)	
Very Good	132 (5.5)	58 (3.7)	
Excellent	28 (1.2)	20 (1.3)	
Missing	162 (6.7)	644 (41.9)	

Table 3 CONTINUED: Comparison of CMAP Patients With and Without Complete Adherence Data

Variable	With Complete Adherence Data (n=2417)	Without Complete Adherence Data (n=1550)	p-value*
Self-Reported Health Now Compared to One Year Ago (n, %)			**<.001**
Much Worse	203 (8.4)	103 (6.6)	
Somewhat Worse	565 (23.4)	249 (16.1)	
About the Same	1157 (47.9)	386 (24.9)	
Somewhat Better	223 (9.2)	105 (6.8)	
Much Better	108 (4.5)	56 (3.6)	
Missing	161 (6.7)	651 (42.0)	
Primary Diagnosis (n,%)			**<.001**
Hypertension	1543 (63.8)	643 (41.5)	
Diabetes/Blood Sugar	256 (10.6)	188 (12.1)	
Heart Disease	232 (9.6)	146 (9.4)	
Depression	71 (2.9)	122 (7.9)	
Asthma/Respiratory	52 (2.2)	83 (5.4)	
Other/Missing	262 (10.9)	368 (23.7)	

* Significant at $p \leq 0.05$

Calculation of Adherence Measures

The three adherence measures, MPR, CSA, and ASR, were calculated for the 2417 patients with complete data (including calculating weighted MPR and CSA) using the methods described earlier. Table 4 shows descriptive statistics for the three adherence measures. Where applicable, the three adherence measures will be expressed as a percent in order to allow for easy interpretation. The mean CSA and ASR for the study sample were very similar at 80.2% and 80.3%, respectively, while the mean MPR was almost 10% less than the other two measures at 70.5%. The medians all differed, with MPR (72.3%) at the lowest, followed by CSA (82.7%) and ASR (91.7%) with the highest. The ranges for the two electronic pharmacy adherence measures reveal that some individuals have calculated adherences of over 500%. A recent paper by Krousel-Wood et al limited MPR and CSA to a maximum of 100%, and several other researchers have argued that adherence measures should be capped at 100% (31, 74) To determine if capping the two measures at 100% would greatly change the descriptive statistics, all values of both CSA and MPR over 100% were set to exactly 100% (Table 5). This change does not appear to have the effect of greatly reducing the means, with MPR dropping 0.8% and CSA dropping 1.8%. An advantage of capping the adherence measures at 100% appears to be that the data are less skewed (closer to 0), with kurtosis measures closer to three than the original uncapped data. CSA and MPR capped at 100% will therefore be used for all future analysis where adherence is not dichotomized into adherent/not-adherent.

Table 4: Descriptive Comparison of MPR %, CSA %, and ASR % (n=2417)

	MPR %	CSA %	ASR %
Mean	70.5	80.2	80.3
SD	23.6	25.6	26.4
Range	(3.4, 427.4)	(3.4, 506.1)	(0, 100.0)
Standard Error	0.5	0.5	0.5
Median	72.3	82.7	91.7
Mode	90.9	90.9	100.0
Variance	559.3	656.1	698.8
Skewness	1.4	4.1	-1.7
Kurtosis	21.9	56.9	2.1

Table 5: Descriptive Comparison of MPR %, CSA %, and ASR % with adherence truncated at 100% (n=2417)

	MPR %	CSA %	ASR %
Mean	69.7	78.4	80.3
SD	20.9	18.4	26.4
Range	(3.4, 100.0)	(3.4, 100.0)	(0, 100.0)
Standard Error	0.4	0.4	0.5
Median	72.3	82.7	91.7
Mode	100.0	100.0	100.0
Variance	436.6	338.9	698.8
Skewness	-0.5	-1.2	-1.7
Kurtosis	-0.4	1.2	2.1

Tests of Normality

In order to determine whether parametric or nonparametric procedures should be used to compare the three adherence measures, tests for normality were performed on each of the three measures. Figures 1-3 show the histograms for the three adherence measures, with both CSA and MPR presented with and with out being cut off at 100%. The Adherence Self-Report measure does not appear normally distributed, while MPR and CSA both appear skewed regardless of the data being capped at 100%. Table 6 shows both the Kolmogrov-Smirnoff and Shapiro-Wilk tests for normality. The results of both tests are shown because the cut-off to use the Shapiro-Wilk test is normally 2000 observations, and the current dataset has 2417 (121). Regardless, the results of both procedures indicate that all three measures differ significantly ($p<0.05$) from a normal distribution. These findings are further supported by Stem & Leaf, P-P, Q-Q, and Boxplot diagrams that can be found in the Appendix.

Figure 1: MPR Histograms (original data and cut-off at 100%)

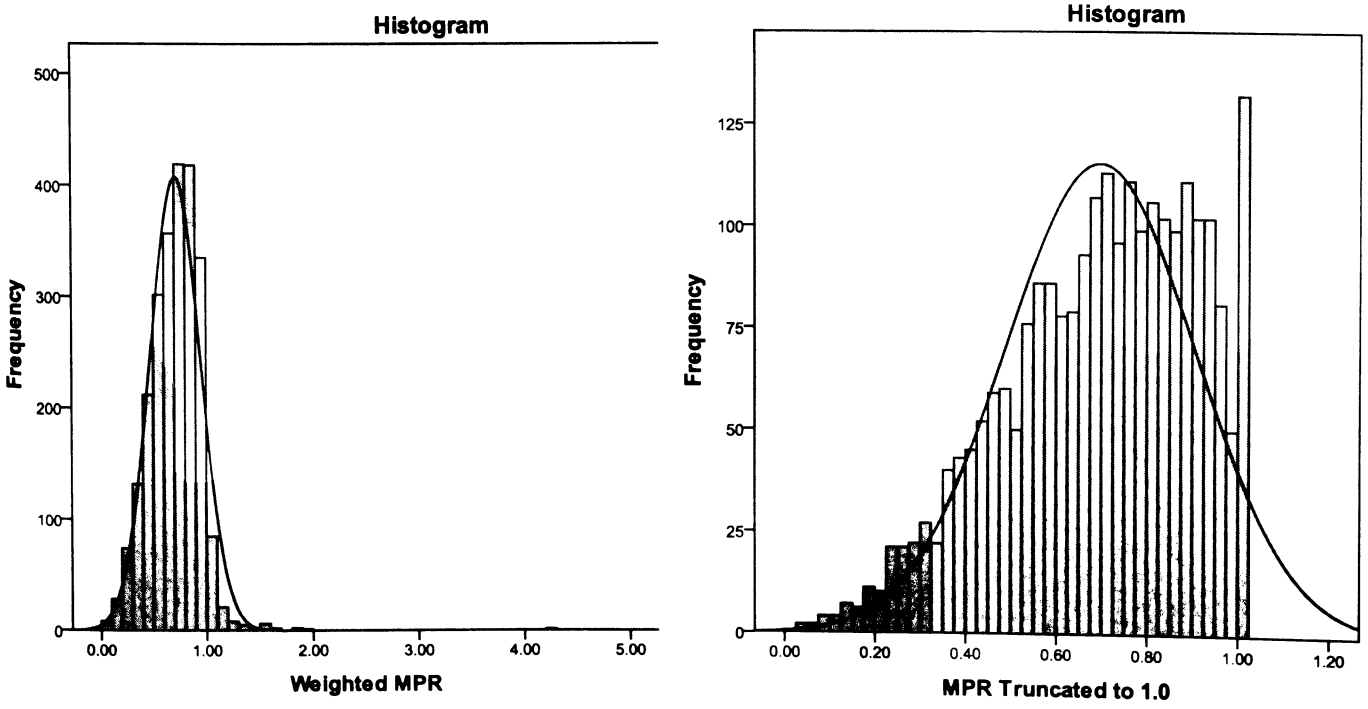

Figure 2: CSA Histograms (original data and cut-off at 100%)

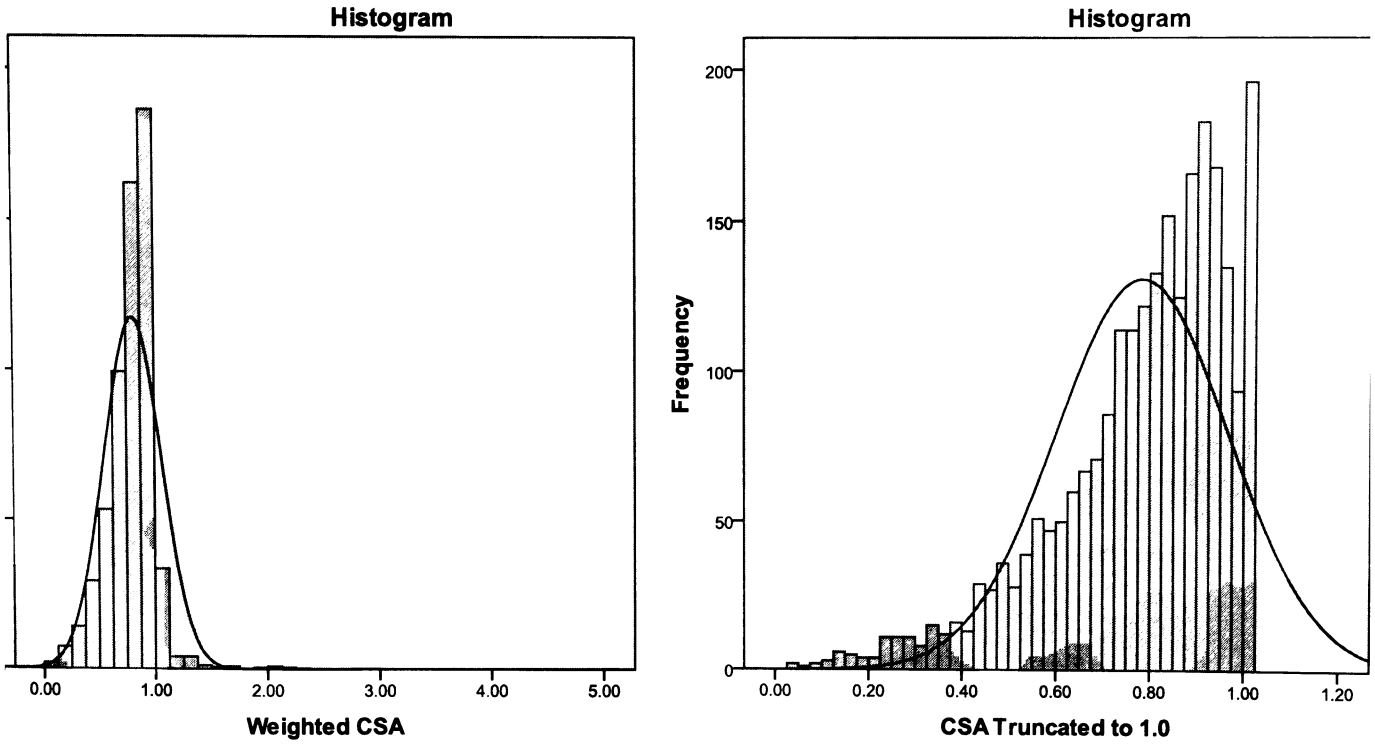

Figure 3: ASR Histogram

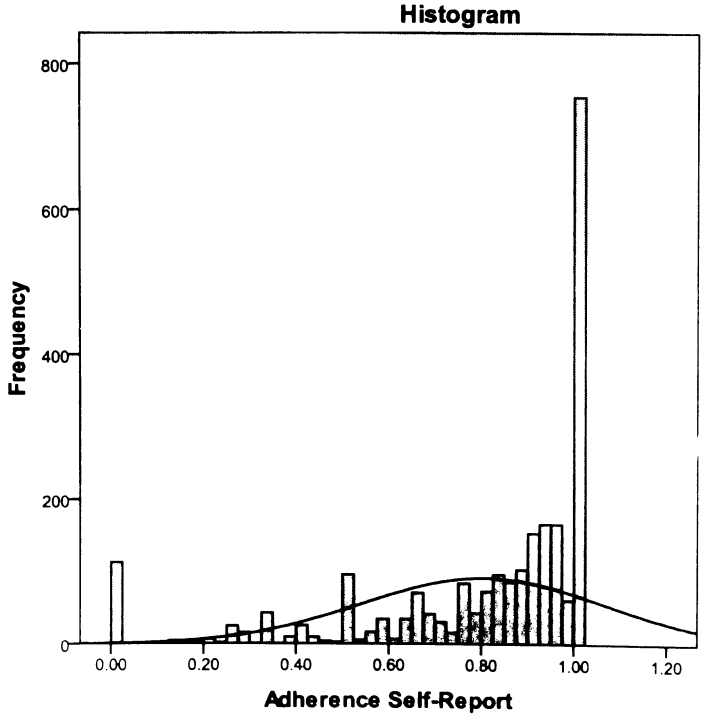

Table 6: Tests of Normality for MPR%, CSA%, and ASR%*

	MPR %	CSA %	ASR %
Kolmogrov-Smirnov	0.074**	0.12**	0.23**
Shapiro-Wilk	0.96**	0.90**	0.75**

*MPR% and CSA% are cut-off at 100%

** Indicates that the distribution of the measure is significantly different than the normal distribution at ($p<.001$)

Cut-points of Adherence Measures

The adherence measures will be dichotomized at a cut-point of 80%, with those less than the cut-point considered "non-adherent" and those above the cut-point considered "adherent." In order to ensure that 80% is the correct cut-point, four additional cut-points of adherence will be used. Table 7 presents the distribution of adherent and non-adherent patients at five different cut-points of adherence; 70%, 75%, 80%, 85%, and 90%. The 80% cut-point, shown first as it is the most commonly used cut-point when dichotomizing adherence, shows adherence rates of 55.9% for CSA, 36.5% for MPR, and 67.1% for ASR. This relationship continues at all cut-points, with ASR the highest and MPR the lowest. MPR has the largest range of adherence, varying from 19.3% at a cut-point of 90% to 54.0% at the 70% cut-point.

Table 7: Distribution of adherence among five cut-points of CSA %, MPR %, and ASR %

	80%		70%		75%		85%		90%	
	≥	<	≥	<	≥	<	≥	<	≥	<
CSA	55.9	44.1	74.0	26.0	65.8	34.2	44.1	55.9	32.1	67.9
MPR	36.5	63.5	54.0	46.0	45.5	54.5	28.0	72.0	19.3	80.7
ASR	67.1	32.9	76.6	23.4	73.9	26.1	61.6	38.4	53.8	46.2

Test of Proportions

McNemar's Test of Binomial Proportions (McNemar's) was used to compare the proportions of adherent and non-adherent patients between each of the three adherence measures to determine if they significantly differ. The adherent/non-adherent cut point was set initially set at 80% (see Methods), however a sensitivity analysis was performed to determine if varying the cut point affected the relationship between the adherence measures. The results in Table 8 show the test for significance at cut-points of adherence at 80%, as well as 70%, 75%, 85%, and 90%. For all comparisons of adherence measures (CSA vs. MPR, MPR vs. ASR, CSA vs. ASR) and cut points of adherence the McNemar chi-square statistic was significant at the $p<.05$ significance level, indicating that the three measures all differed from each other. Varying the adherence cut point did not affect the relationships, except in the comparison of CSA and ASR at the 70% cut-point where the chi-square was at its lowest (5.18). However, the p-value of $p=0.023$ indicates that the proportions still significantly differed. Some trends were observed, however, in the patterns of discordant pairs in the comparisons. At all adherence cut points there were more discordant pairs when MPR $< X\%^{*}$ and CSA $\geq X\%^{*}$, which agrees with our descriptive analysis showing that calculated CSA yields higher adherence values than calculated MPR. There were also more discordant pairs when ASR $\geq 80\%$ and both MPR and CSA $<80\%$, concurring with the histograms in Figures 1-3 which illustrate that ASR is skewed toward 100%.

Tests of Rank Correlation

Although the proportions of adherent/non-adherent patients significantly differed between the adherence measures, it is important to see if correlation exists. Spearman's rank-correlation coefficient was calculated between each of the measures using ranks of the original weighted data truncated at 100% (Table 9).

* X can be substituted with any of the adherence cut points (70%, 75%, 80%, 85%, 90%)

Table 8: Outcomes of McNemar's Test of Binomial Proportions across Adherence Measures and Varying Cut-points of Adherence (n=2417)

80%

	MPR					ASR					ASR				
CSA		<80%	≥80%	X^2	p=value		<80%	≥80%	X^2	p=value		<80%	≥80%	X^2	p=value
	<80%	1060	5	458.3	<.001	CSA <80%	432	633	73.27	<.001	MPR <80%	519	1016	424.2	<.001
	≥80%	475	877			≥80%	362	990			≥80%	275	607		

70%

	MPR					ASR					ASR				
CSA		<70%	≥70%	X^2	p=value		<70%	≥70%	X^2	p=value		<70%	≥70%	X^2	p=value
	<70%	626	3	476.1	<.001	CSA <70%	214	415	5.18	<.023	MPR <70%	284	829	269.6	<.001
	≥70%	487	1301			≥70%	351	1437			≥70%	281	1023		

75%

	MPR					ASR					ASR				
CSA		<75%	≥75%	X^2	p=value		<75%	≥75%	X^2	p=value		<75%	≥75%	X^2	p=value
	<75%	820	6	478.3	<.001	CSA <75%	287	539	42.62	<.001	MPR <75%	359	959	382.3	<.001
	≥75%	498	1093			≥75%	344	1247			≥75%	272	827		

85%

	MPR					ASR					ASR				
CSA		<85%	≥85%	X^2	p=value		<85%	≥85%	X^2	p=value		<85%	≥85%	X^2	p=value
	<85%	1340	10	369.1	<.001	CSA <85%	593	757	163.2	<.001	MPR <85%	666	1074	493.9	<.001
	≥85%	400	667			≥85%	334	733			≥85%	261	416		

90%

	MPR					ASR					ASR				
CSA		<90%	≥90%	X^2	p=value		<90%	≥90%	X^2	p=value		<90%	≥90%	X^2	p=value
	<90%	1634	7	293.7	<.001	CSA <90%	814	827	243.2	<.001	MPR <90%	896	1054	544.7	<.001
	≥90%	316	460			≥90%	302	474			≥90%	220	247		

The correlation between CSA and MPR was high at 0.903, which was significant at $p<0.001$. The correlations between CSA and ASR and MPR and ASR were lower at 0.163 and 0.093, respectively. However, due to the large sample size, both the CSA and MPR comparisons to ASR were significant at $p<0.001$. In order to ensure that truncating CSA and MPR did not affect the correlation, the test was performed on the original weighted data and there was virtually no difference in the outcomes.

Tests of Agreement

Once correlation has been established, the next step is to see if there is agreement between the measures of adherence. Agreement was calculated using the kappa statistic, as shown in Table 10. At all cut-points of adherence, the kappa statistic for agreement between MPR and CSA was significant. The strongest agreement between MPR and CSA occurred at the cut-point of 90%, where Kappa was 0.658, while the lowest was 0.579 at a 70% cut-point. The agreement between CSA and ASR was significant as well at all cut-points, although the kappa was generally low and varied from .091 at 90% to .149 at 70%. The agreement between MPR and ASR only reached significance at the 70% cut point (.041), and never reached significance for the other cut-points with kappa's ranging from -.002 to .024. This appears to agree with the trends seen in Table 6, where we see less discordant pairs in the tables with MPR vs. CSA than we do in the other tables.

Table 9: Comparison of CSA, MPR and ASR using Spearman's Rank Correlation Coefficient (n=2417)

		CSA	MPR	ASR
Correlation Coefficient	CSA	1.000	.903	.163
Sig. (2-tailed)*			.000	.000
Correlation Coefficient	MPR	.903	1.000	.093
Sig. (2-tailed)		.000		.000
Correlation Coefficient	ASR	.163	.093	1.000
Sig. (2-tailed)		.000	.000	.

* All p <0.001

Table 10: Agreement between CSA, MPR and ASR using Cohen's Kappa at Varying Cut-points of Adherence (p-values in parentheses)

		CSA	MPR	ASR
	CSA		**.615 (.001)**	**.142 (.001)**
80%	**MPR**	**.615 (.001)**		.022 (.185)
	ASR	**.142 (.001)**	.022 (.185)	
	CSA		**.579 (.001)**	**.149 (.001)**
70%	**MPR**	**.579 (.001)**		**.041 (.022)**
	ASR	**.149 (.001)**	**.041 (.022)**	
	CSA		**.595 (.001)**	**.139 (.001)**
75%	**MPR**	**.595 (.001)**		.024 (.165)
	ASR	**.139 (.001)**	.024 (.165)	
	CSA		**.642 (.001)**	**.121 (.001)**
85%	**MPR**	**.642 (.001)**		-.002 (.90)
	ASR	**.121 (.001)**	.002 (.90)	
	CSA		**.658 (.001)**	**.091 (.001)**
90%	**MPR**	**.658 (.001)**		.007 (.651)
	ASR	**.091 (.001)**	-.007 (.651)	.

*Comparisons in **BOLD** are statistically significant at p≤ .05*

RESEARCH QUESTION 2

Unadjusted Analysis

Below are the results of the unadjusted comparison of each possible predictor with each of the three adherence measures. Within each adherence measure, five cut-points are examined to determine if altering the cut-point alters the unadjusted relationships. All analyses were performed in SAS Proc Logistic, with Wald X^2 statistics and p-values presented in Tables 10-12. Significance was set at $p \leq 0.25$ in order to insure that as many predictors as possible are eligible to be entered in the stepwise multivariable logistic regression.

CSA

In the unadjusted comparisons in Table 11, age was significantly associated with CSA at all cut-points, as were self-reported current health (HEALTH), total number of refills received (REFILLS), total number of medications received (MEDS), race, work status and primary diagnosis. Average monthly income was not associated with CSA at any cut-point, with all p-values >0.25. The remaining variables' association with CSA were dependent on the cut-point, however trends existed where education was significant at all cut-points except 90%, total number of days patient received medication (LOS) was significant at all cut points except 85%, and marital status was significant at 70%-80%, but not at 85%-90%. Self-reported health status compared to one-year ago (HEALTHYR) and gender were both marginally associated with CSA at varying cut-points, with all p-values approaching p=0.25 (range p=0.139 – p=0.246). The strongest unadjusted associations occurred between CSA and REFILLS (Wald X^2 range: 21.826 – 186.46), Age (5.47 – 59.99), and Race (32.00 – 58.33), while some of the weaker associations occurred with Monthly Income (0.07 to 0.60) and HEALTHYR (0.003 – 1.68).

MPR

Table 12 shows the comparison of each of the variables with MPR at the various pre-determined cut-points. Similar to the results observed with CSA, MEDS, Race, Work Status and Primary Diagnosis were all significantly associated with MPR at all cut-points. However, both age and HEALTH were only significant at four of the five cut points of MPR, unlike CSA where they were associated at all five cut points. Marital status is significant at 75%, 85%-90% but with p-values approaching 0.25. Education, monthly income and gender do not appear to be associated with MPR at any cut-point except for marginal significance at 90% for education (p=0.043), 75% for monthly income (p=0.236) and at 70% for Gender (p=0.210). The largest Wald X^2 values occur for MEDS (range 41.57 – 110.13) and LOS (25.89 – 121.94) for the continuous variables, while Race (13.91 – 45.20) and Primary Diagnosis (8.60 – 30.06) have the highest for the categorical predictors.

ASR

Each of the variables in Table 13 appears to be highly significantly associated with ASR at all cut-points of adherence, except for Monthly Income and Primary Diagnosis. Primary Diagnosis is significant at all cut-points except for 90%, and Monthly Income is significant at cut-points of 70% and 75%, but has p-values greater than p=0.25 at 80%-90% cut points. The largest Wald statistic occurs for LOS (248.36– 338.99), REFILLS (246.77 – 303.18), and age (171.14 – 208.54), work status (136.48 – 187.39) and marital status (95.55 – 120.32).

Table 11: Unadjusted comparisons of CSA with continuous and categorical predictors of the CMAP sample

		Cut Points of CSA									
		80%		70%		75%		85%		90%	
Continuous Predictors	***Valid n***	**Wald X^2 [a]**	**p-value[b]**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**
Age	2417	**46.42**	**<.001**	**54.25**	**<.001**	**59.99**	**<.001**	**26.28**	**<.001**	**5.47**	**.019**
Education	2417	**9.50**	**.002**	**9.15**	**.003**	**8.75**	**.003**	**3.26**	**.071**	0.83	NS
Monthly Income	2416	0.07	NS	0.60	NS	0.38	NS	0.60	NS	.017	NS
Current Health Status (HEALTH)	2325	**10.31**	**.002**	**3.04**	**.081**	**3.84**	**.050**	**13.77**	**<.001**	**4.11**	**.043**
Health Status Compared to One Year Ago (HEALTHYR)	2320	0.29	NS	0.003	NS	0.14	NS	0.27	NS	**1.68**	**.195**
Total # of Refills Received (REFILLS)	2417	**119.18**	**<.001**	**186.46**	**<.001**	**173.43**	**<.001**	**71.76**	**<.001**	**21.82**	**<.001**
Total # of Medications Received (MEDS)	2417	**6.84**	**.009**	**16.00**	**<.001**	**2.21**	**.137**	**31.34**	**<.001**	**48.61**	**<.001**
Total Number of Days Patient Received Medications (LOS)	2417	**5.69**	**.017**	**31.89**	**<.001**	**16.52**	**<.001**	0.03	NS	**10.96**	**<.001**
Categorical Predictors	***Valid n***	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**
Race	2417	**54.76**	**<.001**	**58.33**	**<.001**	**57.10**	**<.001**	**38.67**	**<.001**	**32.00**	**<.001**
Gender	2417	**2.19**	**.139**	0.83	NS	0.40	NS	**1.35**	**.246**	0.36	NS
Marital Status	2417	**12.38**	**.015**	**16.97**	**.002**	**15.44**	**.004**	4.81	NS	2.15	NS
Work Status	2417	**40.02**	**<.001**	**38.81**	**<.001**	**40.32**	**<.001**	**28.04**	**<.001**	**9.14**	**.104**
Primary Diagnosis	2417	**29.41**	**<.001**	**33.89**	**<.001**	**47.91**	**<.001**	**27.23**	**<.001**	**19.88**	**.001**

BOLD indicates significance at $p \leq 0.25$

[a] From PROC LOGISTIC unadjusted analysis

[b] Significance set at $p \leq 0.25$

NS = Not Significant

Table 12: Unadjusted comparisons of MPR with continuous and categorical predictors of the CMAP sample

		Cut Points of MPR									
		80%		70%		75%		85%		90%	
Continuous Predictors	***Valid n***	**Wald X^2 [a]**	**p-value[b]**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**
Age	2417	**1.63**	**.202**	**8.48**	**.004**	**3.22**	**.073**	0.86	NS	**2.36**	**.124**
Education	2417	0.069	NS	3.34	.068	0.61	NS	0.66	NS	**4.08**	**.043**
Monthly Income	2416	**1.15**	**NS**	**1.26**	**NS**	**1.41**	**.236**	0.36	NS	0.38	NS
Current Health Status (HEALTH)	2325	**6.66**	**.010**	**10.50**	**.001**	**11.43**	**.001**	**2.80**	**.095**	0.76	NS
Health Status Compared to One Year Ago (HEALTHYR)	2320	0.49	NS	0.14	NS	0.36	NS	**3.13**	**.077**	**6.83**	**.009**
Total # of Refills Received (REFILLS)	2417	0.76	NS	**30.63**	**<.001**	**11.70**	**<.001**	**5.68**	**.017**	**27.81**	**<.001**
Total # of Medications Received (MEDS)	2417	**89.14**	**<.001**	**41.57**	**<.001**	**65.85**	**<.001**	**110.13**	**<.001**	**109.90**	**<.001**
Total Number of Days Patient Received Medications (LOS)	2417	**69.49**	**<.001**	**25.89**	**<.001**	**43.15**	**<.001**	**118.35**	**<.001**	**121.94**	**<.001**
Categorical Predictors	***Valid n***	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**
Race	2417	**28.15**	**<.001**	**45.20**	**<.001**	**41.35**	**<.001**	**22.42**	**<.001**	**13.91**	**<.001**
Gender	2417	0.044	NS	**1.57**	**.210**	0.91	NS	0.69	NS	0.71	NS
Marital Status	2417	3.03	NS	**6.18**	**.186**	4.47	NS	**6.07**	**.194**	**7.04**	**.134**
Work Status	2417	**13.96**	**.016**	**15.75**	**.008**	**12.60**	**.027**	**14.77**	**.011**	**15.31**	**.009**
Primary Diagnosis	2417	**23.65**	**<.001**	**30.06**	**<.001**	**25.55**	**<.001**	**12.53**	**.028**	**8.60**	**.126**

BOLD indicates significance at $p \leq 0.25$

[a] From PROC LOGISTIC unadjusted analysis

[b] Significance set at $p \leq 0.25$

NS = Not Significant

Table 13: Unadjusted comparisons of ASR with continuous and categorical predictors of the CMAP sample

		Cut Points of ASR									
		80%		70%		75%		85%		90%	
Continuous Predictors	***Valid n***	**Wald X^2 [a]**	**p-value[b]**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**
Age	2417	**206.10**	**<.001**	**198.95**	**<.001**	**208.54**	**<.001**	**203.87**	**<.001**	**171.14**	**<.001**
Education	2417	**16.72**	**<.001**	**19.21**	**<.001**	**21.40**	**<.001**	**21.67**	**<.001**	**26.01**	**<.001**
Monthly Income	2416	1.16	NS	**3.29**	**.070**	**2.13**	**.144**	0.50	NS	0.083	NS
Current Health Status (HEALTH)	2325	**31.86**	**<.001**	**22.64**	**<.001**	**27.63**	**<.001**	**36.20**	**<.001**	**37.86**	**<.001**
Health Status Compared to One Year Ago (HEALTHYR)	2320	**24.00**	**<.001**	**32.49**	**<.001**	**27.91**	**<.001**	**23.07**	**<.001**	**13.33**	**<.001**
Total # of Refills Received (REFILLS)	2417	**291.32**	**<.001**	**246.77**	**<.001**	**253.16**	**<.001**	**303.18**	**<.001**	**249.13**	**<.001**
Total # of Medications Received (MEDS)	2417	**116.24**	**<.001**	**120.49**	**<.001**	**115.47**	**<.001**	**104.19**	**<.001**	**69.15**	**<.001**
Total Number of Days Patient Received Medications (LOS)	2417	**337.78**	**<.001**	**301.48**	**<.001**	**308.76**	**<.001**	**338.99**	**<.001**	**248.36**	**<.001**
Categorical Predictors	***Valid n***	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**
Race	2417	**14.83**	**<.001**	**17.78**	**<.001**	**18.78**	**<.001**	**21.14**	**<.001**	**17.40**	**<.001**
Gender	2417	**24.30**	**<.001**	**35.82**	**<.001**	**30.62**	**<.001**	**18.95**	**<.001**	**13.61**	**<.001**
Marital Status	2417	**120.32**	**<.001**	**105.82**	**<.001**	**110.34**	**<.001**	**118.99**	**<.001**	**95.55**	**<.001**
Work Status	2417	**177.24**	**<.001**	**168.88**	**<.001**	**187.39**	**<.001**	**171.49**	**<.001**	**136.48**	**<.001**
Primary Diagnosis	2417	**14.80**	**.011**	**18.42**	**.003**	**15.76**	**.008**	**9.13**	**.104**	3.62	NS

BOLD indicates significance at $p \leq 0.25$

[a] From PROC LOGISTIC unadjusted analysis

[b] Significance set at $p \leq 0.25$

NS = Not Significant

Correlation of Independent Variables

The variables LOS, MEDS, and REFILLS were all found to be highly correlated during exploratory analyses (Table 14). The Pearson correlation coefficients, each highly statistically significant ($p<0.0001$), were the highest between LOS and REFILLS at 0.810, followed by REFILLS and MEDS at 0.610 and MEDS and LOS at 0.520. This indicated a potential to introduce collinearity into the model when entering all three as independent variables in the multivariable logistic regression model. Collinearity may result in a lack of statistical significance of individual independent variables while the overall model may be strongly significant particularly for small and moderate sample sizes. Multicollinearity may also result in wrong signs and magnitudes of regression coefficient estimates, and consequently in incorrect conclusions about relationships between independent and dependent variable (122)." Preliminary model building in SAS when all three were entered as independent variables indicated an unstable model with potential collinearity (high standard error estimates and a highly significant Hosmer-Lemeshow Goodness of Fit test indicating poor model fit). In order to eliminate this problem, it was determined that LOS would not be included in the model-building, and REFILLS would serve as a substitute since the two were highly correlated. Additional concern existed regarding keeping both REFILLS and MEDS in the analysis, as they were also highly correlated. However, rationale exists that, although highly correlated, the variables are in fact measuring different attributes of medication taking and both should be considered (see Discussion for explanation of the use of REFILLS). Therefore in order to eliminate potential for additional collinearity issues, both variables were dichotomized at their median (MEDS=MEDCAT, REFILLS=REFILLCAT) (123) Chi-square analyses indicated that the recoded MEDCAT and REFILLCAT variables were significantly associated with each of the

three adherence measures in similar patterns as the continuous MEDS and REFILLS variables (Table 15). Notable differences did occur at 80% for both CSA and MPR, where MEDCAT was not significant while MEDS was significant; however it is preferred to keep the MEDCAT variable categorical due to the collinearity potential.

Table 14: Pearson Correlation Coefficient Comparisons of Highly Correlated Predictor Variables

	LOS	MEDS	REFILLS
LOS	1.00	0.52	0.81
MEDS	0.52	1.00	0.61
REFILLS	0.81	0.61	1.00

Table 15: Unadjusted comparisons of CSA, MPR, ASR with MEDCAT and REFILLCAT

		Cut Points of CSA									
		80%		70%		75%		85%		90%	
	Valid n	**Wald X^2 [a]**	**p-value [b]**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**
MEDCAT	2417	0.23	NS	**15.52**	**<.001**	**4.89**	**.027**	**10.21**	**.001**	**26.80**	**<.001**
REFILLCAT	2417	107.39	**<.001**	**159.40**	**<.001**	**147.45**	**<.001**	**64.08**	**<.001**	**15.75**	**<.001**
		Cut Points of MPR									
		80%		70%		75%		85%		90%	
	Valid n	**Wald X^2 [a]**	**p-value [b]**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**
MEDCAT	2417	**57.11**	**<.001**	**13.96**	**<.001**	**32.97**	**<.001**	**74.87**	**<.001**	**94.07**	**<.001**
REFILLCAT	2417	0.279	NS	**25.33**	**<.001**	**9.88**	**.002**	**4.77**	**0.029**	**19.84**	**<.001**
		Cut Points of ASR									
		80%		70%		75%		85%		90%	
	Valid n	**Wald X^2 [a]**	**p-value [b]**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**	**Wald X^2**	**p-value**
MEDCAT	2417	**125.17**	**<.001**	**132.12**	**<.001**	**120.97**	**<.001**	**107.37**	**<.001**	**77.68**	**<.001**
REFILLCAT	2417	**291.15**	**<.001**	**208.63**	**<.001**	**231.99**	**<.001**	**316.19**	**<.001**	**249.13**	**<.001**

BOLD indicates significance at p≤0.25
[a] From PROC LOGISTIC unadjusted analysis
[b] Significance set at p≤0.25
NS = Not Significant

Predictors of Adherence

In order to ensure comparability between all of the adherence measure models, a single sample size of 2292 CMAP participants with complete data for all variables were included in the multivariable logistic regression analysis. The modeling was performed in SAS Proc Logistic using the stepwise option. The level of significance for an adjusted variable to remain in the model was set at $p \leq 0.05$. Using the results found in the adjusted analyses, significant predictors of adherence and the interactions between them were entered into the model one at a time and remained in the model if they were significant after adjusting for the other variables in the model. Due to the large extent of literature demonstrating its significance in predicting adherence, age was forced into all of the models.

CSA

The step-wise modeling procedure yielded a similar final model for all cut-points of CSA except for 90% (Table 16). At the other four levels of CSA, four main effects (Age, Race, MEDCAT, REFILLCAT) and one interaction (MEDCAT*REFILLCAT) were significant at the $p<.05$ level and were entered into the final model. A ten-year difference in age yielded a significant Odds Ratio range of 1.11 to 1.17, indicating older individuals have greater adherence at all cut points of CSA with the exception of 90%. A strong race relationship is observed at all cut-points with 1.78 (90%) to 2.28 (70%) times higher adherence in Caucasian CMAP participants versus African-American CMAP participants. Although both MEDCAT and REFILLCAT are significantly associated with CSA, the interaction between the variables is also significant at cut points of 70%-85%. The direction of the Odds Ratios indicates a unique relationship is being observed within the MEDCAT*REFILLCAT interaction term. CMAP participants who received 4 or more medication while in enrolled in the program are significantly

less likely (OR Range: 0.28 – 0.75) to be adherent than those with 3 or fewer medications, regardless of the number of times they refilled those medications. Conversely, participants who received 30 or more refills, regardless of the number of medications they received while enrolled, were much more likely to be adherent (OR Range: 2.38 – 9.24) than participants who received 30 or fewer refills. The interaction effect is observed for individuals who received 4 or more medications, where adherence was worse for those that refilled those 4 or more medication 30 or more times versus those that refilled those 4 or more medications fewer than 30 times (OR 0.29 vs. 0.59 at CSA=80%). Participants who received 30 or more refills were much more likely to be adherent if they had received 3 or fewer medications while enrolled rather than if they had received 4 or more medications (OR 5.67 vs. 2.75 at CSA=80%). The interaction between MEDCAT and REFILLCAT disappeared at CSA cut at 90%, indicating that the effect of MEDCAT on CSA is no longer dependent on REFILLCAT and vice versa at that cut point. When using 90% as the cut point, the MEDCAT OR of 0.42 (CI 0.34, 0.51) indicates that participants receiving 4 or more medications are less likely to be adherent, and the REFILLCAT OR of 2.14 (CI 1.72, 2.66) suggests that those receiving 30 or more refills were more likely to be adherent.

In order to determine which cut point of CSA produces the best fitting model for the CMAP data, the Aikake Information Criterion (AIC) provided by SAS is shown. The model with the highest AIC is at 85% (AIC = 3135.406) while the lowest is at 70% (2486.677). All of the models had Hosmer-Lemeshow goodness of fit chi-squares with $p>0.05$, indicating all of the models fit the data reasonably well.

Table 16: Odds Ratios and 95% Confidence Intervals for Predictors of CSA at Varying Cut Points of Adherence

	80%		*70%*		*75%*		*85%*		*90%*	
AIC	**3051.73**		**2486.68**		**2835.36**		**3135.41**		**2873.53**	
Hosmer-Lemeshow Goodness of Fit (p-value)[b]	**8.61 (NS)**		**6.23 (NS)**		**4.56 (NS)**		**3.68 (NS)**		**8.89 (NS)**	
Adjusted R-Square	**0.13**		**0.17**		**0.15**		**0.10**		**0.07**	
	OR	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Continuous Predictors										
Age										
60 vs. 50	1.15	(1.09, 1.21)	1.15	(1.08, 1.22)	1.17	(1.10, 1.23)	1.11	(1.05, 1.18)	NS*	
Categorical Predictors										
Race										
Caucasian vs. African-American	2.03	(1.69, 2.43)	2.28	(1.87, 2.78)	2.13	(1.77, 2.57)	1.82	(1.52, 2.18)	1.78	(1.46, 2.17)
Total # of Medications Received (MEDCAT)										
≥ 4 vs. < 4 Medications	[c]		[c]		[c]		[c]		0.42	(0.34, 0.51)
Total # of Refills Received (REFILLCAT)										
≥ 30 vs. < 30 Refills	[c]		[c]		[c]		[c]		2.14	(1.72, 2.66)
Interactions										
Medications* Refills[a] (MEDCAT*REFILLCAT)									NS	
≥ 4 vs. < 4 Medications when Refills <30	0.59	(0.47, 0.73)	0.75	(0.60, 0.95)	0.68	(0.54, 0.85)	0.49	(0.39, 0.62)		
≥ 4 vs. < 4 Medications when Refills ≥30	0.29	(0.18, 0.46)	0.37	(0.18, 0.79)	0.31	(0.17, 0.56)	0.28	(0.19, 0.42)		
≥ 30 vs. < 30 Refills when Medications <4	5.67	(3.54, 9.10)	9.24	(4.46, 19.14)	7.46	(4.15, 13.40)	4.13	(2.80, 6.10)		
≥ 30 vs. < 30 Refills when Medications ≥4	2.75	(2.16, 3.50)	4.57	(3.41, 6.12)	3.40	(2.64, 4.39)	2.38	(1.86, 3.05)		

[a] Refers to the interaction between number of medications (≥ 4 vs. <4) and number of refills (≥ 30 vs. <30)

b A p-value <.05 signifies that the model may not be a good fit (119)

[c] Individual variable odds ratios are not shown when an interaction term exists

* Age was forced into the model for .9 because it was significant at all other cut-points of adherence

NS= Not Significant at p≤0.05

Note: The following predictors were included in the stepwise modeling but were not significant at p≤.05 and were not included in any of the CSA final models:: Education, Monthly Income, Current Health Status, Health Status Compared to One Year Ago, Gender, Marital Status, Work Status, Primary Diagnosis

MPR

A step-wise modeling procedure for determining significant predictors of MPR yielded four different models dependent on the cut point chosen (Table 17). Age was not significantly associated with MPR in any of the models, but as stated earlier, was included because of a priori hypotheses that age would be statistically associated based on previous research. Race was the only main effect that was significant at all cut points, with significant odds ratios ranging from 1.62 (CI 1.28, 2.05) at 90%, to 1.84 (CI 1.54, 2.20) at 70%. A significant effect was also observed for MEDS at all cut-points, but a significant interaction with REFILLS appears at the 70%, 75%, and 85% cut points of MPR. The direction of the relationship between the MEDS and REFILLS interaction term is identical to what was observed with CSA, with the exception MPR cut at 85% where the number of refills is not associated with adherence for those receiving 4 or more medications. A significant relationship was detected between Primary Diagnosis and MPR at cut points of 70% and 75%, but with only certain disease-disease relationships having significant odds ratios. Higher adherence is seen in participants with a diagnosis of hypertension or heart disease vs. those participants having a diagnosis of hypertension (OR: 1.35 & 1.38). Participants with respiratory illness have lower adherence than all of the other diagnoses at the 70% cut point (OR range: 2.06 – 3.71), but at MPR cut at 75% adherence does not differ between those with a diagnosis of respiratory and those with a diagnosis of diabetes. At a cut point of 80%, MEDCAT (OR=0.40, CI 0.33-0.49) and REFILLCAT (OR=1.58, CI 1.28-1.95) are significantly associated with MPR, while their interaction is not. The REFILLCAT association with MPR disappears at the 90% cut point, but MEDCAT remains significant (OR=0.33, CI 0.27-0.41). In assessing the best fitting model, MPR with a cut point of 90% yields the lowest AIC (2227.74), followed by 85% (2730.98) and 80% (3030.82).

Table 17: Odds Ratios and 95% Confidence Intervals for Predictors of MPR at Varying Cut Points of Adherence

	80%		70%		75%		85%		90%	
AIC	3030.82		3167.28		3165.43		2730.98		2227.74	
Hosmer-Lemeshow Goodness of Fit (p-value)[b]	8.22 (NS)		10.05 (NS)		4.78 (NS)		3.33 (NS)		7.31 (NS)	
Adjusted R-Square	0.065		0.085		0.083		0.068		0.078	
	OR	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Continuous Predictors										
Age										
60 vs. 50	NS		NS		NS		NS		NS	
Categorical Predictors										
Race										
Caucasian vs. African-American	1.70	(1.41, 2.05)	1.84	(1.54, 2.20)	1.82	(1.51, 2.19)	1.67	(1.36, 2.06)	1.62	(1.28, 2.05)
Total # of Medications Received (MEDCAT)										
≥ 4 vs. < 4 Medications	0.40	(0.33, 0.49)	[c]		[c]		[c]		0.33	(0.27, 0.41)
Total # of Refills Received (REFILLCAT)										
≥ 30 vs. < 30 Refills	1.58	(1.28, 1.95)	[c]		[c]		[c]		NS	
Primary Diagnosis*	NS						NS		NS	
Hypertension vs. Diabetes			1.35	(1.02, 1.78)	1.38	(1.03, 1.83)				
Heart Disease vs. Diabetes			1.80	(1.23, 2.64)	1.65	(1.13, 2.42)				
Hypertension vs. Respiratory			2.78	(1.51, 5.13)	2.76	(1.44, 5.27)				
Diabetes vs. Respiratory			2.06	(1.07, 3.96)	NS					
Heart Disease vs. Respiratory			3.71	(1.92, 7.19)	3.31	(1.66, 6.61)				
Depression vs. Respiratory			2.90	(1.35, 6.27)	2.90	(1.31, 6.42)				
Other vs. Respiratory			2.72	(1.42, 5.21)	2.60	(1.31, 5.15)				
Interactions										
Medications* Refills[a] (MEDCAT*REFILLCAT)	NS								NS	
≥ 4 vs. < 4 Medications when Refills <30			0.60	(0.48, 0.75)	0.54	(0.43, 0.68)	0.46	(0.35, 0.59)		
≥ 4 vs. < 4 Medications when Refills ≥30			0.30	(0.19, 0.45)	0.27	(0.18, 0.40)	0.28	(0.20, 0.40)		
≥ 30 vs. < 30 Refills when Medications <4			3.48	(2.29, 5.28)	3.05	(2.09, 4.45)	1.71	(1.22, 2.40)		
≥ 30 vs. < 30 Refills when Medications ≥4			1.73	(1.36, 2.19)	1.53	(1.20, 1.95)	NS			

[a] Refers to the interaction between number of medications (≥ 4 vs. <4) and number of refills (≥ 30 vs. <30)

[b] A p-value < .05 signifies that the model may not be a good fit

[c] Individual variable odds ratios are not shown when an interaction term exists

NS= Not Significant at p≤0.05

Note: The following predictors were included in the stepwise modeling but were not significant at p≤.05 and were not included in any of the MPR final models:: Education, Monthly Income, Current Health Status, Health Status Compared to One Year Ago, Gender, Marital Status, Work Status

ASR

Table 18 shows the results of stepwise modeling of Adherence Self-Report (ASR) yielding four different final models dependent on the cut point of ASR used. At cut points of 70% and 75% the models consisted of Age, HEALTHYR, Race, Gender, MEDCAT, and REFILLCAT. Gender, for the first time in any of the adjusted analyses, is significantly associated with adherence in both models, with higher adherence observed in females vs. males with OR=1.46 (CI: 1.16,1.84) at 70% and OR= 1.35 (CI: 1.08, 1.68) at 75%. The direction of the relationships between Age, Race, and REFILLCAT with ASR are similar to what was observed with CSA, with older age, Caucasian race, and greater or equal to 30 refills being positively associated with adherence. However, the significant OR for MEDCAT and ASR is in the opposite direction as was observed between MEDCAT and CSA and MEDCAT and MPR. In this analysis, at ASR cut points of 70%, 75%, and 80% (the only cut points where MEDCAT is significant), participants receiving 4 or more medications are MORE likely to be adherent (OR range 1.32, 1.46). Self-reported HEALTHYR is also significantly associated with ASR at 70%, 75%, and 80%, with higher adherence in participants reporting improved health compared to one year ago. HEALTH, for the first time, also appears as a significant predictor of ASR at 80%, 85%, and 90%, where adherence increases as self-reported health increases. The lowest AIC, indicating the best model fit, is observed at ASR cut at 70% (1976.72).

Table 18: Odds Ratios and 95% Confidence Intervals for Predictors of ASR at Varying Cut Points of Adherence

	80%		70%		75%		85%		90%	
AIC	**2364.66**		**1976.72**		**2131.51**		**2507.49**		**2774.57**	
Hosmer-Lemeshow Goodness of Fit (p-value)[b]	**8.14 (NS)**		**12.17 (NS)**		**14.67 (NS)**		**5.52 (NS)**		**10.63 (NS)**	
Adjusted R-Square	**0.30**		**0.31**		**0.30**		**0.30**		**0.22**	
	OR	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Continuous Predictors										
Age										
60 vs. 50	1.42	(1.33, 1.51)	1.43	(1.33, 1.54)	1.43	(1.34, 1.54)	1.40	(1.32, 1.49)	1.35	(1.27, 1.43)
Current Health (HEALTH)										
Fair vs. Poor	1.40	(1.24, 1.58)	NS		NS		1.30	(1.15, 1.48)	1.37	(1.22, 1.53)
Health Status Compared to One Year Ago (HEALTHYR)										
Somewhat Better vs. About the Same	NS		1.44	(1.26, 1.64)	1.39	(1.22, 1.57)	1.19	(1.05, 1.35)	NS	
Categorical Predictors										
Race										
Caucasian vs. African-American	1.56	(1.27, 1.93)	1.89	(1.49, 2.38)	1.84	(1.47, 2.30)	1.76	(1.43, 2.17)	1.53	(1.26, 1.85)
Gender										
Female vs. Male	NS		1.46	(1.16, 1.84)	1.35	(1.08, 1.68)	NS		NS	
Total # of Medications Received (MEDCAT)										
≥ 4 vs. < 4 Medications	1.33	(1.07, 1.65)	1.49	(1.17, 1.89)	1.32	(1.05, 1.66)	NS		NS	
Total # of Refills Received (REFILLCAT)										
≥ 30 vs. < 30 Refills	5.81	(4.43, 7.62)	7.83	(5.24, 11.31)	6.52	(4.74, 8.98)	5.63	(4.50, 7.04)	3.53	(2.91, 4.29)

[a] Refers to the interaction between number of medications (≥ 4 vs. <4) and number of refills (≥ 30 vs. <30)

[b] A p-value <.05 signifies that the model may not be a good fit

NS= Not Significant at p≤0.05

Note: The following predictors were included in the stepwise modeling but were not significant at p≤.05 and were not included in any of the ASR final models: Education, Monthly Income, Marital Status, Work Status, Primary Diagnosis

RESEARCH QUESTION 3

Utilization Data

A total of 815 (33.7%) of the 2417 patients with adherence data used in Question 2 had complete data available on the number of ED visits and hospitalizations in the 6 months before and after enrollment into the CMAP and will be used in this analysis. In order to be considered to have complete data, patients had to have given written permission to obtain their medical records from one of the three hospitals where complete data were obtained and indicated that they only used those three hospitals for any of their emergent or long-term care. Therefore, of the remaining 1602 patients without complete utilization data, 509 (31.8%) indicated use of a hospital where data could not be obtained and the remaining 1093 (68.2%) did not grant permission for the CMAP to access their medical records.

Comparison of CMAP Patients With and Without Utilization Data

T-tests and chi-square procedures were used to compare whether the 815 CMAP patients with complete utilization data differ from the 1602 CMAP patients with missing or incomplete utilization data. Table 19 contains the comparison of the two groups across several demographic and health variables. T-tests indicated that the samples significantly differ in age, with a mean age of 62.9 for the sample with utilization data and 60.6 for the sample without ($p=0.001$), as well as in total education ($p=0.003$) and total number of medications received ($p<0.001$). Chi-square tests revealed statistically significant differences in race, employment, self-report health, self-reported health compared to one year ago, and primary diagnosis (all $p<0.001$). The differences in age and education, although significant, do not appear to have any practical differences with the age difference less than two years, and the education difference being less

than half a grade (9.9 vs. 10.3). The differences in race are a bit more pronounced, with 70.1% vs. 64.2% of the utilization missing group reporting Caucasian race. The utilization missing group has higher rates of employment (11.0% vs. 5.8%) and unemployment (20.8% vs. 12.6%), but lower rates of being retired (36.3% vs. 44.8%) and receiving disability (24.4% vs. 28.8%). There was no statistically significant difference between the two samples in total income, gender, and marital status. Although there is a statistically significant difference in the mean MPR and ASR %, they are practically equal with only 2.6% and 4.1% differences, respectively. The mean CSA adherence was identical between the two groups.

Table 19: Comparison of CMAP Patients With and Without Complete Utilization Data

Variable	With Complete Utilization Data (n=815)	Without Complete Utilization Data (n=1602)	p-value*
Mean Age (SD)	62.9 (16.2)	60.6 (15.9)	**0.001**
Education (SD)	9.9 (3.0)	10.3 (2.8)	**0.003**
Total Income (SD)	$505.73 (362.2)	$501.72 (392.2)	NS
Number of Medications (SD)	4.6 (2.7)	3.8 (2.3)	**<.001**
Gender (n, %)			NS
Male	258 (31.7)	450 (28.1)	
Female	557 (68.3)	1152 (71.9)	
Race/Ethnicity (n, %)			**0.003**
Black or African-American	292 (35.8)	479 (29.9)	
Caucasian	523(64.2)	1123 (70.1)	
Other	0 (0.0)	0 (0.0)	
Marital Status (n,%)			NS
Single	104 (12.8)	215 (13.4)	
Married	232 (28.5)	485 (30.3)	
Divorced	137 (16.8)	289 (18.0)	
Separated	49 (12.8)	215 (13.4)	
Widow	293 (36.0)	497 (31.0)	
Other/Missing	0 (0.0)	2 (0.1)	

Table 19 CONTINUED: Comparison of CMAP Patients with and without Complete Utilization Data

Variable	With Complete Utilization Data (n=815)	Without Complete Utilization Data (n=1602)	p-value*
Employment (n, %)			**<.001**
Unemployed	103 (12.6)	334 (20.8)	
Employed (Full or Part Time)	48 (5.8)	176 (11.0)	
Disability	235 (28.8)	391 (24.4)	
Retired	365 (44.8)	582 (36.3)	
Never Worked	56 (6.9)	103 (6.4)	
Other/Missing	8 (1.0)	16 (1.0)	
Self-Reported Health (n, %)			**<.001**
Poor	189 (23.2)	353 (22.0)	
Fair	335 (41.1)	743 (46.4)	
Good	144 (17.7)	331 (20.7)	
Very Good	37 (4.5)	95 (5.9)	
Excellent	6 (0.7)	22 (1.4)	
Missing	104 (12.8)	58 (3.6)	
Self-Reported Health Now Compared to One Year Ago (n, %)			**<.001**
Much Worse	82 (10.1)	121 (7.6)	
Somewhat Worse	172 (21.1)	393 (24.5)	
About the Same	338 (41.5)	819 (51.1)	
Somewhat Better	72 (8.8)	151 (9.4)	
Much Better	46 (5.6)	62 (3.9)	
Missing	105 (12.9)	56 (3.5)	
Primary Diagnosis (n,%)			**<.001**
Hypertension	526 (64.5)	1017 (63.5)	
Diabetes/Blood Sugar	72 (8.8)	184 (11.5)	
Heart Disease	107 (13.1)	125 (7.8)	
Depression	14 (1.7)	57 (3.6)	
Asthma/Respiratory	14 (1.7)	38 (2.4)	
Other/Missing	82 (10.1)	181 (11.3)	
Mean Adherence (%)			
CSA	80.2	80.2	NS
MPR	68.8	71.4	**<.001**
ASR	83.0	78.9	**<.001**

* Significant at $p \leq 0.05$

Contingency Tables and Tests of Proportions to Explore Utilization Data

Tables 20 and 21 show the contingency tables comparing the number of Emergency Department (ED) visits and Hospitalization in the six month period before and after enrollment into the CMAP. The shading in the tables shows the differences pre and post-enrollment, with the non-shaded area on the diagonal indicating no difference. A visual analysis of the ED visit table shows the majority of patients (548 out of 815: 67.2%) did not have an ED visit before or after enrollment. More patients had an ED visit prior to enrollment, with 633 (77.7%) reporting zero visits pre-enrollment compared to 654 (80.2) with zero visits post. In general, however, the differences between the number and frequency of ED visits before and after enrollment appear to be small. The contingency table of hospitalizations, however, appears to show a much clearer difference between pre and post-enrollment utilization. In the 6-months before joining CMAP, 519 of the 815 (63.7%) participants did not have an overnight hospitalization, while that jumped to 637 of the 815 (78.2%) in the 6-months after joining. This difference persists for each comparison of the number of hospitalizations (1, 2, 3, ≥4), with the number post-enrollment being lower.

To confirm the descriptive findings observed in the contingency tables, McNemar's Test of Binomial Proportions was used. Table 22 shows the ED visit data collapsed down to yes (one or more ED visits) and no (zero ED visits) for both before and after enrollment. The chi-square statistic comparing the proportion of those that had a visit pre and not a visit post to those that had a visit post and not a visit pre (the discordant pairs) is not significant at the $p \leq 0.05$ level, indicating that there isn't a statistically significant difference in ED visits. The comparison of hospitalizations pre and post-enrollment (Table 23), however, shows that a statistically significant ($p < 0.001$) larger proportion of patients had an overnight hospital stay in the period

before enrollment and not one after. A total of 188 of the 815 (23.1%) had an overnight hospital stay in the 6-months prior to enrollment, but only 70 of 815 (8.5%) had an overnight hospital stay in the 6-months after enrollment.

Table 20: Contingency Table of Emergency Department (ED) Visits Pre and Post Enrollment in CMAP (n=815)

	# of ED Visits Post Enrollment				
# of ED Visits Pre Enrollment	**0**	**1**	**2**	**>=3**	**N**
0	***548***	67	11	7	633
1	76	***23***	8	8	115
2	20	12	***6***	8	46
>=3	10	6	1	***4***	21
N	654	108	26	27	815

Table 21: Contingency Table of Hospitalizations Pre and Post Enrollment in CMAP (n=815)

	# of Hospitalizations Post Enrollment					
# of Hospitalizations Pre Enrollment	**0**	**1**	**2**	**3**	**>=4**	**N**
0	***449***	59	5	3	3	519
1	145	***32***	9	5	3	194
2	30	12	***10***	3	1	56
3	7	5	5	***5***	1	23
>=4	6	7	2	3	***5***	23
N	637	115	31	19	13	815

Table 22: McNemar's Test of Emergency Department Visits Pre and Post Enrollment

ED Visit Pre Enrollment	ED Visit Post Enrollment		
	Yes	No	Total
Yes	76	106	182
No	85	548	633
Total	161	654	815

$X^2 = 2.31$
p value = NS

Table 23: McNemar's Test of Hospitalizations Pre and Post Enrollment

Hospitalizations Pre Enrollment	Hospitalizations Post Enrollment		
	Yes	No	Total
Yes	108	188	296
No	70	449	519
Total	178	637	815

$X^2 = 53.97$
p value < 0.001

Results of Poisson Regression Analysis

To determine whether adherence, taking into account utilization in the period prior to enrollment, can predict utilization post-enrollment, Poisson methods were employed. Each of the three adherence measures (CSA, MPR, ASR) were examined at various cut-points (70%, 75%, 80%, 85%, and 90%) to look for trends in the relationships between the adherence and pre-enrollment count interaction, as well as the various covariates. The final models are presented in Tables 23-28 below for each of the adherence measures, first for ED visits and followed by hospitalizations.

Emergency Department Visits

CSA

Age was significantly associated with the count of ED visits at all cut-points when examining the data using the CSA adherence measure (Table 24). In the CMAP sample at a CSA cut-point of 80%, those less than age 40 were 3.94 (95% CI: 2.67, 5.82) times as likely and those that were aged 40 to ≤60 were 2.28 (95% CI: 1.68, 3.08) times as likely to have an ED visit than the oldest group who were ≥ age 60. A race effect was also significant at all cut-points, with African-Americans anywhere from 1.33 (CSA 80%) to 1.40 (CSA 70%) times more likely to have an ED visit post enrollment than Caucasian CMAP participants. Education was also associated with ED visits after joining CMAP, with those participants having completed 11^{th} grade or less in school almost twice as likely to have a visit than those with a High School Diploma/GED or above (Odds Ratio Range: 1.85 to 1.89). Race and primary diagnosis were both not significant in all CSA models. The main variable of interest, the interaction between CSA adherence at the various cut-points and the count of ED visits prior to enrollment was not significant in any of the models. The CSA adherence measure alone (without taking into account

pre-enrollment visits) was also examined, and found to not be significant at any of the cut-points (results not shown).

MPR

Similar results as to those seen with CSA are observed over the various cut-points of MPR in Table 25, with age, race, and education all significantly associated with ED visits after enrollment. The odds ratio estimates of these three variables are almost identical for MPR as they were with CSA, with all MPR odds ratios within 0.1 of the CSA odds ratios. However, the adherence interaction with ED visits pre-enrollment is significant at the 85% and 90% cut-points of MPR, unlike CSA. In this analysis, individuals with MPR adherence less than 85% were 1.69 times as likely (95% CI: 1.02, 2.81) and individuals with MPR adherence less than 90% were 1.96 times as likely (95% CI: 1.08, 3.54) to have an ED visit after joining CMAP if they had 0 ED visits prior to enrollment. In contrast, for those patients that had one ED visit or more prior to enrollment, there was no effect of adherence on the outcome.

ASR

The analysis of ASR and ED visits at the five cut-points of adherence is presented in Table 26. The same three covariates (age, race, and education) are related to ED visits post-enrollment as was found with CSA and MPR. The direction of the odds ratios are the same, and the magnitude of the associations are also similar in the three measures with the exception of age < 40 vs. ≥ 60 which appears to be slightly less at each of the cut-points compared with the other two measures of adherence (ASR OR at 80% = 3.34 vs. CSA OR at 80% = 3.94). The interaction effect at all cut-points between ASR adherence and pre-enrollment ED visits was not significant.

Table 24: Outcomes of Poisson Regression Analysis of CSA as a Predictor of Emergency Department Visits After Joining the CMAP Program (with covariates) (n=815)

	CSA Cut-points									
	80%		70%		75%		85%		90%	
Predictors	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Age (Categories)										
<40 vs. ≥60	3.94	(2.67, 5.82)	4.14	(2.80, 6.12)	3.85	(2.61, 5.68)	4.08	(2.76, 6.02)	3.99	(2.71, 5.88)
≥40 to <60 vs. ≥60	2.28	(1.68, 3.08)	2.32	(1.72, 3.13)	2.26	(1.67, 3.06)	2.32	(1.71, 3.14)	2.32	(1.72, 3.15)
Race										
African-American vs. Caucasian	1.33	(1.02, 1.73)	1.40	(1.07, 1.83)	1.35	(1.04, 1.76)	1.35	(1.03, 1.76)	1.37	(1.04, 1.80)
Gender										
Males vs. Females		NS		NS		NS		NS		NS
Education (Last Grade Completed)										
≤11th Grade vs. ≥ 12th Grade/GED	1.87	(1.41, 2.49)	1.85	(1.40, 2.46)	1.87	(1.41, 2.49)	1.87	(1.41, 2.49)	1.89	(1.43, 2.51)
Primary Diagnosis										
Hypertension vs. Other		NS		NS		NS		NS		NS
Diabetes vs. Other										
Adherence (CSA*ED Visit Pre)										
Non-Adherent vs. Adherent at 0 ED Visit Pre Enrollment		NS		NS		NS		NS		NS
Non-Adherent vs. Adherent at 1 ED Visit Pre Enrollment										

NS= Not Significant at p≤0.05

Table 25: Outcomes of Poisson Regression Analysis of MPR as a Predictor of Emergency Department Visits After Joining the CMAP Program (with covariates) (n=815)

	MPR Cut-points									
	80%		70%		75%		85%		90%	
	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Predictors										
Age (Categories)										
<40 vs. ≥60	3.99	(2.71, 5.88)	3.78	(2.54, 5.63)	3.80	(2.59, 5.57)	3.72	(2.53, 5.47)	3.59	(2.45, 5.26)
≥40 to <60 vs. ≥60	2.32	(1.71, 3.14)	2.21	(1.62, 3.02)	2.22	(1.65, 3.00)	2.20	(1.63, 2.97)	2.10	(1.56, 2.83)
Race										
African-American vs. Caucasian	1.39	(1.06, 1.83)	1.34	(1.02, 1.76)	1.36	(1.03, 1.79)	1.36	(1.04, 1.77)	1.39	(1.08, 1.81)
Gender										
Males vs. Females		NS		NS		NS		NS		NS
Education (Last Grade Completed)										
≤11th Grade vs. ≥ 12th Grade/GED	1.86	(1.40, 2.47)	1.94	(1.45, 2.61)	1.90	(1.44, 2.53)	1.90	(1.43, 2.51)	2.08	(1.56, 2.77)
Primary Diagnosis										
Hypertension vs. Other		NS		NS		NS		NS		NS
Diabetes vs. Other										
Adherence (MPR*ED Visit Pre)										
Non-Adherent vs. Adherent at 0 ED Visit Pre Enrollment		NS		NS		NS	1.69	(1.02, 2.81)	1.96	(1.08, 3.54)
Non-Adherent vs. Adherent at 1 ED Visit Pre Enrollment								NS		NS

NS= Not Significant at p≤0.05

Table 26: Outcomes of Poisson Regression Analysis of ASR as a Predictor of Emergency Department Visits After Joining the CMAP Program (with covariates) (n=815)

	ASR Cut-points 80%		70%		75%		85%		90%	
	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Predictors										
Age (Categories)										
<40 vs. ≥60	3.34	(2.27, 4.92)	3.67	(2.48, 5.42)	3.68	(2.49, 5.44)	3.47	(2.35, 5.13)	3.55	(2.41, 5.23)
≥40 to <60 vs. ≥60	2.06	(1.53, 2.77)	2.17	(1.60, 2.93)	2.17	(1.61, 2.94)	2.10	(1.55, 2.84)	2.10	(1.55, 2.84)
Race										
African-American vs. Caucasian	1.38	(1.07, 1.77)	1.36	(1.05, 1.75)	1.34	(1.04, 1.74)	1.35	(1.05, 1.74)	1.33	(1.02, 1.71)
Gender										
Males vs. Females		NS		NS		NS		NS		NS
Education (Last Grade Completed)										
≤11th Grade vs. ≥ 12th Grade/GED	1.98	(1.50, 2.61)	1.93	(1.46, 2.56)	1.92	(1.45, 2.54)	1.97	(1.49, 2.61)	1.92	(1.45, 2.55)
Primary Diagnosis										
Hypertension vs. Other		NS		NS		NS		NS		NS
Diabetes vs. Other										
Adherence (ASR*ED Visit Pre)										
Non-Adherent vs. Adherent at 0 ED Visit Pre Enrollment		NS		NS		NS		NS		NS
Non-Adherent vs. Adherent at 1 ED Visit Pre Enrollment										

NS= Not Significant at p≤0.05

Hospitalizations

CSA

Poisson models of CSA and overnight hospitalizations(Table 27) show an association of age, but in the opposite direction observed in ED visits. Here, those patients ≥ age 60 were more likely to have a hospitalization in the period after enrollment compared to patients <40 years old (OR Range: 2.13 – 2.49). There were no observed differences between any of the other age groups. Race was a significant predictor of hospitalization after enrollment at all CSA cut-points except 90%, which was not significant. The magnitude and direction of the odds ratio relationships between race and hospitalizations are the same as in CSA ED visits. An interesting effect was observed for the main predictor of interest at the 70% cut-point of CSA, where adherent patients were 1.68 (95% CI: 1.04, 2.71) times as likely to have a hospitalization post-enrollment if they didn't have a hospitalization pre-enrollment. This association is marginally significant, and the implications of such a relationship are explored in the Discussion section.

MPR

The relationship between the interaction of interest (MPR and pre-enrollment hospitalizations) and covariates with the outcome of hospitalizations post-enrollment is explored in Table 28. Age is significantly associated with the outcome at cut-points 75%-90%, but not at 70%. At MPR cut at 75%, the oldest group was 2.49 times as likely to have a hospitalization after joining the CMAP then the youngest age group. At both 80% and 85% cut-points the oldest age group was more likely to have a hospitalization than the middle age group, although only marginally significant (p=0.492 at MPR cut at 85%). At all cut-points except for 80%, patients with African-American race were significantly more likely to have a hospitalization after enrolling in the CMAP (OR Range: 1.29 – 1.50). The adherence interaction variable here is marginally

significant at the MPR cut-point of 70%, with adherent individuals 1.48 (95% CI: 1.01-2.18) times as likely to have a hospitalization after enrolling if they didn't have a hospitalization prior to enrolling.

ASR

Finally, the models containing the hospitalization data at the five pre-determined cut-points of ASR are shown in Table 29. Our main predictor, the adherence and hospitalization pre-enrollment interaction, is not significant at all cut-points of ASR, indicating no association of adherence on post-enrollment hospitalization. Similar age and race trends as the other measures of adherence were found, with the oldest age group and African-American race both significantly associated with an overnight hospital stay after enrollment. A marginal difference was observed within primary diagnosis at the 85% ASR cut-point, where those with a diagnosis other than hypertension were 1.37 times as likely to have a post-enrollment hospitalization. This effect, however, only appeared at this adherence cut-point and was highly non-significant at the other cut points of ASR.

Table 27: Outcomes of Poisson Regression Analysis of CSA as a Predictor of Hospitalizations After Joining the CMAP Program (with covariates) (n=815)

	CSA Cut-points									
	80%		70%		75%		85%		90%	
	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Predictors										
Age (Categories)										
≥60 vs. <40	2.41	(1.27, 4.57)	2.13	(1.12, 4.03)	2.20	(1.16, 4.15)	2.44	(1.29, 4.62)	2.49	(1.31, 4.73)
≥60 vs. ≥40 to <60		NS		NS		NS		NS		NS
Race										
African-American vs. Caucasian	1.35	(1.05, 1.74)	1.42	(1.09, 1.86)	1.41	(1.08, 1.84)	1.34	(1.03, 1.73)		NS
Gender										
Males vs. Females		NS		NS		NS		NS		NS
Education (Last Grade Completed)										
≤11th Grade vs. ≥ 12th Grade/GED		NS		NS		NS		NS		NS
Primary Diagnosis										
Hypertension vs. Other		NS		NS		NS		NS		NS
Diabetes vs. Other										
Adherence (CSA*Hospitalization Pre)										
Adherent vs. Non-Adherent at 0 Hospitalizations Pre Enrollment		NS	1.68	(1.04, 2.71)		NS		NS		NS
Adherent vs. Non-Adherent at 1 Hospitalizations Pre Enrollment				NS						

NS= Not Significant at p≤0.05

Table 28: Outcomes of Poisson Regression Analysis of MPR as a Predictor of Hospitalizations After Joining the CMAP Program (with covariates) (n=815)

	MPR Cut-points									
	80%		70%		75%		85%		90%	
	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Predictors										
Age (Categories)										
≥60 vs. <40	2.62	(1.38, 4.98)		NS	2.49	(1.31, 4.75)	2.56	(1.35, 4.86)	2.51	(1.32, 4.76)
≥60 vs. ≥40 to <60	1.45	(1.05, 2.00)		NS		NS	1.39	(1.00[a], 1.93)		NS
Race										
African-American vs. Caucasian		NS	1.50	(1.15, 1.95)	1.30	(1.01, 1.68)	1.29	(1.00[b] 1.67)	1.32	(1.03, 1.71)
Gender										
Males vs. Females		NS		NS		NS		NS		NS
Education (Last Grade Completed)										
≤11th Grade vs. ≥ 12th Grade/GED		NS		NS		NS		NS		NS
Primary Diagnosis										
Hypertension vs. Other		NS		NS		NS		NS		NS
Diabetes vs. Other										
Adherence (MPR* Hospitalization Pre)										
Adherent vs. Non-Adherent at 0 Hospitalizations Pre Enrollment		NS	1.48	(1.01, 2.18)		NS		NS		NS
Adherent vs. Non-Adherent at 1 Hospitalizations Pre Enrollment				NS						

NS= Not Significant at p≤0.05

[a] Rounded from 1.0026 (p=0.482)

[b] Rounded from 1.0016 (p=0.492)

Table 29: Outcomes of Poisson Regression Analysis of ASR as a Predictor of Hospitalizations After Joining the CMAP Program (with covariates) (n=815)

	ASR Cut-points									
	80%		70%		75%		85%		90%	
	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Predictors										
Age (Categories)										
≥60 vs. <40	2.27	(1.20, 4.30)	2.26	(1.19, 4.28)	2.16	(1.14, 4.10)	2.25	(1.19, 4.27)	2.34	(1.24, 4.42)
≥60 vs. ≥40 to <60		NS		NS		NS		NS		NS
Race										
African-American vs. Caucasian	1.52	(1.17, 1.99)	1.50	(1.15, 1.97)	1.53	(1.17, 2.00)	1.54	(1.18, 2.01)	1.38	(1.06, 1.79)
Gender										
Males vs. Females		NS		NS		NS		NS		NS
Education (Last Grade Completed)										
≤11th Grade vs. ≥ 12th Grade/GED		NS		NS		NS		NS		NS
Primary Diagnosis										
Other vs. Hypertension		NS		NS		NS	1.37	(1.01, 1.86)		NS
Other vs. Diabetes								NS		
Adherence (ASR*ED Visit Pre)										
Adherent vs. Non-Adherent at 0 Hospitalizations Pre Enrollment		NS		NS		NS		NS		NS
Adherent vs. Non-Adherent at 1 Hospitalizations Pre Enrollment										

NS= Not Significant at p≤0.05

VIII. DISCUSSION

Research Question 1

In the current study, among a sample of older, chronically ill, indigent patients utilizing a medication access program, three different methods of calculating patient medication adherence were compared. The original population of the CMAP included almost 4000 patients, but only 2417 of them had usable electronic pharmacy prescription refill data and self-reported adherence data from interviews with a program pharmacist. The 2417 were older, less educated, poorer, more likely to be widowed than the 1550 that did not have adherence data. Additional analysis revealed that of 1168 patients with an Adherence Self-Report interview but no prescription refill data, 755 (64.6%) only had an initial interview and most likely never filled a prescription. With almost two-thirds of the patients without adherence data never filling a prescription after enrolling in the program, these CMAP patients may be different somehow than those with adherence data. At enrollment into the CMAP the patient receives a prescription benefits card, but it is up to that patient to use it at his/her pharmacy the next time they fill/refill a prescription. As the group without adherence data is younger and earns significantly more per month, it's possible that these individuals did not utilize the discount prescription card and paid out of pocket for prescriptions. Another possibility is that those who didn't fill a prescription were healthier and so may have signed up for the program for a single prescription (rather than for a chronic care prescription) or in case they needed the service, but never actually used it. Unfortunately due to an excessive amount of missing self-reported health (41.9%) and primary diagnosis (23.7%) data, it is impossible to tell from the available data alone if these individuals were healthier in addition to be being younger. The samples clearly differ, and therefore it

should not be assumed that the adherence data and adherence calculations for the 2417 are representative of the larger CMAP population.

When looking at the descriptive statistics of CSA, MPR, and ASR, it's clear that the three measures have some similarities that justify an in-depth comparison, including similarities in means, modes, standard deviations, and variances. The 9.7% difference in the calculated mean adherence of CSA (80.2%) and MPR (70.5%) in the CMAP sample is almost identical to the 10.3% difference between CSA (86.2%) and MPR (75.9%) found by Karve et al in a group of almost 5000 older diabetics receiving Medicaid benefits in rural Arkansas (75). This similarity reinforces that the measures were calculated correctly and that the levels of adherence are around what would be expected in a similar population. The means of CSA and ASR were nearly identical, as were the magnitude of the differences between MPR and ASR and CSA and MPR, leading to hope that CSA and ASR would be highly correlated. Truncating CSA and MPR at 100% was attempted to remove the variability introduced by having adherence's over 100% (and as high as 506%), which led to large reductions in the variance, kurtosis, and skew of the two measures without greatly affecting the means. However the plots and the tests for normality of the three measures clearly show that their distributions are all significantly differ from normal even after truncating. Hence the decision to dichotomize the adherence measures for the remainder of the analysis was justified not only due to the precedent set in the literature, but also due to CSA, MPR, and ASR being non-normally distributed continuous variables.

The decision to use multiple cut-points when examining adherence measures is not new and has been used previously by Wetzels and colleagues and most recently by Tam et al (32, 124). It provides the advantage of looking at whether varying the definition of adherence changes the relationship the adherence measures has with another variable. In the CMAP

population, varying the cut-points in 5% increments between 70% and 90% greatly influences the proportion of adherent and non-adherent patients. When adherence is cut at 70%, CSA and ASR have similarly high rates of adherence (74.0% and 76.6%, respectively), while MPR is much lower (54.0%). At the highest cut-point of 90%, about half of patients are adherent (53.8%) as measured by ASR, one-third (32.1%) as measured by CSA and one-fifth (19.3%) as measured by MPR. The plots of the adherence measures explain why the ranges of proportions are much larger than the 20% range in cut-points, as CSA, MPR, and ASR data are all generally clustered in the 70%-100% ranges. This large variation in the proportion of patients considered adherent based on cut-points further supports exploring these cut-points when looking at the relationships between the adherence variables.

All of the tests to determine if the three measures were comparable showed that they appear to differ regardless of the chosen cut-off value of adherence. All of the two-way McNemar's comparisons were significant, indicating that the proportions of adherent and non-adherent patients differed between the measures. However, McNemar's test only takes into account discordant pairs, and a visual inspection of the data shows that each of the comparisons have more pairs that agree than disagree. Next, a comparison of the data using the Spearman Correlation Coefficient showed that there is indeed a very strong correlation between CSA and MPR (0.903), as would be expected with two similar methods of calculating adherence using the pharmacy dataset. Instead, the correlations of interest here are the relationships between both CSA and MPR with ASR, which are weak at around 0.163 (CSA and ASR) and 0.093 (MPR and ASR). These findings of a slight correlation are similar to the results observed by Wang who found Spearman correlations of 0.15 (CI: 0.01, 0.28) in a similar analysis of pharmacy vs. self-reported adherence data (125). The observed correlations in the CMAP sample were statistically

significant due to the large sample size of the study, but the coefficient's proximity to 0 indicates that they may not be clinically useful or meaningful. Finally, the kappa statistic was used to explore the level of agreement between the measures. Kappa looks at reproducibility, and here is determining the level of agreement between CMAP patient adherence as defined by each of the measures. Reinforcing our findings from the other two tests, the level of reproducibility is small between the self-reported ASR and both CSA and MPR, not varying greatly at the different cut-points. The largest kappa between ASR and CSA, 0.149 at the 70% cut-point, is nearly identical to the kappa of 0.19 observed by Thorpe and colleagues when comparing electronic pharmacy data and self-reported adherence among chronically ill male veterans (126). Generally, in order to use a measure interchangeably, we would expect to have kappa statistics higher than 0.75, and the current results do not approach that.

The results of the analysis show that it would not be recommended to use ASR as a substitute for either of the calculated adherence measures from electronic pharmacy data without further study. Further study of the psychometric properties of the pharmacist interview questionnaire including comparisons to other validated instruments to measure adherence is required (127, 128). These findings are not entirely surprising given that patients often over-report medication taking behavior (85, 86, 125), and electronic pharmacy refill data can sometimes underestimate adherence (129). Garber, in a review of the literature examining adherence, found that self-reported adherence measures were only highly concordant with electronic measures in 17% of studies (89). Additionally, the ASR measure is based on a single question asked of patients every 6-months, while CSA and MPR are usually based on multiple refills/data points. The similarities between CSA and MPR were expected, but large enough differences exist between the two measures (kappa=0.658) that using them interchangeably

should be questioned Further analysis is warranted to determine whether CSA or MPR is a better measure of adherence for the CMAP population.

Research Question 2

A key component of adherence, apart from measuring it, is determining who will or will not be adherent so that interventions can be tailored for those patients with suboptimal compliance. While performing the unadjusted analyses in order to determine which predictors would be entered into the multivariable model predicting adherence, several patient variables emerged as being associated with each of the adherence measures. Strong unadjusted relationships existed between CSA, MPR, and ASR with age, number of refills, number of medications, total number of days of medication received, race, work status, and primary diagnosis. Apart from work status, most of these variables were hypothesized to be associated with the adherence measures based on previous research. Varying the cut-point of the adherence measures appears to alter the unadjusted relationships with many of the predictors, but not in any discernable clear pattern where one cut-point would be preferred over another. Note that almost every variable at each cut-point of ASR was significant, but many of these relationships went away in the adjusted analysis.

The multivariable logistic regression analysis revealed strong collinearity between "number of refills" (REFILLS), "number of medications" (MEDS), and "total number of days of medication received" (LOS) as predicators of adherence. Intuitively, it stands to reason that the three of these variables are strongly related, as all are measuring medication taking behavior. A particular problem exists with the LOS variable because it is strongly related to both REFILLS and MEDS, but it is also the denominator in the MPR calculations. Therefore the choice to

eliminate LOS, and to dichotomize the REFILLS and MEDS variables reduces the collinearity of the relationships between adherence and the other predictors. The analysis found race was the one variable that was significant over the five cut-points of all three adherence measures, with adherent CMAP patients about two times more likely to be Caucasian than African-American. This was not surprising given that race is traditionally associated with adherence, however the hypothesis that the similar socioeconomic status and geographic area of the CMAP population would eliminate any race effect on adherence is unfounded. Krousel-Wood found similar race differences in a study of adherence measures within a comparable rural-Louisiana population, as did Hyre and colleagues in an urban health clinic in Louisiana, perhaps indicating the need for further study to determine if geographic variables related to culture and healthcare access are contributing to this lower adherence (77, 130). In a study of similarly aged minority Medicaid recipients in California, the researchers found that African-American patients were 1.5 times as likely to become non-adherent, underscoring that racial differences often related to access exist when looking at predictors of adherence (131). Further analyses of the data (not shown) stratifying on race did not reveal any major differences between the races in any of the other variables, indicating that factors contributing to African-American non-adherence were most likely not measured and/or analyzed in this study.

The next strongest predictor of any of the adherence measures was age, where adherent CMAP patients were 1.15 times (MPR at 80%) and 1.45 (ASR at 80%) more likely to be ten years older than non-adherent CMAP enrollees. Given that older chronically ill adults are more likely to be affected by their illness and feel the consequences of medication non-adherence, this result is not surprising. The CMAP results agree with a recent study of diabetics enrolled in commercial HMO found that younger age was one of the only significant factors ($p=0.025$) to

predict non-adherence, as did a study of similarly aged hypertensive veterans (39, 132). As most of the CMAP patients were aged 50 or older, the finding of an age association with CSA and ASR would seem to indicate that adherence continues to increase as an individual ages, and that even in the older populations there are opportunities to impact adherence. MPR was not associated with age in the adjusted analysis, which agrees with the marginal significance observed in the unadjusted regression analysis. Interestingly, the lack of association between MPR and age may provide one of the best clues as to why MPR may not be an appropriate measure of adherence in this CMAP sample. Age and MPR have the strongest unadjusted association at the MPR cut-point of 70% (p=0.004), which is the cut-point of MPR when most CMAP patients are considered "adherent", while age and CSA have the weakest association at CSA=90% (p=0.019) which is the CSA cut-point when most CMAP patients are "non-adherent." This would seem to indicate that if age is truly associated with adherence, and since MPR underestimates adherence compared to CSA, that the MPR measure is distorting the relationship between age and adherence. In spite of these findings, MPR should not be discounted as a usable measure without further evidence that it may not be capturing adherence correctly.

The dichotomized variables for number of medications (MEDCAT) and number of refills (REFILLCAT) were significantly associated with all three adherence measures, dependent on the cut-point, in the adjusted analysis. For ASR, adherence was associated with taking less than four medications (compared to taking greater than or equal to four medications), and with having more than 30 refills (compared to having less than 30 refills). These results give the impression that those CMAP patients who are in the program longer (as measured by refills) and who have filled multiple medications have better adherence. In the two pharmacy refill measures of adherence, an unanticipated significant interaction effect was observed between MEDCAT and

REFILLCAT at three of five cut-points of MPR and four of five cut-points of CSA. At the 80% cut-point of CSA non-adherent CMAP patients were more likely to have received four or more medications while enrolled, and those that refilled those medications 30 or more times have an OR=0.29, while those that received four or more medications and refilled those medications fewer than 30 times have an OR=0.59. Conversely, at 80% CSA, adherent CMAP enrollees are 2.75 times as likely to have 30 or more refills and have filled four or more different medication, but are 5.67 times as likely to have 30 or more refills and have filled fewer than four medications. When significant, the direction of the relationships in this interaction is the same for both MPR and CSA and the magnitudes are similar. It stands to reason that this effect is real and makes sense, where adherence is higher in patients who are on a small stable number of prescriptions but refill those prescriptions many times. This interaction is an important finding because it may help to explain why the relationship between number of medications and adherence is inconsistent in the literature, as the mitigating effect of the number of refills is causing the discrepancy. Studies by Chapman, Siegel, Grant and O'Leary, and Grant et al where the relationship between number of medications and adherence was explored, none of the authors collected or reported on refill data (39, 59, 96, 97).

Note on Using Refills as a Predictor of Adherence

To address any concerns in using refills as a predictor of CSA since the number of refills is in the denominator of the CSA calculation, its relationship with all three variables was examined. Scatter-plots of refills and each of the three adherence measures showed a strong linear trend, with all three adherence measures increasing with more refills (see Appendix). Refills was then regressed on each of the three measures as continuous variables, using Proc GLM and all three

adherence measures were significantly associated with refills in a single linear regression model. This shows that the effect of refills as a predictor of CSA is not due to an artificial mathematical relationship, but the true relationship that refills has on adherence. Additionally, each of the final prediction models were changed to remove adherence and re-run (not shown), and this did not effect the Odds Ratio and p-values of the relationship between the other variables (age, race, etc) and the adherence measures. This is important, because one would expect that if refills was causing an artificial relationship, once it was removed from the CSA model, it would effect the relationship those variables had on adherence. But here, removing refills did not effect the OR or p-values for any of the three adherence measures. A more in-depth explanation can be found in the Appendix.

Other predictors were significant at certain cut-points of ASR, but many of the significant relationships observed in the adjusted analysis disappeared during multivariate modeling. Current self-reported health, self-reported health compared to one year ago, and gender all are significantly associated with ASR at three or fewer cut-points, with higher adherence in females and those reporting better health. Primary diagnosis was significant at two cut-points of MPR, with adherent participants more likely to have hypertension or heart disease than diabetes. The fact that these relationships only appear at certain cut-points lead the authors to believe that these relationships may be spurious and further exploration is necessary. Caucasian race and older age are the only predictors that appear to be consistently significantly associated with adherence regardless of the measure used, while the MEDCAT/REFILLCAT interaction seems to indicate that the relationship between adherence and medications is predicated on the relationship to refills in predicting CSA and MPR.

Research Question 3

The final analysis looked at whether the three adherence measures are related to emergency department (ED) use and hospitalizations in the 6-month period after enrolling in the program, taking into account the number of ED and hospitalizations in the 6-month period before enrollment. Using the 6-month period before enrollment enables the author to explore the relationship between adherence and utilization while accounting for the CMAP patient's history, unlike previously published analyses. Obtaining CMAP patient protected medical data was often difficult, as discussed in the Limitations section below, leading to a large reduction in sample size with complete data for this final analysis. A comparison of characteristics between those with utilization data and those without found that while they do indeed differ in important characteristics such as age, race and education, many of these differences are small.

The initial analysis of the 815 CMAP patients with utilization data seems to indicate that there was not a statistically significant reduction in ED visits in the period after enrollment compared to the period before enrollment, however a significant difference does exist in overnight hospitalizations. Although important to examine, the absence or presence of a relationship between ED visits and hospitalizations pre and post enrollment does not effect examining the relationship with adherence, as adherence may alter the relationship between pre and post utilization.

Here, adjusting for several covariates, the relationship between the interaction of adherence and pre-enrollment ED visits was significantly associated with ED visits after enrollment at the upper two cut-points of MPR. Although this interaction was only significant at those two points, the importance of the direction and the magnitude cannot be understated.

Other studies, mentioned earlier, found similar associations with electronic measures of adherence and ED visits but none had taken into account utilization prior to the period of adherence being measured. The association of MPR and ED utilization are backed by results obtained by Hepke, Martus and Share, who found a similar protective effect of higher adherence on fewer ED visits in a diabetic sample (44). The CMAP findings are especially important because one of the original intentions of the program was to provide individuals with low-cost prescription medications so they would be adherent and be less likely to seek emergent care. A results paper published in 2005 by Lefante et al on the first year of CMAP pharmacist interviews found that adherence significantly increased over time once CMAP participants began meeting regularly with the program pharmacists (23). Without data beyond the first 6-months of the program, it's difficult to know if the effect of increased self-reported adherence would lead to an even greater decline in ED visits in the CMAP population. Further research would be needed to examine this issue, with access to the data being the largest barrier.

Together with the results of the Lefante paper, the current research shows the importance of monitoring adherence and using targeted interventions to improve adherence. There have been several large studies to implement interventions to help improve patient adherence to prescriptions medications, with mixed results. A 2003 meta-analysis of 41 behavioral interventions to improve adherence found an overall effect size of 0.07 for improving adherence, while Schedebauer found no intervention of the eight examined helped improve compliance to lipid-lowering medications.(133, 134) Very recently, a group out of the Medical University of South Carolina conducted a trial to compare 3 strategies to improve adherence (135). One of the three groups included phone contacts with a pharmacist, but none of the interventions differed from usual care. These results are contrary to the CMAP findings of improved adherence over

time as found in the earlier program paper, where adherence was measured using ASR. Perhaps a future analysis would be to model adherence over time using the two electronic measures, MPR and CSA, to see if adherence improves over time and if it correlates to the physician reviews.

A lower number of ED visits with higher adherence, a natural extension of these results, would result in significant cost savings at the current average expense of $651 per visit for those 65 and older (136). Lower adherence has also been found to predictive of an almost two-fold increase in utilization-related costs for non-adherent patients enrolled in an insurance plan in Maryland, with the authors concluding that adherent patients incurred 12.5% lower medical costs overall (104). Non-adherence can also lead to a higher risk of adverse events and drug-related emergencies, as Yee found when examining ED visits in an elderly veteran population. She found that medication non-adherence accounted for 19% of drug-related ED visits, many of which led to a longer hospitalization (107). Any reduction in costs for this chronically ill population of older adults in Central Louisiana is crucial, as many are living below the poverty threshold. The CMAPs attempt to improve adherence to reduce emergency department use appears to have been successful in the first six-months, leading to substantial cost-savings in reduced ED usage. Persistance of this effect should be examined, as well as total estimated cost-savings.

Unfortunately, the opposite direction of the association of adherence and hospitalizations was found. Surely surprising, adherent CMAP participants appear to be more likely to have a hospitalization if they didn't have one prior to enrolling. This significant odds ratio relationship only occurred at the extreme lowest cut-point of adherence for both MPR and CSA and closely approached non-significance. Although this finding shouldn't be dismissed, it is contrary to

results achieve by Hepke, Lau, Kane and others who found that increased hospitalization are associated with lower drug adherence (almost always dichotomized at 80%) (43, 44, 137). Also, it's possible that this relationship could be an anomaly that is occurring in the first six-months of the program and would not persist beyond. Similar to ED visits, without this data available it is impossible to tell. The likelihood also exists that hospitalizations are related to many factors, with patient adherence only accounting for some of them (discussed below in Strengths and Limitations). Despite not being the main variables under study, the other covariates that were significantly associated with utilization post-enrollment, including race and age, are similar to the results obtained in the other studies (64).

STRENGTHS and LIMITATIONS

The main strength of the current study is the large amount of prospectively collected data on the population under study. With sample sizes in the hundreds or thousands, depending on the analysis, the power to detect even small associations is increased. Additionally, a large amount of data were available on demographics, self-reported health, medication acquisition, hospital utilization, and patient interviews with program pharmacists, allowing for the analysis of numerous variables and adherence. The homogeneity in socio-economic status and income of the population was also an advantage because it allowed for the comparisons to focus on differences not related to monthly income and earnings. CMAP patients were also similarly located in a rural area of Louisiana that identifies itself as a collective state region (the Cenla in CMAP refers to "Central Louisiana"), consequently reducing any geography-related bias.

Using various cut-points for each of the adherence measures allowed the authors to look at how varying the definition of adherence can affect relationships with other variables. By

varying the cut-point we were able to observe the hypothesized result of an association of adherence and pre-enrollment ED visits that we would not have other seen if MPR was fixed at 80%, as in most studies. Another advantage of varying the cut-point was that in the analysis of predictors of adherence it reinforced that certain relationships would persist between adherence and the predictor variables even at the different cut-points, such as race and age.

One of the main limitations of the study is the use of the adherence measures overall, and not by condition. The difficulty in stratifying the adherence data by medication class or condition for which it was used came from the rather large distribution of classes of medication available to program participants. While this large selection of medications to treat a host of chronic conditions surely made for a better medication access program, it created the problem of having too many classes to analyze separately. Additionally, the main research question in our first analysis was whether the self-reported ASR was similar to the electronic pharmacy measures, and the ASR data is overall and not medication specific. As a result, the three adherence measures used in this study were more an overall indication of medication taking behavior rather than looking at any adherence associated with one particular disease or condition. This may be one of the reasons why very few significant associations were found with primary diagnosis in any of the analysis predicting the adherence measures – the grouping of medication classes to an overall adherence may have diluted any client disease-specific or medication class-specific relationships with adherence.

There are some built-in limitations with using electronic measures such as MPR and CSA, as the formulas don't necessarily allow for real-life scenarios that can influence adherence. There are many medications that are not taken regularly (i.e. anti-migraine) or in doses that can always be measured (inhalers), and these medications were eliminated when identified in the

data cleaning stage. Adherence calculations can also be affected if medication samples are given to the patient by the doctor, if the physician writes a prescription so that the patient can get a larger dose refilled but the dosing instructions don't change, or if a patient switches back and forth between medications due to adverse reactions.

A limitation in the analysis of question 3 data was the large amount of missing utilization information due to lack of access to medical records. At each interview (initial and follow-up) all patients were asked to sign authorizations to allow the CMAP program to obtain the patient's medical records for any hospitals that they had used for emergency care or hospitalizations in the previous 6 months. For unknown reasons, many CMAP participants either chose not to sign medical record release authorizations or did not recall having used a hospital for any care. Data are not available on patient refusal rates in the current sample, however no fewer than two local hospitals refused to release patient records even after having made arrangements prior to the start of the CMAP and being provided with the signed authorizations for medical record release. Additionally, the hospitals that did cooperate were hesitant to release full utilization information, including not releasing ICD-9 diagnosis codes. While there is no reason to think that a systematic bias was introduced by only obtaining data from some of the hospitals, it is impossible to know if those patients that didn't sign a release or claimed to not have used a hospital in the previous 6-months are different than those with utilization data. Without utilization data for the complete CMAP cohort to know if the lack of a relationship between adherence and hospitalizations is real or due to an unknown bias in data collection and reporting.

Missing ICD-9 codes also make it impossible to know the true reasons why a CMAP participant visited the ED or was hospitalized. It is very possible that most ED visits and hospitalizations were the results of accidents, falls, and other medical issues unrelated to

adherence (138). Examining the relationship of adherence on overall utilization in the CMAP sample most likely contributed to the contradictory results obtained, and more detailed data on the reasons for the visits and hospitalizations could help to bring forth the true relationship.

Another concern with the analysis in question 3 is that the adherence measures being used are for the entire length of enrollment while utilization is being looked at over only the first 6 months after enrollment. The reason for using overall adherence and not adherence measured only in the 6-month period after enrollment is because ASR is only collected once every 6-months, and many patients did not have multiple refills in the first 6 months. Therefore the adherence measures used in the Poisson analysis, as stated earlier, are more of an overall measure of medication taking behavior (i.e. a characteristic of the patient) rather than just in a pre-defined period. The lack of association between the self-reported health and adherence may be deceiving because the health variables are a mean of the responses over each of the patient CMAP interviews. It is possible that as adherence fluctuated so did self-reported health, but using the mean of both eliminated the ability to see that relationship.

Finally, the major limitation of this study is that it may not be generalizable to the larger United States chronically ill, indigent, older adult population. There was a sizable amount of missing data for adherence and utilization, and the comparisons of those with and without data showed that significant differences do exist between them. This would limit the applicability of the findings to those individuals who had complete data, rather than the entire CMAP cohort or beyond.

VIII. CONCLUSIONS

This study of adherence in a rural medication access program with older adult participants found that a self-reported measure of adherence does not correlate or agree well with two commonly used electronic measures of adherence. Varying the cut-points of commonly used adherence measures can change the relationships those adherence measures have with other variables. Age and race were found to be CMAP patient characteristics that may predict adherence, while a particularly interesting association was found with higher adherence in patients who take fewer medications but refill them many times. The marginally significant relationship observed between adherence and utilization shows that a non-adherent CMAP patient without an ED visit pre-enrollment is almost twice more likely to have an ED visit post-enrollment than an adherent CMAP patient without an ED visit pre-enrollment. Therefore this appears to be one of the first studies to find the association between adherence and ED utilization taking into account utilization prior to the period of adherence being measured. Recent studies have found that adherence is associated with outcomes related to risk reduction and improved health, further underscoring the need for continued study (139, 140, 141, 142). With increased recognition in the scientific community of the significance of the relationship of adherence and health, studies such as this one become an important contributor to the overall field of knowledge.

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APPENDIX

- List of Abbreviations
- Complete List of Primary and Secondary Diagnoses for CMAP Participants
- Normality Plots for CSA %, MPR %, and ASR %
- Scatter-plots of Refills with MPR, CSA, and ASR
- SAS Results of Refills regressed on CSA, MPR, and ASR

List of Abbreviations (in order they appear in the document)

CSA	Continuous Single-Interval Measure of Medication Availability
MPR	Medication Possession Ratio
ASR	Adherence Self-Report
ED	Emergency Department
ADHD	Attention Deficit Hyperactivity Disorder
MRA	Medication Refill Adherence
HMO	Health Maintenance Organization
LDL	Low-density Lipoprotein
HBA_{1c}	Hemoglobin A_{1c}
CMAP	Cenla Medication Access Program
HIPAA	Health Information Portability and Accountability Act
GED	General Equivalency Diploma
OR	Odds Ratio
CI	Confidence Interval
SD	Standard Deviation
HTN	Hypertension
DM	Diabetes Mellitus
ICD-9	International Classification of Disease Version 9

Complete List of Diseases Conditions for CMAP Adherence Sample (n=2417)

Primary Diagnosis		Frequency	Percent
Valid	High Blood Pressure/Hypertension	1543	63.80
	Diabetes/Blood Sugar	256	10.60
	Heart Disease	232	9.60
	Depression	71	2.90
	Asthma/Respiratory	52	2.20
	Arthritis/Gout	46	1.90
	Epilepsy/Seizure	42	1.70
	Thyroid Disease	32	1.30
	Stroke	22	.90
	High Cholesterol	21	.90
	None	13	.50
	Cancer/Malignancy	12	.50
	Anxiety/Nerves	9	.40
	Glaucoma/Cataracts	6	.20
	Kidney Disease	5	.20
	Ulcers/GERD/Hiatal Hernia	5	.20
	Bi Polar	4	.20
	Lupus	4	.20
	Parkinson's Disease	4	.20
	Breast Cancer	3	10
	Liver Disease	3	10
	Missing	2	10
	Colon Cancer	2	.10
	Emphysema	2	10
	Fibromyalgia	2	10
	Hormones	2	.10
	Schizophrenia	2	.10
	Alzheimer	1	.00
	Alzheimers	1	.00
	Anemia	1	.00
	Back Injury	1	.00
	CHF	1	.00
	COPD	1	.00

	Degenerative Disc Disease	1	.00
	Hansen's Disease	1	.00
	HIV +	1	.00
	HIV/Aids	1	.00
	Leukemia	1	.00
	Multiple Sclerosis	1	.00
	Osteoporosis	1	.00
	Paralysis	1	.00
	Peripheral Artery Disease	1	.00
	Post Polio Syndrome	1	.00
	Pre-Leukemia	1	.00
	Psychosis	1	.00
	Pulmonary Disease	1	.00
	Renal Failure	1	.00
	Total	2417	100.0

	Secondary Diagnosis	Frequency	Percent
Valid	Diabetes/Blood Sugar	447	18.50
	None	385	15.90
	Heart Disease	314	13.00
	High Blood Pressure/Hypertension	293	12.10
	High Cholesterol	287	11.90
	Arthritis/Gout	141	5.80
	Depression	110	4.60
	Asthma/Respiratory	102	4.20
	Thyroid Disease	93	3.80
	Ulcers/GERD/Hiatal Hernia	53	2.20
	Anxiety/Nerves	39	1.60
	Osteoporosis	25	1.00
	Glaucoma/Cataracts	22	.90
	Epilepsy/Seizure	19	.80
	Stroke	10	40
	Kidney Disease	9	40
	Parkinson's Disease	8	.30
	Emphysema	6	.20
	Missing	5	.20

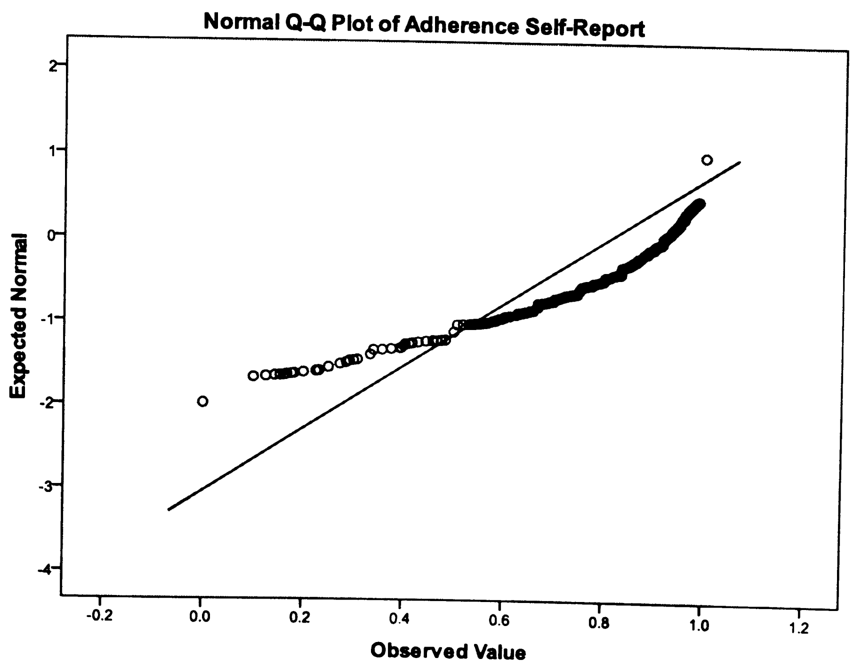
Cancer/Malignancy	5	.20
Prostate Problems	3	10
Stomach Problems	3	10
Bi Polar	2	10
Fibromyalgia	2	10
Hepatitis	2	10
Hormones	2	10
Liver Disease	2	10
Lupus	2	.10
Alzheimer's	2	10
Migraine	2	.10
Missing	1	.0
Anemia	1	.0
Back Problems	1	.0
Bipolar	1	.0
Bowels (Diarrhea)	1	.0
Bronchitis	1	.0
CHF	1	.0
Grave's Disease	1	.0
Hepatitis C	1	.0
Hypokalemia	1	.0
IBS	1	.0
ADHD	1	.0
Multiple Sclerosis	1	.0
Muscular Degeneration	1	.0
Prostate	1	.0
Psoriasis	1	.0
Pulmonary Fibrosis	1	.0
Renal Failure	1	.0
seizures	1	.0
Shingles	1	.0
stomach adhesions	1	.0
Triglycerides	1	.0
Vasculitis	1	.0
Total	2417	100.0

Normality Plots for CSA %, MPR %, and ASR %

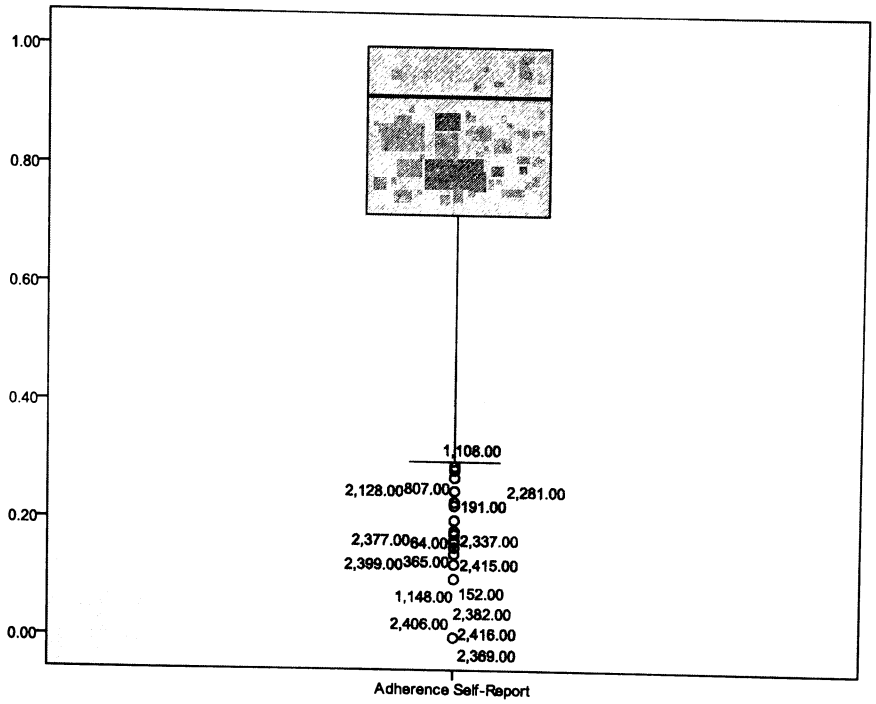
ASR Stem-and-Leaf Plot

```
 Frequency     Stem &  Leaf

   173.00 Extremes     (=<29)
    48.00        3     033333
    11.00        3     7&
    36.00        4     00012&
     7.00        4     &
   102.00        5     000000000000&
    37.00        5     788&
    57.00        6     00122234
    94.00        6     56666666789
    66.00        7     000112234
   127.00        7     5555555556777899
   169.00        8     000001112333333333344
   189.00        8     555556666677777788888899
   287.00        9     000000011111111122222233333333444444
   259.00        9     55555555555555666666677777778888
   755.00       10     000000000000000000000000000000000000000000000000000000000000000000000000000

& denotes fractional leaves.
```

ASR Normal Q-Q Plot



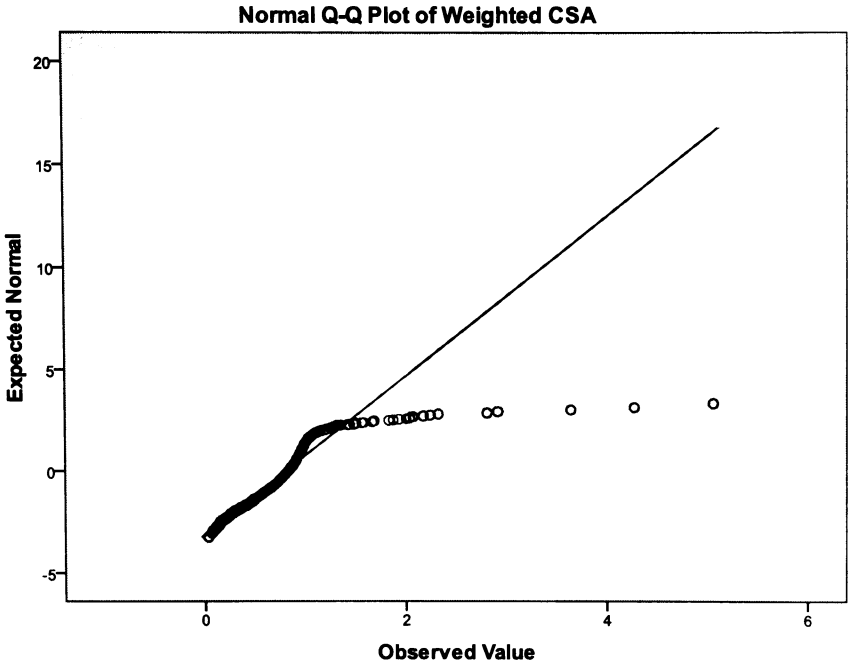
ASR Box-Plot



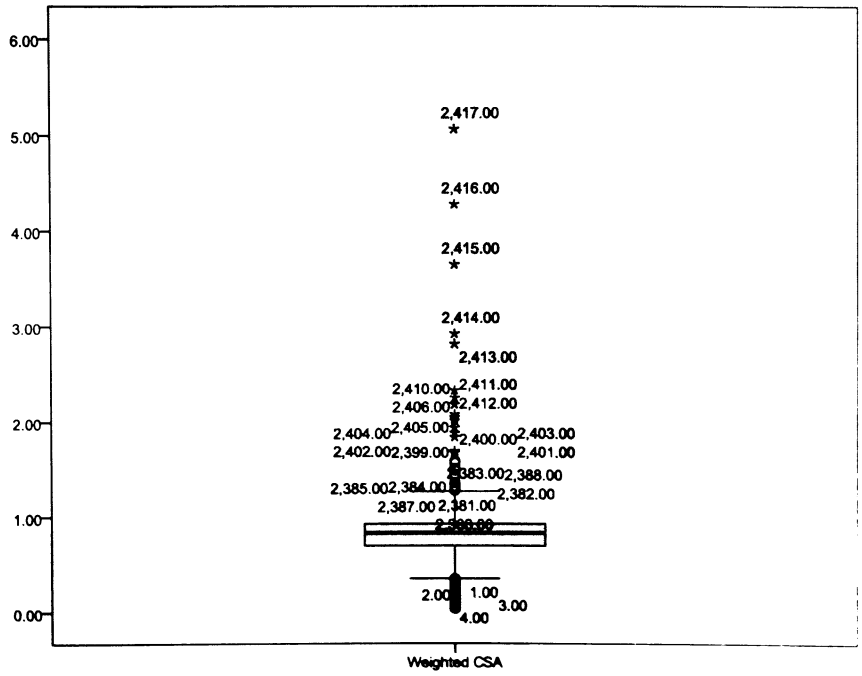
CSA Stem-and-Leaf Plot

```
 Frequency    Stem &  Leaf

    83.00 Extremes    (=<35)
    28.00        3    5678899
    42.00        4    0112334444
    61.00        4    55666778888999
    69.00        5    0001112223334444
    97.00        5    55556666677777888888999
   111.00        6    000011112222222333333344444
   138.00        6    555556666666677777778888888999999999
   197.00        7    000000001111111122222222223333333333333334444444444
   239.00        7    555555555566666666666777777777777788888888888899999999999
   285.00        8    000000000000000111111111111222222222222333333333333333334444444444444444
   291.00        8    555555555555556666666666777777777777777888888888888888888999999999999999
   351.00        9
000000000000000000000001111111111111111122222222222222233333333333333333344444444444444444
   229.00        9    555555555555566666666666667777777777778888888888899999999
   196.00       10    00000000000000000000000000000000000000000000000000000000

 Stem width:     10.00
 Each leaf:       4 case(s)
```

CSA Normal Q-Q Plot



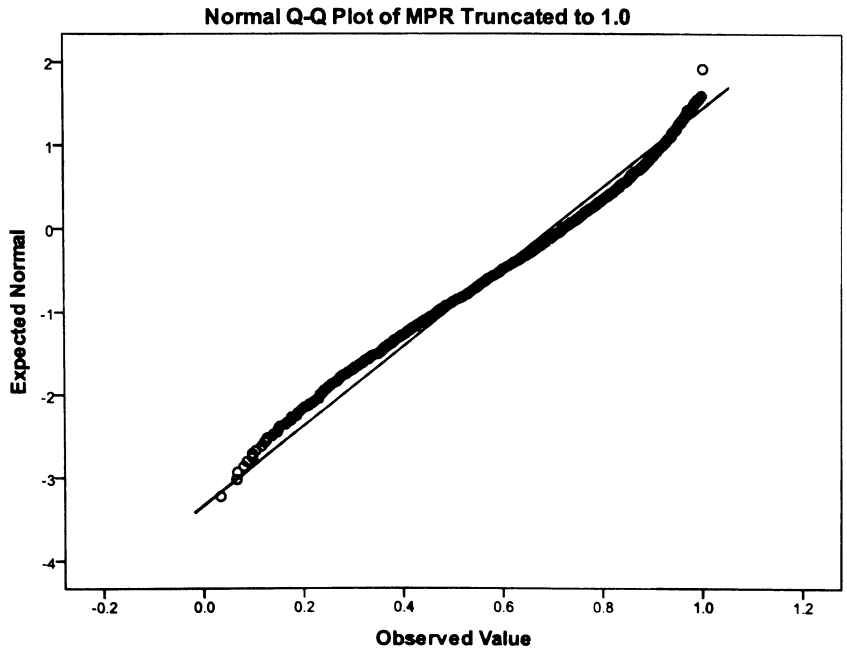
CSA Box-Plot



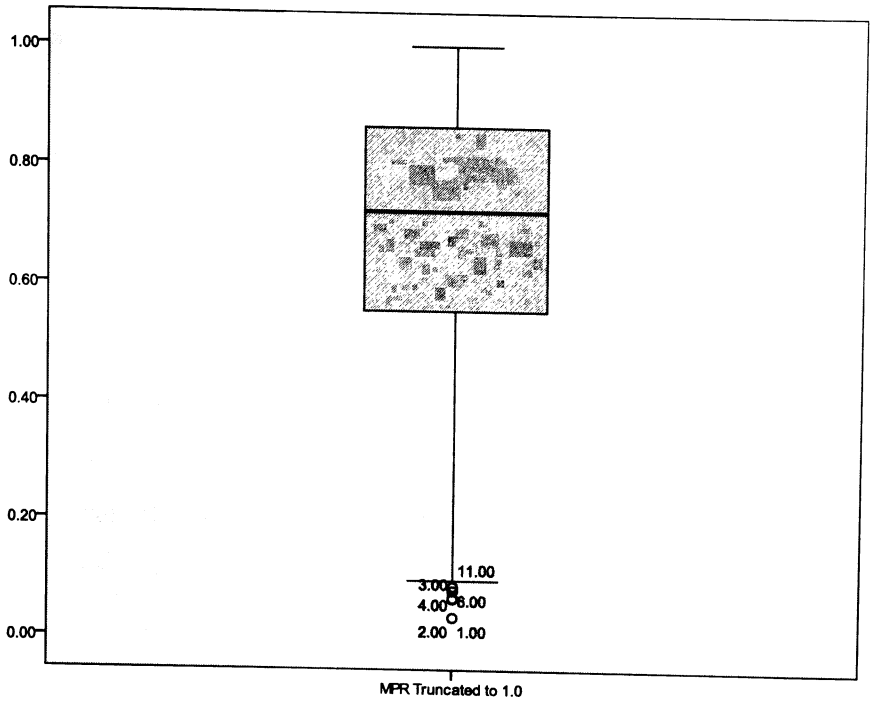
MPR Stem-and-Leaf Plot

```
Frequency    Stem &  Leaf

    6.00 Extremes    (=<9)
    2.00        0    9
   11.00        1    124&
   17.00        1    56789
   31.00        2    0112333444
   41.00        2    55566777788899
   51.00        3    000011112222333344
   83.00        3    555556666677777888888999999
   97.00        4    00000001111112222223333334444444
  115.00        4    55555556666666667777777788888889999999999
  130.00        5    000000000111111222222233333333333344444444444
  169.00        5    555555555556666666666667777777778888888889999999999999999
  160.00        6    0000000000111111111112222222223333333333334444444444
  200.00        6    55555555556666666666666777777777777778888888888888899999999999999
  205.00        7    000000000000011111111111111222222222222222333333333333333444444444444
  214.00        7    5555555555555555666666666666666677777777777788888888888888899999999999999
  208.00        8    000000000000011111111111111222222222222222333333333333333344444444444
  210.00        8    555555555555555556666666666677777777777888888888888888999999999999
  204.00        9    000000000000000000011111111122222222222222333333333333333444444444444
  131.00        9    55555555556666666666666677778888888889999
  132.00       10    00000000000000000000000000000000000000000000

Stem width:     10.00
Each leaf:       3 case(s)

& denotes fractional leaves.
```

MPR Normal Q-Q Plot

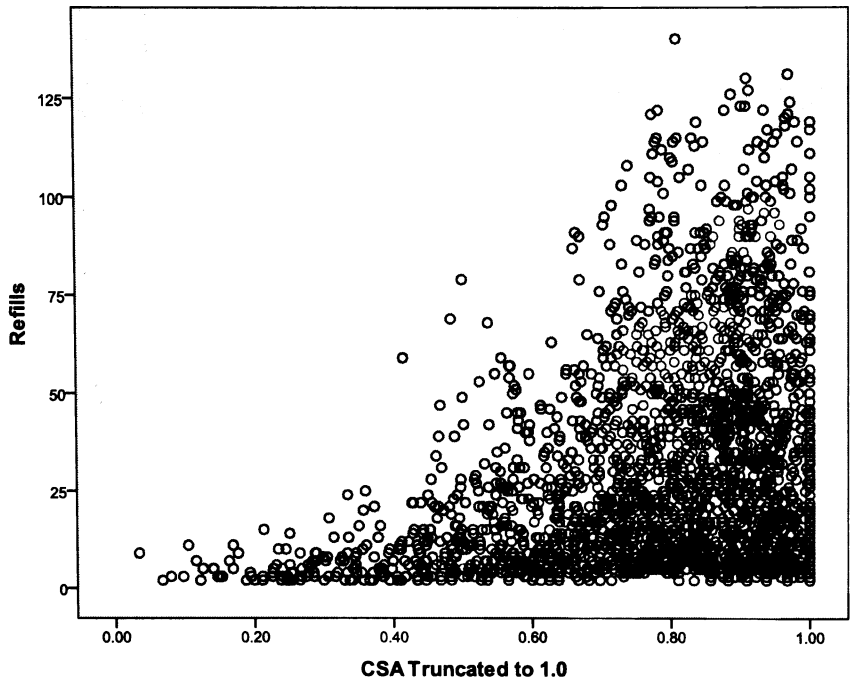


MPR Box-Plot

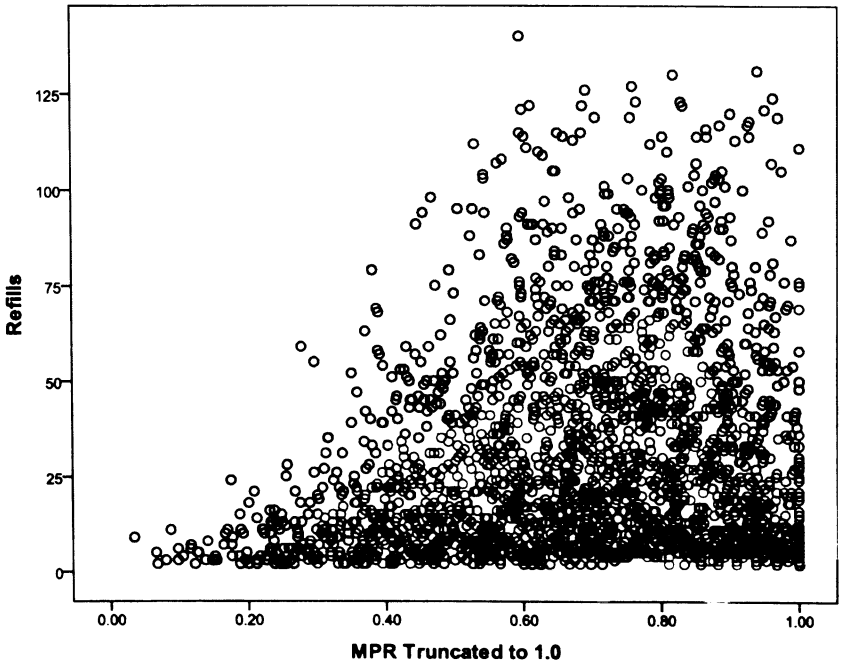

1.00
0.80
0.60
0.40
0.20
0.00
11.00
3.00
4.00
6.00
2.00
1.00
MPR Truncated to 1.0

Scatter-plots of Refills with MPR, CSA, and ASR

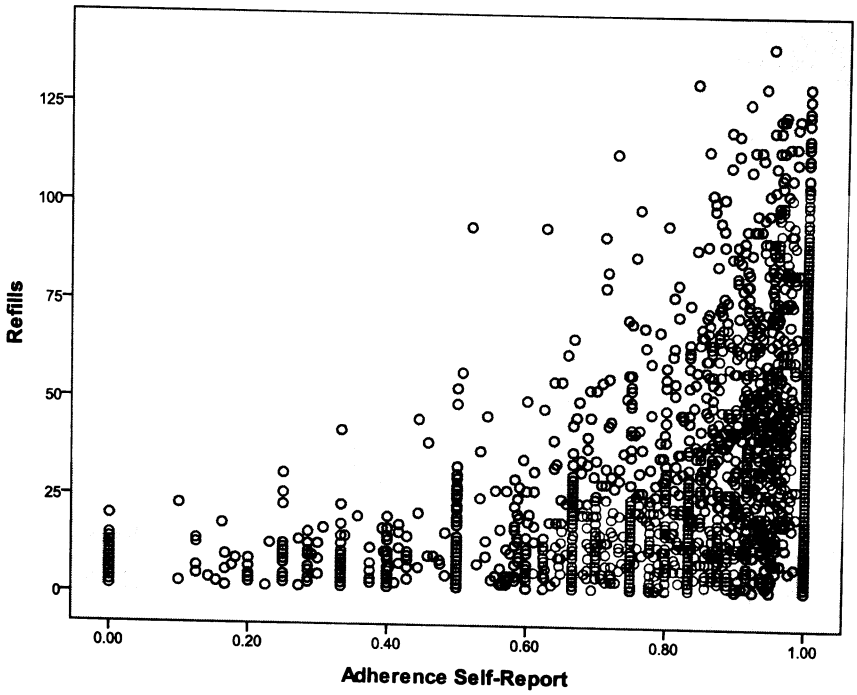
CSA



MPR



ASR


Refills
125
100
75
50
25
0
0.00
0.20
0.40
0.60
0.80
1.00
Adherence Self-Report

SAS Results of Refills regressed on CSA, MPR, and ASR*

CSA

	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	0.75	0.0076	98.58	<.0001
Refills	0.0016	0.00019	8.53	<.0001

MPR

	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	0.68	0.0071	95.46	<.0001
Refills	0.00081	0.00017	4.67	<.0001

ASR

	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	0.69	0.0074	93.47	<.0001
Refills	0.0037	0.00018	20.51	<.0001

*using PROC GENMOD