Prescription Refill Compliance Validation Study

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ABSTRACT

Numerous studies have demonstrated that noncompliance causes increased morbidity and mortality from a wide variety of illnesses. Solutions to the problem require systematic evaluation of the determinants of noncompliance and identification of subgroups of patients who are vulnerable so appropriate interventions can be designed. Population-based research methods are needed to evaluate this problem.

Compliance research has been enhanced by the evolution of sophisticated techniques for measuring compliance. One method, prescription refill compliance, has the advantage of being unobtrusive and available in automated databases. Unfortunately the validity of prescription refill compliance has not been well established. Only two validation studies have been conducted, in predominately male populations with two diseases, and analyzed without adjustment for variables that could modify the outcome or confound the association between compliance and outcome.

This study was undertaken to address the problems in previous studies and to expand the scope of refill compliance validation to a variety of chronic diseases. A prospective dynamic cohort study in patients with primary hypothyroidism, type 2 diabetes and atrial fibrillation was conducted to evaluate the association between refill compliance and laboratory measurements of therapeutic effects of drugs (levothyroxine, oral hypoglycemic drugs, and warfarin, respectively). Compliance was measured over 30-day time periods preceding a laboratory test of the study drug's effect (TSH, $HgbA_{1c}$, or INR) utilizing a computer-generated daily log of laboratory tests and of drug supply. The association between laboratory tests and compliance was evaluated with multivariate linear regression analysis within a generalized estimating equations framework, adjusted for demographic and disease

factors known to modify the effectiveness of the drugs (e.g. renal function).

The study showed that refill compliance is a valid measure of compliance. The adjusted correlations between refill compliance and therapeutic effects for hypothyroid (r=0.31) and diabetic patients (r=0.24) were similar to those reported in previous studies and represent an upper biological threshold on the capacity of a respective drug to modify clinical outcomes. The correlation in atrial fibrillation patients (r=0.06) suggested that refill compliance is unsuitable for drugs like warfarin that have a narrow therapeutic index or require frequent dose changes.

RÉSUMÉ

De nombreuses études ont démontré que l'inobservance au traitement augmente le risque de mortalité et morbidité relatives à différents problèmes de santé. Une évaluation systématique des causes de l'inobservance ainsi qu'une identification des sous-groupes de patients qui y sont sujets sont nécessaires afin de développer des interventions appropriées. Des méthodes de recherche fondées sur les données démographiques sont nécessaires pour bien évaluer le problème.

L'intérêt pour la recherche sur l'inobservance au traitement a été fortement stimulé par le développement de méthodes de mesure de plus en plus sophistiquées. L'une de ces méthodes, basée sur le renouvellement d'ordonnances, présente l'avantage d'être à la fois aisément disponible dans les grandes bases de données administratives et non-intrusive pour le patient. Malheureusement, la validité de cette méthode n'a pas encore été clairement établie. Deux études de validation ont été réalisées jusqu'à présent, auprès de populations essentiellement masculines aux prises avec deux maladies. Lors de l'analyse, ces études n'ont cependant pas considéré le rôle de certains facteurs de confusion pouvant altérer les résultats.

Cette étude vise à pallier aux failles des études précédentes et à élargir les connaisances actuelles concernant la validité de l'utilisation des renouvellements d'ordonnances comme mesure d'observance au traitement en regard de certains problèmes de santé chroniques. Une étude a été faite de cohorte prospective dynamique de patients souffrant d'hyperthyroidisme primaire, de diabète de type 2 et de fibrillation auriculaire mettant en relation l'observance au traitement basée sur les renouvellement d'ordonnances et certaines mesures physiologiques en lien avec les effets thérapeutiques des médicaments (soit la levothyroxine, les médicaments hypoglycémiques oraux et la warfarine). L'observance au traitement a été effectuée sur des périodes de trente jours précédant une analyse de l'effet

des médicaments étudiés (TSH, $HgbA_{1c}$, or INR) en utilisant un rapport quotidien des tests en laboratoire et d'approvisionnement de médicaments généré par ordinateur.

L'association entre les mesures physiologiques et l'observance au traitement a été mesurée par des techniques d'analyse de régression linéaire tirées d'un modèle généralisé d'équations linéaires ajusté selon des facteurs démographiques ainsi que des facteurs de maladies qui affectent l'efficacité des médicaments (par ex. la fonction rénale).

L'étude démontre que la méthode des renouvellements d'ordonnances constitue une mesure valide de l'observance au traitement. Les coéfficients de corrélation ajustés obtenus pour les patients traités pour l'hypothyroidie (r=0.31) et pour le diabète (r=0.24) sont comparables à ceux précédemment rapportés dans des études similaires. Ils démontrent le seuil biologique supérieur atteint par un médicament donné dans la modification des effets cliniques. Le coéfficient de corrélation obtenu pour les patients atteints de fibrillation auriculaire (r=0.06) suggère que la mesure de l'observance au traitement basée sur les renouvellements d'ordonnances n'est pas adéquate pour les médicaments à spectre étroit ou requérant de fréquents ajustements posologiques, telle que la warfarine.

PREFACE

This thesis investigates the validity of refill compliance in three separate patient populations, utilizing the same methodology in each. Chapters 1 and 2 address common issues in testing the validity of refill compliance in general. Chapter 3 outlines the specific questions addressed and the methodology employed. The final two chapters contain the results and the conclusions, relevant to the specific issues of each study population.

Statement of Originality

Several aspects of this study represent original contributions to knowledge. It advances the general knowledge of the validity of refill compliance and its limitations. It is the first to study the validity of refill compliance in samples of patients with hypothyroidism, atrial fibrillation and diabetes. Previous work has been limited to cardiovascular diseases and to male populations. It is also unique in that it assesses factors which influence drug effectiveness, such as renal and liver function, age, and dose of medication. The algorithm developed for this study refines the measurement of compliance through an adjustment in the duration of each prescription for changes in drug dose. The algorithm can be applied in future research of compliance and etiologic research in which quantification of drug exposure is important.

Contribution of Authors

Although the thesis supervisor Dr. Robyn Tamblyn, suggested the topic, the candidate was responsible for conceptualizing, designing, analyzing and reporting the results of this study. The study methodology and algorithm for measuring refill compliance were designed by the candidate. James Burroughs converted the

preliminary algorithm designed and implemented in SAS by the candidate into an elegant and efficient SAS program. Dr. Marianne Ulcickas Yood provided access to her database, and Karen Wells performed the electronic data extraction. The candidate set the parameters of the data extraction and prepared the SAS programs to refine the extract to select eligible study patients. Marie-France Valois assisted with database management and Dr. Gillian Bartlett prepared graphs for the document. Members of the thesis committee guided the candidate through the process.

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CHAPTER 1 INTRODUCTION

Compliance is 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.[1,2] Medication compliance, in the setting of outpatient health care, is adherence to physician instructions for self-administration of medication.

Noncompliance includes many types of behaviors: not having a prescription filled or refilled; taking too little or too much medication; stopping the medication too soon; erratic dosing; and combining medications inappropriately with other medications or alcohol. The consequences of noncompliance to the patient range from inadequate disease-state control resulting from under-dosage to potential toxicity resulting from over-dosage for the individual.

Noncompliance with drug therapy is a public health problem with major health and economic implications. Reported rates of noncompliance in a variety of therapies range from 13-99% among adults and from 25-82% among children.[3] Non-compliance in the treatment of infectious diseases contributes to the development of resistant bacteria, which affects the health of a community.[3] Numerous studies have demonstrated that partial compliance and noncompliance with prescribed medication regimens cause increased morbidity and mortality from a wide variety of illnesses, as well as increased health care costs.[4-7]

Key to investigating the determinants of noncompliance and solutions for this public health problem is an objective, reliable and valid measurement of compliance. Most objective methods of measuring compliance (pill counting, electronic sensors, plasma levels of drug) have proved to be difficult to implement and are often expensive. Each of these methods of measuring compliance is imperfect and seriously compromised because patients may modify their compliance when they

are aware that it is being monitored.[8] Furthermore, these methods of measuring compliance are unsuitable for large population studies and where multiple drugs are used.

Prescription refill compliance, another objective method of measuring compliance, is both unobtrusive and suitable for large longitudinal population studies. Longitudinal prescription refill pattern studies have led to interesting observations. For example, 40% of patients fail to fill lipid-lowering drug prescriptions after one year in spite of the well-known benefit of this therapy.[9]

Unfortunately the validity of using prescription refill rates to measure compliance has not been well established. Two construct validation studies have been conducted in only two diseases in very homogeneous populations.[10;11] These studies correlated refill compliance with intended therapeutic effect of the drug (e.g. change in blood pressure). In each study, the correlations between refill compliance and therapeutic effect of the drug were modest, in part because the methods used to determine the quantity and duration of drug supply likely led to an overestimation of compliance. Neither study included all of the variables that could influence the therapeutic effect or confound the estimate of the association between compliance and therapeutic effect in their analysis. Both studies were conducted in Veteran Administration medical centers and in study populations that were 98% male, thus they have limited external validity. The present study was undertaken to address the problems identified in previous refill validation studies and expand their scope by addressing refill compliance validation in a variety of chronic diseases and heterogeneous patient populations.

CHAPTER 2 LITERATURE REVIEW

2.1 Prevalence and Scope of Noncompliance in Chronic Illness

It appears that patients rarely take 100% of their prescribed medication. Successive comprehensive reviews of the compliance literature have documented that poor compliance is a prevalent and significant problem in most diseases. In 1976, Sackett and Haynes published a seminal review of the compliance literature. They reviewed 371 publications and reported on 204, which provided sufficient information to assess and score the rigor with which six methodological issues central to the investigation of compliance could be evaluated. These included study design, sample selection and specification, description of the illness, description of the therapeutic regimen, completeness of the definition of compliance, and adequacy of the measurement of compliance. The studies measured compliance in pediatric and general medicine illnesses as well as the specific conditions (hypertension, peptic ulcer disease, diabetes, rheumatoid arthritis, dental disorders, glaucoma, acute otitis media, postnatal care, myocardial infection, prophylaxis for rheumatic fever, contraception, oral iron therapy in pregnancy, tuberculosis, streptococcal pharyngitis, and psychiatric disorders). They reported a weighted average compliance rate of 54% (median 56%, range 19-84%) in studies of chronic therapy for prevention and treatment of different illnesses and conditions.[1]

The second review of compliance literature was published in 1984 by Richard Greenberg. He reviewed more than 100 articles and book chapters for data on compliance to medication dosing directions, and reported on 57 comprehensive studies. Thirty-six of the studies limited data to compliance with one particular drug. Twenty-three studies evaluated compliance in patients receiving antibiotics, five in antacid regimens, while the remainder dealt with medication regimens for heart failure (n=3), hypertension (n=3), asthma (n=1), juvenile rheumatoid arthritis (n=1),

immunosuppression (n=4), psychiatric or neurological disorders (n=3), placebo, or other types of illnesses (n=13). Twenty-four studies (42%) evaluated compliance in the pediatric age group, 32 studies (56%) involved only adult populations, and one included both age groups. Overall compliance with medication treatment in this review was 56%.[12]

Two reviews of the compliance literature in the 1990s concurred with these early estimates of the extent of noncompliance with medication therapy in chronic diseases. In 1992, Morris and Schultz concluded that the average rate of compliance tends to converge to 50% for long-term therapy and compliance behavior tends to decline over time, regardless of disease.[13] In 1995, Coambs and colleagues published a review of the prevalence and consequences of noncompliance in Canada. They found that for all types of medication as a whole, approximately 50% of patients are noncompliant with their prescribed regimen; 33% of them either do not fill their prescription, or fill it but do not take the medication; and 17% of them take their medication, but not precisely as prescribed. Thus, only 50% of patients who receive prescription medications are compliant with medication instructions.[14]

Years of research have systematically documented the existence of substantial noncompliance and provided evidence that it occurs in any medical setting or geographic location.[15] A 10% sample of compliance literature between 1980 and 1996 reported on studies conducted on five continents in multiple disease states (cardiovascular, infectious diseases, respiratory psychiatry, oncology, endocrinology, glaucoma, rheumatology and others).[15] Compliance literature in a multitude of chronic diseases, medications, countries and age groups, confirms the broad scope of problems with compliance and that the magnitude of the problem is unchanged over time. Noncompliance remains a public health problem in the beginning of the twenty-first century.

2.2 Impact of Noncompliance

There is consistent evidence for both acute and chronic conditions that compliance deteriorates over time, especially when the patient is asymptomatic or in remission.[1] Treatment adherence is particularly difficult to sustain when patients feel well and when drug adverse reactions are more troublesome than the asymptomatic condition being treated or the condition averted through prophylactic treatment.[16] Furthermore, because poor compliance dampens the effectiveness of the treatment, patients become dissatisfied with their care because they are not cured or they are bothered by side effects.[17]

Chronic disease is often poorly controlled despite extensive education programs aimed at increasing medication compliance.[18-20] Findings for diseases such as hypertension and diabetes show that only 25% of patients followed recommended guidelines to control the disease and prevent complications.[21] Moreover, the following noncompliance rates for the following chronic `diseases have been reported: asthma, 20%; diabetes, 40-50%; epilepsy, 30% to 50%; hypertension, 40%; and psychoses and related mental disorders, 40%.[22]

Patients often experience treatment fatigue and choose to take drug holidays from treatment (even in life-threatening diseases such as AIDS) without discussing the option with the treating physician.[23;24] Sub-optimal compliance ultimately contributes to drug resistance, which leads to restriction of future drug regimens for the patient, and to the potential transmission of drug-resistant organisms in AIDS and tuberculosis.[24-26] In other chronic diseases, drug holidays can contribute to dire consequences. Kruse, et al. reported that consecutive drug holidays with diuretic therapy were followed by deterioration of congestive heart failure due to severe pulmonary congestion.[23] In both infectious and non-infectious chronic illnesses, the consequence of noncompliance is the loss of therapeutic benefit of the medication

eventually resulting in a threat to patient well-being, and in some diseases a threat to their lives.[24]

Adherence to prescribed medications is hampered by a variety of factors including forgetfulness, misunderstanding (e.g. that treatment can be stopped when the symptoms resolve), disbelief of the diagnosis, unwillingness to take medication, cost, and initial adverse reactions or other side effects attributed to the drug.[14] Unfortunately, patients rarely report difficulties in adhering to a prescribed treatment unless they are experiencing troublesome adverse events.[14]

The prevalence of troublesome adverse events as a cause of noncompliance is not well documented, but information is available on adverse events and noncompliance resulting in hospitalization. The extent and pattern of hospital admissions caused by adverse drug reactions or dose-related therapeutic failures was studied prospectively in England in a population-based survey of 1999 consecutive admissions to six medical wards. Treatment failures were defined as a lack of therapeutic effect that could be ascribed to: noncompliance; recent dose reduction/discontinuation; interaction; inadequate dose; or inadequate monitoring of therapeutic response. The prevalence of drug-related hospital admissions was 11.4%, of which 8.4% were caused by adverse drug reactions and 3.0% by treatment failures. Noncompliance accounted for 66% of the treatment failures.[7;27] Hospitalizations related to noncompliance appear to be both potentially avoidable and have costly consequences.[7]

Noncompliance has been estimated to account for 10% of hospitalizations and 23% of nursing home admissions in the United States.[6] Additional health care costs occur because noncompliance appears to health care professionals to be non-responsiveness to treatment. Physicians may increase the dose of the medication (possibly increasing side effects), changing medicines, or ordering new tests to

confirm the diagnosis.[17] Altogether, hospital and nursing home admissions, lost productivity, premature deaths, and excessive treatments associated with noncompliance are estimated to cost the US more than $100 billion every year.[6] If compliance with prescription-drug regimens could be improved, the United States' health care expenditures might see a net annual savings of more than $80 billion; similar savings might be realized in Canada.[6]

Aside from increased health care costs, there are other negative health outcomes of noncompliance: patients do not recover or their condition worsens. For example, women who took less than 75% of the beta-blocker medication following a heart attack were 2.5 times more likely to die than compliers.[28] Noncompliance with drug therapy for contagious diseases such as tuberculosis and AIDS may cause the pathogen to become resistant to treatments, encourage the spread of the disease, and increase the threat to public health.[3]

2.3 **Compliance Research**

Over 1,200 articles have been published on the topic of compliance in the last twenty-five years.[29-31] Compliance research has focused on the determinants of noncompliance and strategies to improve compliance.[13] In the past quarter century this research has diverged into two streams. Basic compliance research has focused on understanding the nature of the problem, determinants, and risk factors without a focus on solutions. Applied compliance research has focused on interventions, without regard to unraveling the underlying mechanisms of the problem. Each discipline relies on the advances of the other to guide its research and each shares responsibility and credit for advancements in methodologies applied to compliance research and in particular, the measurement of compliance. The following examination of compliance research is organized into three sections: basic compliance research, applied compliance research, and methodology, with

emphasis on the measurement of compliance.

2.3.1 Basic Compliance Research

Initially, basic compliance scientists attempted to identify the features of a disease, the patient, or the treatment which might act as barriers to compliance. They have searched for demographic factors and personality traits that distinguished the noncompliant patients from compliant. In 1976 Sackett and Haynes critically reviewed the methodology and results from the previous 16 years of compliance research. In their systematic review of compliance studies in a large variety of illnesses, no clear relationship emerged between race, gender education, intelligence, marital status, occupation, income, or ethnic group and compliance.[1] Morris and Schultz included the work of Sackett and Haynes and subsequent studies in their 1992 review of the literature. They reported that scientists have looked at more than 200 variables seeking potential associations with compliance. None of the variables is consistently predictive of compliance or noncompliance.[13]

Demographic characteristics, though studied extensively over three decades, are poor predictors of compliance. Noncompliance is distributed democratically in all subgroups of patients regardless of age, sex, ethnic background, geographic location, educational level, marital status or religious persuasion.[13-15;23]

Disease characteristics have also proven to be poor predictors of compliance.[13] The one exception is psychiatric disorders (i.e. schizophrenia, manic depressive disorder and depression). People with these mental illnesses consistently manifest very low compliance rates.[13;14;32;33] Furthermore, depression interferes with compliance with non-psychiatric medications. A meta-analysis of the effects of anxiety and depression on compliance reported that depressed patients were three times as likely as non-depressed patients to be noncompliant (OR: 3.03, 95% CI:

1.98 to 4.95) while anxiety had no effect.[34]

Features of the medication regimen such as dosing frequency and complexity of the administration process have consistently shown to affect compliance.[1318] Regimens that involve taking the medication with food, at a particular time of day, or more frequently than twice a day consistently have lower rates of compliance in multiple settings;[12;35] however, a simple medication regimen is not the sole answer to compliance problems.[36]

A positive doctor-patient relationship was initially thought to be a key factor in compliance.[1] This created interest in the role of patient satisfaction with the health care provider as a mediator between information provision, recall and adherence. A number of surveys suggest that many patients are dissatisfied with their health care provider, but few studies have addressed the impact of dissatisfaction on compliance.[31] One large study showed that the patient-doctor relationship affects compliance only when the relationship is negative. This study of compliance of 800 outpatients, found that good "bedside manner" is an important factor associated with patient satisfaction with health care but there was no clear associated with good compliance. However, when the patients' expectations are not met, there is a negative impact on compliance. Dissatisfaction with attributes of the practitioner or the amount of information and explanation provided may act as a barrier to adherence.[31;37]

Sociobehavioral features; family stability, social support systems, and the presence of a care giver in the home have been found to be positively associated with compliance.[38-40] The premise that sicker patients are more likely to take medications as directed because of the perceived need to treat their condition effectively has not been supported by compliance research.[41] Even the threat of death from cancer or kidney rejection after a transplant operation does not assure

good compliance with immunosuppressant medication in all patients.[16] However, negative beliefs about health care do seem to influence compliance. In a 1993 study conducted by the Upjohn company, the most common reason given by patients for not taking medication was the belief that they did not need it.[14] In Western society there is a proliferation of ideas about health and illness, and these combined with the dominant culture of individualism, work against compliance.[14]

After decades of research, very little consistent information is available, except that people often do not take their medications as prescribed. The assumptions and methodology employed in compliance studies may partially contribute to this dilemma.

Two assumptions seem to be pervasive in basic compliance research. The first is that noncompliant behavior can be viewed as a trait. A dichotomous distinction between compliant and noncompliant patients fails to take into account the variability of patients' drug use behavior over time may obscure the detection of time-dependent relationships in drug use behaviors. Recent studies of compliance in which patterns of drug taking have been measured prospectively by electronic monitors studies shown that compliance is a dynamic process, and that compliance changes over time.[35] The dynamic nature of compliance suggests that it is a state rather than a trait.

The second assumption is that noncompliers and compliers are similar to one another in all other respects save that noncompliers received less treatment than compliers. There is evidence that contradicts this assumption as well.[2] For example, in a randomized double-blind clinical trial of prevention therapies for coronary heart disease, men who were more noncompliant with the placebo treatment died at almost twice the rate of men who complied with the placebo treatment (28% versus 15% over 5 years, $P < 0.001$.[42] One might have concluded

that ingested placebo had a positive benefit but it is more likely that there were underlying differences between compliers and noncompliers. A similar study conducted in women showed that compliance with either placebo or a beta-blocker drug had a favorable effect on reducing mortality following a myocardial infarction.[28] It is likely that drug compliance is one of many behaviors adopted by people who are engaged in life style changes associated with positive health outcomes.

Many scientists feel the search for determinants of noncompliance has been disappointing, primarily because of the approach of converting compliance into a binary outcome.[18] Dichotomous measures may be particularly inappropriate if compliance distributions for a single drug assume fundamentally different shapes (i.e., normal skewed normal, bimodal, flat, U-shaped, etc.) in different populations, or if these distributions vary for different drugs in a single population.[10] An outspoken critic of this approach stated, "Compliance is variable, not dichotomous; arbitrary boundaries between good and not-good are meaningless and, in any case, drug-dependent."[23]

Lastly, the point of demarcation of compliance and noncompliance is inconsistent across studies. Some researchers divide their sample populations into compliers and non-compliers based on statistical measures such as the median or mean levels of medication taken.[13] Alternatively, a few scientists have determined the level of compliance that positively or negatively impacts the desired health outcome to define compliance versus noncompliance. Unfortunately, the level of compliance associated with positive and negative health outcomes has been established in only a few diseases, such as hypertension.[43] When the level of compliance necessary for positive drug effects is unknown, the division of compliance and noncompliance is often arbitrarily assigned by the investigators as a percentage of the total amount of drug prescribed.[44;45] The lack of consistency in defining compliance has hindered basic compliance research.

Collectively, the body of basic compliance research has provided some direction for applied compliance research; however, the complexity of the compliance problem and methodological issues cited have impeded the development of a universal solution to the problem. Contemporary compliance research examines patterns of compliance in longitudinal studies and in health outcomes, using objective measurement tools.

2.3.2 Applied Compliance Research

Applied compliance research scientists seem to prefer the term "adherence" to "compliance." Adherence denotes a more active patient-physician treatment collaboration than compliance.[46] Most drug regimens allow for some flexibility and patient discretion in how, when, and if the drugs are taken. One of the primary ways in which patients attempt to assert control over their illness is through independent adjustment of the dosage and schedule of their medications. The patients' goal in this process is not to subvert their doctors, but to regulate their own lives and to reconcile their treatment with their understanding of the disease.[15]

Applied compliance research scientists have investigated specific interventions that have improved understanding of patient and health care provider behavior.[47] These intervention studies have been predominantly randomized trials of educational, behavioral and affective approaches to modifying patient compliance. Educational interventions include verbal or written information about disease management. Behavioral interventions focus on changing, shaping and reinforcing specific behavioral patterns by such methods as contracting. Affective strategies such as counseling or family support attempt to influence compliance through appeals to emotions or social relationships. Interventions directed at the providers of health care (physicians, nurses and pharmacists) are less common and focused on providing patient education.[44]

Roter and colleagues published a meta-analysis of a variety of study designs used in intervention studies conducted between 1975 and 1994. They reviewed 153 studies represented in 162 publications. An effect size, the Pearson correlation coefficient representing the association between compliance intervention (intervention group versus comparison group) and compliance outcome, was calculated for all studies and used as an estimate of the strength or magnitude of each intervention's effect. Compliance was assessed or imputed in the studies through many means. The compliance measurements included health outcomes (e.g. BP, hospitalizations), direct measurements of compliance (e.g. tracer substances, physiological indicators), indirect measures of compliance (e.g. pill count, prescription refills), subjective measures (e.g. reports of patients or others) and utilization indicators (e.g. appointment keeping, utilization of preventative services).

No single strategy or pragmatic focus had a clear advantage over others. Overall, intervention programs were generally effective, but programs with a combined educational and behavior focus were more so than single-focus interventions. Interventions that were especially effective included affective, behavioral, and educational components. Interventions showed stronger benefits for patients with particular diseases (diabetes, asthma, cancer, hypertension and mental illness) but the strength of the association may have been a function of the number of studies conducted in the specific diseases. Table 2.3.2.1 summarizes the results from "Effectiveness of Interventions to Improve Compliance: A Meta-Analysis" by D.L. Roter, et al.

Table 2.3.2.1. Effect of Compliance Intervention Programs on Various Measurements of Compliance

Programmatic Focus	Compliance Measurement and Weighted Effect Size				
	Health Outcome[A]	Direct[B]	Indirect[C]	Subjective[D]	Utilization[E]
	Estimate of Correlations (R's) with Z score in parentheses*				
Educational	.13 (5.1)	.23 (4.2)	.35 (9.5)	.14 (8.1)	.19 (15.2)
Educational/behavioral	.18 (6.7)	.23 (3.8)	.83 (17.3)	.20 (9.7)	.16 (12.0)
Affective	.18 (3.2)	.31 (4.0)		.07 (1.5)	.18 (2.9)
Educational/affective		.19 (2.5)		.22 (4.5)	.37 (4.7)
Behavioral	.20 (5.4)	.17 (3.9)	.27 (16.8)	.20 (4.3)	.18 (18.9)
Behavioral/affective	.20 (3.4)			.22 (6.1)	
Educational/behavioral/ affective	.24 (3.6)	.34 (4.4)			.38 (4.9)
Provider intervention	.03 (1.0)		.46 (5.6)	.02 (1.0)	.06 (17.3)

* Z scores >4.0 is significance at P <0.05

A. Measures of disease severity (e.g. pain), survival, hospitalization

B. Drug tracer substances and physiological indicators of drug effect (e.g. cholesterol or weight change)

C. Pill count, prescription refill, or electronic monitors of drug use

D. Patient report or reports of other of compliance and chart review

E. Appointment keeping or utilization of preventative services (e.g. vaccinations or cancer screening)

Their report also noted the effects of intervention programs on different methods of measuring compliance. Not all indicators of compliance are equivalent; the measures tap different dimensions of the compliance. The effect of interventions on direct compliance measures was stronger than that for subjective measures or health outcomes overall. Interventions had the strongest effect on indirect indicators of drug use. The two indirect compliance measures, pill counts and refill records, showed substantially different patterns of effect (Table 2.3.2.2) Pill counts

generally overestimate compliance and can bias assessments of an association. This difference could also mean that compliance intervention had a much greater effect on refill behavior than actual pill consumption. However, because the pill count and refill data are from different studies, one cannot be sure the difference is due to the outcome measured rather than to other study factors. Interestingly, the estimated correlation coefficient was smaller in both methods of direct measurement in non-randomized trials compared to randomized trials. As the less obtrusive measure of compliance, refill compliance might be the better measurement to assess the effectiveness of compliance intervention programs.

Table 2.3.2.2 Measurement of Compliance in Non-Randomized Versus Randomized Studies: Estimated Correlations of Compliance Intervention and Outcome

	Pill Count	Refills
Randomized	r= 0.26	r=0.79
Non-randomized	r=0.13	r=0.62

Compliance studies are diverse and definitions of the success of interventions designed to improve compliance vary from outcome-oriented markers of compliance to subjective perceptions.[44] Standardizing the measure of compliance would lead to advancement in applied compliance research.

The standard for study design of adherence interventions is the randomized controlled trial, which evaluates attempts to produce a health outcome benefit, and not merely an increase in adherence.[48] Haynes and colleagues' systematic review of randomized trials of interventions reported between 1993 and 1995 reported that even the effective interventions with respect to improved adherence did not lead to

substantial improvements in health benefits. Randomized controlled trials of unconfounded compliance interventions with at least 80% follow-up of participants, and with one or more measures of both medication adherence and treatment outcome were included in their analysis. The authors were unable to calculate effect sizes because of the differences across studies in multiple clinical disorders, interventions, adherence measures and reporting, and outcome measures. In four studies, three of hypertension and one in acute infection, the interventions of education, simplified dosing, work-site care and home monitoring neither enhanced compliance nor improved the health of the patient.[43;49-51] Three studies showed that using simplified dosing, reminder systems, self-monitoring and counseling improved compliance but not health outcome.[47;49;52] Two studies of family counseling and close follow-up did not show improved compliance, but the patients experienced improvement in their health state (possibly due to the closer follow-up in the intervention group).[53;54] Four studies of different complex and labor-intensive interventions demonstrated an improvement in both compliance and health outcome but did not identify the components of the program that contributed to their success.[33;55-57]

In 2000, the Cochrane Collaborative Group reported on their extensive review and meta-analysis of compliance interventions and concluded that 10 of 19 interventions for long-term treatments in 17 trials effected improvements in adherence, but only nine interventions led to improvements in treatment outcomes. The review included 106 published studies and found 17 unconfounded by other interventions, with at least 80% follow-up participants, and with one or more measures of both medication adherence and treatment outcome. For long-term regimens, studies with initially positive findings were required to have at least 6 months follow-up from the time of patient entry; negative trials with shorter follow-ups were included on the grounds that initial failure was unlikely to be followed with success. Almost all of the interventions were complex, including combinations of

more convenient care, information, counseling, reminders, self-monitoring, reinforcement, family therapy and other forms of additional supervision or attention. Even the most effective interventions did not lead to large improvements in adherence or treatment outcomes.[45]

"With the astonishing advances in medical therapeutics during the past two decades, one would think that studies on the nature of noncompliance and on the effectiveness of strategies to help patients overcome it would flourish."[29] Indeed, these studies have not led to solutions or to greater advances.[29] Some studies have investigated specific interventions that have led to substantial and meaningful increases in compliance and subsequent improvement in patient health status.[31;48;58] Most published studies of compliance tend to be fragmented by diagnostic categories and discipline perspectives (e.g. sociology, medicine).[48] Insight into adherence difficulties in one disease has not been integrated into compliance interventions in other diseases, although there is clearly some common ground.[44] In addition, researchers have proceeded with studies without regard to a theoretical framework of compliance. Although we know that people do not take their medications consistently, we do not know specifically why this happens. One reason for this lack of understanding is that compliance research has been dominated by the perspective of the health professional. To better understand medication taking behavior, research needs to investigate a patient's decision-making process and the reasons for those decisions.[13] Further, it is difficult to generalize information learned about compliance in one disease to other diseases because of the different effects of compliance with one class of drugs on different health outcomes. The relationship between compliance and drug effectiveness is thus a complex one.[59]

2.3.3 Methodologies

Both basic and applied compliance researchers have concluded that methodological problems in compliance research account for the limited scientific advancement in this field.[29;48] Methodological problems of concern are study design flaws in basic compliance research, study execution in the case of applied compliance research, and techniques of measuring compliance in both.

2.3.3.1 *Study Designs*

2.3.3.1.1 Cohort Studies

The preferred study design for basic compliance research has been a descriptive cohort study which investigates different characteristics of compliers vs non compliers with the goal of predicting which groups of people are at risk for the consequences of poor compliance.[60] Dissatisfaction with simple dichotomization appears to be leading toward an evolution in methodology. Because the distinction between good and bad compliance is virtually impossible to make except by examining eventual outcomes in relation to compliance, it is usually easier to classify patients into "bands of compliance" - for example, those who take 95-105% of their prescribed dose - to facilitate descriptive analyses.[61]

Scientists who view compliance as a dynamic process rather than a fixed behavior are studying compliance longitudinally with follow-up for one year or more. The study of the dynamics of compliance over time offers unique opportunities for both drug effectiveness evaluation and compliance research.[23] Basic compliance research appears to be shifting its focus to patterns of compliance, identifying patterns that are most likely to have detrimental effects on health outcomes (e.g.

drug holidays) and determining risk factors that are associated with poor compliance and adverse outcomes that are amenable to change.[61]

Descriptive cohort studies do not generally report considerations of sample size and power in the methodology summary. Too often, the studies were conducted in populations that are too small (fewer than 50 subjects) to detect even clinically important effects. More recent studies are being conducted in larger cohorts, which provide greater power to detect patterns of compliance and risk factors associated with suboptimal compliance.

Compliance studies continue to use multiple methods of measuring compliance: patient interviews; pill counts; measurement of medicines in blood and urine; and medication monitoring systems. Each method has specific limitations. None of these methods alone is accepted as the gold standard but, if two or more are used together, a more accurate estimate of compliance is likely.[62] The lack of standard measurement methods, in particular, has hampered major progress in compliance determinant research with regard to both descriptive and explanatory sides of the problem.[23;62]

2.3.3.1.2 Randomized Control Trials

The study design for applied compliance research has been well established; the randomized control trial focused on health outcome endpoints. Because these studies are expensive and difficult to do, investigators often initially choose or ultimately end with a small sample size and have low power to detect potentially important effects.[29;47;48] Some studies may have been unable to detect a difference because of a ceiling effect created by participation bias. For example, in Freidman's study of interactive computer-based telephone monitoring and counseling's effect on compliance, the mean baseline compliance of the study

population was 93%.[52] Most studies failed to assess adherence after the intervention had been discontinued, precluding assessment of durability of the effect in studies with positive findings.

Randomized studies are often flawed in the execution of the study. Some studies do not take steps to prevent investigators from influencing the treatment assignment of individual patients.[59] Many of the studies in the reported in the Cochran meta-analysis did not take steps to prevent contamination bias.[47;47;50;55;60] Contamination bias occurs when health care providers care for patients in each treatment arm, know the study objectives, and can influence the outcomes of the study. This occurred in two compliance intervention studies conducted in patients with hypertension in which blood pressure control was the outcome. The treating physicians were both aware of the study objectives and were allowed to adjust the anti-hypertensive medication as needed.[29] Both the experimental and standard treatment groups had improved blood pressure control in each study.[47;50] Similarly, in studies where the intervention was education, the level of information shared with all patients increased.[60;63] Contamination bias confounds the assessment of a compliance intervention.

Another common study flaw is failure to give equal attention to the control group. Control patients receive standard care, but the intervention group may be visited in their homes, or more frequent contact with a health care provider.[54] Health problems are detected early and serious problems averted with frequent contact by health care providers. Detection bias is an important study design consideration, especially if the evaluation of the effectiveness of a compliance program is based on the number of hospitalizations.

Each of these biases leads to an underestimation of the magnitude of change in compliance or outcomes as a result of the intervention. To further illustrate the complexity of the problem, methodologies of each of the randomized trails included in the Cochran Collaborative Compliance and the Haynes-McKibbon-Kanani meta-analyses are presented in tabular form in Appendix 1.

2.3.3.2 *Common Biases in Compliance Research*

2.3.3.2.1 Selection Biases

The greatest challenge in human research is assembling a study population that is representative of the target population, and this is even more of a challenge in applied compliance research. Two forms of selection bias are common to compliance research: participation bias and lost-to-follow-up.

The study population of non-randomized studies can be biased when study participants are selected from a cohort of patients who are currently taking the medication of interest. Patients who have ceased therapy after only one prescription or never obtain a supply of medication are excluded from the study and thus bias the estimate of interest toward the null (See Figures 2.4.1.1.1 and 2.4.1.1.2).

In randomized studies, patients who agree to participate in a study of interventions to improve adherence are generally more adherent and more motivated to take their medications than are those who refuse to participate.[64] Although the randomization process facilitates an unbiased assessment of the effectiveness of the interventions, participation bias creates a ceiling effect which makes it difficult to detect improvement in compliance.[29] Participation bias also diminishes the external

validity of intervention studies because it affects the degree to which the sample population represents the target population.

Another form of selection bias, loss to follow-up can occur after the study population is assembled. For example, in the study by Cote et al., there was a 21% dropout out from the study because of noncompliance. Both types of selection bias attenuate the assessments toward the null.[118]

2.3.3.2.2 Information Biases

Two forms of information biases can be present in compliance studies: detection bias and observation bias. Detection bias is present in studies in which the outcome surveillance procedures are more thorough in the treatment group than the control group (as described in Section 2.3.3.1.2). Observation bias occurs when people are aware that their behavior is being observed and take steps to enhance their behavior and thus bias the study results.[8] Kruse and Weber showed that observation bias is operative in compliance research. They investigated the utility of a microprocessor-based method of continuous monitoring of compliance in 10 patients who were informed and 20 who were not informed of the nature and purpose of the monitoring. Compliance was 94.7% in the informed group and only 77.2% in the uninformed patient group.[65] Observation bias creates a ceiling effect in randomized control trials, but does not bias the assessment of the intervention. If a non-randomized study has a control group which is unaware of the study and an experimental group that is aware, observation bias threatens the internal validity of the study.

Maintaining the blinding of evaluators can produce problems that challenge the validity of the results of any study. Patients often break the blind by volunteering their treatment assignment. The knowledge influences the health care provider's

assessment of outcome in studies, when the outcome assessments are subjective (e.g. disease severity).[33;53;54;66]

Detection and observation biases create errors in measurement of outcome and compliance. Measurement error that is non-differential or random merely attenuates the estimate of effect, but differential measurement error can lead to invalid results. Information biases can be minimized by standardizing detection procedures, using objective measurements and adequately blinding subjects and observers.[67]

2.3.3.3 *Measurement of Compliance*

Compliance is difficult to quantify: pill counts are often impractical, patient reports may be unreliable, electronic monitoring is obtrusive, and measurement of drug presence in body fluid or drug effectiveness (e.g. blood pressure control) may only reflect the patient's recent ingestion of certain medications. There is no standard measurement of compliance, which is a major obstacle to understanding compliance through research.

Measuring compliance is a challenge because of three methodological problems inherent in compliance research: participation bias, observation bias, and the white coat effect. Assessment of compliance will always be spuriously high because the non-compliant patients frequently refuse to participate in studies (participation bias). Additionally, patients are prone to feign compliance, because they are aware that their compliance is being measured (observation bias). Both subjective and objective methods of measuring compliance can be modified by the patients' attempts to appear compliant. Even electronic sensors that monitor when the cap

of the medication bottle is removed are not immune to creative acts of deception by the patient.[64]

The white coat effect (a visit to the physician) is a well-documented surveillance bias in adherence research. Studies utilizing electronic monitoring of compliance have noted a significant decline in compliance with a prescribed regimen between clinic visits and enhanced compliance in anticipation of clinic visits and following a visit.[68] Consequently, when compliance is measured by traditional methods such as asking patients about their level of compliance, pill counts, and drug levels, the level of compliance may be overestimated because of the white coat phenomenon.

There are multiple subjective and objective means of measuring compliance. Subjective measures include patient report and clinician assessment of the patient's report of compliance. Although many methods have been developed to assess compliance subjectively, none has evolved to be a standard. Subjective measures of compliance are most likely to overestimate compliance because patient recall is frequently inaccurate and limited to recent activities. On average, people are able to accurately recall daily activities such as dietary intake for only seven days.[69] Patient report of compliance is biased by a reluctance to admit 'improper' behaviors and/or by the desire to please the health care providers.[70] Thus, studies of compliance based on subjective measurement are limited by participation bias, recall bias, and white coat effect, and are unsuitable for large population studies.

Objective measures of compliance have shortcomings as well. Objective measures of compliance can be subdivided into direct and indirect measurements of drug consumption. Direct measurement of compliance involves testing the quantity of drug in the blood or urine. The greatest limitation of using drug levels is the fact that so many other variables exist that may alter drug levels (e.g. dose, concomitant

medications, and changes in function of the organs of elimination). The timing of the test in relationship to the last dose is critical to evaluating adequate dosing and compliance. Taking a dose of a drug (especially a drug with a short half-life) a few hours before laboratory testing can spuriously raise drug levels. Although a drug level of zero clearly signifies no recent drug ingestion with any drug, serum drug levels are not a useful measurement of compliance.[62] The drug assay methods are highly specific (e.g. absence of a trace of drug signifies noncompliance), but not sensitive to varying levels of compliance. Suitable assays exist for a limited number of drugs, and the expense of these tests make them impractical for large or longitudinal studies. Participation bias and white coat effect are also limitations in this direct method of measuring compliance.

Indirect objective compliance measures include pill counts, electronic sensors and prescription refill compliance. Pill counts have been used extensively, but this method has also been shown to overestimate compliance.[71] Patients can and do discard extra pills prior to pill count checks in order to appear compliant. Sackett and Haynes compared unannounced home pill counts with pill counts at scheduled visits and found compliance was consistently higher when measured by pill counts on a scheduled visits.[43] Pill counts at clinic visits do not show a strong correlation (r=.09) with compliance as measured by microelectronic monitoring systems[72] or by serum assay (r=.16).[73] However, when obtained during home visits, without forewarning the patients, correlations with clinical outcomes were higher (r=.30), thus illustrating the impact of observation bias.[55] Compliance measures can be manipulated by the patient, are unreliable, and therefore less likely to be valid.

A more reliable measure of compliance utilizes sensors within bottle caps which record the time and date the medication bottle is opened. Microelectronic monitoring systems are expensive and require computer software to view and analyze the results. The results can be misleading, if the patient opens the bottle

but does not ingest the medication or transfers the drug to another container. Data are lost if the patient loses the bottle.[62] Patients must consent to electronic monitoring, so assessment of compliance will always be spuriously high since it excludes most noncompliant patients.[58] Eisen et al. reported that a large proportion of eligible patients (76%) declined to participate and 13% of patients who initially agreed to participate subsequently withdrew from a simple study to determine the relationship between prescribed daily dose frequency and medication compliance using electronic monitoring of compliance.[64] This suggests that participation bias may be a systematic problem with electronic monitoring. Furthermore, this method of measuring compliance is unsuitable for population studies and where multiple drugs are used. It can be useful in clinical trials of single therapies where it is important to know the pattern of drug intake during the day.

Another indirect method of measuring compliance, prescription refill rates, is a more widely used method because information is more readily available for large populations and has the advantage of being unobtrusive. The inherent methodological problems in compliance research (white coat effect, participation bias and observation bias) are not present when prescription refill databases are used for research. Analyzing automated records of prescriptions actually filled allows for use of pharmacy or insurance claims databases to define continuity of medication use and gaps in therapy and to allow monitoring of a large number of patients without extra investment in data collection.[9] Prescription refill compliance measurement has several limitations, however. It is useful only where data on all prescriptions filled for each patient are stored in a central database. Another limitation is that this approach is limited to patients on chronic therapy. Refill compliance is not useful for monitoring compliance with intermittent or short-term therapy, such as antibiotics.

Ideally, compliance should be measured longitudinally. Patient-initiated drug holidays occur in many fields of therapy and have diverse clinical consequences.[3] Compliance may change radically throughout the life. For example, a diabetic patient who is passively compliant with parental wishes as a child may rebel by rejecting treatment during adolescence. In early adult life, the rewards of a healthy lifestyle may seem to be a compelling reason to strive for compliance, but in old age the burdens of treatment may exceed the perceived benefits of longevity.[74]

Each method of measuring compliance has its limitations, and these limitations are summarized in the Table 2.3.3.3.1.

Table 2.3.3.3.1 Compliance Measures and Their Limitations

Limitations	Subjective		Objective			
	Patient Report	Clinician Rating	Indirect			Direct
			Pill Count	Electronic Monitor	Refill	Drug levels
Prone to participation bias	x	x	x	x		
Time limit for accurate assessment	1 week	1 week				48 hours
Prone to observation bias	x	x	x	x		
Unable to determine patterns of compliance	x	x	x			x
Expensive				x		x
Biased by white coat effect	x	x	x			x
Unsuitable for large or longitudinal population studies	x	x	x	x		x
Accurate estimate of compliance	Over-estimate	Over-estimate	Over-estimate	Assumed accurate	?	?
Suitable for limited number of drugs				Single drug	Chronic therapy	x
Able to monitor only single therapies				x		x
Obtrusive and can be manipulated by the patient	x	x	x	x		x

The ideal method of measuring compliance in chronic illness should provide both the absolute level as well as the pattern of compliance over a prolonged period. It should be unobtrusive and non-invasive; it should be easily applicable to large numbers of patients, inexpensive, capable of yielding immediate results and resistant to manipulation by the patient.[61] Additionally it should be reliable and valid.

An unobtrusive measure of compliance is needed to reduce the impact of observation bias. Refill compliance measurements offer the only solution to this methodological problem. Pharmacy prescription profile-based methods for monitoring compliance have a distinct advantage in that patients are not aware that their compliance is being monitored, but the utility of this research tool depends upon its validation.

2.4 **Evidence of Validity of Refill Compliance**

There is some evidence that compliance measured by prescription refills is a valid indicator of patient adherence. Two studies designed specifically to validate this measurement of compliance were published in 1980 and 1988. Both were construct validation assessments in which the correlation between prescription refill compliance and a measure of the effect of drug consumption (serum drug levels or physiologic effect) was used to judge the validity of refill compliance. Correlations in these two studies between refill compliance and physiological effects between ranged 0.14 to –0.63; variations in estimated association may be attributable to features of the design of the studies.

2.4.1 Validation Study Design Challenges

There are three primary components of validation studies of refill compliance: study population, treatment outcome, and measurement of compliance that can influence the results of the study. Careful attention to each is required to evaluate the construct validity of refill compliance.

2.4.1.1 *Study Population Issues*

The study population can be either too small in size to have sufficient power for detecting an association or too homogenous. For example, to achieve 80% power and 0.05 level of significance, the number of patients required to detect an association, of $r \geq 0.30$ is 67, for $r \geq 0.40$ is 37, and for $r \geq 50$ is 23.[75;76] Studies conducted in small study populations have the power to detect only strong associations.

Underestimation of the true association between compliance and an outcome can occur because of participation bias. Participants in compliance studies tend to be more compliant than those who refuse to participate. Under-representation of noncompliant patients will cause an underestimation of the association because the range of compliance will be restricted. The following two graphic presentations illustrate this point. A linear relationship is evident between compliance and treatment outcome in the hypothetical population (Figure 2.4.1.1.1). When the noncompliant patients are removed (i.e. patients who choose not to participate), the linear relationship disappears (Figure 2.4.1.1.2.)

Ideally, validation studies should be conducted in sample populations that represent the range of compliance that may actually exist among persons in the target population, so that the results are internally and externally valid. To enhance the understanding of compliance, the target population should represent the general population of persons using medications. However, in the absence of a general representative population, multiple select populations with low rates of non-participation may serve the same function.

Figure 2.4.1.1.1
Total Study Population

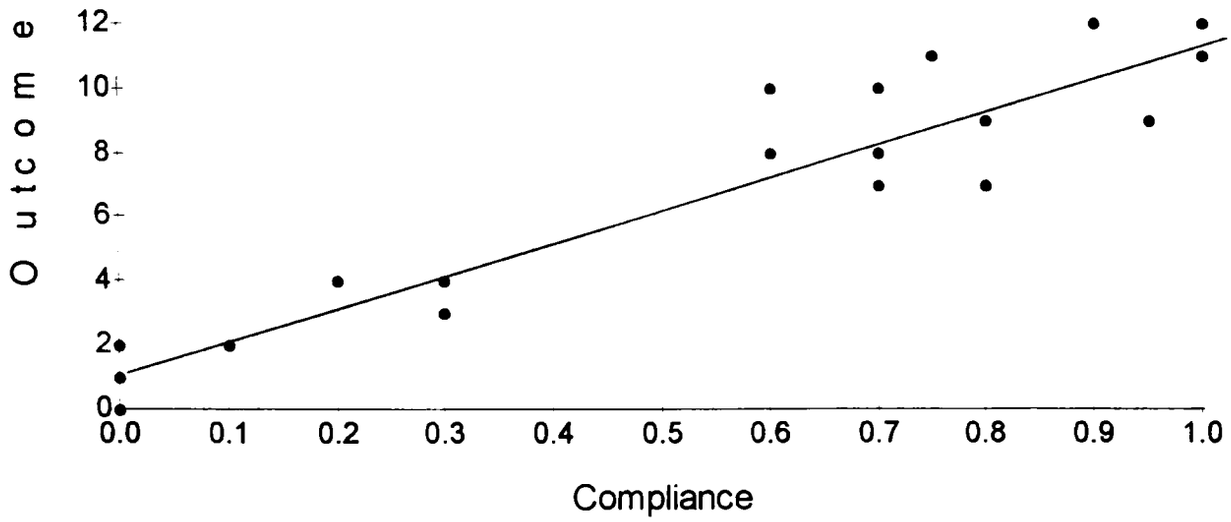
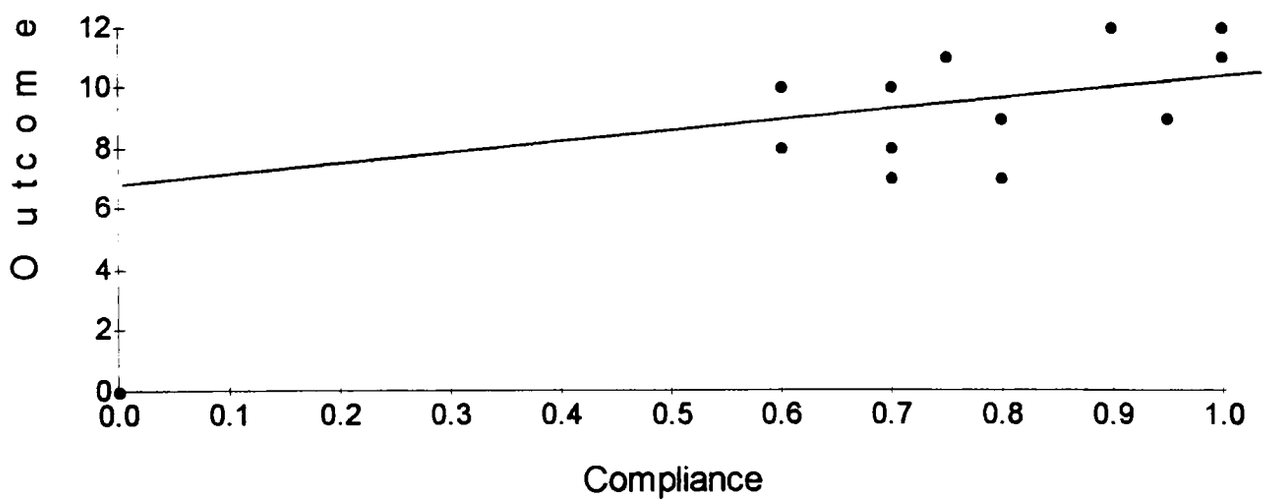


Figure 2.4.1.1.2
Participating Study Population



2.4.1.2 *Outcome Measurement Issues*

Treatment outcome is generally a valid biological indicator of either the therapeutic effect of the drug (e.g. blood pressure level) or the blood level of the drug. Reliability is the key feature of the test of treatment outcome that is necessary to provide a credible estimation of the association between a treatment outcome and compliance. Variability in the outcome stems from a variety of factors, such as diet, circadian rhythms, and dose changes. Steps can be taken to minimize these sources of variance in the outcome measurement, so that changes in the outcome are more likely to represent changes in compliance. Some variability results from intrinsic biological variability that cannot be measured or controlled. The impact of random error due to intra-subject variability is reduced by aggregating the measurement of outcomes for each patient (e.g. average blood pressures). Between-subject variance attributable to factors other than medication compliance can be reduced by restriction of the population (e.g. patients who have similar disease severity, such as diabetic patients who are not receiving insulin rather than all diabetic patients). Another solution is to measure (by valid and reliable methods) potential effect modifiers and confounders and control for these factors in the analysis. If unmeasured or unrestricted, other factors which can influence the level of the outcome will increase "unexplained" variability in outcome measurement. The net result is that the association will be underestimated because of "random error."

2.4.1.3 *Refill Compliance Measurement Issues*

Non-random error in measurement is a serious threat to the validity of any measurement tool. Non-random error can be insidious in the measurement of both the numerator and denominator of refill compliance (Figure 2.4.1.3.1). Refill

compliance is generally calculated as the sum of days of drug supply obtained and available for consumption over a time interval, divided by the total days from the beginning to the end of the time period.[65] Compliance is likened to a rate of events in a period of time (e.g. miles per hour, cases per year).

Figure 2.4.1.3.1 Refill Compliance Formula

Compliance = Σ days of drug supply / (end of time period – beginning of time period)

Problems arise when the numerator (days of drug supply) is measured without attention to the corresponding and appropriate denominator of person-time (calender days). Problems occur because of left- and right-sided censoring, early refills, stock piling of medication, and changes in the treatment regimen. As a result, the numerator can be over- or under-estimated. The denominator is a period of time can that can be fixed or dynamic. Each choice has the potential to bias the measurement of compliance.

2.4.1.3.1 Numerator Issues

The numerator can be underestimated and overestimated because of changes in the treatment regimen. The most common treatment change is a switch to a new dose of the same drug or another drug in the same therapeutic class. A switch in therapy usually represents the end of the current regimen before the current supply of the medication is exhausted. Some changes are not measurable, such as switches to over-the-counter drugs and physician directions to reduce or increase the frequency of dosing without issuing a new prescription. Failure to adjust the duration of drug supply for changes in treatment will usually overestimate the total days of supply (the numerator) and thus overestimate compliance (unless the physician advises the patient to increase the dose per day without a new

prescription).

Inaccurate counting of the numerator is inevitable when a compliance study is conducted in a cohort of patients who are prevalent users of the drug of interest, because they have an unknown amount of medication on hand at the beginning of the study. Left-sided censoring underestimates the days of drug supply and deflates the numerator.

Underestimation of the numerator can occur when the patient receives a supply of drug that is not recorded in the prescriptions claims database. Drug dispensed during periods of hospitalization, prescriptions filled in the hospital pharmacy at the time the patient is discharged from the hospital, use of over-the-counter rather than prescription drugs, or free samples can create an underestimation of the total days supply of medication as well.

For the numerator to be accurate, the duration of a drug supply days should be adjusted for early prescription refills. For example, if each prescription contains 30 days of medication and a refill is obtained the 25th day after beginning the first prescription, the days of drug supply duration should be 60 days (30 days followed by 30 days), not 55 days (25 days followed by 30 days). The duration of available drug (days of supply) should also be augmented to account for the extra tablets that the pharmacist sometimes adds to the amount dispensed beyond the required (e.g. Dispensing 100 pills for 90 days of therapy, because the manufacturer-supplied bottle has 100). Failure to accurately count the supply days in the numerator can lead to an underestimation and invalid measurement of compliance.

2.4.1.3.2 Denominator Issues

The denominator is the number of days between two time points, the start and end

of the observation period (T1 and T2). The starting point (T1) is often the first prescription of an inception cohort, and an arbitrary time point for a cohort of prevalent medication users. The ending time point (T2) can be one of several dates: the last day of a fixed period of follow-up (e.g. 6 months from first prescription); the date of the last prescription; or the date of the last outcome measurement. Table 2.4.1.3.1 shows that the calculation of compliance yields different rates with each option (77%, 83%, and 102%). The differences are created by varying the size of the denominator and by right-sided censoring.

The fixed follow-up example in Table 2.4.1.3.1 shows that the patient had 50 days of drug supply in 60 days of follow-up. Initially, this seems to be an accurate measurement of compliance. However, if the patient obtained another 30-day supply of drug on Day 54, when the previous prescription ran out, it would create a dilemma. Counting this prescription in the numerator would inflate the numerator and ignoring it would deflate the numerator.

Table 2.4.1.3.1 Three Options for Determining the End of the Compliance Observation Window and Compliance Calculation for Each Option

Time and Events				**Options for End of Compliance Observation Window**		
Date	Time in days	Clinic Visits Blood Pressure	Prescription Daily dose and Days of supply	Fixed Follow-up 60 days	Last Outcome	Last Prescription
Jan 1	0	150/92	1daily x 30 days	T1	T1	T1
Jan 15	15	166/84				
Feb 3	34	148/80	1 daily x 20 days			
Feb 18	49	136/82			T2	
Mar 1	60			T2		
Mar 6	65		1 daily x 30days			T2
Compliance Calculation			Numerator	50	50	50
			Denominator	60	49	65
			Compliance	83%[a]	102%	77%

A. If another prescription was filled before the end of the 60 days it might be counted in the numerator.

The next option, ending with the last outcome can also lead to measurement error. Consider the example in Table 2.4.1.3.1 above in which the last measure of outcome (BP) was on Feb18th and so the denominator is 49 days. It would be erroneous to assume that the prescription dispensed on Feb 3rd would be consumed by Feb 18th. If the patient took the drug once daily without fault, it would last until Feb 22nd. Compliance was overestimated in this example because it was assumed that all drug prescribed during the study follow-up was consumed in that time period.

When the ending point (T2) is the last prescription refill, it provides reassurance that the therapy was not discontinued by physician, but selects the more compliant patient population for study, and the association between compliance and outcome is affected by the uneven right-sided censoring. Both compliance and outcome information are censored at different points in time therefore the numerator and denominator are measured over different periods of time. In the "Last Prescription" option example above, T2 is on March 6th and the last BP is on February 18th. The problem is that the temporal association between BP and compliance is ambiguous because compliance is measured both before and after the outcome.

2.4.1.3.3 Temporality Issues

Ideally, compliance and outcome should be measured in the same time period. Uneven right-sided censoring can also obscure the temporal association between outcome and compliance. In the example below, both BP and T2 occurred on the same date the data are censored at the same time point. The temporal relationship between compliance and outcome is clear, and we can infer that drug compliance during the period between T1 and T2 could be associated with the level of BP.

BP

T1 T2

When the BP measurement occurs before the end of the compliance period (T2), there is temporal ambiguity because compliance (post BP measurement), is included in the measurement of compliance and the estimated association between compliance and blood pressure.

T1 BP T2

A biased inference can occur if the temporal sequence between exposure (compliance) and outcome (BP) is reversed, i.e., if the study outcome actually precedes and causes the hypothesized exposure.[67]

The outcome measurement and last prescription often do not occur on the same day, and so a daily compliance log to measure compliance obviates errors in measuring compliance and temporal distortion. Creating a daily compliance log of drug supply and outcomes events enables investigators to measure the two events at the same point in time. Daily compliance logs are a recent development in compliance research that offer some advantages over aggregate measurements of compliance. Table 2.4.1.3.2 is an example of a daily compliance log that enables one to see the affect of uneven censoring on measuring compliance. On Feb 18th, compliance is 46/49 (94%) for 3 days during the observation period, the patient was without a supply of drug. This is a more accurate calculation of compliance.

Table 2.4.1.3.2 Daily Compliance Log Example

Date	Time in Days	Prescriptions	Drug Supply (0=no 1=yes)	Outcome
Jan1	1	30 tabs, 1 daily	1	BP 150/92
Jan2	2		1	
↓*	↓		↓	
Jan 15	15		1	BP 166/84
↓	↓		↓	
Jan 30	30		1	
Jan 31	31		0	
Feb 1	32		0	
Feb 2	33		0	
Feb 3	34	20 tabs, 1 daily	1	BP 148/80
↓	↓		↓	
Feb 18	49		1	BP 136/82
↓	↓		↓	
Feb 22	53		1	
Feb 23	54		0	
↓	↓		↓	
Mar 1	60		0	
↓	↓		↓	
Mar 6	65	30 tabs, 1 daily	1	

* Arrows represent repetition of information on subsequent calender days

Failure to adjust the expected date of refilling for changes in therapy, stock piles of medication and other factors that influence the expected duration of a supply of drug can underestimate compliance and bias the association and thus the validity of the study. Table 2.4.2 summarizes the impact of the impact of each of the design

features (and flaws) on the results of validation studies.

Table 2.4.1.3.3 Summary of Study Features and Their Impact on Studies of Construct Validation of Refill Compliance

Study Feature	**Yes**	**No**
Study Population Features		
Largely compliant patients due to participation bias	Under-estimation of association	Reasonable estimate of association
Sample size small	Powered to detect only strong associations	Power to detect significant associations
Cohort of new users of the medication	Adequate estimate of association	Left-sided censoring leads to errors in measuring compliance because of an unknown supply of medication on hand.
Restricted by demographic features of patients	Limited generalisablity	External validity
Features of Treatment Outcome Measures		
Disease state is stable and therefore changes in outcome represent changes in compliance	Adequate estimate of association	Non-differential misclassification under-estimates association; potential for systematic error and biased estimates of association.
Test of outcome is reliable; e.g. not influence by circadian rhythms or white coat effect.	Adequate estimate of association	Random error in outcome measurement, under-estimate of the association
Restriction of concomitant therapies and other variables which affect treatment outcome or adjustment in analysis	Adequate estimate of association	Under-estimates association due to random error or potential bias due to confounding
Features of Compliance Measures		
Adjusts duration of therapy for early refills and dose modifications	Reasonable estimate of association	Biased estimate of association due to non-random under-estimation of compliance.
Right-sided censoring of compliance with the last prescription	Selects a more complaint population and biases estimates the association, direction unknown	Reasonable estimate of associations
Right-sided censoring of compliance and outcome on the same date	Reasonable estimate of associations	Uneven censoring creates temporal ambiguity which could bias the association

2.5 REFILL COMPLIANCE VALIDATION STUDIES

Validation is an ongoing process that involves the development of a body of evidence to justify the descriptive, explanatory or predictive interpretations of a test or measurement.[77] The validation studies described in the next section provide some evidence to justify the interpretation of compliance behavior based on prescription refill compliance.

Theoretically, a patient's behavior is in compliance with their physician's recommendations when the patient consumes their medication as it was prescribed. The components of this behavior include a decision making process regarding the physician's recommendation for medication treatment, obtaining a supply of the medication, and consuming the medication in the manner prescribed.[74] Although the behavior can not be observed, it can be linked to other attributes associated with compliant behavior such as obtaining the medication, removing pills from the medication bottle, and experiencing the benefits (or consequences) of drug consumption. If the relationship between the indicator of compliance (e.g. timeliness of refills) and drug ingestion is strong, it can lead to useful inferences about compliance.

In refill compliance construct validation studies, the therapeutic effect derived from ingesting the medication or the resulting levels of the drug in the blood is correlated with measures of refill compliance. The underlying assumptions are that: 1) the drug is effective, and 2) high levels of refill compliance are associated with the desired therapeutic outcome derived from consuming the medication.

2.5.1 Primary Construct Validation Studies

Two construct validation studies have been conducted in the same Veteran's Administration hospital (predominately male patients). The first study by Inui and colleagues in 1980 demonstrated significant correlations between refill compliance of hydrochlorothiazide and propranolol with expected physiologic effects of these drugs on blood pressure and heart rate. The study populations were random samples of patients thought to be chronic users of the two drugs, so as to avoid assumption of non-compliance in patients who discontinued therapy on advice from their physician. The study was a retrospective record review so the patients were not aware that their compliance was being measured. Eligible patients had pharmacy file prescription data that indicated that one or more drugs were to be taken on a regular schedule for at least six months after the original prescription was written. Patients were excluded from the propranolol group if they were receiving concomitant medications known to affect heart rate. The observation period for each patient began when medical or pharmacy records indicated that the patient had been given a prescription for propranolol or hydrochlorothiazide, which had the option of four 30-day refills and ended 155 days after the prescription was recorded in the medical record. Compliance was determined from pharmacy records by dividing the number of refills actually obtained by the amount of refills possible. Their semi-continuous measure of compliance had six possible values:

Number of prescriptions filled	Level of compliance
0	0%
1	20%
2	40%
3	60%
4	80%
5	100%

A second compliance index, *the effective dose*, was calculated only in the propranolol study group by multiplying the prescribed daily dose times the observed proportion of compliance (e.g. 40mg dose x 0.80 refill compliance =32 mg *effective dose*).

The study found statistically significant correlations between hydrochlorothiazide compliance and mean diastolic blood pressure (r = -0.63, 95% CI= -0.31 to -0.82). For the propranolol treatment group, the correlation coefficient was r = -0.27 (95% CI= -0.58 to 0.12) for the relationship between propranolol compliance and resting pulse and r = -0.41 (95% CI= -0.68 to -0.03) for *effective dose*. Thus, both groups provided evidence of construct validity of refill compliance, but the propranolol effective dose analysis highlighted the importance of measuring effect modifiers such as dose in the measurement of outcomes in compliance studies. There were several strengths in this study. The study population was unaware that their compliance was being assessed thus avoiding observation bias. Confounding was controlled by restriction; the propranolol group was not receiving other drugs that modified heart rate and the hydrochlorothiazide group had controlled blood pressure at the outset of the study thereby limiting treatment modification as a potential confounder for outcome assessment. The investigators used the average diastolic blood pressure and pulse rate over the study period in the analysis and

thus reduced random error in the measurement of the outcome for each subject. The limitation of the study was that compliance was potentially overestimated when the last refill was obtained near the end of the observation period and the authors assumed that the excessive drug supply was consumed in the observation period. If this occurred, it would have biased the estimate of association toward the null.

In 1988, Steiner and colleagues reported a second construct validation in two study populations.[78] They compared refill compliance for phenytoin, a drug for the treatment of seizure disorders, with serum phenytoin levels and refill compliance with anti-hypertensive drugs with diastolic blood pressure. Random samples were drawn from a cohort of eligible patients who had to have sufficient pharmacy and medical record data for study; they were excluded if they had fewer than three refills or fewer than 180 days between the first and last refill and less that two outcome measurements. These criteria acted to select a more compliant patient cohort.

Refill compliance was measured from the first prescription during the study period to the date of the first refill immediately after the last measurement of outcome (serum phenytoin or diastolic blood pressure). Uneven right-sided censoring creates an inflation of the numerator, and overestimates compliance and the temporal relationship is ambiguous as described in section 2.4.1.3. There is no indication that drug administration during periods of hospitalization or changes in drug dose were considered in their assessment of drug supply. Compliance rates were often greater than 100% in this study in part because of two hospital policies. The hospital encouraged physicians to issue prescriptions for 90-day drug supplies and required that they write new prescriptions every six months. Since the patient received the drug free of charge, there was no incentive to decline the extra supply of medication. Surplus medication supplies may further inflated the numerator.

The first of the two study populations was a stratified random sample of seizure disorder patients with low and normal serum levels of phenytoin and all patients with toxic levels, based on their average phenytoin levels during the study period. Serum phenytoin levels were obtained in asymptomatic patients, but more commonly for patients with recent seizures or suspected drug toxicity. The study reported statistically significant correlation coefficients for phenytoin compliance and mean serum phenytoin level (r= 0.31, 95% CI= 0.04 to 0.54) for all 52 patients. Fifteen percent of the patients had mean compliance scores of greater than 110%. Measurement error probably resulted in underestimated associations. When the over-compliant patients were excluded, the association was stronger, (r=0.37, 95% CI=0.08 to 0.60).

The second study population was a treatment inception cohort of 73 randomly selected hypertension patients. The investigators estimated the correlation of the mean compliance and mean diastolic blood pressure (DBP) for each visit during the study period for each patient. To control confounding due to disease variability, the study period began after the patients' DBP reached the customary therapeutic goal of 90 mm Hg. For patients receiving multiple anti-hypertension drugs, each refill of each drug contributed to a composite measure of compliance. Compliance was a time-weighted measure of supply of medication divided by the days of observation. For example, if the patient obtained 150 days worth of drug A over a 200 day period and 120 days worth of Drug B over 100 days the index of compliance would be ((0.75 x 200) + 1.20 x 100)/(200 + 100), or .90. On average, the patients were taking 1.58 medications. The resulting correlations between mean blood pressure and compliance ranged from r= -0.14 (95% CI= -0.35 to 0.09) for all patients to r= -0.19 (95% CI= -0.42 to 0.06) for patients with "controlled" blood pressure throughout the study (also presented in Table 2.5.1.2).

This study had many strengths and weaknesses. One of the strengths of this study

was that the study groups were random samples of a potential study cohort, and patients were unaware that compliance was being assessed, thus avoiding observation bias. Unfortunately, the eligibility criteria which excluded patients fewer than 3 refills eliminated the less compliant patients. The hypertension population was restricted to patients with controlled DBP in order to control confounding due to changes in the disease. These patients were a treatment inception cohort which reduced the likelihood of underestimating the numerator due to left-sided censoring. Random error in measuring the compliance and the two outcomes (DBP and phenytoin levels) due to intra-subject variability was reduced by using average levels of the outcome for each patient and correlating these values with mean compliance over time the entire observation period.

There was a broad distribution of outcomes in the phenytoin study because a stratified sampling procedure selected patients with high, normal and low phenytoin levels, thus enhancing the probability of demonstrating the relationship between outcome and compliance but likely overestimated the magnitude of the association in the general population. It is plausible that the patients in the high level group may have had more phenytoin levels and adjustments of dose, which would have lead to errors in measuring compliance numerator if one fails to adjust the duration of therapy for changes in dose of treatment. Phenytoin has a long half-life, and therefore phenytoin levels are not influenced by recent ingestion of medication and the white coat effect. However, phenytoin levels are affected by the dose of phenytoin and many concomitantly administered medications, such as phenobarbital. It is difficult to predict the impact of failure to measure this effect modifier/potential confounder on the estimation of the association.

The major weakness of the Steiner study was the over-estimation of compliance in both study populations. Measurement error was derived from several sources in this study, all of which likely created an underestimation of the relationship between

compliance and outcome. Overall, the range of patient compliance was reported as 0.3-1.63. All patients (compliant and partially compliant) had an opportunity to obtain an over-supply of medication, and this can be viewed as a source of random error in measurement of compliance which would have likely to underestimated the association between compliance and outcome. It may also be viewed as an invalid measurement of compliance for 'stock piling' and uneven right-sided censoring caused the measurement of compliance to systematically overestimate drug consumption. The authors reported that "as medication oversupplies became more extreme, measures of phenytoin levels fell and mean DBP rose," suggesting that the patients were not consuming the surplus medication.[78] Table 2.5.1.1 permits an examination of their results in more detail and in particular the impact of including the over-compliant patients in the analysis.

Table 2.5.1.1 Steiner's Results With and Without Over-Compliant Patients

	Patients with Compliance >1.1. Included	**Patients with Compliance >1.1 Excluded**
Hypertension Patients		
All hypertension patients	r=-0.14 N=73	r=-0.30 N=49
Controlled - at least one DBP < 90 during follow-up	r= -0.19 N=64	r=-0.38 N=42
Phenytoin Patients	r= 0.31 N=52	r= 0.37 N=44

There was a stronger correlation in the controlled hypertension patient group as compared with the more heterogeneous group (all hypertension patients). The changes in blood pressure less likely reflect changes in compliance than physicians' efforts to improve blood pressure control, by maneuvers such as dose modification. When compared with Inui's study results (r= -0.63) in hypertension with a single drug (hydrochlorothiazide) the results are in the same direction.

Steiner's study underestimated the association. The differences in the two studies are the number of drug therapies, and the different methodology for calculating compliance.

Steiner and his colleagues developed a method for calculating compliance that elucidates the variability in obtaining medications over time by calculating three indices of compliance: ratio of days supply, time between prescription refills (MED-TOTAL), and days without medication (MED-OUT) which is not merely the reciprocal of MED-TOTAL. Since patients may comply to varying degrees with different medications in the same treatment regimen, they also developed a summary measure of compliance for all drugs in the treatment regimen, weighting each by the duration of its observation.

Comparison of the two different methods of calculating compliance is necessary to evaluate the results of these two validation studies. Inui's observation period was fixed for each patient while Steiner's study had a variable observation period for each patient, which was actually the time between the first and last refill. The following is an illustration of the two methods of calculating refill compliance for a single drug.

Table 2.5.1.2 Comparison of Two Methods of Calculating Refill Compliance

Inui Method	**Steiner Method** (Columns 2-5)			
Study Day **Rx #**	Study Day	Number of days between refills Time differences between rows of column 2.	Days with a drug supply in each time interval Also number of daily doses in the RX	Days without drug available during each time interval Column 3 – Column 4 (positive values only)
Day 0 **#1**	Day 0	20	30	0
Day 20 **#2**	Day 20	45	30	15
Day 65 **#3**	Day 65	65	30	25
Day 130 **#4**	Day 130	26	30	0
	Day 156 The first prescription filled following the last outcome measurement the study		Drug supply in the last RX is not included in the calculation of compliance	
Maximum number of Rx's possible was five.		Σ= 156 Days in Time Period (to first Rx after last outcome)	Σ= 120 Days of Drug Supply Available	Σ = 40 Days without Drug
4/5 Rx's = 80% Compliance	**Steiner Compliance Summaries**: MED-TOTAL: (Σ days supply available/ Σ days in time period) = 120/156 or .77% MED-OUT: (Σ days without drug available/ Σ days in time period) = 40/156 or 26%			

The obvious difference in the two methods is the unit of assessment: number of prescriptions filled versus days supply of medication obtained. An important difference between Steiner's method and Inui's method of calculating compliance is in the determination of the time interval or the denominator. Steiner's method is

more likely to inflate the numerator because the numerator days are not always included in the denominator and it assumes that all drug dispensed in the denominator period is consumed in that time period. The final difference is Steiner has two indices of compliance, MED-TOTAL and MED-OUT which facilitate research to explore patterns of compliance over time.

Both methods failed to adjust the duration of drug supply for dose modification by the physician with a new prescription. The studies also have limited generalizability as they were conducted in predominately male populations. Nonetheless, both studies provide some evidence of construct validation of refill compliance, and the magnitude of the associations were likely attenuated by methodological issues.

2.5.2 Secondary Construct Validation Studies

A few compliance intervention studies have correlated outcomes with refill compliance indices and lent support to the validity of refill compliance measures. Each of the studies was conducted in subjects that had relatively high compliance at the start of the study and thus are limited by participation bias and a ceiling effect. Still, each study provides insight into the methodology and validity of refill compliance.

In 1971 Roth, Caron, and Hsi reported on their efforts to find a measure of compliance that would offer a more accurate assessment than clinician's judgement of patients' compliance with treatment of peptic ulcer.[119] The study population was composed of patients who were participating in a non-randomized intervention study evaluating a peptic ulcer treatment program that included 11 clinic visits over two years and two physician visits at the patient's home. Therefore, the results of this validation study are likely to be affected by observation and participation bias.

Two measures of compliance, total number of atropine tablets prescribed and total number obtained through filling prescriptions during one year (i.e. only numerator count), were correlated with the presence of urinary metabolites of one of the drugs in the patient's treatment regimen, atropine.

The investigators reported a correlation between percent positive urinary atropine tests and the number of tablets of atropine obtained by a patient to be r=0.47 (95% CI = 0.24 to 0.65) and noted slightly higher correlation for those who obtained their medication free (a smaller subset of patients). The correlation between number of tablets prescribed and the atropine outcome was r=0.01 (95% CI = -0.25 to 0.26).

This study had many limitations. The study population was likely to be more compliant because they were participating in a treatment intervention study. This leads to an underestimation of the association between compliance and outcome. The measure of outcome was not a valid test of continuous atropine use. It was only sensitive to atropine consumption within the previous 12 hours and was likely to overestimate the outcome because the white coat effect. Even a negative test was only an indicator of having missed the most recent dose of atropine. Finally, compliance could have been underestimated because the patients could obtain their medication from multiple pharmacies.

The next secondary study was designed to evaluate the effectiveness of a non-randomized intervention program to improve drug documentation in medical records. Bond, et al.[120] demonstrated a statistically significant association between diastolic blood pressure and compliance with a variety anti-hypertensive therapies. The source population was patients from the medical centers' rheumatology and renal clinics. An individual who was not aware of the study objectives extracted data from medical and pharmacy records. The study population consisted of a

randomly selected control group and was assessed six months prior to initiation of a pharmacist drug management service. Intervention patients were evaluated 9 months and 4.75 years after the intervention was initiated. The investigators analyzed the association between compliance and outcomes with the Phi (ö) correlation coefficient, which is based on the chi square test group. The outcome was the percentage of patients whose average blood pressure over the follow-up period was less than 145 mm Hg systolic and 95 mm Hg diastolic. Compliance was reported as the percentage of patients who were compliant with all medications. Compliance and noncompliance were determined by whether or not a patient had refilled a prescription for a long-term medication within a seven-day period before or after the 30-day prescription would have been exhausted. A patient was classified as "compliant" if they obtained all refills within the 7-day window.

The study strengths include a study population who was not aware that their adherence was being assessed, and a random sample of control patients who did not receive the intervention. The control group was needed for evaluation of the intervention, not the validation of refill compliance, but it provides a good example of the effect of participation bias. There were significant differences in the percentage of patients who were compliant between the control group (14%) and study group (80%). Although no details were provided, the investigators had access to information that would allow adjustment of the compliance measurement for dose changes early refills, and discontinuation of therapies. Errors in the measurement of compliance and outcome are likely to have been random errors as data extractions from the medical and pharmacy records were done by individuals who were blinded to the purpose of the study. By using average summary measures for the individual of outcome and compliance, the impact of random measurement error is neutralized. The main limitation of this study is that the impact of potential confounders on the estimation of association was not addressed. Renal failure, a cause of secondary hypertension, was present in most of the

patients from the renal clinic and may have been absent from the arthritis clinic patients. Renal clinic patients were reported to be receiving complex medical regimens, which can also affect compliance. The impact of these confounders on the results is difficult to predict.

In 1991, Steiner et al. correlated propranolol refill compliance with resting pulse rates in 25 male patients taking a variety of beta-blocking drugs in a treatment intervention study.[121] The intervention was a gradual reduction in antihypertension medications until the DBP rose to above 95 mm Hg followed by increase in antihypertension medications to achieve blood pressure control. The authors hypothesized and found that patients who had been partially compliant and well-controlled blood pressure could have their antihypertension medications reduced without loss of blood pressure control. Steiner's measurement of compliance was modified for this study. Compliance was measured for each drug for a fixed time period; and was measured as a summary index of the entire antihypertension regimen that weighted the compliance for each drug in the regimen by the time span over which the drug had been supplied. If the patient obtained 150 days worth of drug A over a 200 day period and 120 days worth of Drug B over 100 days the index of compliance would be ((0.75 x 200) + 1.20 x 100)/(200 + 100), or 90%. For analysis of the intervention, compliance was divided into 6 strata, (< 80%, and 80 to 120%) in increments of 10. Stratum classifications were correlated by Spearman's correlation with resting heart rate. There was a statistically significant association between refill compliance and resting pulse (r=-0.49, 95% CI = 0.12 to 0.74),

One strength of this study is that restriction was used to control for pharmaceutical modifiers of the outcome (heart rate). Patients taking drugs known to affect heart rate were excluded from the study. Another strength is that although the measurement of pulse rate is subject to random error, it is minimized by averaging

repeated measurements of the outcome in a defined time window. Using 6 strata to reflect average compliance rather than an average value in the analysis may have further reduced the variance in the measurement of compliance.

As in all intervention studies, participation bias was present and likely created a restriction in the compliance range (a ceiling effect) and thus attenuated the relation between compliance and outcome. As in previous studies, Steiner did not adjust the drug supply for changes in dose or periods of hospitalizations. The range of compliance was 30% to 170%; median compliance was 95%. The reasons for overestimation of compliance included inflated numerator due to stockpiling, and uneven right-sided censoring. The time period for counting numerator days was longer than that for the denominator (uneven censoring).

The final study was reported by, Steiner, et.al in 1993.[114] This study retrospectively evaluated the relationship between refill compliance and drug levels of digoxin by review of medical and pharmacy records as a substudy of a larger study. The objective of the larger study was to determine whether larger prescriptions ($\geq$ 90 day supply) enhance the acquisition of a variety of maintenance medications. The substudy population consisted of 86 patients receiving digoxin for congestive heart failure or EKG documented arrhythmias. The outcome was digoxin levels and the confounders were serum creatinine, body weight and digoxin dose. Compliance was measured as the total days' supply divided by the days between the first and last digoxin prescriptions. The partial correlation coefficient was 0.23 (95% CI = 0.04 to 0.44) after adjusting for serum creatinine, body weight and prescribed dose. Although over-compliance rates were high (mean compliance 124.4%) it was not associated with digoxin toxicity in this study. Only three cases of digoxin toxicity occurred, and none were associated with consumption of more digoxin than prescribed. Restated, over-compliance (> 100%) was not associated with the expected outcome of drug toxicity suggesting that the method for the calculation of

compliance overestimated drug consumption.

One of the strengths of this study is that the drug levels were not likely to be elevated because of the "white coat effect." Digoxin is a drug with a long half-life (> 24 hours) and drug levels are reflective of long-term compliance. Additionally, the analysis included covariates that modify the level of digoxin. The study population was not affected by either observation or participation bias. However, the study population was based on a subgroup from the hospital that was evaluating the use of 90-day prescriptions. Physicians were more likely to issue 90-day prescription in compliant patients with stable disease. This was a potential population selection bias that could have influenced and likely attenuated the compliance-outcome association.

A weakness of the 1993 Steiner study is that the observation period (first to last prescription) selects a more compliant patient group and this can lead to an underestimation of the compliance-outcome relationship. Compliance was probably overestimated as in the previous studies reported by this investigator. Errors in the measurement of compliance may have led to underestimation of the association between compliance and outcome. Finally, in this study and the previous three studies by Steiner, the population was predominately male and so the results have limited external validity.

Each of the secondary validation studies was an analysis of compliance in a subset population participating in an intervention study. The reported associations between health outcome and indices of compliance may underestimate the association because the studies were conducted within study populations motivated to adhere to the prescribed drug therapy. Only one of the studies addressed confounders in the analysis of the association. Yet, each study provides

convergent evidence that refill compliance is correlated with health outcomes and indirect evidence of medication consumption. For further comparison of these studies, Table 2.5.3.1 summarizes each study and the impact of each of the design features (and flaws) on the study results.

2.5.3 Summary of Previous Validation Studies

In summary, the two validation studies and four supportive studies reviewed have reported a range of correlations (r=.14 to r=.86). The reasons for the discrepancies may be explained by the different methods of calculating compliance.

Features of the study design can lead to spurious results in all studies. Studies in which validation was the main object have been designed with forethought. Inui and Steiner attempted to control the impact of dose adjustment on the outcome measure by restricting their study population to those that exhibited signs of stable disease. This is an important design feature for future validation studies; it reduces the "noise" or random error in the assessment. Although Inui et al. documented the impact of modifiers of the drug's effectiveness, like dosage, on the association of compliance and health outcome, Steiner did not measure or adjust for any other factors in his initial validation study. Both studies were conducted in predominately male patients with cardiovascular disease, and therefore have limited generalizability.

Each of the supportive studies was an analysis of a subset population participating in an intervention study and therefore subject to participation bias and observation bias. The reported associations between health outcome and indices of compliance may have been underestimated because the studies were conducted within study populations motivated to adhere to the prescribed drug therapy. Only one study

addressed potential confounders and modifiers of the association. The methods for measuring compliance were varied, but none of the studies reported that there was an adjustment in days of medication supply (numerator) for dose changes, switching of drugs in the same therapeutic group, early refills, or for periods of hospitalization. Many studies overestimated compliance because compliance and outcome were measured at two different time points and thus created a numerator that was inappropriately larger than the denominator.

2.5.4 Gaps in Refill Validation Studies

The collective body of knowledge regarding the validity of refill compliance as a measurement of compliance is limited to studies conducted predominately in male patients with cardiovascular diseases. There is insufficient evidence that it is a valid measure of compliance in both genders and other diseases conditions. Nevertheless, valuable lessons can be extracted from prior research to refill compliance to conduct further validation research and to refine the methods of measuring.

While most investigators agree that refill compliance is best determined by the proportion of days of drug supply dispensed in a particular time period, the methods of calculation for both the numerator and denominator vary. Refinements in the method of calculating the duration of therapy have evolved in recognition of the fact that patients often obtain a new supply of medication before the current prescription is depleted and that physicians modify chronic therapy over time. Generally, compliance researchers have developed methods for adjusting the duration of therapy for presumed early refills and switching to another drug in the same therapeutic class, but not for changes in dose. Christensen, et al. confirmed the importance of adjusting the duration of drug supply (numerator) for changes in

treatment by comparing prescription refill data with medical chart review. They observed that high and low compliance rates were associated with dosage changes. Among over-compliers, 42% had dosage changes noted in the chart. Among under compliers, 43% had dosage changes. They concluded that compliance based on days of supply, ignoring dose, is not a valid way of measuring compliance.

The methodology developed for this validation study is an algorithm that adjusts the duration of therapy for apparent changes in drug dose. The algorithm program looks forward and backward from the time of each prescription to determine if the current prescription is probably an early refill, probably intended to replace the current prescription (a switch), or probably intended to be taken concurrently with the previous prescription (an addition). This algorithm and other similar ones also creates a daily log of available drug, so that an individual patient's compliance in any window of time can be determined. Daily logs of drug availability offer investigators many options for future health care research and after treating physicians the opportunity to evaluate an individual patient's pattern of compliance with appropriate software and links to automated pharmacy databases on their office computers. More importantly, refill compliance methodology can be used to quantify drug exposure in future epidemiological research.

This validation study has been undertaken primarily to expand refill compliance validation to a variety of diseases and patient groups while addressing the shortcomings of the past studies. A secondary objective of this study was to validate a new refill compliance measurement methodology that adapts the duration of therapy in the case of early refills or changes in dose, and to compare this approach with methods used by previous investigators.

Table 2.5.3.1 Construct Refill Compliance Validation Studies and Their Limitations

Author	Study Population and Medication	Outcome Measure and Limitations	Measure of Compliance and Limitations	Crude/ Adjusted association	Study Limitations
Primary Validation Studies					
Inui,et al. 1980	Population: 25 randomly sampled patients with diastolic blood pressure (DBP) below 90. Follow-up duration: 155 days Medication: Hydrochlorothiazide	Mean diastolic blood pressure (DBP) over 155-day observation period. Changes in DBP were more likely to reflect changes in compliance because BP was controlled at start of study.	Compliance: number of refills obtained in 155 days after original prescription divided by the number of prescriptions possible. Potential measurement error: Compliance could be over-estimated when patient obtains last refill near the end of the observation period.	r=0.-63 p<.05 95% CI= -.31 to -.82	98% male subjects - results are not generalizable Measurement Bias; Over-estimation of compliance can lead to random or systematic measurement error.
	Population: 27 random sample of patients (with evidence of chronic use of propranolol) and not on other drugs that affect heart rate. Follow-up duration: 155 days Medication: Propanolol	Average resting pulse rate over 155-day observation period.	Compliance: the number of refills obtained in 155 days after original prescription divided by the number of prescriptions possible Effective Dose: prescribed daily dose x proportion of days compliant Potential measurement error: Compliance could be over-estimated when patient obtains last refill near the end of the observation period	Compliance r=-0.27 p<.05 CI= -.58 to 0.12 Effective Dose r=-0.41 p<.05 CI= -.68 to –.03	98% male - results are not generalizable Measurement Bias: Over-estimation of compliance can lead to random or systematic measurement error.

Author	Study Population and Medication	Outcome Measure and Limitations	Measure of Compliance and Limitations	Crude/ Adjusted association	Study Limitations
Primary Validation Studies (Continued)					
Steiner et.al 1988	Population: A random sample of 52 patients with low, and normal mean serum levels of phenytoin and all patients with toxic levels Mean Follow-up: 15 ± 4 months Medication: Phenytoin	Mean serum phenytoin Measurement Error: Dose and concomitant therapies that modify phenytoin levels were not measured, controlled and used in the analysis, thereby creating an underestimation of the association.	Days of phenytoin supply/ days between first and last prescription Measurement Error: Failure to adjust for dose changes and hospitalizations can underestimate compliance. Hospital policies encouraged stockpiling and which lead to an overestimation of compliance.	All patients: r=0.31 CI=0.04 to 0.54 Patients with compliance < 1.1 r=0.37 CI=0.08 to 0.60	100% male subjects - results are not generalizable Study population is compliant therefore association will be underestimated. Measurement Bias: Failure to measure effect modifiers of outcome can lead to an under estimation or over estimation of the association.
	Population: 73 newly treated hypertension patients; 64 with DBP < 90 during follow-up Mean follow-up: 14 ± 5 months Medication: Anti-hypertensive medications Average of 1.58 drugs per patient	Overall mean diastolic blood pressure over the entire observation period	Days of phenytoin supply/ days between first and last prescription. Compliance was not adjusted for hospitalization, dose changes, switching or additions of new drugs. This can under-estimate compliance (random error) Hospital policies encouraged stockpiling and which lead to an overestimation of compliance	All patients r=-0.14 CI=- 0.09 -0.36 Controlled DBP r=-0.19 CI= 0.06 -0.42 Patients with compliance <1.1 All levels of DBP: r=-0.30 CI=--0.02-0.54 Controlled DBP: r=-0.38 CI=-0.09-0.61	96% male subjects - results are not generalizable Study population is compliant therefore association will be likely underestimated Measurement Bias: Errors in measuring compliance can lead to an underestimation of the association.

Author	Study Population and Medication	Outcome Measure and Limitations	Measure of Compliance and Limitations	Crude/ Adjusted association	Study Limitations
Secondary Validation Studies					
Roth, Caron, and Hsi, 1971	Population: 59 peptic ulcer patients 75% male 56% in lowest SES strata Follow-up: up to 24 months Medication: Atropine (½ life 1-2 hours)	Atropine metabolites in urine Measure confirms only recent ingestion of atropine and thus is a poor measure of long-term compliance (white coat effect) Overestimates compliance	Total number of prescribed pills in one year Total number of pills obtained Measurement error: Prescriptions could have been fill at other pharmacies. Compliance was underestimated by sum of tablets obtained. Drug cost confound the measurement of compliance	Total prescribed pills r=.01 CI = -.25 to .26 Total pills obtained r=0.47 CI=.24 to 65 Clinic attendance r=.22 CI=-.04 to .45	Study population; participation and observation bias underestimate or overestimate associations. Measurement Bias: Outcome influenced by 'white coat effect and likely underestimates the association. Over-estimation of compliance can lead to random or systematic measurement error. Confounding: Failure to adjust for confounding in the analysis biased the results
Bond & Monson 1984	Population: 96 renal and arthritis patients randomly sampled control and an inter-vention groups Follow-up:12 months Medication: Unspecified Anti-hypertensive therapy	Percent of patients with controlled BP BP was considered to be controlled if readings averaged less that 145 systolic and 95 diastolic. Effect modifiers and confounders were not addressed in the analysis.	Compliance was defined as the patient that always obtained a refill within 7 days before or after the 30-day supply would be exhausted. All other refill patterns were considered to be non-compliance. Measurement error: random error in measurement of compliance and outcome were neutralized by using averages in the analysis.	Control group ö=0.65 p<.001 Intervention group at 9 months ö=0.67 p<.001 Intervention group at 4.75 years ö=0.89 p<.001	Study Population: Participation bias in the intervention group underestimates the association Confounding: Failing to stratify the analysis may bias the results.

Author	Study Population and Medication	Outcome Measure and Limitations	Measure of Compliance and Limitations	Crude/ Adjusted association	Study Limitations
Secondary Validation Studies (Cont'd)					
Steiner, et al, 1991	Population: 25 patients in an intervention program to reduce therapy for patients with controlled hypertension. Follow-up: 6 months Medication: Beta-blocker therapy (propranolol, atenolol, nadolol, prazosin)	Resting pulse rate Restriction of effect modifiers: Patients were excluded from the study if they were taking drugs that affect heart rate.	Weighted sum of all anti-hypertensive drugs supplied/ 180 days divided into 6 compliance levels Measurement errors: Compliance could be over-estimated if patient obtains last refill near the end of study. Compliance was not adjusted, dose changes, causing and under-estimation of compliance (random error) Hospital policies encouraged stockpiling, which lead to an overestimation of compliance	r=-.49 p=.02 CI = 0.12 to 0.74	Study Population: Not generalizable; 100% male patients Participation and observation bias underestimate associations. Measurement Bias: Random errors in measuring compliance can lead to an underestimation of the association

Author	Study Population and Medication	Outcome Measure and Limitations	Measure of Compliance and Limitations	Crude/ Adjusted association	Study Limitations
Steiner, et al, 1993	Population: 86 patient subset of 176 patients in an observational study of 30-day vs 90-day prescription use. Mean follow-up: 9 ± 5 months Medication: Digoxin	Serum digoxin Modifiers of diogixin level (creatinine, dose, and weight) measured and included as covariates in the analysis.	Sum of days of digoxin supplied/ sum of days to first to last digoxin prescription Compliance was not adjusted, dose changes, causing and under-estimation of compliance (random error Hospital policies encouraged stockpiling, which lead to an overestimation of compliance	r=0.25 p=.03 CI=0.04 to 0.44 adjusted for serum creatinine, weight and dose	Not generalizable; male patients Study Population; Eligible subjects had to demonstrate a minimal level of compliance to be included in the study; therefore association will be underestimated by restriction in range Potential Confounder: This analysis was based on a subgroup from the hospital that allowed 90-day prescriptions. Physicians were more likely to issue 90-day prescription in compliant patients with stable disease.

CHAPTER 3 METHODS

3.1 Study Objectives

The primary objective of this study was to determine the construct validity of prescription refill as a measurement of compliance in a variety of diseases and patient groups while addressing the shortcomings of past studies. A secondary objective of this study was to validate a new refill compliance measurement methodology that adapts the duration of therapy in the case of early refills or changes in dose, and to compare this approach with methods used by previous investigators

3.2 Overview of Study Design

A prospective dynamic cohort study was conducted to determine the construct validity of refill compliance through analysis of the association between refill compliance and laboratory outcomes indicative of the therapeutic effects of the respective drugs. Three cohorts were drawn from a population of adult patients continuously enrolled in a health maintenance organization (HMO). Compliance was measured using prescription refills for inception cohorts of patients who started treatment for one of the following diseases: primary hypothyroidism, type 2 diabetes, and atrial fibrillation. These disorders were selected because they require chronic drug therapy and interruption of therapy is generally an indication of non-compliance, rather than discontinuation of therapy due to improvement in health status. As compliance may change over time, repeated assessments of the relationship between refill compliance and laboratory outcomes were conducted for each patient over a one to four year follow-up period. The association between

refill compliance and laboratory outcomes was assessed using multivariate linear regression models in the following three groups:

Disease Condition	Study Drug	Laboratory Outcome
Hypothyroidism	Levothyroxine	TSH
Type 2 Diabetes	Oral hypoglycemic drugs	$HgbA_{1c}$
Atrial Fibrillation	Warfarin	Prothrombin time (INR)

These groups were chosen to minimize the bias in assessments of outcome and compliance due to "white coat" effect. Since the therapeutic effect of drugs is usually related to the amount of drug circulating in the blood, drugs with long half-lives (i.e. 24 hours or more) are more suitable for construct validation studies. The homoeostatic relationship between the drug's half-life, the amount of drug within the body, and the clearance of the drug from the body (steady state) is more constant for drugs with long half-lives.[79] The serum level of the drug is fairly stable after the patient has taken the drug long enough to reach steady state. Like water slowly dripping into a full bath tub and slowly leaking out of the drain, taking a few extra doses of drugs just prior to a clinic visit will not remarkably change the serum concentrations of these drugs.[61] Thus, laboratory measurement of the therapeutic effect of drugs with a long half-life is more representative of drug use in the prior month than might be the case for drugs with shorter half-lives.

The study drugs levothyroxine and warfarin, used in the treatment of hypothyroidism and atrial fibrillation respectively, are drugs with long half-lives.[79] Although most diabetes drugs have short half-lives, the measurement of therapeutic effect in diabetes, with glycosylated hemoglobin ($HgbA_{1c}$) reflects the glucose level in the blood over several weeks. Glycosylation occurs continuously within red blood cells and is a direct reflection of the average glucose concentration to which

the cell was exposed throughout the 120 days of its life span.[80] Measurement of glycosylated hemoglobin content therefore provides a useful means of assessing the degree of chronic hyperglycemia that existed in a patient over the preceding 4-8 weeks, and is not affected by acute changes in plasma level of glucose due to sporadic compliance with therapy and abrupt changes in diet.[80]

3.2 Hypotheses

3.2.1 Relationship Between Compliance and Laboratory Outcomes

Drug therapy for hypothyroidism and diabetes is intended to decrease the values of TSH and $HgbA_{1c}$. On the other hand, the goal of anticoagulant therapy for atrial fibrillation is increase INR values. Therefore, it was hypothesized that: higher levels of compliance would be associated with lower levels of TSH in the hypothyroid patients; lower levels of $HgbA_{1c}$ in the diabetic patients; and higher levels of INR in the atrial fibrillation patients.

3.2.2 Modification of Compliance-Laboratory Outcome Relationship by Dose

Previously, Inui reported that dose was a modifying factor in the association between compliance and pulse rate in patients taking propanolol.[10] He found that the dose-response curve of propanolol was attenuated by compliance level. For levothyroxine and warfarin, it was assumed that the dose-response relationships with TSH and INR levels, respectively, would also be attenuated by compliance.[81-83] Although the diabetic drugs do not have a strong dose-response relationship, in this study low dose levels reflect single drug therapy and high dose levels reflect multiple drug therapy. Therefore, it was hypothesized that the association between compliance and laboratory values would be modified by the dose prescribed.

Specifically, it was hypothesized that high levels of compliance would show a weaker association with laboratory values in patients on lower doses of drug than higher doses.

3.2.2 Modification of Compliance-Laboratory Outcome Relationship by Time

It was hypothesized that the association between compliance and laboratory values would be reduced by treatment time in the diabetic population because diabetes is a progressive disease.[84] High levels of compliance were expected to have less impact on laboratory values ($HgbA_{1c}$) with longer treatment time in the diabetic patients. Dose, time, and the interaction of the two variables were expected to modify the compliance-laboratory outcome relationship in diabetes. However, hypothyroidism and atrial fibrillation are not progressive diseases and therefore treatment time was not expected to modify the compliance-laboratory outcome relationship.[82;85-87]

3.4 **Ethical Considerations**

The study proposal was submitted to the Henry Ford Health Science Center Human Rights Committee (Institutional Review Board) by Dr. Christine Johnson, Research Director of the Biostatistics and Research Epidemiology on behalf of the candidate. The committee ruled that the study was void of human rights issues and approved the study on 13 July 1999 (Appendix 2, IRB Approval).

3.5 **Assumptions**

3.5.1 Relevant Time Period of Compliance Measurement

Two assumptions influenced the selection of a relevant time window for measuring refill compliance. The first assumption was that an individual's compliance changes over time.[13] The second assumption was that measurement of mean compliance over an extended time period such as a year may not reflect an individual's compliance in the time period immediately prior to the laboratory test. Although there could be a delay between a period of non-compliance and the resulting effect on laboratory outcomes, compliance was measured during the 30 days prior to the date of the laboratory test of interest in each study population.

3.5.2 Intra-patient Variability in Compliance

It was assumed that most patients vary their patterns of compliance over time. Even rather compulsive patients take drug holidays, or encounter obstacles in taking their medication as prescribed.[1;13;23;61] Therefore, multiple measurements of the refill compliance and laboratory outcome were used for each patient over the course of the study to provide a more stable estimate of the association, and to test the hypothesized modification of treatment time on the compliance-laboratory outcome relationship in diabetes.

3.5.3 Frequent Laboratory Testing

Frequent laboratory testing in a short time period is often an indication of a new problem in the treatment of the illness. Subsequent testing after an initial abnormal value often represents monitoring an intervention, such as administering vitamin K

for an abnormally high INR. A pattern of frequent laboratory testing over a short time span was assumed to indicate that the patient's physiologic state had been altered either by disease progression or inadequate compliance. When testing occurred frequently (i.e. within 3 days of the previous test), only the first laboratory test in the series was used in the analysis and the time window of compliance observation ended with the first laboratory test in the series. Therefore, time windows for measuring compliance excluded periods of repeated testing. To determine if frequent laboratory testing confounded or modified the relationship between refill compliance and laboratory outcome, the intensity of testing within each time period of observation was characterized as standard or frequent testing for the disease and the impact of including this variable on the estimated regression coefficients for the compliance-outcome relationship was tested in multivariate regression models. (See Section 3.7.6.2 for definitions of standard and frequent testing.)

3.6 **Study Populations**

3.6.1 Source Populations

The source population consisted of adults who were continuously enrolled from 1 January 1995 to 30 June 1999 in the Health Alliance Plan of Michigan, a health maintenance organization (HMO). Patients could enter the cohort at any time after 1 January 1995. Elilgible patients had to be continuously enrolled until 30 June 1999 to ensure that complete information was available on their medication and health care use. Study data were derived from integrated automated claims databases of prescriptions, hospitalizations and outpatient visits claims, and computerized laboratory records. Anonymized but unique patient identifiers were

used to link sequential prescription and laboratory data for the same patient and to protect the individual patient's privacy.

3.6.2 General Eligibility

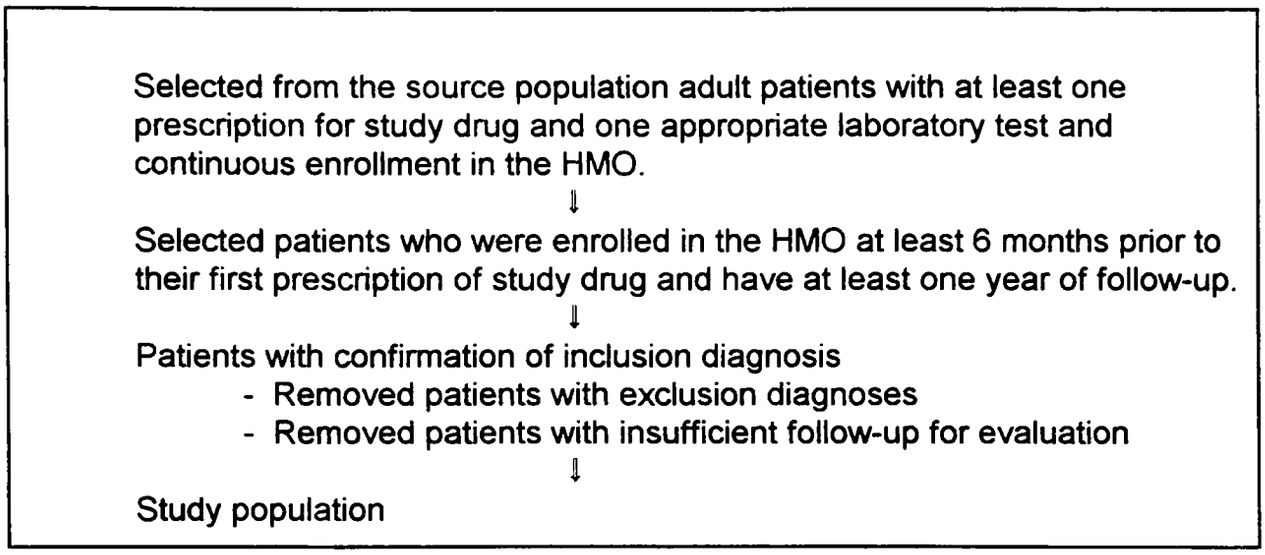
Adult patients (≥ 18 years of age) were included in the study if they had been enrolled in the HMO for at least six months before the first prescription of one of the study drugs. This criterion permitted restriction of the study population to those for whom new use (incident) versus prior use (prevalent) of a study drug could be determined. Accurate counts of drug supply are more easily determined in incident users than would be possible with prevalent drug users. Furthermore, inaccurate counts are more common among prevalent users because they invariably have a supply of study drug at home, prior to the first prescription information in the database (i.e. left-sided censoring of drug supply data).

New users of prescription drugs commonly experience a period of dosage adjustment with frequent laboratory testing to evaluate the effectiveness of treatment.[80] Therefore the first three months after receipt of the initial study drug prescription were considered the dosage adjustment period and this period was excluded from the analysis of compliance.

To be eligible, study patients also had to have at least one year of follow-up after receipt of their first prescription of study drug, to allow sufficient opportunity to assess the association between refill compliance and laboratory outcome. Inclusion and exclusion diagnoses were determined by hospital discharge or outpatient ICD-9 diagnoses (International Classification of Disease, 9th Revision).[88] Patients were included if they had inclusion diagnoses in the 6 months before or three months after the first prescription of study drug. Patients were excluded if

they had exclusion diagnoses at any point in the study. Pregnant patients (ICD-9 codes 630-679) were excluded because during pregnancy, non-essential drug therapy is often modified or discontinued to protect the fetus. Figure 3.6.2.1. outlines the steps which were followed to select members of the study population from the source population.

Figure 3.6.2.1 Derivation of Study Populations



3.6.3 Dynamic Eligibility

During periods of institutionalization, compliance is not usually a matter of choice and medication dispensed during hospital stays would not be recorded in the HMO prescription claims data files. For this reason, periods of hospitalization and 30 days following discharge were excluded from the analyses. The 30-day grace period was added to account for the impact of an extra supply of medication

provided at discharge, which would not be captured in a database of claims for prescriptions dispensed from community-based pharmacies, and to allow time for complete recovery from illness.

3.6.4 Hypothyroid Patient Population

Hypothyroidism is a clinical state characterized by deficiency of thyroid hormone resulting in a slowing of metabolism. It is usually due to thyroid failure or auto-immune thyroiditis (Hashimoto's thyroiditis) but may be secondary to hypothalamic or pituitary deficiency. Medical management of hypothyroidism includes life-long thyroid hormone replacement and monitoring of thyroid stimulating hormone (TSH) levels.[89]

To be potentially eligible, patients had to have an elevated TSH test result (>5.5 IU/dl, the upper limit of normal range for TSH) prior to starting levothyroxine therapy. Eligible patients had to have a diagnosis of hypothyroidism in either hospital discharge diagnostic codes or outpatient diagnostic codes (ICD-9 codes 244.9 or 245.2) and one TSH test after the 3-month dose-adjustment period.

Patients were ineligible for the study if they had a hospital discharge ICD-9 code for thyroid cancer (ICD9-193), thyroid nodules (ICD-9 codes 241.9, 242.1-241.4), or thyroiditis (other than Hashimoto's thyroiditis, ICD-9 code 245.2), since these patients would be receiving chronic levothyroxine therapy to suppress the thyroid gland (ICD-9 codes 240-243 and 245-250). Patients were also excluded if hypothyroidism was secondary to pituitary hypofunction or due to ablation of the thyroid gland by surgery or radiation therapy for hyperthyroidism or thyroid cancer (ICD-9 codes 244-244.8). Post-ablation patients have secondary hypothyroidism which differs from primary hypothyroidism patients in two ways. First, they require

very high doses of levothyroxine if the thyroid was totally destroyed or removed. Second, if they retain some functioning thyroid tissue, the speed at which the remaining tissue resumes function is quite variable, so their dose adjustment period is sometimes prolonged. [80]

3.6.5 Type 2 Diabetes Patient Population

Type 2 diabetes is a form of diabetes that can be treated without insulin. It is usually managed with dietary restrictions and oral hypoglycemic drugs, and is monitored by regular $HgbA_{1c}$ testing.[80]

Potentially eligible patients had to have at least one prescription for an oral hypoglycemic drug, one $HgbA_{1c}$ test after the 3-month dose-adjustment period, and were not concurrently taking insulin. Patients were excluded from the study if they required insulin therapy, had pancreatic cancer (ICD-9 code 193), or gestational diabetes (ICD-9 code 157). Patients who required insulin subsequent to the first prescription for an oral hypoglycemic drug were excluded from further evaluation after starting insulin therapy so as to avoid the complexity of the interaction between compliance with injectable and oral therapy, which are pharmacologically different classes of drugs that effect $HgbA_{1c}$. The impact of excluding these patients was probably negligible since only 7% of the study population was concurrently treated with insulin. When diabetic patients were taking oral or inhaled steroid drugs which significantly affected the course of the disease, they were considered temporarily ineligible for study. Compliance and laboratory data during periods of concurrent steroid use were excluded from the analyses.

The final diabetic study population consisted of patients who received a prescription for an oral hypoglycemic drug and who had at least two outpatient visits for which

an ICD-9 (ICD-9 codes 250.0 or 252.2) diagnosis of diabetes was recorded. Type 2 diabetes is a disease that usually does not require hospitalization, so the more reliable hospital ICD-9 discharge diagnosis could not be used to identify patients for the study. Medical records were previously used to confirm this method of determining the presence of a diabetes diagnosis (as part of another study) in a subset of 1,307 Health Alliance Plan of Michigan HMO patients. In that study, the diagnosis was determined by less stringent criteria: either a prescription for an oral hypoglycemic drug or two outpatient visit ICD-9 diagnostic codes for diabetes. The diagnosis of diabetes was confirmed by a chart review in over 98% of the patients identified through medication and patient encounter administrative databases of the HMO.[90]

3.6.6 Atrial Fibrillation Patient Population

Atrial fibrillation is the most common abnormal rhythm of the heart.[87] Persistent atrial fibrillation occurs in patients with cardiovascular disease, most commonly with mitral valve disease, hypertension, chronic lung disease and a variety of miscellaneous cardiac abnormalities, although idiopathic atrial fibrillation can occur.[80] The three principal goals of therapy are restoration and maintenance of normal sinus rhythm, ventricular rate control and prevention of thromboembolism.[87] The primary morbidity associated with atrial fibrillation, embolic stroke, may be prevented by anticoagulant therapy with warfarin.[24]

Potentially eligible patients were identified as having at least one prescription for warfarin and one INR measurement (prothrombin time measured using international normalized ratio), a measure of the physiologic effect of warfarin. To be eligible for the study, patients had to have diagnoses of atrial fibrillation (ICD-9 code 427) in either hospital discharge diagnostic code or outpatient medical visit diagnostic

codes and at least one INR test after the 3-month dose-adjustment period. Patients were excluded if they had hospital discharge diagnostic codes for primary pulmonary hypertension (ICD-9 code 416.8), acute myocardial infarction (ICD-9 code 410), rheumatic heart disease (ICD-9 code 397), heart value replacement (ICD-9 codes 996 and V43.3), or venous thrombosis, or any thromboembolism (ICD-9 codes 415, 451-454). These patients were considered ineligible because they may not require chronic anticoagulant therapy.

The validity of these diagnostic data used to select the study population has not been scientifically investigated for each diagnosis. However, hospitals in the Henry Ford Medical Care system used for these HMO patients each have quality assurance review committees. Hospital discharge diagnostic coding is subject to quality assurance review, and therefore considered to be more reliable than outpatient diagnostic coding, which does not undergo any formal review process.

3.7 **Measurement**

3.7.1 Databases

This study was conducted among members of a health maintenance organization, the Health Alliance Plan (HAP) of Michigan. The data requested were extracted from a central repository, Corporate Data Store (CDS), which contains data on patient encounters at Henry Ford Hospital and all Henry Ford Health Services satellites utilized by HAP. The relational database on CDS stores information on patient populations and clinical care. These databases contain data from 1988 to the present, with over 2.5 million encounters added each year. A personal computer interface is used to access the various databases using Structured Query Language (SQL). SQL queries are used to retrieve data from CDS in a summary

report format or in a format compatible with popular software packages such as Lotus 1-2-3 or dBASE for manipulation in statistical packages such as SAS.

CDS databases track covered patient lives through provider-aligned patient panels, HAP membership files and a Master Patient Index. A unique medical record number serves as a lifetime patient identifier. Databases capturing clinical care include ambulatory care visits (outpatient clinic and emergency department), hospital admissions and operating room procedures. Diagnoses and procedures are identifiable through ICD-9-CM. Other databases include clinical laboratory, cardiology tests, neurological tests and radiology. Claims data, including pharmacy (all obtained prescriptions), are available for HAP members, providing a comprehensive resource of medical care provided for that population. The prescription claims database contains information on all prescription drugs dispensed to HMO members at community pharmacies. Each prescription claim record includes the patient identification number, date of birth, drug brand name, NDC (National Drug Code) number, prescribed days of supply, quantity dispensed, strength, units, dosage form, prescriber and pharmacy numbers, and date of service. The laboratory database includes patient identification number, date of test, test name, test result, and normal ranges for the test. Laboratory data are transferred to the database directly from machines that generate the laboratory test results.

The physician claims database contains patient identification number, physician number, medical services provided by physicians on a fee-for-service basis, ICD-9 codes, and date of visit. The hospitalization record contains patient identification number, date of birth, admission date, discharge date, admission and discharge ICD-9 codes, indicator for primary and secondary diagnostic codes, and details about charges.

3.7.2 Measurement of Compliance

3.7.2.1 *Fairchild Method for Refill Compliance Measurement*

Compliance was measured over 30-day time periods preceding a laboratory test of the study drug's effect (INR, TSH, or $HgbA_{1c}$) utilizing a daily log of laboratory tests and of drug supply. A computer-generated listing of drug supply and laboratory test results on each day that the patient was in the study facilitated the calculation of compliance in the 30 days prior to each laboratory outcome. (See Table 2.4.1.3.2 Daily Compliance Log Example). Compliance was calculated by dividing the number of days in which the patient had drug available in the observation period by 30 (the number of days in the observation period). To simplify the measurement and analyses, each 30-day time window was discrete, not overlapping another time window of observation. Thus, a second and subsequent measurement window was considered for each patient only if it was 31 days or more after the end of the previous window.

The follow-up period for measuring compliance began after the 90-day dose adjustment period and therefore the first time window was at least 120 days after starting therapy. Compliance measurement was terminated on the date of the last laboratory test prior to the last prescription because the duration and dose of subsequent prescriptions were utilized to determine the duration of overlapping prescriptions.

The duration of each prescription in days was determined by dividing the quantity dispensed by an estimate of number of tablets per day prescribed. The number of tablets per day was estimated by dividing the quantity of drug dispensed by supply days and rounding that quotient to the nearest half-tablet (e.g. ½, 1, 1½ tablets per

day). Tablets of levothyroxine and warfarin are scored so that they can be easily broken in half. The following is an example of the calculated duration of a prescription in which 100 tablets were dispensed to be taken over 30 days:

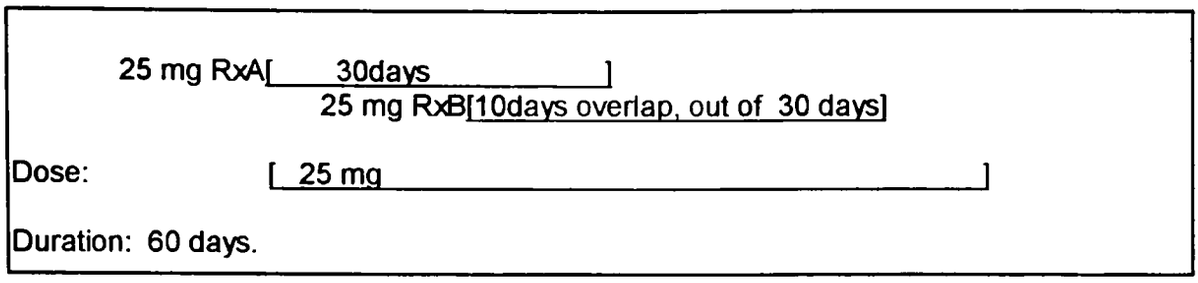
Quantity=100	Supply days=30
Tablets per day:	100/30 = 3.3, rounded to the nearest half-tablet = 3
Duration:	100/3 tablets per day = 33 days

The duration of each prescription can be inaccurate if one fails to account for factors that affect the duration of drug supply such as changes in dose and early refilling of prescription. The difficulty in measuring prescription refill compliance from a database without the benefit of medical records is in understanding a physician's intent when a prescription is filled before the previous one is expected to be totally consumed (over-lapping prescriptions of the same drug). To determine the duration of overlapping prescriptions, the dose of each overlapping prescription was compared with that of the previous and subsequent prescriptions to determine if the new prescription represented a dose adjustment or an early refill. There are at least three explanations why a patient might have refilled a prescription at least one day or more before the previous prescription was exhausted and each affects the duration of drug supply different. The three possibilities are:

A. Early Refill - Patients often refilled a prescriptions before their current prescription runs out to avoid disruption in therapy. In the database, when a prescription's duration overlapped that of the previous prescriptions, it was assumed to be an early refill if the dose of the prescription was identical to that of the previous prescription and next prescription. In other words, if there was no apparent change in dose, the overlapping prescription was assumed to be an early refill. The duration of the two overlapping prescriptions was the sum

of the duration of both prescriptions (see Figure 3.7.3.2.1). In a daily log of drug supply, the overlapping days were added to the end of the second prescription.

Figure 3.7.3.2.1 Early Refill



B. Dose Addition - Occasionally, physicians write two prescriptions for different strengths of the same medication to be taken concurrently. Intending for the patient to take 75 mg of a drug, a physician may write a prescription for 50 mg tablets and another for 25 mg tablets. Occasionally, the pharmacy does not have 75 mg tablets on hand and dispenses two bottles of medication for 25 mg and 50 mg tablets. In the database, two overlapping prescriptions were assumed to be dose additions when the sum of the doses of the two prescriptions was approximately equivalent to the dose of the next prescription. In other words if a patient had filled a prescription for 25 mg tablets shortly after filling a prescription for 50 mg tablets, it was assumed that the two prescriptions were supposed to be taken concurrently if the dose of the subsequent prescription was for 75 mg. It was assumed that the two prescriptions were intended to be taken together, when the sum of the doses of prescriptions A and B was approximately equivalent to the dose of the next prescription (C). In mathematical terms if Dose A + Dose B = Dose C ($\pm$ dose approximation factor) then the doses were added together. The dose approximation factor served as a means of determining if the sum of Dose A and Dose B were *approximately* equivalent to Dose C. An approximation factor was needed because of the

limited dose formulations available for dose titration. When 75 mg tablets of the drug are not available and a single tablet daily regimen is optimal, 80 mg tablets may be the best alternative. Thus, two overlapping prescriptions of 25 mg and 50 mg were assumed to be dose additions if the subsequent prescription was 75 mg $\pm$ a dose approximation factor of 5mg. (See example in Figure 3.7.3.1.1)

The dose approximation factor was derived by evaluating a subset of 10 patients in each study population with two prescriptions on the same day. A time line with the start and stop times of each prescription was drawn manually. By examining the dose of each prescription before and after each of the overlapping prescriptions, it was possible to discern whether the second of the two overlapping prescriptions was probably a dose addition, dose change, or early refill. This exercise also facilitated the selection of a range of the dose approximation factors that might be suitable in the algorithm for each drug. The dose variation values that most often yielded the expected results were 20 mcg for levothyroxine and 5 mg for warfarin and the diabetic drugs. Therefore, to determine if two overlapping prescriptions were meant to be taken together, it was first determined that the doses of the two overlapping prescriptions were approximately equal to the dose of the subsequent prescription using the following formula:

Dose A + Dose B = Dose C $\pm$ 20 mcg for levothyroxine

Dose A + Dose B = Dose C $\pm$ 5 mg for warfarin

Dose A + Dose B = Dose C $\pm$ 7 mg for hypoglycemic drugs

Duration was determined differently if the two prescriptions were filled on the same day or different days. If the two prescriptions were filled on the same day and of equal length (e.g., 30-day prescriptions), the duration was determined by the

duration of only one of the two prescriptions (See Figures 3.7.3.1.1 and 3.7.3.1.3). Alternatively, if the two prescriptions dispensed on the same day were of unequal length, the duration was determined by the prescription with the shorter prescription length, which was the period during which the patient had sufficient drug supply to take medication from the two prescriptions together on a daily basis (See example in Figure 3.7.3.1.2).

If the two prescriptions were filled on different days, the duration of the combined dose was determined by the number of days during which the two prescriptions overlapped. (See example in Figure 3.7.3.1.4). Figures 3.7.3.1.1 through 3.7.3.1.4 are four graphic examples of dose additions:

Figure 3.7.3.1.1 Dose Addition
Two Prescriptions Filled on the Same Day

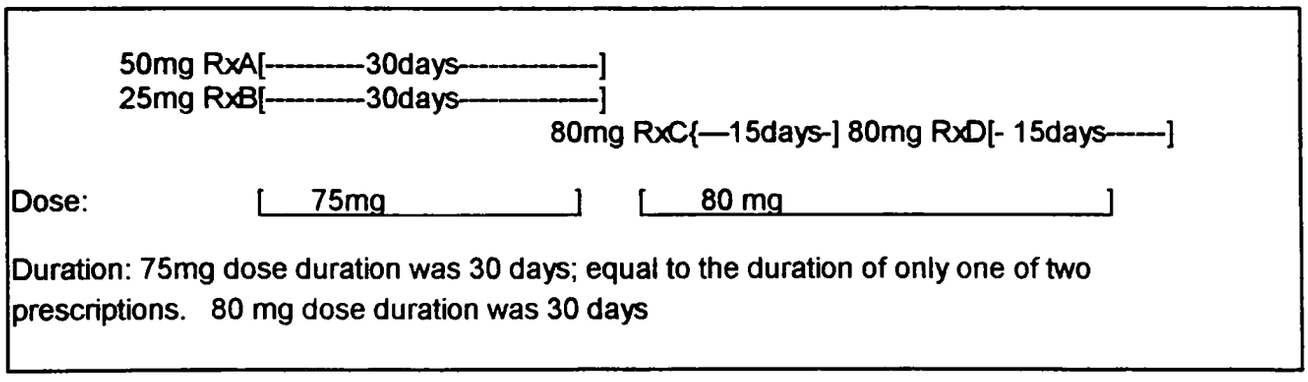


Figure 3.7.3.1.2 Dose Addition
Two Prescriptions Filled on the Same Day

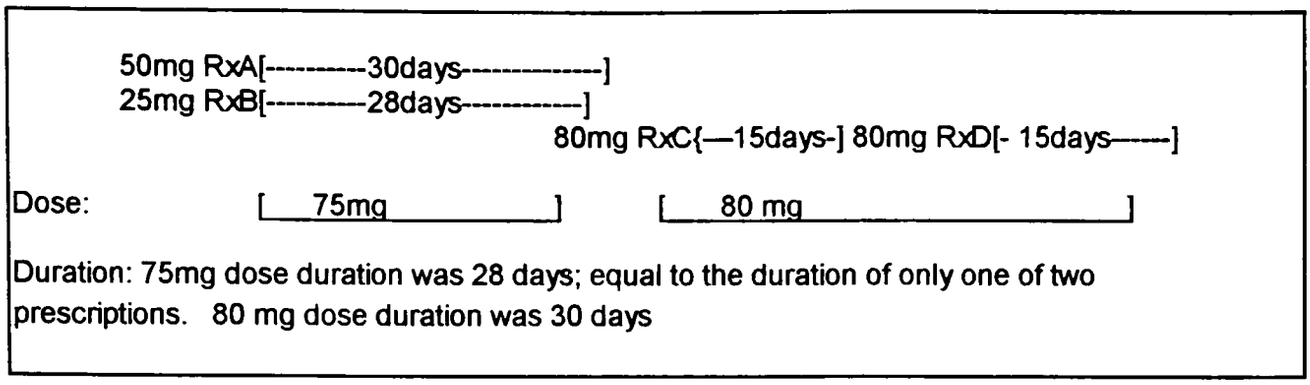


Figure 3.7.3.1.3 Dose Addition
Repetition of Two Prescriptions Filled on the Same Day

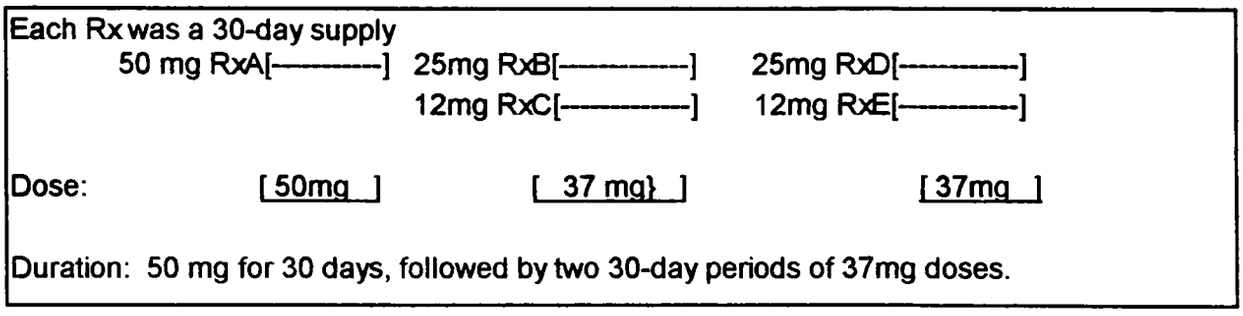
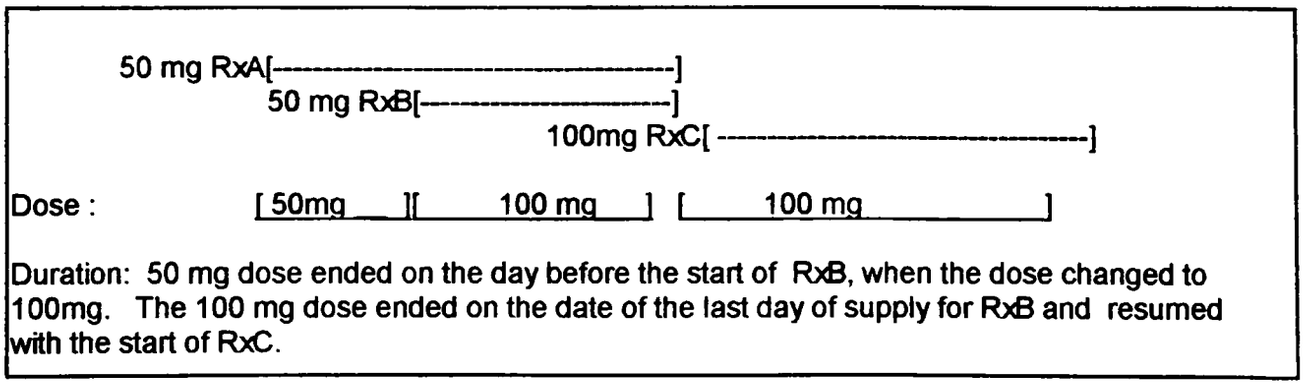


Figure 3.7.3.1.4 Dose Addition
Overlapping Prescription Filled on Separate Days



C. Dose change - A new prescription for a different strength of medication can also be an indication that the physician has changed the dose and intended for the patient to stop taking the previous prescription. When two overlapping prescriptions were of different doses and the sum of the doses of the two prescriptions (plus or minus the dose-approximation factor) was not equal to the dose of the subsequent prescription, they were assumed to be a dose change.

If two overlapping prescriptions were determined to be a switch in dose and the prescriptions were filled on different dates, the duration of the first prescription was terminated on the day before the prescription for the new dose began, for it was assumed that patients started the new dose on the day they filled the prescription (Figure 3.7.3.3.1). However, if the overlapping prescriptions were filled on the same day, it was assumed that the two prescriptions were meant to be taken sequentially, and that the smaller dose was meant to be taken (entirely) before beginning the larger dose (Figure 3.7.3.3.2).

Figure 3.7.3.3.1 Simple Dose Change
Two Prescriptions Filled on Different Dates

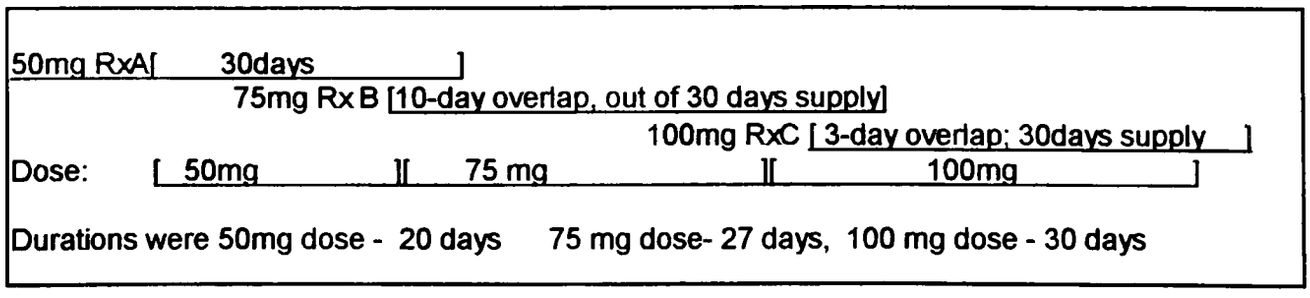
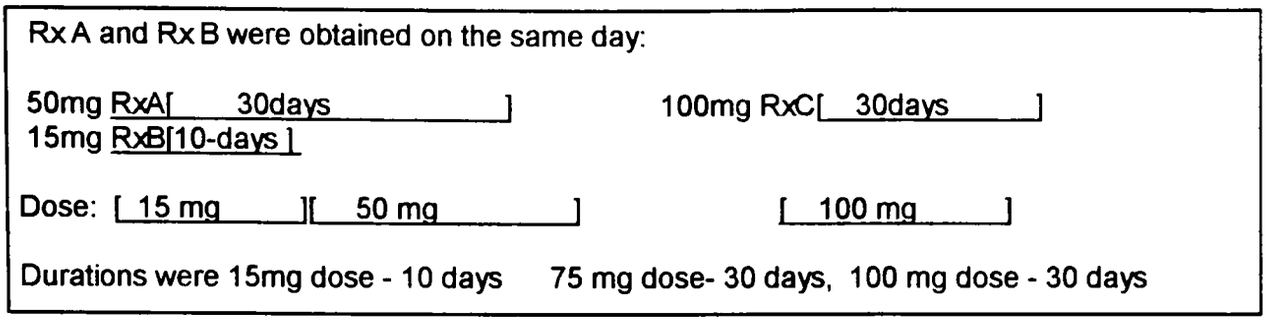


Figure 3.7.3.3.2 Sequential Dose Changes
Two Prescriptions Filled on the Same Date



3.7.2.2 *Steiner Method of Refill Compliance Measurement*

Compliance was also measured using the method developed by Steiner, from the date of the first prescription to the date of the last prescription following the last laboratory test in the follow-up period. Duration of drug supply was based solely on the "supply days" data in the prescription claims data base. The total supply days of each prescription (excluding the supply days of the last prescription) was summed over the study observation period (numerator) without adjustment for dose additions, dose changes or surplus supplies of the study drug (e.g. 100 tablets for 3 months of therapy). Compliance was calculated as the ratio of the total days of drug supply in the study observation period divided by the length of the study follow-up period (days between first and last prescription).

In order to compare the two methods of compliance measurement, compliance should have been assessed in the same time span, as much as possible. The observation period began at the start of the first time window, 30 days before the first laboratory test after the 90-day dose adjustment period, the starting point for

measuring compliance. The observation period ended on the date of the first prescription after the last laboratory measurement in the study period. In the Steiner method, the denominator is measured over a longer time period than the Fairchild method because of the inherent differences in the two methodologies.

3.7.3 Study Drug Dose

When there was no overlap in duration of prescriptions, the dose per day was the product of the tablets per day multiplied by the strength of the tablet (e.g. 3 tablets/day x 50 mg = 150 mg/day). When there was an overlap, daily doses were determined using a computer algorithm developed to determine if overlapping prescriptions were more likely to be early refills or changes in the treatment regimen (i.e. dose change or dose addition) and calculated the daily dose accordingly, as described in Section 3.7.2.1.1).

The algorithm created to assess prescription duration can calculate the dose and duration of only one generic drug or one class of drugs in which the range of dosages of each drug is narrow. The diabetic study drugs are twelve generic drugs that have a broad range of dosage strengths (0.5 to 1000 mg tablets) so it was necessary to standardize the doses to enable the algorithm to detect changes in dose and measure the duration of drug supply. The dosage strengths were categorized to three levels: high-15 mg, medium -10 mg and low- 5mg. Medium dose was assigned to drugs with only one dose strength, and medium and high doses were assigned to drugs with only two dose strengths.

Standardization of the oral hypoglycemic drugs was plausible because each of the drugs is effective in treating diabetes and each has a somewhat flat dose response curve. Increases in dose produce modest changes in the effectiveness of the

drug.[91-98] Table 3.7.3.1 describes the usual dosage strength of each drug and the standardized doses employed in the study.

Table 3.7.3.1 Standardized Hypoglycemic Drug Dose

Hypoglycemic drug	Dose Strengths	Standardized Dose
Glimepiride	1, 2, 4 mg	5, 10, 15 mg
Chlorpropamide	100, 250 mg	10, 15 mg
Glyburide	1.25, 2.5, 5 mg	5, 10, 15 mg
Glyburide, Micronized	1.5, 3, 6 mg	5, 10, 15 mg
Metformin	500, 850, 1000 mg	5, 10, 15 mg
Glipizide	5, 10 mg	10, 15 mg
Glipizide XL	5, 10 mg	10, 15 mg
Repaglinide	0.5, 1 mg	10, 15 mg
Acarbose	25, 50, 100 mg	5, 10, 15 mg
Troglitazone	200, 300, 400 mg	5, 10, 15 mg
Tolbutamide	500 mg	10 mg
Tolzamide HCL	100, 250, 500 mg	5, 10, 15 mg

In the analysis, dose was treated as a time-dependent covariate. Dose was defined by the last dose prior to the laboratory test at the end of the time window because the level of the laboratory outcome (TSH or INR) is influenced most by the dose the patient is taking just prior to testing. When the patient had no available drug for the 30-day observation window, the dose was zero.

3.7.4 Computer Algorithm for Prescription Duration and Dose Calculation

A computer program was written in SAS to calculate the probable intended duration and dose of all prescriptions. After several iterations it became evident that an algorithm could be used to discern whether two prescriptions had overlapping durations and whether overlapping prescriptions were probably an early refill, dose addition or switch in dose by examining the dose and duration of the previous and subsequent prescriptions. The initial step of the algorithm was to determine if the duration of two prescriptions was overlapping. If the prescriptions were not overlapping in duration, the calculation of duration and dose of each prescription was completed as described in Sections 3.7.2.1.1 and 3.7.3.

When there was an overlap, duration and daily doses were determined for each study drug using a logical sequence. In the first step, the program looked for evidence that the two prescriptions constitute a dose addition and were meant to be taken together. If it was not a dose addition, the next step was to look for evidence that the second prescription was an early refill. Finally, if there was no evidence that it was an early refill or a dose addition, the second prescription was presumed to represent a dose change. Compliance might have been underestimated by the algorithm because the default setting for a change in dose. Therefore a sensitivity analysis was conducted in the diabetic study population who had the highest percentage of dose changes.

The program also created a day-by-day listing of dose of drug and laboratory test results on each day that the patient was in the study so that compliance could be calculated in the 30 days prior to each laboratory outcome. (See Table 2.4.1.3.2: Daily Compliance Log Example). The program was tested at various stages of development with contrived data designed to test the limitations of the program.

After the program executed with 100% accuracy, it was tested in the hypothyroid patient population. In its final form, it was checked multiple times throughout the follow-up period of15 patient computer records from each study population with two prescriptions on the same day. The test involved manually drawing a time line of each prescription (start and stop times) and determining the probable intended dose by examining the prior and subsequent doses. Independent comparison of manual and computer base calculations of days supply and dose with 135 overlapping prescriptions showed an agreement of 91.8% (95% CI=78%-100%).

3.7.5 Laboratory Outcomes

The therapeutic effect of each of the three study drugs was measured by laboratory tests for INR, TSH and $HgbA_{1c}$. These tests were performed in medical laboratories by automated procedures for obtaining and recording the results in an electronic database (machine to machine data transfer). In addition, following the recommendations for frequency of recalibration of each machine for each test, the laboratories ran control samples daily. If the results are not satisfactory the machines were recalibrated.

The fourteen laboratories in the Henry Ford Medical Care system were all certified by the American College of Pathology (CAP) and Clinical Laboratory Improvement Amendments (CLIA), a division of the US Health Care Finance Administration. Quality assurance testing of the laboratory procedures is required for laboratory certification. The American College of Pathologist provides challenges 3 times per year. For each test, five specimens are provided to be analysed and the results are forwarded to CAP. In addition, every 18 months the institution's quality assurance records are reviewed, and every 2 years there is a physical inspection of the facility

by CAP. The CLIA evaluation process is similar, but differs in that there are legal and financial ramifications for failing to meet minimum standards.

3.7.5.1 *Thyroid Stimulation Hormone (TSH)*

In hypothyroidism, the impaired thyroid gland is not synthesizing sufficient thyroid hormone, which leads to hypersecretion of thyroid stimulating hormone (TSH) from the pituitary gland. Measurement of serum TSH concentration is useful in the diagnosis and management of hypothyroidism.[80] The method employed by the Henry Ford Medical Center laboratories to assess TSH is a two-site sandwich immunoassay using direct chemiluminescence technology. The system automatically performs dispensation of the two reagents into the samples; incubates them for 7.5 minutes at 37° C ; separates, aspirates, and washes the cuvettes with reagent water; dispenses acid and base reagent to initiate the chemiluminescent reaction; and reports the results. Replicate analysis using control materials yields a coefficient of variation of $\leq$ 5%. The test results may be unreliable in patients routinely exposed to animals or to animal serum products.[99]

3.7.5.2 *Glycosylated Hemoglobin A_{1c} ($HgbA_{1c}$)*

Glycosylated hemoglobin ($HgbA_{1c}$) is a component of hemoglobin found to be elevated in diabetic patients. Determination of HbA_{1c} is based on turbidimetric immuno-inhibition using a hemolyzed whole blood sample. The amount of $HgbA_{1c}$ in the sample is inversely proportional to the amount of turbidity formed. Replicate analysis using control materials yields a coefficient of variation of $\leq$ 5%. The test results may be unreliable in cases of hemolytic anemia or in iron deficiency anemia since $HgbA_{1c}$ can not be calculated if the patient's hemoglobin is below 6 g/dl.[99]

3.7.5.3 *International Normalized Ratio (INR)*

International Normalized Ratio is a system of international reference standard for thromboplastins which was adopted by the World Health Organization in 1983 in order to standardize prothrombin time reporting. It is a ratio of the patient prothrombin time and control time, "PT ratio", which is standardized in international units (ISI).[99] The control time represents the mean of the normal population distribution for each laboratory and ISI is the international sensitivity index. The ISI value represents the responsiveness of PT to the reduction in vitamin K-dependent coagulation factors II, VII, and X as measured with a given thromboplastin in the PT test system. Prothrombin time is determined by automated photo-optic instrumentation. Replicate analysis using control materials yields a coefficient of variation of $\leq$ 2.5%. Many drugs that interact with warfarin may exert an effect on coagulation and INR (see Table 3.7.2.4.1).

3.7.5.4 *Repeated Assessment of Laboratory Outcomes*

As described in section 3.5.3, it was assumed that a pattern of frequent laboratory testing was a sign of that the patient's physiologic state was altered by disease or inadequate compliance. When a test was done within 3 days of the previous test, it was ignored in the analysis. Only the first test in a series of frequently occurring tests was included in the data.

In each study population, the association between laboratory outcome and compliance was assessed with only one laboratory value in each time window of compliance observation. Although sometimes multiple laboratory measurements occurred within the time window, only the last laboratory test in the time window was used in the analyses.

3.7.5.5 *Laboratory Outcomes for Comparing Fairchild and Steiner Methods*

For the Steiner method, the means of all laboratory outcomes (TSH, $HgbA_{1c}$, and INR) within the study period, following the 3-month dose adjustment, were used to determine the association of refill compliance and laboratory outcome.

3.7.6 Measurement of Potential Effect Modifiers and Confounders

Potential effect modifiers and confounders were selected a priori based on a review of pharmacological and medical literature relating to the properties of each drug. The primary sources of information were Goodman and Gilman's the Pharmacological Basis of Therapeutics and Medscape, an electronic database of drug literature.[79 100] Patient characteristics such as: age, gender, renal function, liver function and obesity influence the metabolism and elimination of the drug and therefore were measured as potential confounders.[79;101] Dose, duration of therapy and frequency of laboratory testing were assessed as potential effect modifiers.

The pharmacodynamics of drug therapy is also affected by concomitant drug therapy. Concurrent treatment with some medications increase and others decrease the effectiveness of the study drugs. Another influencing factor is changes in the disease state. The frequent testing occurs most often when laboratory test results are abnormal and may be a surrogate for a change in the disease. Therefore, concurrent medications that modify the effectiveness of the study drugs and frequency of laboratory testing were considered potential confounders.

Characteristics of the drug treatment, dose of the study drug and duration of treatment (since date of first prescription), were considered potential drug effect

modifiers and potential confounders of the relationship between refill compliance and outcome. Compliance has been shown to change over time; therefore treatment time, in this study, was thought to be potentially associated with compliance. As the effect of medication therapy on disease control may also change over time, it is plausible that duration of therapy may be a modifier of the relationship between refill compliance and laboratory markers of disease control. Time is also a surrogate for disease progression in diabetes and so it is potentially associated with the laboratory outcome. Increased complexity of the drug regimen is a predictor of poor compliance.[64] High doses of drug often require complex treatment regimens (more than one tablet daily). High doses were also expected to have a large impact on the laboratory outcome than lower doses. Therefore, both time on treatment and dose were considered potential confounders and effect modifiers.

3.7.6.1 *Treatment Time*

Treatment time was calculated for each time window of measurement of compliance and outcome. Each window ended with a laboratory test, so the last date of the window was also the date of the laboratory test. Treatment time was determined by subtracting the date of the first study drug prescription from the date of the last laboratory test in the observation period and dividing by 30 in order to expressed treatment time in months.

3.7.6.2 *Frequency of Laboratory Testing*

The number of laboratory tests recorded between the beginning and end of each time window of compliance observation was counted. Frequent laboratory testing was defined as more than one TSH or $HgbA_{1c}$ and more than two INR per time

window respectively, for each disease. Frequency of testing within each time window was treated as a time-dependent covariate and assessed as a potential confounder and effect modifier.

3.7.6.3 *Age, Gender and Obesity*

Demographic information, date of birth and gender were provided in the HMO databases based on beneficiary registration information completed by the patients. Age was the patient's age on June 30, 1995, irrespective of the year of entry. Age was treated as a fixed variable, not changing over time. It could not be treated as a time-dependent variable in the analyses because of its collinearity with treatment time.

Obesity was determined by outpatient or hospital discharge diagnosis (ICD9-278 or 259.9). It was assumed that obesity significant enough to be noted in diagnostic coding, was unlikely to change over the course of the study. In the analysis, it was treated as present or absent.

3.7.6.4 *Hepatic and Renal Function*

Hepatic and renal function were determined, respectively, by the last albumin and creatinine laboratory test results that were recorded prior to laboratory test measurement of outcome. Test result values were treated as continuous variables in the analysis. In cases where there was no measure of albumin or creatinine, it was assumed that the patient had normal hepatic and renal function, and the midpoint of the normal range for albumin (4.3 g/dL) or creatinine (1.0 mg/dL) was assigned for missing values. During each time window, the creatinine and albumin value most proximal to the last date of each time window was utilized. When there

was no creatinine and/or albumin in test within the time window, the last value was carried forward.

Measurement of serum creatinine is useful in the diagnosis and treatment of acute and chronic renal disease and in monitoring renal dialysis. Replicate analysis of creatinine using control materials yields a coefficient of variation of $\leq$ 2.5%.[99] Creatinine can be elevated due to ingestion of hydantoin, large doses of ascorbic acid, and cephalosporin antibiotics. Low creatinine can be attributed to debilitation.

Albumin is a protein that constitutes 55-65% of total plasma protein. It maintains oncotic plasma pressure and is a source of endogenous amino acids. Albumin binds and solubilizes various compounds, e.g. bilirubin, fatty acids, and toxic heavy metal ions as well as numerous pharmaceuticals, which is the reason why lower albumin concentrations in blood may have a significant effect on drug distribution and metabolism. Hypoalbuminemia is caused by several factors. Liver disease is the most common cause of hypoalbuminemia but this problem is also seen in tissue damage due to severe burns, protein malnutrition, Crohn's disease, neoplastic disease, or proteinurea as a consequence of nephrotic syndrome.[102;103] The test for albumin is a colorimetric assay, similar to that of creatinine. Replicate analysis using control materials yields a coefficient of variation of $\leq$ 2%.[99] The results may be unreliable, however if the specimen is not processed within 4 hours after the sample is drawn.

3.7.6.5 *Concomitant Medication*

The presence of concomitant therapy with a drug known to interact with the study drug was recorded as present or absent.[100] Table 3.7.4 lists all concomitant drugs that were considered to possibly interact with the study drugs and the direction of

the interaction.[79;100] In the analysis, two variables were created in each time window: the number of concomitant medications that increase the effect of the study drug and the number of drugs that decrease the effects of the study drug each window. The start and stop dates of each concomitant medication prescription were compared with start and stop dates of each time window. If the dates over-lapped by one day or more, the concomitant drug was considered present.

Table 3.7.6.5.1 Concomitant Drugs that Interact with Study Drugs

Study Drug	Drugs that increase the effect of study drug	Drugs that decrease the effect of study drug
Levothyroxine	Asparaginase, clofibrate, flurosemide, 5-fluorouracil, mefenamic acid,salicylates, methadone, perphenazine, phenytoin, phenylbutazone, and tamoxifen.	Estrogens, birth control pills, androgens corticosteroids, and amiodarone.
Glimepiride Chlorpropamide Glyburide Glyburide, micronized Metformin Glipizide Glipizide XL Repaglinide Acarbose Troglitazone Tolbutamide Tolzamide HCL	Nonsteroidal anti-inflammatory drugs, antifungal azoles drugs, clofibrate, nifedipine, salicylates, sulfinpyrazone, monoamine oxidase inhibitors,and beta adreneric blocking drugs.	Thiazide diuretics, corticosteroids, phenothiazines, thyroid hormone supplements, estrogens, oral contraceptives, rifampin, diazoxide, epinephrine and beta blockers.
Warfarin	Allopurinol, amiodarone, androgens, azoles antifugal drugs, dyiridamole, antiarrythmics, cefamandole, cefoperazone, cefotetan cimetidine, chloramphenicol, clofibrate, danazol, diazoxide, diflunisal, disulfiram, heparin, erythromycin and other antimicrobial, ethacrynic acid, fluoxetine, flutamine, glucagon, ibuprofen, isoniazid, ketoprofen, lovastatin, meclofenamate, mefenamic acid, methylthiouracil, miconazole, moxlctam, neomycin (oral), pentoxifylline, phenybutazone, piroxicam, propranolol, propoxyphene, propylthiouracil, salicylates, streptokinase,	Aminoglutethimide, antithyroid drugs, barbiturates, corticosteroids, carbamazine, glutethimide, griseofulvin, methaqualone, methimazole, meprobamate, nafcillin, oral contraceptives containing estrogen, primidone, rifampin, vitamin K.

3.8 Analysis

Descriptive statistics were used for data cleaning, and to examine the distribution of each of the study variables. Graphs were constructed of the distributions of independent and dependent variables in each time window. Histograms of laboratory outcomes (TSH, INR, and $HgbA_{1c}$) showed outliers with very high values at each time window and so the log of each laboratory value was used to reduce their impact.

Relationships between all variables were then examined. To identify potential problems of collinearity, associations among all of the independent variables were estimated using Pearson product moment correlation coefficients. Crude associations between the laboratory outcome and each of the independent variables that might have potentially confounded or modified the association between the study drug and outcome were evaluated initially using simple linear regression for each time window and then re-examined incorporating all repeated measurements in multivariate analyses.

The multivariate analyses were conducted using linear regression within a generalized estimating equation (GEE) framework, in which laboratory outcomes and refill compliance measures in the preceding 30 days represented repeated measurements for the same patient.[104] Residuals from the multiple measurements of laboratory outcome of adjacent windows of measurement were assumed to be more correlated than the residuals from those more distant in time. Therefore, an autoregressive first order correlation structure was used to represent the dependence among these residuals.

Potential modifiers of the relationship between laboratory tests and refill compliance were first evaluated by comparing the estimated betas for the compliance-laboratory outcome relationship above and below mean values of the hypothesized modifying variables (dose, time of treatment and frequency of laboratory test). To formally test potential modification of the compliance-outcome relationship, the potential effect modifier variables were centered ($x-\bar{x}$) and then an interaction variable (e.g. compliance x effect modifier) was created using the centered values to prevent collinearity of terms in further analyses. Multivariate analyses were conducted using linear regression within a GEE framework.[104]

Confounding in the relationship between compliance and laboratory outcome was evaluated by determining if the estimated regression coefficient of the laboratory outcome compliance relationship was changed by inclusion of potential confounders. Changes in the estimated beta for compliance by 15% was defined as the threshold for evidence of confounding.

The assumption that the relationship between the laboratory outcome and refill compliance was linear was tested by adding a squared term for compliance to the full model of all variables. If the p-value of the squared term was significant at the .01 level, the next step was to graph the predicted laboratory values for various levels of compliance using the estimated slope and beta for compliance. When the relationship was non-linear within the range of values observed in the sample, the squared term was added to the full model, and its contribution to enhancement of fit in the overall compliance outcome relationship was assessed by changes in the partial correlation coefficient.

The primary goal of the study was accomplished by determining the strength of the association between refill compliance and laboratory outcomes and to compare the correlations between compliance and similar physiologic outcomes reported in previous studies. Normally one would use a partial r (or r^2) to measure the association while controlling for the effects of other variables which have an important relationship with the dependent variable. To the author's knowledge, there is no published way to assess partial correlation coefficients using GEE multivariate analysis of repeated measures. An analogy of the standard formulae for overall and squared partial correlation coefficient was employed:

Overall r^2 = (SSY-SSE) / SSY
Partial r^2 =[SSE(reduced) - SSE(full)] / SSE (reduced)

Where:

SSE (reduced) = residual sum of squares of model without variables of interest
SSE (full) = residual sum of squares of full model

Partial correlation coefficients (r^2) were calculated for patient characteristics, and then treatment characteristics and compliance in a sequential fashion to examine the contribution of each set of variables to the explanation of variance in laboratory values. The basic model included only patient characteristic variables (age, gender, renal and hepatic function, obesity and concurrent medications). Partial correlation coefficients were calculated for 1) base model variables; 2) compliance and base variables; and 3) compliance, dose, time and interactions, and base model variables.

CHAPTER 4 STUDY RESULTS

4.1 Study Populations

4.1.1 Assembling the Study Populations

The target populations were patients with primary hypothyroidism, type 2 diabetes, and atrial fibrillation. The study populations were treatment inception cohorts of patients receiving chronic treatment for these disease conditions. The source populations were sequentially screened for the presence of eligibility, inclusion, and exclusion criteria as described in Chapter 3, Section 3.6. The percentage of the source population retained at each step in the screening process are described in Table 4.1.1.1.

Although each study population was substantially smaller than the source population, the study populations remained large enough to detect a correlation between refill compliance and laboratory outcome of $r \geq 0.15$ at 0.01 level of significance with 90% power.[75;76] Of the patients screened, 56% of the diabetics and 52% of the atrial fibrillation patients were eligible for study. The greatest reduction in sample size in the diabetics was because patient did not have a $HgbA_{1c}$ value after the dose adjustment period. Because the HMO recommended $HgbA_{1c}$ testing on an annual basis, patients enrolled during the last year of eligibility had abbreviated follow-up and limited opportunity for further $HgbA_{1c}$ testing after the dose-adjustment period. The greatest reduction in the atrial fibrillation and hypothyroid patients was due to concurrent ineligible diagnoses. Atrial fibrillation occurs primarily in conjunction with a variety of cardiovascular disorders; many of which disqualified the patient from inclusion in the study. The hypothyroid study population was restricted to patients with primary hypothyroidism. Consequently,

only a small proportion (38%) of the hypothyroid patients screened were retained for study.

Table 4.1.1.2 compares the characteristics of hypothyroid patients included and excluded from the hypothyroid study population. The two groups were quite similar in terms of gender, age, and the treatment they received (dose of levothyroxine, prescriptions filled, and number of laboratory tests). The mean TSH level was higher in the excluded patient group as might be expected in patients with a variety of thyroid disorders. There were two other notable differences between the two patient groups. A small portion of the excluded patients filled only one prescription for levothyroxine (5%) and had only one TSH test (0.2%), suggesting that possibly they were noncompliant or that the diagnosis was subsequently proven to be incorrect. Potentially non-complaint patients made up less than 5% of the excluded patient group and less than 1% of the source population. Bias introduced by the exclusion of a small number of noncompliant patients would likely be negligible.

Table 4.1.1.1 Progression from Source Population to Study Populations
Proportion of Persons Remaining After
Application of Each of the Eligibility Criteria

Progressive steps:	Disease Conditions		
	Hypothroidism **N (% of source population)**	**Diabetes** **N (% of source population)**	**Atrial Fibrillation** **N (% of source population)**
Source Population ⇓	3054	5645	906
Eligibility screen ⇓	2809 (92%)[A]	4925 (87%)[B]	Not applicable
Eligibility confirmed by ICD-9 diagnosis ⇓	2559 (84%)	4332 (78%)	820 (91%)
Ineligible determined by ICD-9 diagnosis ⇓	1371 (45%)[C]	4282 (76%)[D]	518 (57%)[E]
Patients with one or more lab test following dose adjustment period ⇓	1175 (38%)	3175 (56%)	468 (52%)
Study Population	1175	3175	468

A. Patients with abnormal TSH before first levothyroxine prescription

B. Patients with no insulin therapy within 6 months of first prescription for a oral hypoglycemic drug

C. Hypothyroid patients with ineligible diagnoses : acquired hypothyroidism (N=492), thyroidtoxicosis (N=248), thyroiditis (N=245) , nodular goiter (N=77), pregnancy (N=65), thyroid cancer (N=34), and other thyroid disorders (N=27).

D. Ineligible diabetic patients : pregnancy (N=14), pancreatic cancer (N=2). In addition, $HgbA_{1c}$ 34 patients had concurrent insulin therapy

E. Atrial fibrillation patients with ineligible diagnoses: myocardial infarction (N=121), thrombosis (N= 118), pulmonary heart disease (N= 27), pacemaker (N=21), and heart valve disease (N=15).

Table 4.1.1.2 Comparison of Characteristics of Hypothyroidism Patients Included and Excluded From Study

Population Characteristics	Included Patients N= 1175	Excluded Patients N=923
Mean age in years	49.7	47.2[A]
Percentage of female patients	80%	80%
Percentage of patients with only one prescription for levothyroxinec	0%	5%
Mean number of prescriptions filled per year	7.8	7.1
Mean levothyroxine dose	79 mcg	81 mcg
Percent of patients on stable levothyroxine dose (i.e. coefficient of variation=0%)	52%	30%
Number of patients with only one TSH test	0%	0.2%
Mean number of TSH tests per year	5.8	4.2
Mean TSH value	10.9 IU/dl [B]	12.7 IU/dl

A. Excluding 11 patients who were children

B. TSH values prior to and during the levothyroxine dose adjustment period were included in the calculation of mean TSH and therefore the resulting mean TSH differs from those reported in subsequent tables.

4.1.2 Dynamic Eligibility

The study populations were further reduced in size by dynamic eligibility. A patient was deemed ineligible during times when compliance was not a matter of choice (i.e. hospitalization) and when the patients took other medications which significantly affected the course of the disease (i.e. diabetic patient taking insulin or steroid drugs). A small percentage of patients were removed from the study when the period of temporary ineligibility overlapped a time window during which

compliance and laboratory outcome were measured. Table 4.1.2.1 shows further reductions in the sample size because periods of temporary ineligibility overlapped every time window for an individual patient.

Hypothyroid patients were hospitalized infrequently and therefore there was only a 3% reduction in population size due to temporary exclusions. Twenty percent of the diabetic patients were hospitalized, but the hospitalization dates rarely coincided with a window of compliance and outcome measurement. More often, temporary exclusion of diabetic patents occurred as a consequence of concurrent drug therapy that would confound the association between Hgb_{A1c} and compliance. In total, the diabetic study population was reduced by only 2% because of dynamic eligibility. Atrial fibrillation patients were hospitalized frequently; 49% of the patients were hospitalized at least once during the study. There was a 12% reduction in the atrial fibrillation study population because of dynamic eligibility.

Table 4.1.2.1 Dynamic Eligibility and Temporary Exclusions Resulting in Reduction in Sample Size

Time Windows Excluded due to Dynamic Ineligibility	**Disease Conditions**		
	Hypothyroidism N =1175 (% of study population)	**Diabetes N =3175 (% of study population)**	**Atrial Fibrillation N =468 (% of study population)**
Number of time windows of observation excluded because of temporary ineligibility			
Total number of windows[A]	3415	10123	3547
Mean excluded windows per patient Mean	0.3	0.1	1.3
Range	0 - 1	0 - 8	0 - 27[B]
Patients with excluded windows	% N	% N	% N
0	97% 1140	91% 2911	86% 402
1	3% 35	6% 180	1% 5
2	0.5% 7	1% 41	2% 8
3		0.8% 24	1% 5
4		0.2% 9	1% 7
5 or more		0.6% 19	9% 41
Reasons for temporary ineligibility			
Patients hospitalized	13% N= 154	20% N=621	49% N=228
Hospitalizations per patient Mean	0.23	0.34	1.13
Range	0 - 7	0 - 16	0 - 19
Hospitalization frequency per patient	% N	% N	% N
0	87% 1021	80% 2563	51% 240
1	9% 104	12% 391	21% 98
2	2% 23	4% 128	13% 61
3	0.8% 9	1% 47	7% 31
4	0.7% 8	0.8% 27	3% 15
5 or more	0.8% 10	0.8% 28	5% 23
Windows excluded due to concurrent drug therapy	none	473[C]	none
Final Study Population: Patients with at least one eligible time window	97% N=1140	98% N=3105	88% N =410

A. Windows of compliance observation 30-day periods preceding a laboratory test (TSH, INR or Hgb_{A1c}).

B. Frequent hospitalizations in this population resulted in a high rate of temporary ineligibility.

C. 473 windows were excluded for 268 patients (1.1%) because of concurrent steroid drug therapy;13% of steroid use was inhaled steroids.

4.1.3 Characteristics of the Study Populations

The characteristics of the patients in each study population are summarized in Tables 4.1.3.1 and 4.1.3.2. Table 4.1.3.1 describes patient status before the start of the study and Table 4.1.3.2 describes the patient characteristics during the course of the study.

4.1.3.1 *Hypothyroid Patient Study Population*

Hypothyroid patients in the study population were 80% female, and the mean age was 49 years. Only a small proportion of patients had prior hospitalizations (5%), abnormal renal (1%) or hepatic dysfunction (1%), suggesting that these patients were in good health. Over the course of the study, hypothyroid patients had a small number of hospitalizations and stable creatinine and albumin levels. A small percentage of patients were taking concurrent medications that would increase (5%) or decrease (5%) the effect of levothyroxine on TSH. The mean TSH during the course of the study was 8.2 IU/L which was above the target of less than 7 IU/L in accordance with treatment guidelines.[80] This study population had the highest mean rate of compliance (76%) during the first window of compliance assessment. Compliance improved over the course of the study to 83% at the end of follow-up.

4.1.3.2 *Diabetic Patient Study Population*

Diabetic study patients had nearly equal representation of males and females with a mean age of 56.8 years. Only a small percentage of the study patients had abnormal renal (2.6%) or hepatic function (0.6%) or hospitalizations (7%) in the six months prior to the onset of the study. Yet, by the end of the study, the number of patients with abnormal renal function increased from 2.6 to 3.6%. Seven percent

of the patients were concurrently taking medications that increase the effect of hypoglycemic drugs on $HgbA_{1c}$ while 20% were taking concurrent medication that decreases the hypoglycemic effect of diabetic drug therapy. The mean $HgbA_{1c}$ during the course of the study was 8.1% which was above the target of less than 7.5% in accordance with the treatment guidelines.[105] Over the course of the study, average compliance in the diabetic patients improved slightly (from 0.70 to 0.77). The mean $HgbA_{1c}$ was 8.1% near the target of the treatment guidelines of <8% published by the HMO. Twenty percent of the patients were hospitalized at least once during the study.

4.1.3.3 *Atrial Fibrillation Study Patient Population*

Atrial fibrillation is a disease that most often accompanies comorbid states. Although idiopathic atrial fibrillation occurs, this abnormal rhythm is most often secondary to another cardiovascular disease.[80] Sixty-five percent of the patients hospitalized prior to the start of the study had cardiovascular diagnoses (ICD-9 codes 396-459.1). Hospitalization rates were quite high both in the six months prior to the start of treatment (42%) and during the study (49%). Patients in this study population were older (mean age 69.3) than the other study populations. They quite frequently used concurrent medications known to influence the effects of the study drug, warfarin. This is partly explained by the fact that elderly patients have more co-morbidities that require drug therapy and in part because warfarin-related interactions are among the most widely studied drug interactions. Atrial fibrillation patients also had a higher prevalence of abnormal liver and renal function tests than the two younger study populations (hypothyroid and diabetic patients).

Table 4.1.3.1 Characteristics of Study Populations Six Months Prior to Study Entry

Population Characteristic	Disease Conditions					
	Hypothroidism N=1140		Diabetes N=3105		Atrial Fibrillation N=410	
Age in years Mean (SD)	49.7 (14.5)		56.8 (12.8)		69.3 (11.2)	
Percent female	80%		49%		43%	
Percent obese	8%		15%		7%	
Concomitant taken medications prior to initiation of study drug which might:	%	N	%	N	%	N
- Increase effect of study drug	95%	1084	93%	2964	70%	280
0	5%	53	7%	207	25%	101
1	0.3%	3	0.1%	4	5%	20
2 or more						
- Decrease effect of study drug	95%	1088	79%	2494	95%	389
0	5%	52	20%	631	5%	20
1			2%	50	0.2%	1
2 or more						
Patients hospitalized	%	N	%	N	%	N
	5%	59	7%	211	42%	171
Number of hospitalization with a primary discharge diagnosis of:	%	N[A]	%	N[A]	%	N[A]
Infection	10%	6	17%	19	2%	4
Neoplasm	20%	12	10%	25	2%	6
Endocrine & metabolic dis.	54%	32	74%	189	5%	13
Mental & neurologic dis.	7%	4	2%	5	2%	5
CV disorder	5%	3	5%	13	65%	169
Respiratory disorder	0%	9	0%	0	4%	11
Other disorder	3%	2	2%	4	20%	51
Renal Function: Mean (S.D.)	86.6 (38)		86.6 (25)		106 (101)[C]	
Creatinine[B] Range	35 - 970		26 - 539		35 - 1821	
in µmol/L % Abnormal	1.6%		2.6%		7.8%[C]	
Liver Function: Mean (S.D.)	43.2 (2.1)		43.1 (2.2)		41.4 (2.4)[C]	
Albumin[B] Range	25 - 53		20 - 54		29 - 50	
in g/L % Abnormal	1%		0.6%		1.5%	

A. Some patients were hospitalized more than once.

B. These tests are abnormal if creatinine is greater than 115 µmol/L and if albumin is below 35g/L.

C. Because of missing data, renal and hepatic function tests results were based on 382 and 212 (97% and 48%, respectively) of the atrial fibrillation patients.

Table 4.1.3.2 Characteristics of Study Populations During the Follow-up Period

Population Characteristic	Disease Conditions		
	Hypothroidism N =1140	**Diabetes** N =3105	**Atrial Fibrillation** N =410
Duration of study drug therapy in months Mean (S.D.)	21.1 (11.9)	22.1 (12.7)	17.4 (11.4)
Range	3.9 - 52.8	4.4 - 55.0	4 - 47.9
Windows of compliance-outcome measurement per patient Mean (S.D.)	3.0 (2.0)	3.3 (2.4)	8.6 (7.3)
Range	1 - 12	1 - 17	1 - 32
Frequency of lab tests per window	% N	% N	% N
1	99% 3494	99% 10589	35% 1460
2	0.06% 21	0.03% 35	47% 1976
3		<0.01 % 2	13% 543
4			4% 168
5 or more			1% 65
Study drug dose over all time windows.	Levothyroxine [A] mcg	Hypoglycemic [A] mg	Warfarin [A] mg
Mean (S.D.)	78.9 (45.6)	19.3 (17.3)	5.8 (5.0)
Range	0 - 400	0 - 135	0 - 35
Refill Compliance: Mean (S.D.)			
First window	0.76 (0.37)	0.70 (0.39)	0.57 (0.41)
Last window	0.83 (0.31)	0.77 (0.35)	0.50 (0.43)
Overall compliance	0.80 (0.34)	0.76 (0.36)	0.56 (0.41)
Laboratory outcome values	TSH IU/dl	$HgbA_{1c}$ %	INR%
Mean (S.D.)	8.2 (20.2)	8.1 (1.9)	2.4 (0.5)
Range	0.2 - 644 [B]	2.3 - 22.9 [B]	0.8-27.3 [B]
Renal Function-Creatinine [C] in µmol/L Mean (S.D.)	85 (41)	86 (26)	100 (65)
Range	35 - 1175	9 - 628	35 - 2245
% Abnormal	2.2	3.6	10.0
Liver Function - Albumin [C] in g/L Mean (S.D.)	43.3 (2.4)	43.1 (2.6)	41.8 (2.7)
Range	24 - 50	21 - 55	31 - 50
% Abnormal	1.0	1.1	2.2
Patients hospitalized	13% N= 154	20% N= 621	49% N= 228

A. Levothyroxine and warfarin dosing is individualized; recommended starting doses are 50 mcg and 5 mg respectively. Recommended starting dose varies with each hypoglycemic drug.

B. High values were confirmed by repeated testing. Includes testing done during and outside of windows of compliance measurement. Therapeutic laboratory goals were TSH <7.5, $HgbA_{1c}$ <8.0, INR >2

C. These tests were considered abnormal if creatinine was >115µmol/L and albumin was <35g/L.

4.1.3.4 *Algorithm Results*

A daily log of available drug supply was essential for assessing the relationship between compliance and laboratory outcomes for compliance measurements in the 30 days prior to testing. The algorithm developed for this study facilitated creation of a daily log of available drug and a more accurate counting of duration of available drug supply of overlapping prescriptions. Table 4.1.3.4.1 shows the frequency of overlapping prescriptions and the resulting adjudication by the algorithm into three categories: early refills, dose additions, and dose changes.

The majority of overlapping prescriptions were determined to be early refills in all study populations by the algorithm. As expected, hypothyroid and atrial fibrillation patients had infrequent modifications of dose (dose additions or dose changes). After the initial period of dose adjustment, the dose level of levothyroxine and warfarin generally remains constant because these disease conditions do not worsen over time.[106] On the other hand, diabetes is a progressive disease and dose adjustments were expected throughout the study period.[94] After the initial treatment fails, treatment alternatives include changing the drug therapy to another oral hypoglycemic drug with a different mechanism of action or adding a second therapy to the current regimen. Changing to an alternative oral hypoglycemic drug was reflected by the algorithm as a dose change; and adding a second drug to the current regimen was reflected a dose addition. The dominant adjudication (15%) of overlapping prescriptions in diabetic patients was a dose change (See Table 4.1.3.4.1). Overlapping prescriptions were most frequently determined to be a dose change by the algorithm in the diabetic population, even when the criterion for determining dose additions was relaxed. The criterion could be relaxed by changing the dose-approximation factor [Dose A + Dose B $\pm$ 7 mg]. When the dose-approximation factor was changed from 7 mg to 15 mg (doubled), 11% of the prescriptions were dose changes and 8% dose additions. The consequences of

using the original and more lenient dose approximation-factor for the diabetic population on the compliance-laboratory outcome relationship were examined in secondary analyses.

Table 4.1.3.4.1 Frequency of Prescription Refills and Overlapping Prescriptions

	Disease Conditions					
	Hypothyroidism N=1140		**Diabetes N=3105**		**Atrial Fibrillation N=410**	
Total number of refills	16, 760		70146		5629	
Average number of refills per patient	14.7		22.6		13.7	
	Percentage of total prescriptions					
	%	N	%	N	%	N
Early refills[A]	34%	5771	29%	20597	20%	1129
Dose changes[A]	8%	1299	15%[B]	10879	4%	222
Dose additions[A]	1%	199	4%[B]	2720	5%	283
All overlapping prescriptions	43%	7269	48%	34196	29%	1634

A. Refer to Section 3.7.2.1.1 for definitions of early refill, dose change, and dose addition.

B. 11% were categorized as dose changes, 8% were characterized as dose additions, when a more generous dose-approximation factor was used to determine dose additions.

4.2 Refill Compliance-Laboratory Outcome Relationship

Plots of the distribution of laboratory test results (See Appendix 3) indicated that the laboratory measures were skewed with a long right tail. Further investigation of the

outliers confirmed that the data were not errors, but true outliers. From a clinician's perspective a two-fold change in a laboratory parameter at the upper end of the laboratory test range is not clinically equivalent to a similar change at the lower end of the range. To reduce the impact of the outliers in the modelling procedure, the log of each laboratory test results was used in the analyses.[107]

The unadjusted associations between logged laboratory parameters and compliance were assessed with Pearson's correlation and linear regression within a GEE framework. In all populations, the direction of the association was as expected. Drug therapy for hypothyroidism and diabetes is intended to decrease the values of TSH and $HgbA_{1c}$ and so negative regression coefficients were expected. A positive correlation was expected for atrial fibrillation patients for the goal of anticoagulant therapy is to increase INR values. In each analysis, the direction of the regression coefficient was appropriate for the population. The strength of association between compliance and laboratory outcomes appeared to be strongest in hypothyroid patients ($r= -0.23$, regression coefficient (β) = -0.82, $p<0.0001$), weaker in diabetic patients ($r=-0.08$ and $\beta = -0.05$, $p<0.0001$), and not statistically different from zero ($r=0.004$ and $\beta = 0.010$, $p=0.51$) in the atrial fibrillation patients. These crude measures of association (unadjusted for covariates) suggested that the association between compliance and laboratory outcomes varied across the three populations.

4.2.1 Assessment of Potential Effect Modifiers

Three treatment characteristics were hypothesized to influence the refill compliance-outcome relationship: dose, treatment time, and frequency of laboratory testing. To evaluate potential effect modifiers, stratified multivariate analyses were conducted by dividing each patient population into two groups: those above and those equal to or below the mean level of dose and treatment time.

Laboratory testing was also divided into two groups: frequent and standard laboratory test frequency. Standard testing was defined as one or two INR's, one $HgbA_{1c}$, or one TSH in a 30-day window. Testing more often than standard testing was considered to be frequent testing. The refill compliance-outcome relationship was estimated for each stratum and the resulting differences in the stratum-specific regression coefficients (beta) for compliance were compared. The statistical significance of these potential interactions was tested in multivariate models which included other patient characteristic variables (age, gender, obesity, renal function, hepatic function, and concomitant drugs). Hypothesized two-way and three-way interactions were tested in a multivariate linear regression model within a GEE framework. The results of the stratified analysis and interaction evaluation are presented in Table 4.2.1.1.

4.2.1.1 *Assessment of Potential Effect Modifiers in Hypothyroid Patients*

The relationship between compliance and log TSH appeared to be modified by drug dose. There was a two-fold increase in the size of the compliance regression coefficients for low-dose and high-dose levothyroxine indicating that the relationship between refill compliance and TSH was stronger for patients on higher doses of levothyroxine. (Table 4.2.1.1). The interaction between dose and compliance for hypothyroidism was statistically significant and therefore was interpreted as evidence of effect modification. This interaction was depicted in linear plots of the predicted logged TSH values at all levels of compliance for three doses of levothyroxine (25 mcg, 100 mcg, and 175 mcg) in Figure 4.2.1.1. The slope between compliance and TSH increase with higher doses of levothyroxine. High levels of compliance were predicted by the model to have less impact on TSH values in patients on lower doses of drug than higher doses. In other words, patients who consumed more of their medication were more likely to have greater reductions in TSH when prescribed higher doses of levothyroxine than patients

prescribed low doses of levothyroxine. Treatment time and laboratory testing frequency did not modify the relationship between compliance and log TSH.

4.2.1.2 *Assessment of Potential Effect Modifiers in Diabetic Patients*

In diabetic patients, the relationship between compliance and log $HgbA_{1c}$ appeared to be modified by two covariates, dose and treatment time. There was a 1.9-fold increase in the size of the compliance regression coefficients for low-dose and high-dose oral hypoglycemic drugs and a 1.7-fold increase for short and long treatment time. Furthermore, there was a 1.5-fold difference or more in the regression coefficients for compliance in patients on low-dose and high-dose oral hypoglycemic drugs in both short and long treatment time groupings (Table 4.2.1.1). The covariates representing compliance*time, dose*time and compliance*dose interactions were statistically significant in the multivariate analysis.

The interaction between compliance and time contributed in a meaningful and statistically significant manner in predicting logged $HgbA_{1c}$. The interaction was depicted in linear plots of the predicted logged $HgbA_{1c}$ values at all levels of compliance (Figure 4.2.1.2) for three treatment time periods (12, 24, and 36 months). Higher levels of compliance had more impact on $HgbA_{1c}$ values in patients treated for longer time periods than shorter time periods. In other words, compliance in the first year of treatment was not as influential on $HgbA_{1c}$ values as it was at later stages of the disease. In the early stages, disease control was achievable with single drug therapy and moderate compliance. As the disease progresses, compliance becomes a more important factor in disease control.

Treatment time also modified the association between dose and $HgbA_{1c}$. There was a stronger association between dose and $HgbA_{1c}$ for persons who had received

hypoglycemic therapy for a longer period of time. With disease progression, patients were more likely to receive either high doses of a single drug or receive combination drug with two or more hypoglycemic drugs with different mechanisms of action therapy. When a patient was taking two or more oral hypoglycemic drugs concurrently, the dose of each drug was added together as though the patient was taking a single generic drug. Therefore, there was a stronger association between dose and $HgbA_{1c}$ for patients who had received hypoglycemic therapy for a longer time period and were either on high doses of a single drug or receiving dual drug therapy.

Both compliance and dose were predicted to have more impact on $HgbA_{1c}$ with longer treatment time. Frequent laboratory testing was not an effect modifier in diabetes.

4.2.1.3 *Assessment of Potential Effect Modifiers in Atrial Fibrillation Patients*

In atrial fibrillation patients, dose also appeared to modify the relationship between patient compliance and INR results. There was a change of direction in the regression coefficients for compliance in patients on low dose and high dose warfarin signifying that dose was a potential effect modifier of the association between compliance and INR in atrial fibrillation patients (Table 4.2.1.1). However, the interaction between dose and compliance was not statistically significant, indicating that dose was not an effect modifier in atrial fibrillation patients.

Another potential modifier of the association between compliance and INR results was the frequency of laboratory testing. There was a change of direction of the compliance regression coefficient between standard (1-2 INR per month) and more frequent testing. The interaction between compliance and laboratory test frequency

was statistically significant in the multivariate regression model (see Table 4.2.1.1). The interaction is depicted in linear plots of the predicted logged INR at all levels of compliance for standard and frequent laboratory testing (Figure 4.2.1.3). As expected, the slope for standard testing was positive, indicating that high levels of compliance predicted higher levels of INR. The slope for frequent testing was steeper than the slope for standard testing and paradoxically negative. This paradoxical effect of increased compliance with warfarin associated with lower levels of INR is not biologically plausible. It suggested a systematic difference in the patient's disease state during periods of frequent INR monitoring. Periods of frequent testing may have represented some other unmeasured clinical phenomenon and therefore were unlikely to provide information on compliance-INR relationship. The decision was taken to exclude windows of frequent testing from the evaluation of the compliance-INR relationship.

4.2.1.4 *Summary of Assessment of Potential Effect Modifiers*

In summary, the relationship between compliance and laboratory outcome was modified by dose and treatment time in diabetic patients and by dose in the hypothyroid patients. In atrial fibrillation patients, the relationship between compliance and laboratory outcome was modified by frequency of laboratory testing. The paradoxical effects associated with periods of frequent testing led to the decision to limit assessment of the compliance-INR relationship to windows of standard testing. There was no evidence that frequency of laboratory testing modified the association between compliance and laboratory outcomes in hypothyroid or diabetic patients. Nor was there evidence of effect modification by dose or treatment time in atrial fibrillation patients.

Table 4.2.1.1 Evaluation of Potential Effect Modifiers
Stratified Analyses and Analyses Involving Full Models with Interaction Terms

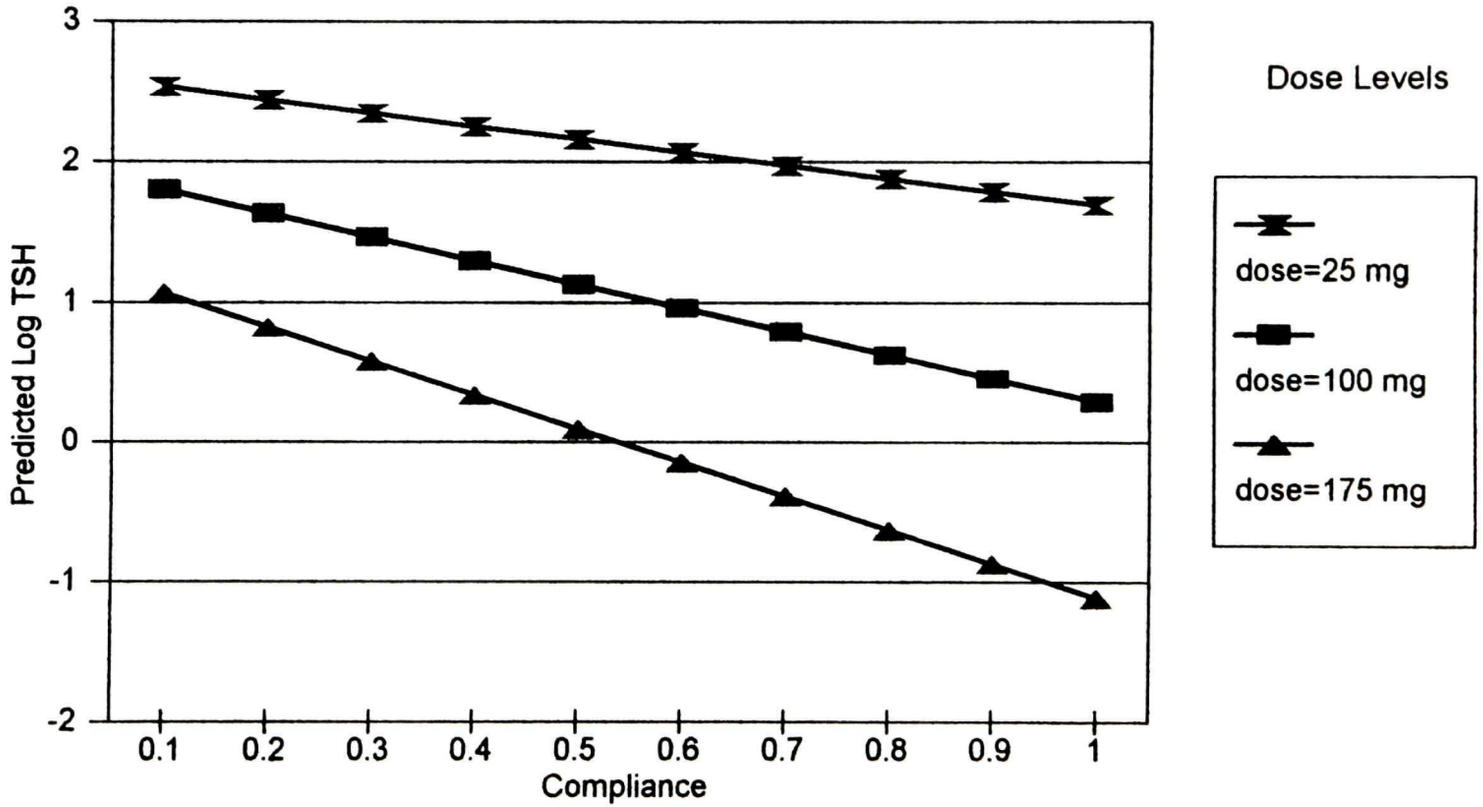
Levels of Potential Modifiers	Disease Conditions					
	Hypothyroidism		Diabetes		Atrial Fibrillation	
	Compliance Coefficient[A]	P-value	Compliance Coefficient	P-value	Compliance Coefficient	P-value
Low dose	-0.58	<0.0001	-0.06	<0.0001	-0.03	0.39
High dose	-1.11	<0.0001	-0.04	0.003	0.01	0.69
Short treatment time	-0.7	<0.0001	-0.04	<0.0001	0.01	0.67
Long treatment time	-1.06	<0.0001	-0.07	<0.0001	0.01	0.57
Low dose, short treatment time	-0.51	<0.0001	-0.06	<0.0001	-0.03	0.39
Low dose, long treatment time	-0.76	<0.0001	-0.08	<0.0001	-0.01	0.83
High dose, short treatment time	-0.93	<0.0001	-0.02	0.17	0.01	0.83
High dose, long treatment time	-1.41	<0.0001	-0.01	<0.0001	0.02	0.63
Standard lab testing frequency	-0.70	<0.0001	-0.05	0.61	0.02	0.15
Frequent lab testing[B]	Number too small to estimate beta		Number too small to estimate beta		-0.12	0.04
P-values of interaction terms in multivariate analyses						
Compliance* Dose	<0.0001		0.01		0.17	
Compliance*Time	0.14		0.004		0.96	
Time*Dose	0.11		<0.0001		0.06	
Compliance*Dose*Time	0.11		0.30		0.09	
Compliance* Lab testing frequency[B]	–		--		0.05	

A. Regression coefficients for the association between compliance and laboratory outcome represented change in log of laboratory test per unit increase in refill compliance (from 0-1).

B. Frequent testing is > 2 INR per time window.

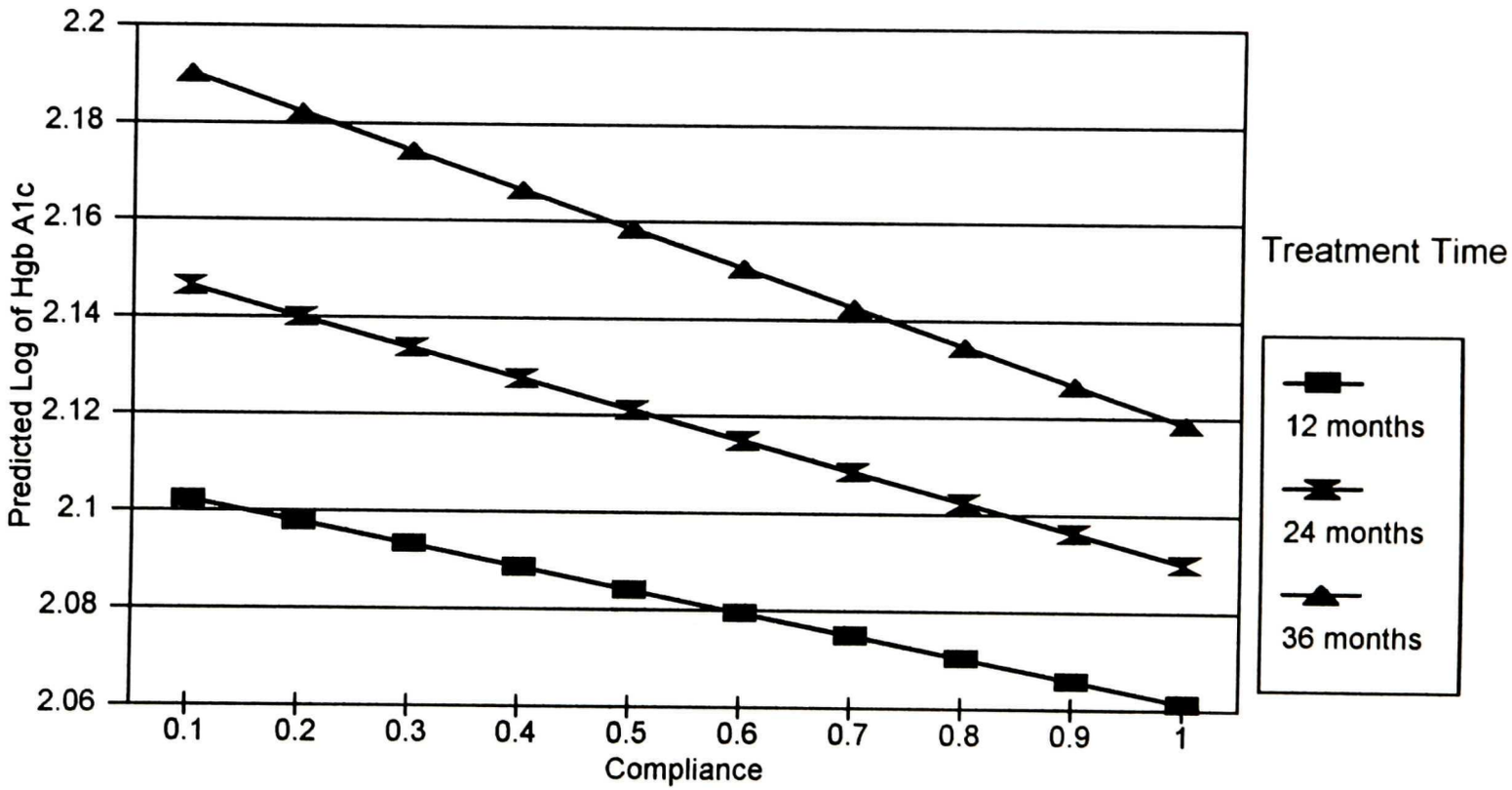
Figure 4.2.1.1 Hydrothyroid Patients Effect Modification

Relationship of Compliance and Log TSH at Different Levels of Dose



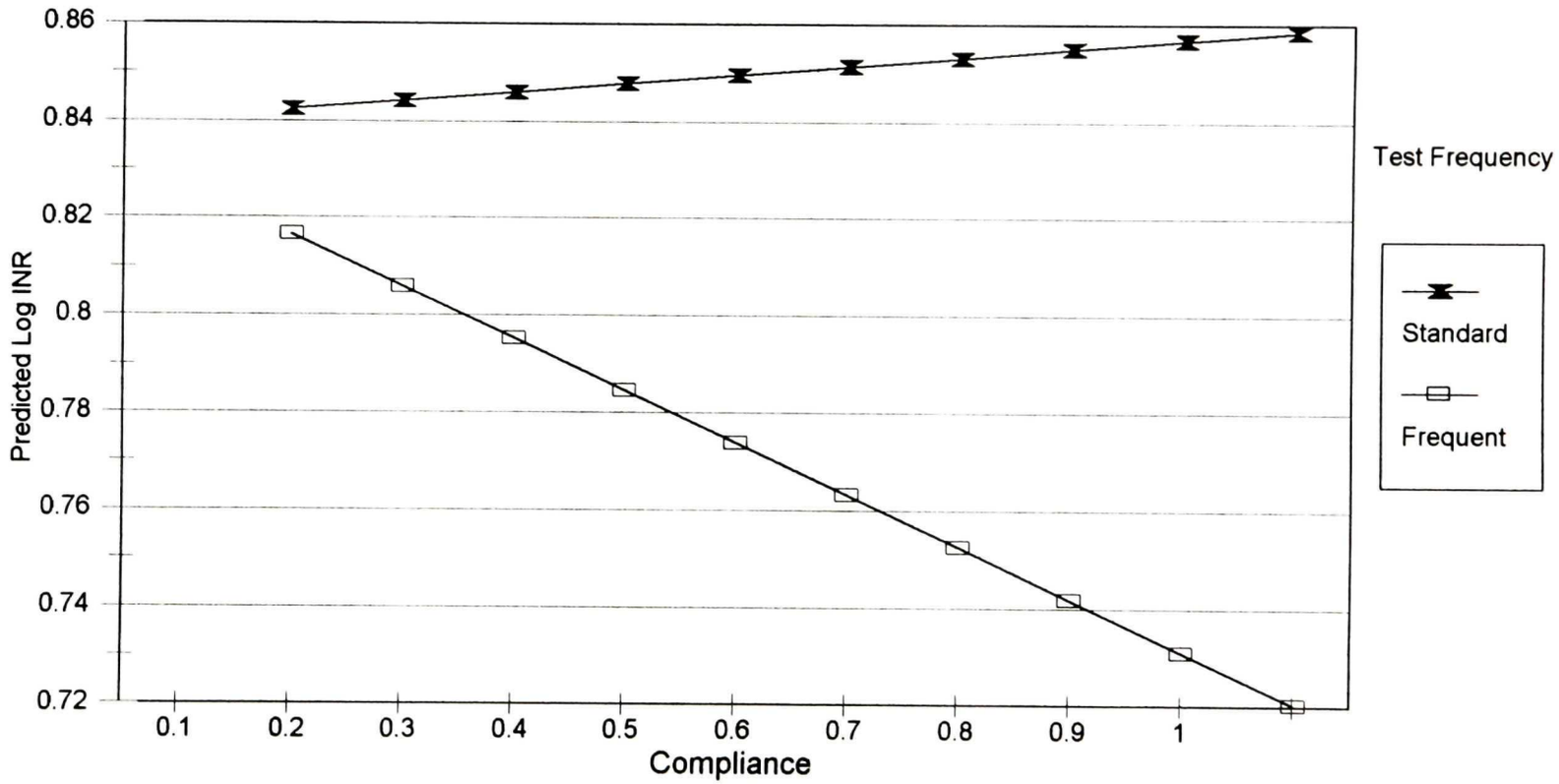
Figures 4.2.1.2 Diabetic Patients Effect Modification

Relationship of Compliance and Log $HgbA_{1c}$ at Different Times After Beginning Treatment



Figures 4.2.1.3 Atrial Fibrillation Patients Effect Modification

Relationship of Compliance and INR at Different Laboratory Testing Frequencies



4.2.2 Assessment of Confounding

All patient and treatment variables were evaluated for potential confounding. Patient variables included age, gender, renal function, liver function, obesity and concomitant medications known to modify the pharmacodynamics and effectiveness of the study drugs. Treatment variables included study drug dose and time of treatment since first prescription. Potential confounders were identified by examining the associations between laboratory outcome, compliance, and patient and treatment characteristics estimated using Pearson's and Spearman correlation coefficients and crude (unadjusted) bivariate linear regression analysis (see Tables 4.2.2.1 and 4.2.2.2) within a GEE framework. In the atrial fibrillation patients effect modification by the frequency of INR testing produced effects in opposing directions, therefore confounding was evaluated separately for standard and frequent testing.

Potential confounders were covariates which were correlated with both logged laboratory outcomes and compliance. Dose was associated with logged laboratory outcomes in all populations (TSH: r= -0.24, $HgbA_{1c}$: r= 0.16, and INR r= 0.04). The modest and positive correlation of dose and $HgbA_{1c}$ may be an artifact of the study methodology. The dose-response association has been reported to be almost flat for most of the oral hypoglycemic agents.[91-96;98] Dose was also correlated with compliance in all study populations (hypothyroid: r= 0.41, diabetic: r= 0.29, and atrial fibrillation: r=0.31). The dose-compliance correlations were stronger than those of dose-laboratory outcome because both dose and compliance were zero if there was no drug available for the patient to take during the time window for measuring compliance. Dose appeared to meet the definition of a potential confounder. Since it was independently associated with both compliance and outcome and not a priori considered to be in the pathway between compliance and outcome.[69]

The presence of confounding was confirmed by determining if there was a 15% or more change in the regression coefficient representing the relationship between compliance and laboratory outcome when patient and treatment characteristics were included in the model.[108] Table 4.2.2.3 shows the changes in the estimated compliance laboratory outcome association when characteristics of the patient and treatment regimen were included in the model.

When dose was included into the multivariate model, the regression coefficients changed from -0.82 to -0.47 (43% change) in the hypothyroid patients; from -0.05 to -0.06 (20% change) in the diabetic patients; and from 0.03 to 0.02 (33% change) in the atrial fibrillation patients during windows of standard testing. Dose affected the compliance regression coefficient (beta) for refill compliance in all populations and thus was included as a confounding variable in the relationship of compliance with laboratory measurements of the physiologic effect of drugs.

Table 4.2.2.1 Identification of Potential Confounders
Correlation of Compliance and Potential Confounding Variable

Independent Variables	Disease Conditions							
	Hypothyroidism		Diabetes		Atrial Fibrillation			
					Standard Testing[A]		Frequent Testing[A]	
	R[B]	P-value	R	P-value	R	P-value	R	P-value
Dose	0.41	<0.001	0.29	<0.001	0.31	<0.001	0.32	<0.001
Age	0.02	0.22	0.08	<0.001	-0.1	0.004	-0.14	<0.001
Gender[C] 0=male 1=female	0	0.91	0.03	0.003	0	0.97	0	0.84
Renal function (Creatinine)	0	0.07	0	0.03	0	0.69	0.04	0.27
Liver function (Albumin)	0	0.08	0.01	0.25	0	0.27	0.04	0.27
Obesity[C] 0=absent 1= present	0	0.79	0	0.85	-0.1	0.001	0.07	0.1
Time on study drug treatment (in months)	0	0.56	0.08	<0.001	0	0.18	0.01	0.78
Concurrent drug that increases effectiveness	0	0.88	0.03	0.002	0	0.46	0	0.92
Concurrent drug that decreases effectiveness	0.03	0.08	0.1	<0.001	0.01	0.95	-0.1	0.2

A. Of the 3547 windows, 2952 (83.2%) had standard, and 595 (16.6%) had frequent INR testing.

B. Pearson's product moment correlation coefficient

C. Spearman's correlation test results

Table 4.2.2.2 Identification of Potential Confounders
Estimated Regression Coefficient for Unadjusted Association Between Laboratory Outcome and Potential Confounding Variable

Independent Variables	Disease Conditions					
	Hypothyroidism Outcome: Log TSH		Diabetes Outcome: Log $HgbA_{1c}$		Atrial Fibrillation (Standard Testing)[A] Outcome: Log INR	
	$\hat{\beta}$[B]	P-value[B]	$\hat{\beta}$	P-value	$\hat{\beta}$	P-value
Dose of study drug prior to laboratory test	-0.01	<0.0001	0.001	<0.0001	0.001	0.83
Age	0.001	0.47	-0.003	<0.0001	0.004	0.08
Gender 0=male[C] 1=female	-0.228	0.002	0.013	0.0481	-0.029	0.55
Renal function (Creatinine)	0.094	0.28	-0.043	<0.0001	0.015	0.26
Liver function (Albumin)	-0.094	0.38	-0.007	0.49	0.033	0.14
Obesity 0=absent[C] 1= present	0.18	0.07	0.009	0.02	-0.07	0.26
Time on study drug treatment (in months)	0	0.45	0.004	<0.0001	-0.006	0.25
Concurrent drug that increases effectiveness	0.098	0.36	0.024	0.05	-0.023	0.45
Concurrent drug that decreases effectiveness	0.08	0.53	-0.007	0.14	0.05	0.39

A. There were insufficient data for convergence within GEE analysis when applied to windows of frequent testing.

B. Linear regression within a GEE framework was used to estimate regression coefficient (β) and p-value for each independent variable

C. Reference group for analyses.

Table 4.2.2.3 Evaluation of Potential Confounders: Estimated Regression Coefficients for the Compliance and Laboratory Outcome Relationship with the Addition of Covariates

Potential Confounding Variables Added to the Model with Compliance	Disease Conditions			
	Hypothyroidism	Diabetes	Atrial Fibrillation Compliance Coefficient	
	Compliance Coefficient[A]	Compliance Coefficient	Standard Testing[B]	Frequent Testing[B]
None (Compliance alone)	-0.82	-0.05	0.03	-0.11
Dose	-0.47	-0.06	0.02	-0.12
Dose + treatment time	-0.47	-0.06	0.02	-0.12
Dose + treatment time + demographics[C]	-0.45	-0.06	0.02	-0.11
Dose + treatment time + demographics + metabolic[D]	-0.44	-0.06	0.02	-0.13
Dose + treatment time + demographics + metabolic[D] + concomitant medications	-0.44	-0.06	0.02	-0.13

A. Regression coefficient for the association between compliance and laboratory outcome of laboratory test value.

B. In the 3547 windows, 2952 (83.2%) had standard, and 595 (16.6%) had frequent INR testing.

C. Demographic variables: age and gender

D. Variables that affected the metabolism and elimination of the study drug include renal function, liver function and obesity.

4.2.4. Linearity of the Association of Compliance and Outcome

A final step in evaluating the appropriateness of a model was to confirm whether the relationship between compliance and outcome was linear. Linearity was tested by including and excluding a first order polynomial variable, compliance-squared, in a full model with all independent variables. The significance of the squared term for compliance in each population in multivariate analysis was assessed. The first order polynomial of compliance was significant only in the diabetic patients. The estimated regression coefficients were used to plot the relationship between refill

compliance and $HgbA_{1c}$ using values within the range observed for refill compliance. The slope of the relationship was flat at the lower end of the compliance range, increasing slightly upward as compliance approached 100%. The inclusion and exclusion of the polynominal term did not change the estimated partial correlation of log $HgbA_{1c}$ and compliance; therefore further model analyses did not include the compliance-squared term.

4.2.5. Evaluation of the Association of Refill Compliance and Laboratory Outcome

To quantify the strength of association between compliance and laboratory outcomes, correlation coefficients (r^2) were calculated for patient characteristics, treatment characteristics and compliance in a sequential fashion (Table 4.2.5.1). In the atrial fibrillation population, the analyses were restricted to periods of standard laboratory testing frequency because of the paradoxical effects observed in periods of frequent testing (see Section 4.2.1.3). The base model included only patient characteristics (age, gender, renal and hepatic function, obesity and concurrent medications). These variables explained less than 1% of the variance of the predicted log TSH in hypothyroid patients (r^2=0.008) and log INR for atrial fibrillation patients (r^2=0.009). However, in diabetes, these variables accounted for 3% the variance in log $HgbA_{1c}$ (r^2=0.031). With the addition of compliance to the base model, there was little change in the proportion of unexplained variance for the diabetic (r^2=0.034) or atrial fibrillation patients (r^2=0.01). However, compliance explained an additional 5% of the variance of the hypothyroid patients (r^2=0.064).

With the inclusion of all variables and treatment effect modifiers in the models used to predict laboratory outcomes in each disease condition there was an overall correlation of r^2=0.10 (r=0.32) in the hypothyroid group, r^2=0.08 (r= 0.30) in the

diabetic group, and r^2= 0.012 (r=0.11) in the atrial fibrillation group. The addition of dose, time of treatment and appropriate interaction terms for each population accounted for 4% and 5% of the unexplained variance in the hypothyroid and diabetic patients, respectively, and <1% in the atrial fibrillation group.

Partial correlations were calculated to measure the proportion of variance explained by compliance and its effect modifiers after adjustment for the effects of the other variables (age, gender, renal and hepatic function, concurrent drugs and obesity). The partial correlations were r=0.31 in hypothyroidism; r=0.24 in diabetes; and r=0.06 in atrial fibrillation.

Table 4.2.5.1 Multiple Correlations of Refill Compliance with Laboratory Outcomes

Independent predictors of physiologic outcome	Disease Conditions		
	Hypothyroidism	**Diabetes**	**Atrial Fibrillation (Standard testing)**
	Overall Correlations		
Base model: Age, gender, renal & hepatic function, and concurrent drugs, obesity [A]	$r^2 = 0.008308$ $r = 0.091$	$r^2 = 0.031285$ $r = 0.177$	$r^2 = 0.009010$ $r = 0.094$
Base model and compliance	$r^2 = 0.063836$ $r = 0.253$	$r^2 = 0.034299$ $r = 0.185$	$r^2 = 0.010231$ $r = 0.101$
Base model, compliance, dose and treatment time effect modifiers	$r^2 = 0.101780$ $r = 0.319$	$r^2 = 0.088388$ $r = 0.297$	$r^2 = 0.012394$ $r = 0.111$
	Partial Correlations *Adjusted for age, gender, renal & hepatic function, concurrent drugs, and obesity*[A]		
Compliance	$r^2 = 0.055993$ $r = 0.236$	$r^2 = 0.002533$ $r = .050$	$r^2 = 0.001230$ $r = 0.035$
Compliance and its effect modifiers (and interactions)	$r^2 = 0.094250$[B] $r = .3067$	$r^2 = 0.058947$[C] $r = 0.243$	$r^2 = .003414$[D] $r = 0.058$

A. Known to be modifiers of the pharmacokinetics and effectiveness of study drugs

B. Interaction term: compliance*dose

C. Interaction terms: compliance*time and dose*time Partial correlation was $r^2 = 0.057116$, $r = 0.239$ when a more generous dose-approximation factor was used to determine dose additions.

D. Analysis was limited to windows of standard testing. When all windows and the interaction term compliance*test frequency were included, the partial correlation was $r^2 = 0.004547$ $r = .067$.

4.2.6 Comparison of Methods of Measuring Refill Compliance

To make a valid comparison with the study methodology, compliance was measured over the same follow-up period by the Fairchild and Steiner methods and compared with the same laboratory values for each patient. Steiner and colleagues measured compliance from the first prescription to the date of the last prescription following the last laboratory test. The Fairchild measurement method was restricted to data beginning after the three-month dose-adjustment period and ending on the date of the last laboratory test.

Because the study follow-up began after the dose-adjustment period, there was left-sided data censoring in the Steiner compliance measurement which contributed to the underestimation of compliance. Steiner's method yielded lower mean compliance in hypothyroid patients (68% vs 80%) and atrial fibrillation patients (46% vs 56%). When the study period for observing compliance was extended backward in time to the first prescription (see last column of Table 4.2.6.1) to eliminate left-sided censoring for the Steiner method, the mean compliance was higher than the Fairchild method in all populations and the correlations with laboratory tests were all diminished except for the hypothyroid patients. The hypothyroid patients had an unexpected higher correlation ($r = -0.19$) by this method, possibly due to a greater reduction in measurement error for compliance assessment when left-sided censoring was corrected. Both Steiner methods showed weaker associations between compliance and laboratory outcome than the Fairchild method in all populations.

Table 4.2.6.1 Comparison of Methods of Measuring Refill Compliance

Observation Period	Fairchild Method	Steiner Method	
Start	Day 1 of first time window	Day 1 of first time window	First prescription
Stop	Last day of last time window	Date of next prescription after last time window	Date of next prescription after last time window
Compliance	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
Hypothyroid patients	0.80 (0.34)	0.68 (0.48)	0.90 (0.26)
Diabetic patients	0.76 (0.36)	0.77 (0.49)	0.88 (0.37)
Atrial fibrillation patients[A]	0.57 (0.41)	0.46 (0.30)	0.61 (0.28)
Range of compliance			
Hypothyroid patients	0-1	0.02- 5.31	0.02- 2.31
Diabetic patients	0-1	0.06- 3.10	0.07- 2.84
Atrial fibrillation patients[A]	0-1	0.01- 1.32	0.01- 1.49
Correlations	R =	R =	R =
Hypothyroid patients	-0.31	-0.003[B]	-0.19[B]
Diabetic patients	-0.24	-0.12[B]	-0.04[B]
Atrial fibrillation patients[A]	0.06	0.07[B]	0.01[B]

A. Restricted to windows of standard laboratory testing

B. Steiner correlations of laboratory outcome and compliance were calculated with Pearson's product moment test.

One difference in the methodologies was the approach of assessing the compliance-outcome relationship. The Steiner method assessed the relationship by correlating mean values of compliance and laboratory outcome of each patient while the Fairchild method utilized a daily log of available medication laboratory outcomes to assess and correlate multiple measures of compliance and outcome for each patient within multiple discrete windows of observation. The Steiner method reduced intra-patient variability in measurement through averaging, whereas this temporal variability in compliance and outcome relationship is included in the analysis in the current study.

Another difference between the two methods is the range of compliance. Compliance ranged between zero and one with the study method. The daily log allowed measurement at any time period and thus captured times when compliance was zero. Compliance, as measured by the Steiner method, was always greater than zero since the measurement always included the drug supply from the first prescription filled in the numerator. Furthermore, Steiner's method assumes that all medication prescribed is consumed sequentially within the observation period. It does not allow for possible discontinuation of one dose, or for replacement with another, nor that two prescriptions were intended to be taken together. Consequently, with Steiner's method compliance levels can be greater than 1.0 (100%). In contrast, compliance never exceeds 1.0 by the Fairchild method because it was assumed that dosing changes modify the duration of available drug supply. Thus, extra days of supply of a drug were reflected in dose changes rather than extended duration of use.

In spite of these differences, the two methods of measuring refill compliance were correlated. The Pearson's product moment correlation between mean compliance values for both methods of measuring refill compliance was estimated. In the Fairchild method, mean of multiple measurements of compliance for each patient was used in order to have a single compliance value for each patient for the Fairchild method. The correlations between the two measurements of compliance were r=0.68 for hypothyroid patients, r=0.64 for diabetic patients and r=0.72 for atrial fibrillation patients. The correlations were indicative of moderate association between the two methods of measuring refill compliance.

CHAPTER 5 CONCLUSIONS

The primary objective of this study were to evaluate the validity of prescription refill as a measurement of compliance by assessing the association between refill compliance and outcome measures of disease control. The secondary objective was to validate a new refill compliance measurement methodology that adapts the duration of therapy in the case of early refills or changes in dose, and to compare this approach with methods used by previous investigators and to compare two methods of measuring refill compliance in a variety of diseases and patient groups. Previous refill compliance validation studies were limited in scope to predominately male populations with cardiovascular disease.[10;11] To broaden the scope of refill compliance validation, compliance was measured using prescription refills in three disease conditions: primary hypothyroidism, type 2 diabetes, and atrial fibrillation.

Drawing from a careful review of the strengths and weakness of previous studies, this investigation measured extraneous variables (e.g. renal function, dose) that affect the metabolism and effectiveness of the drug. The measurement of dose was considered to be important in this study for two reasons. First, it was considered to be a potential modifier or confounder of the association between compliance and laboratory outcomes. Dose was found to modify the effect of compliance on a physiologic outcome in a previous validation study of refill compliance.[10] Dose was also considered to be a potential confounder since both dose and compliance are associated with therapeutic effects of drug therapy. The benefits of any treatment diminish in proportion with the degree of noncompliance and the pharmacologic effect of the drug are frequently attenuated if the minimum therapeutic dose is not reached,.[109] Second, an adjustment in dose may indicate that the previously prescribed dose was discontinued and the supply of medication from that prescription was not consumed. Alterations in dose affect the accuracy of the

calculation of duration of drug supply of over-lapping prescriptions available for consumption.

In chronic illnesses, after physicians titrate the dose of medication to achieve optimal disease control, changes in measures of disease control are likely to reflect changes in compliance. Therefore, the validity of refill compliance was assessed by examining the relationship between compliance and laboratory outcomes while controlling for extraneous factors that might influence the relationship, three months after the start of treatment. The limitation of this approach was that it excluded patients with no laboratory follow-up and early problems with compliance. The likely consequence of was that the association between compliance and laboratory outcomes may have been underestimated.

5.1 Interpretation of Study Findings Regarding Construct Validity

5.1.1 Hypothyroid Patients

Primary hypothyroidism is an endocrine disorder occurring in women four times more frequently than in men.[106] Although it can occur in any age group, the disease is more frequently manifested in the fourth and fifth decades of life. The hypothyroid study population was 80% female with a mean age of 49 years and therefore similar to the target population.

In hypothyroidism, the thyroid gland does not produce sufficient thyroid hormone, which causes the pituitary gland to hypersecrete thyroid stimulating hormone (TSH). Treatment with synthetic thyroid hormone (levothyroxine) ameliorates the deficiency and reduces TSH levels.[80] Therefore, it was hypothesized that in the hypothyroid patients higher levels of compliance would be associated with lower levels of TSH.

The expected negative relationship of lower TSH values with higher levels of compliance was found in the study. Statistically significant negative correlations were found between compliance and TSH when evaluated with Pearson correlations ($r = -23$, $p < 0.0001$) and multivariate analysis (regression coefficient = -0.69, $p < 0.0001$, Appendix 5). The partial correlation between refill compliance and TSH was r=0.31 (95% CI: 0.25 - 0.36). Similar correlations have been reported in other studies of levothyroxine and laboratory outcomes. In a bio-equivalence study of four levothyroxine products (synthetic thyroxine), the association between dose of levothyroxine and TSH levels was r= -0.39 in hypothyroid patients.[110] The maximum potential of levothyroxine to affect changes in TSH (r= -0.39) in hypothyroid patients places an upper limit on the potential strength of the association between levothyroxine compliance and TSH levels. Thus, the study results indicate that refill compliance may be a valid measure of compliance in patients with primary hypothyroidism.

The association between compliance and TSH was modified by the dose of levothyroxine; it was stronger at higher doses levels, as hypothesized. Dose-compliance interaction in this study replicated the findings of Inui and colleagues who also reported that the interaction between dose and compliance was a significant predicator of therapeutic effect.[10]

5.1.2 Diabetic Patients

Type 2 diabetes is a progressive heterogeneous metabolic disorder characterized by a relative deficiency in insulin secretion, resistance to the action of insulin in muscle and other peripheral tissues, and increased rates of hepatic glucose production.[84] It is the most prevalent form of diabetes. The incidence of diabetes was reported to be increased from 2% in the fourth decade to 10-15% in the sixth

decade.[111] Among patients in this study with diabetes 42-44% are male and 56-58% are female. In this study, diabetic patients had a nearly equal representation of males and females with a mean age of 56.8, years and thus were demographically similar to the target population.

The primary goal of treatment in patients with type 2 diabetes is prevention of chronic complications through glycemic control.[105] Initial treatment includes diet and exercise with the goal of maintaining near-normal weight and body fat. When diet and exercise alone fail, the next step is the administration of sulfonylurea or metformin drugs to increase the pancreatic insulin response to blood glucose or reduce insulin resistance and reduce $HgbA_{1c}$.[84] Therefore it was hypothesized that higher levels of compliance would be associated with lower levels of $HgbA_{1c}$ in the diabetic patients receiving hypoglycemic therapy. As predicted, statistically significant negative correlations were found between the compliance and $HgbA_{1c}$ when evaluated with Pearson correlations ($r = -0.08$, $p < 0.0001$) and multivariate analysis (regression coefficient = -0.066, $p < 0.0001$, Appendix 5). The partial correlation between refill compliance and laboratory outcome for diabetic patients was r=0.24 (95% CI: 0.20 -0.27). A comparison with correlation studies of hypoglycemic drug doses and levels of $HgbA_{1c}$ was not feasible because most oral hypoglycemic drugs have a weak dose-response curve. Thus, the biological maximum potential correlation between hypoglycemic medication and $HgbA_{1c}$ has not been established. The partial correlation was not as strong as seen in the hypothyroid population, but was within the range of reported in previous construct validation studies discussed in Chapter 2 (range r=0.15 to r=0.63). The study results provide evidence to support the hypothesis that refill compliance may be a valid measure of compliance in patients with type 2 diabetes.

The association between compliance and outcome in diabetic patients was modified by time of treatment, but in the opposite direction as hypothesized. It was

hypothesized that the relationship between compliance and $HgbA_{1c}$ would diminish over time because diabetes requires more intensive therapy to maintain low levels of $HgbA_{1c}$ as the disease progresses. However, the study results showed that with longer duration of therapy, the association between compliance and $HgbA_{1c}$ was stronger. New diabetics often have a "honey moon" treatment period after starting drug therapy during which diabetes is easily controlled.[112] Compliance may not be an important factor in glycemic control in the first year of treatment. Compliance appeared to be a more important factor in disease control in the later stages of the disease. Improved compliance with all aspects of managing diabetes (i.e. diet and exercise) and more aggressive treatment as the disease progresses over time could explain the effect modification of time on the association of compliance and $HgbA_{1c}$. In addition, patients who were followed for a longer period of time could be systematically different from those with shorter follow-up on some unmeasured attribute that influences compliance and glycemic control.

5.1.3 Atrial Fibrillation Patients

In the Framingham study, the incidence of atrial fibrillation was observed to increase with age, with a male predominance.[111] The chance of developing atrial fibrillation over two decades was 2%.[111] Patients in this study population were predominately elderly (mean age 69.3) and 57% male and thus similar to the target population in demographic composition.

Atrial fibrillation is the most common abnormal rhythm of the heart.[80] Persistent atrial fibrillation occurs in patients with cardiovascular disease, most commonly with mitral valve disease, hypertension, chronic lung disease and a variety of miscellaneous cardiac abnormalities, although isolated atrial fibrillation can occur in elderly patients without underlying cardiac disease.[80] The primary morbidity

associated with atrial fibrillation (stroke) is prevented by anticoagulant therapy with warfarin.[24]

The treatment goal of warfarin therapy is to increase INR values to the range of 1.5-2.5%.[83 113] Therefore it was hypothesized that higher levels of compliance would be associated with higher levels of INR in the atrial fibrillation patients. The study results supported this hypothesis. A weak, but positive correlation was found between the compliance and INR when evaluated with Pearson correlations (i.e. r= 0.04). However, the hypothesized modification of the compliance-outcome relationship by dose was not confirmed. The interaction between dose and compliance was not a significant predictor of INR within the full regression model. However, the association between compliance and INR was modified by the frequency of laboratory monitoring as predicted. Among patients with standard testing, a weak positive, but not significant relationship was evident between compliance and INR in the expected direction (higher INR levels in patients with higher compliance levels). Although for patients with frequent testing, the opposite occurred; increased compliance was associated with decreased INR levels. Frequent laboratory testing was associated with poor treatment control. The negative association may reflect periods of inadequate disease control. The patients may have experienced adverse effects from warfarin leading to bleeding complications; consumed excessive dietary vitamin K reducing the effectiveness of warfarin; or had other unmeasured factors that contributed to inadequate disease control.

The partial correlation between refill compliance and laboratory outcome was r=0.06 (95% CI: -0.07 to 0.016) in periods of standard INR testing. Like levothyroxine, the dose of warfarin had a stronger correlation with plasma levels of warfarin (r=0.51)[113] than with the laboratory measure of drug effect, INR (r=0.20).[83] Biologically, the partial correlation between warfarin compliance and INR was

expected to be approximately r=0.20. However, the partial correlation between compliance and INR, controlling for other variables was not statistically different from zero (r=0.06). This finding suggested that refill compliance may not be a valid measurement of compliance in atrial fibrillation treated with warfarin.

Warfarin is a drug with a narrow therapeutic range. There is a small difference between warfarin serum levels that produce the desired therapeutic effect and those that produce serious side effects (bleeding).[79;80] When side effects occur, warfarin therapy is suspended for a time, or the dose is reduced. Under these circumstances, the supply of warfarin lasts longer than would be predicted by examining pharmacy claims data. Physician prescribed or patient initiated reductions in therapy cannot be detected in prescription databases. Consequently, measurement error of both dose and duration of each prescription was highly probable in this study population.

Another source of measurement error in this population may have stemmed from the frequent periods of hospitalization. Drug supplies given to patients at the time of hospital discharge could not have been determined from the information available. Atrial fibrillation patients in this study and the target population have frequent hospitalizations as a consequence of their comorbidities. The potential for significant measurement error affirms the premise that prescription refill data is unsuitable for measurement of compliance in patients taking warfarin, regardless of the method employed to compute compliance. Furthermore, until automated prescription claims databases in the United States also capture medication dispensed to the patient upon discharge from hospital, refill compliance is an inadequate compliance measurement tool in patients who are hospitalized frequently.

5.1.4 Summary of Evidence for Validity

This study assessed the construct validity of prescription refill as a measurement of compliance in three patient populations. The resulting adjusted partial correlations between refill compliance and laboratory outcome were r=0.31 (95% CI: 0.25 - 0.36) in hypothyroid patients, r=0.24 (95% CI: 0.20 - 0.27) in diabetic patients, and r=0.06 (95% CI: -0.07 - 0.16) in atrial fibrillation patients. Refill compliance was found to be a valid measure of compliance in hypothyroid patients taking levothyroxine and diabetic patients taking oral hypoglycemic medications, but not in atrial fibrillation patients taking warfarin. Construct validation studies which correlated refill compliance with blood levels of drugs yielded similar results. Steiner reported the correlation of refill compliance with serum phenytoin to be r= -0.40 and with digoxin to be r= 0.20.[78;114]

Validation of compliance measurement with electronic monitoring had not been reported in the literature at the time of this study. The methodology is widely accepted as valid because it is viewed as free from measurement error. However, Crammer correlated coefficients of variation in serum concentrations of 23 anticonvulsant drugs and compliance measured by electronic monitoring in an attempt to understand fluctuations in plasma concentrations and found no association with compliance measured with electronic monitors(r=0.07) or with pill counts (r=0.26) and drug serum levels.[35]

Pill counts at clinic visits have not shown a strong correlation (r=0.09) with compliance as measured by microelectronic monitoring systems[72] or by serum assay (r=0.16).[73] However, when obtained during home visits, without forewarning the patients, correlations with clinical outcomes were higher (r=0.30) thus illustrating the impact of observation bias on compliance.[55] Only moderate degrees

of correlation have been found between compliance measurements and clinical outcomes (e.g. diastolic blood pressure)[55] even with most accurate measures (unannounced pill counts on home visits). The modest correlations likely represent an upper biological threshold on the capacity of a respective drug to modify clinical outcomes, as well as the inability to obtain exact measures on drug absorption and distribution in relationship to clinical events.

The burden of evidence in testing construct validity does not arise from a single powerful study, but from a series of studies.[115] Construct validation studies by Steiner and Inui reported correlations of health outcomes and refill compliance of .014 to 0.63. Choo, et al. reported the predictive validity of refill compliance to be r=0.32. Prescription refill compliance during the 12 months prior to study was correlated with compliance measured by electronic monitoring devices for 3-months in hypertension patients.[71] Collectively, the evidence from this study and others demonstrates that refill compliance may be a valid instrument for measuring compliance in patients with disease conditions which require chronic therapy like diabetes and hypothyroidism, but not in disease conditions like atrial fibrillation which are treated with drugs that have a narrow therapeutic index, like warfarin. It is also unsuitable for disease conditions which require acute therapy and patient populations that are hospitalized frequently. The latter condition may be irrelevant in the future if hospital drug dispensation records are integrated with outpatient pharmacy claims records.

5.2 Comparison of Methods of Measuring Refill Compliance

A secondary objective of this study was to validate a new refill compliance measurement methodology that adapts the duration of therapy in the case of early refills or changes in dose, and to compare this approach with methods used by

Steiner and previous investigators. The Fairchild method of measuring refill compliance differed from that of Steiner in two ways. First, the Steiner method assumed that all drug dispensed was consumed and in a sequential fashion. The study method looked for evidence of dose titration, signaling the previous prescription was discontinued or two prescriptions were meant to be taken concurrently, and adjusted the duration of each prescription accordingly. Second, the algorithm created for this study enabled measurement of compliance at the same time point and any period of time through the construction of a daily log of available drug, while the Steiner method was limited to time points between two or more prescriptions. Steiner advocated ending the denominator time on the date of the last prescription after the last outcome measurement. The temporal association between outcome and compliance can be distorted by using dose of subsequent prescription as a mechanism of adjudicating the supply days of overlapping prescriptions. Temporal ambiguity in the compliance-outcome relationship assessment was avoided in the study methodology.

Comparing the methodologies for measuring refill compliance yielded interesting results. The correlations between compliance and outcome were weaker with the Steiner methodology which did not adjust for other factors that influence the association. The most striking difference in the two methods of measuring compliance is that the compliance scales are different. The Fairchild method compliance cannot exceed 1.0 (100%) because the numerator never exceeded the denominator, while Steiner's method has no upper limit. What appeared to be over-compliance by the Steiner method was reflected in dose adjustment by the Fairchild study method because the algorithm adjusted the duration of drug supply days for changes in dose and early refills. Over-compliance on the part of the patient can only be detected an excess drug dose and therefore the algorithm would need to be modified to study drugs in which over-compliance is an important issue.

Although, the two methods were correlated (r=0.68 for hypothyroid patients, r=0.64 for diabetic patients and r=0.72 for atrial fibrillation patients) the Steiner method may have underestimated the association of compliance and laboratory outcome, due to measurement error.

5.3 Study Strengths and Limitations

5.3.1 Strengths

This study had many strengths and limitations. Most importantly, the study expanded the scope of refill validation work to a variety of disease conditions. This facilitated a broader understanding of the nuances and limitations of measuring refill compliance in a stable disease (hypothyroidism), progressive disease (diabetes) and disease influenced by multiple comorbid states (atrial fibrillation).

Several aspects of the study methodology were designed to minimize refill compliance measurement error and establish the appropriate temporal relationship of compliance with measures of disease control. The compliance measurement algorithm utilized in this study may have reduced measurement error by adjusting the duration of drug supply for dose changes and early prescription refills. It also facilitated the exploration of the influence of dose and time on compliance. Utilization of a daily drug log allowed the measurement of compliance and laboratory at the same point in time and thereby avoided temporality issues in the assessment of the compliance-outcome association encountered by Steiner et al. Restriction of the study period to after the dose-adjustment period increased the probability that changes in the outcome reflect changes in compliance rather than changes in the disease or management of drug treatment. Finally, the populations in this study were treatment inception cohorts which enabled a more accurate

accounting of drug supply available to patients, thus eliminating left-sided censoring, and permitted investigation of representative populations of patients with newly initiated treatment.

The study was strengthened by measurement of many factors known to modify the effectiveness of each treatment and it controlled for these factors in the analyses. Laboratory measurements of the effectiveness of drug therapy are often influenced by factors unrelated to patient compliance behavior (e.g. physical characteristics of the patient).[116] This study measured factors known to affect the metabolism of the drug therapy.

Multiple measurements of refill compliance and laboratory outcomes over the course of the study provided more substantial estimates of the refill compliance-laboratory outcome association and facilitated exploration of effect of treatment time on the relationship between refill compliance and laboratory outcome. Linear regression, in a generalized estimating equation framework, addressed the within patient correlation of outcomes and generated robust calculations of the regression coefficients and their standard errors. Calculation of overall and partial correlations were simplistic, but adequate for assessment of construct validity in this study. A more sophisticated method of determining correlations and partial correlations with GEE may be available in the future.

5.3.2 Limitations

5.3.2.1 *Selection Bias*

Selection bias is inherent in refill compliance for the measurement excludes primary noncompliant patients, those who do not fill the initial prescription prescribed by

their doctor. The study design also excluded noncompliant patients who discontinued therapy during the 3-month dose adjustment period. Similarly, noncompliant patients were more likely to drop-out of the study, failing to keep physician appointments and filling prescriptions through out the follow-up period. Additionally, limiting the hypothyroid population to primary hypothyroid patients may have introduced selection bias by excluding potentially noncompliant patients. Of the secondary hypothyroid patients excluded from the study, 5% filled only one prescription for levothyroxine. Selection bias introduced by exclusion of noncompliant patients would bias the estimate of the compliance-laboratory association toward the null.

5.3.2.2 *Information Bias*

Information bias is common to claims databases utilized for epidemiologic research. The HMO database used in this study may have been incomplete. Patients could have obtained medication or laboratory tests through a laboratory or pharmacy outside of the HMO systems but they were not reimbursed for these services. Information bias from missing data was probably small, but may have led to an underestimation of the association between compliance-laboratory outcome. Information bias could have occurred in patients with frequent hospitalizations. Drug dispensed by hospital pharmacies were not counted and may have led to an underestimation of compliance. Excluding the time of hospitalization and 30 days after hospitalization may have attenuated the effect of unmeasured drug supply following hospitalization. Another approach would have been to count the days of hospitalization as fully compliant and included them in the analysis.[117]

Another source of potential measurement error was in the estimation of the intended duration of drug supply. The algorithm determined the duration of over-

lapping prescriptions based on the dose of each prescription. If there was no evidence of an early refill or a dose addition, the second prescription was presumed to represent a dose change. In other words, dose change was the default setting. If each case of dose change were incorrect, and the two overlapping prescriptions should have been dose additions, the duration of available drug supply would have been shorter. Compliance may have been underestimated. Dose changes occurred most frequently in diabetic patients (15% of all prescriptions). However, when the algorithm's dose approximation factor was relaxed in diabetic patients so that dose changes were re-assigned to be dose additions as much as feasible, the resulting estimate of compliance-outcome association was unchanged.

Information bias may have been present in the measurement of some of the covariates. Obesity was determined by an ICD-9 code for obesity, which is usually reserved for morbid obesity. Measures of height and weight would have enhanced the measurement of obesity. When renal and liver function tests were not available, it was assumed that the patients had normal function, which may have not been the case. The impact of underestimating these variables on the study results is unknown.

5.3.2.3 *Confounding*

Although the study design incorporated variables that could effect the association between refill compliance and laboratory outcomes, unknown and unmeasured confounding may have also biased the results of the study.

5.4 Future Refill Compliance Research

This study addressed problems noted in previous validation studies and expanded the scope of refill compliance to new populations and both genders. It also defined two limitations of refill compliance; it was not found to be the optimal method of measuring compliance in patients with frequent hospitalizations or drugs with small therapeutic indexes.

Future refill compliance validation research should expand into validation studies in other diseases, concurrent validation with other measures of compliance and predictive validation. There has been only one study which compared electronic compliance monitoring with refill compliance. Truly effective refill compliance measures will require the development of a method to simultaneously evaluate compliance with multiple drugs. Finally future compliance research should examine patterns of compliance over time and develop interventions for enhancing compliance in relationship to patient, drug and health professional characteristics.

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Appendix 1

Randomized Controlled Intervention Trials of Compliance Interventions

Appendix 1

Randomized Controlled Intervention Trials of Compliance Interventions

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Baily, et al. 1990	Adult Asthmatics 135 Usual care 132 Self-Management Program	Self-Management Program: counseling, written educational material, re-enforcement, and support group	2 Self report questionnaires Skills survey of inhaler use Clinician interview Study Duration 12 months	Percent reduction in emergency visits and hospitalization Percent adherent on each scale without an overall summary measure of adherence Percent patients with asthma symptoms on 4 scales	Selection Bias - 4 x higher drop-out rate in controls group. All subjects may have been recent users of emergency room or recently hospitalized thereby inflating the baseline utilization of health care services. Contamination Bias: control group benefitted from increased emphasis on education.	No difference in emergency visits or hospitalization rates. Both groups showed a decrease in health are utilization 4 measures of adherence demonstrated improved adherence in both groups and significantly greater improvement in the intervention group 2 of 4 asthma rating scales showed statistical difference in group scores

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Baird et al. 1984	Adults Hypertension 196 qd dosing 193 bid dosing	Once-daily vs Twice daily Metoprolol treatment 95 patients Home BP monitoring	Pill counts Spot-check urine drug levels Study Duration: 8 weeks	Percent of patients taking at least 80% of medication by pill count. Percent of patients taking at least 90% of medication by pill count. Office mean heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP)	Selection Bias: Self-selection to participate in a study to measure compliance - overall compliance was higher than expected. Randomization without concealment made it possible for investigator to determine the treatment assign of individual patients Confounding: Home monitoring was not randomly assigned. Measurement Bias: Urinary drug level measurement was neither sensitive nor specific enough to distinguish between two groups of patients who demonstrate a high level of compliance unless it is applied at more frequent intervals, according to authors	Percentage of patients taking at least 80 and 90% of drug was significantly higher by pill count in the once-daily treatment group. The distribution of urinary concentrations of metoprolol did not differ significantly between treatment groups. No drug treatment group nor difference in disease outcomes (HR, SBP, or DBP) No difference in disease outcomes or compliance in patients doing home BP monitoring vs controls

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Becker et al. 1986	Adult Hypertensive patients 85 Regular packaging 86 Special packaging	Special unit dose reminder packaging of medication	Pill counts (Compliant = 80% or more) Self-report (any degree of non-compliance with any antihypertensive drug) Study Duration 3 months	- DBP Self-report of compliance - Pill count percent of recommended dose - Self-report plus DBP Hybrid rule: any patient admitting noncompliance or who had a DBP >100 assumed to be non-compliant. Patients with DBP <100 and claimed to be compliant were assumed to be so	Selection Bias: Compliant patients participate in a compliance study. 48% of all patients reported perfect compliance at baseline. Baseline self-report of compliance and BP control was better in the experimental group. Randomization without concealment made it possible for investigator to determine the treatment assign of individual patients Contamination Bias: Treating physicians were aware that their patients were in a compliance study and that BP control was an endpoint. They were advised to adjust the antihypertensive medication as needed.	No significant group differences were detected for adherence or blood pressure. Both groups showed slightly improved compliance on all measures and diastolic blood pressure. Regression analysis of post-study DBP showed baseline DBP to be the most powerful predictor. The analysis did not include a compliance variable.

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Brown et al. 1997	31 Adult male patients with hyperlipidemia and coronary artery disease	Cross over study of regular QID niacin vs. daily controlled - release niacin in a 3-drug therapy regimen	Pill counts Study Duration 28 months	Percent of recommended dose for each drug Percent achieving target LDL	Selection Bias: Patients demonstrated a high level of compliance in a prior trial of familial atherosclerosis treatment (FATS trial).	Target LDL of $\geq$ 100 was achieved in 83% in the controlled-release niacin vs. 52% receiving regular niacin due to greater drug compliance with the former. Compliance with controlled-release niacin was 10% greater than regular niacin at 4 months and 13% greater at 8 months. Patients taking controlled-release ingested 12% more drug than those taking regular niacin.
Chaplin et al. 1999	Patients receiving anti-psychotic maintenance medication 28 patients in Intervention group 28 patients in ususal care group	Drug education session	Patient interview, Depot medication records Study Duration 6 months	Non-compliance = having missed more than two weeks of anti-psychotic medication Clinical relapse	Selection bias: All patients were very complaint Contamination Bias: control group benefitted from increased emphasis on education in the intervention group.	No difference in compliance after 6 months Both groups significantly gained in knowledge after 6 months, the mean change score was significantly high in the experimental group. No difference in clinical relapses after 6 months

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Colcher & Bass 1972	Children with Strept. Pharyngitis 100 in each treatment group	Education Group 1: IM penicillin Group 2: Oral penicillin Group 3 Oral penicillin plus educational counseling	Antimicrobial activity of urine specimen obtained on Day 9 Ability of urine to inhibit growth of *Sarcina lutea* Study Duration 6 weeks	Percent of compliant patients Percent of patients experiencing clinical relapse and/or treatment failure base on positive throat cultures.	Selection Bias: Randomization without concealment made it possible for investigator to determine the treatment assign of individual patients	Education had a positive effect on compliance. Compliance rates were significantly less in group 2. Relapse rates were significantly less in group 2. Relapse appears to be directly related to not taking penicillin orally for the full 10 days as prescribed
Cote et al. 1997	Adult asthmatics 54 patients Group C 45 patients Group P 50 patients Group S	Self-Manage Group C: no intervention Group P: Action plan based on peak flow monitoring Group S: Action plan based on symptoms	Weighing the used canisters Corticosteroid tab courses Study Duration 12 months	Poor compliance was taking less than 60% of the prescribed dose over one month. Change in hospitalizations emergency room visits Days lost from work or school	Selection bias: 21% dropout rate - non-compliance with the study protocol was the most common reason. Surveillance Bias: All groups had marked improvement in morbidity when comparing the one-year-before with the one-year-after morbidity Recall Bias; measurement of morbidity was diary, collected only every 3 months.	Poor compliance was significantly more common in the control groups at the beginning of the study but after 3 months compliance was similar in all groups at each time point. No group differences in morbidity (hospitalizations, ER visits, oral corticosteriod courses or days lost from work or school)

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Friedman et al. 1996	Elderly Hypertensive 145 standard care 156 intervention	Interactive computer-based telephone monitoring and counseling vs usual care	Pill count during home visits Study Duration 6 months	Adherence $\geq$ 80% of prescribed medication Change in adherence in regression by baseline categorization of adherent-nonadherent Diastolic blood pressure (DBP and SBP)	Selection Bias : 30% refused to participate, 15% in the experimental group and 8% in the control group dropped out Baseline mean adherence was 93% in experimental and 94%in control groups created a ceiling effect	Unadjusted analysis showed little change over 6-months in adherence and no group difference. After adjustment, mean adherence improved 17.7% in the treatment group and 11.7% in the control group (p=.03) Significant group differences in mean DBP were evident with adjustment for age, sex, baseline BP and baseline adherence Mean adjusted SBP did not change except in the subgroup of patients who were non-adherent. Significant group differences were only evidenced in patents who were non-adherent at baseline.

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Haynes et al. 1976	Male hypertensive patients who had inadequate BP control or poor compliance 18 Usual care patients 20 Intervention patients	Adherence counseling, self-monitoring of BP, modest monetary reward for improved BP vs usual care	Pill count during home visits Study Duration 6 months	Percent change in mean adherence Change in DBP	Contamination: Physicians in both groups strove to improve their BP because they were in a study of BP control. Confounding: Physicians were aware of treatment assignment for the experimental group and more likely to have increased medication dose in the experimental group Power: Small sample size may have lead to a Type II error, failing to reject the null hypothesis.	Significant difference in mean compliance 21.3% vs -1.5% in experimental vs control groups Significant decrease in diastolic blood pressure -5.4 vs -1.9 mmHg in both experimental and control groups but the between group differences were not significant
Howland et al. 1990	Patients treated with erythromycin for a variety of infectious diseases 48 controls 50 intervention patients	Drug side effect information provided to the experimental group Control group were only told to take the medication with meals.	Self-report Study Duration 10 days	Mean number of pills taken in 10 days. Mean number of pills taken daily. Percent of patients completing 10 days of therapy. No of patients experiencing side effects	Recall bias. Patients were interviewed 5 to 21 days after treatment to assess compliance and side effects. Confounding of side effects leading to early discontinuation of medication was not reported.	No group differences in any parameter of compliance. 63% failed to take at least one pill. No difference in groups. 35% stopped therapy prematurely. No differences in groups. 36% had side effects ; no group differences in the occurrence of side effects

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Johnson et al. 1978	Adult hypertensive patients 34 patients Intervention 1 33 patients Intervention 2 35 patients Intervention 3 34 patients Usual care	Self-recording of BP and home visits in a 2 x 2 factorial design: 1) Self-BP & home visits 2) Self-BP only 3) Home visits only 4) Neither intervention	Interview Home pill counts Study Duration 6 months	Mean compliance (percent of prescribed medication taken) Change in compliance Change in DBP	Selection Bias: Randomization without concealment made it possible for investigator to determine the treatment assign of individual patients	No significant difference between groups. Greater changes in mean compliance were noted in the subjects with initial compliance of less than 80% (not significant) Significant improvement in DBP noted in both self-recording and home visit groups who reported difficulty remembering to take their medications at the outset of the study.
Kemp et al. 1996	Patients with acute psychosis 22 control patients 25 intervention patients	4-6 sessions of compliance counseling or non-specific counseling (usual care)	Composite compliance based upon a 7 point scale Study Duration 6 months	Mean compliance OR for dichotomous categories: Good compliance , score of $\geq$ 5. Disease severity measures: Brief Psychiatric Rating Scale (BPRS), and Global Assessment of Function (GAF)	Selection bias: 31% refused to participate or were discharged rapidly without an opportunity to participate. The intervention group was significantly more symptomatic than the control group Measurement Bias: Baseline intermediate compliance measures were not made by an unblinded observer; final assessments were made by a blinded researcher.	Insight and compliance improved by 10% in controls and 40% in the intervention group ($p<0.01$) immediately after the intervention. After 6 months the intervention group had 23% improvement and the control group worsened OR =6.3 for improvement in compliance with the intervention No group difference noted in BPRS or GAF

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Kemp et al. 1998	Psychotic patients who were suffering a relapse 35 Control patients 39 Intervention patients	4-6 sessions of compliance counseling or non-specific counseling (usual care) Followed by 3 6, and 12 months	Composite compliance based upon a 7 point scale Study Duration 18 months	Mean compliance Odds ratio for dichotomous categories: Good compliance , score of ≥ 5. Time to re-admission	Same as Kemp et al.,1996 Power: The study lacks statistical power to reject the null hypothesis, but the effect size of readmission suggests a potential impact of the intervention on time to re-admission	Repeated measures parameter estimate showed a significant advantage for the for compliance therapy, that was maintained a at constant level over all post-intervention assessments; a mean difference of 19% between the two groups. Survival analysis showed a clinically significant advantage of the intervention in time to readmission but not statistically significance
Logan et al. 1979	Adult hypertensive patients 225 usual care patients 232 intervention patients	Work-site care by nurse practitioners vs regular care	Self-report via questionnaire Home pill counts for only those who claimed to be compliant Study Duration 6 months	Percent of patients compliant (taking 80% or more of drug) confirmed by home pill count. Change in DBP	Selection Bias: 46% refused to participate. 10% dropped out. Confounding: 94.7% or the intervention group received medication compared with 62.7% of the control group. Contamination: Physicians treating the control group were aware of the purpose of the study and BP control was an outcome.	67.6% of the intervention group and 49.1% of the regular care group were compliant ($p < 0.005$) The intervention group were significantly more likely to reach BP goal. (50% vs 2.9%)

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Logan et al. 1981	Same as above	Same as above	none reported Study Duration 12 months	Cost/change in mm/Hg of DBP	Same as Logan et al. 1979	Mean reduction in DBP was 12.1mmHg in the intervention group and 6.5 mmHg Incremental cost effectiveness ratio of worksite care was less than regular care
Peterson et al. 1984	Teenage and adult epileptic patients 26 Usual care patients 27 Intervention patients	Patient counseling, special medication container, diary of medication intake and seizures, mailed reminders for prescription refills and clinic appointments vs ususal care.	Dose-adjusted plasma levels of anti-convulsant drug (Plasma level divided by prescribed daily dose) Prescription refill frequency Appointment keeping Study Duration 12 months	Change in dose-adjusted plasma level Refill non-compliance was a lapse of 7 days or more between expected dates of prescription renewal at least once in 6 months Appoint keeping non-compliance was one or more missed appointment in 6 months	Measurement Bias: Number of seizures was extracted from the medical records for the control group and from diaries in the intervention group Selection bias: Small sample size resulted in an imbalance of subjects receiving carbamazepine (5 control and 14 intervention patients) Confounding: Failed to control for the extra attention payed to the intervention group by health professionals was much greater (observational bias)	Significant more improvement in compliance and seizure control in the intervention group compared to the control group. Dose-adjusted plasma were significantly higher in patients in the intervention group principally due to shifting from sub-therapeutic to therapeutic plasma levels. Prescription refills show a significant shift in compliance in the intervention group. Appointment keeping showed no change in either group.

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Sackett et al. 1975	230 Untreated male hypertensive patients randomly assigned to two interventions work-site treatment usual care (116 vs 1115 patients) and randomly assigned to education program (115 in each group) Of those who received medication therapy: 25 Usual care patients 37 work-site care patients 28 programmed instruction patients 44 patients received both	Educational program about hypertension Treatment at work site 4 groups randomly assigned to none, one or both interventions	Pill 6 months counts Unscheduled urine test for presence of drug metabolites Potassium and uric acid levels in patients taking diuretics Study Duration 6 months	Compliance = pill counts of 80% or greater at month 6 At blood pressure goal - diastolic BP below 90 mm Hg	Residual confounding: Failed to measure confounders that influence adherence such as side effects, frequency of dosing. Anti-hypertensive drugs available at that time often caused impotence and bothersome urinary frequency that may have cause these steelworkers to stop therapy in order to function at work. Information bias: Physicians were more likely to initiate antihypertensive therapy in the group receiving education (who were presumably more conversant about their disease). Industrial physicians were more likely to treat with medication, for follow-up was simpler.	No group significant differences in compliance No group significant differences in blood pressure control Urine metabolites and serum levels of potassium and uric acid results were not reported in this article.

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Strang et al. 1981	Recently discharged schizophrenic patients 15 usual care patients 17 intervention patients	Family therapy vs individual supportive therapy	Missed appointments Switching to injected depot medication because of poor compliance Plasma levels Composite assessment based on observer and self-report and plasma levels Variability in plasma level/prescribed dose ratio - coefficients of variation, Study Duration 6 months	Percent relapsing in each group	Power: Small sample size may have lead to a Type II error, failing to reject null the null hypothesis. The data suggested that reduction in relapse rates was mediated through enhanced compliance but their was insufficient power to confirm this. Potential Information bias: There was insufficient information on the methodology to know if intervention brought the patient in contact with health care providers more frequently than the control group.	Relapse rates were 6% in family therapy group and 53% in individual therapy group Significantly fewer patients receiving family therapy were non-compliant with appointments, by pill count. Significantly fewer patients in the family therapy group had to be switched to injectable medication. The coefficient of variation tended to show more stable plasma levels among the family therapy patients, but not significant. There was no difference in plasma levels of both groups.

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Xiong et al. 1994	Schizophrenic patients 29 Usual care patients 34 Intervention patients	Family counseling vs standard of care	Time for which the patient took over 50% of recommended dose as reported by family members Study Duration 18 months	Number of months in which patient was over 50% compliant Re-hospitalizations Clinical relapse	Selection bias (minimal) 18% refused to participate Only male participants Measurement biases: Blind was frequently broken as family members spontaneously reported treatment group, when in family counseling group; however evaluators were unaware of the purpose of the study. Clinical relapse without hospitalization was poorly measured Definition of compliance too lax, as it resulted in unrealistically high levels of compliance. A virtual all Chinese patients take less medication than prescribed Direct measurement of compliance by pill count would have been less bias than family member report.	At all three time points (6, 12, and 18-month) re-hospitalized rates were significantly lower and the durations of re-hospitalization were significantly shorter, in the experimental group than in the control group. The statistically significant at the 12 and 18 -month follow-ups and were not explained by differences in drug compliance alone. Compliance was only significantly better in the experimental group at the 12-month follow-up.

Author Year	Population	Intervention	Compliance Measure	Summary Measure	Limitations	Results
Zhang et al. 1994	First-admission male schizophrenic patients 41 Usual care patients 42 Intervention patients	Family counseling vs standard of care	Patient or family member report of compliance Patents taking at least 33% of drug at the time of index discharge for a least at least 6 days per week were classified as compliant Study Duration 18 months	Re-hospitalization Hospitalization-free period Overall functioning	Selection Bias: At baseline, one group had a higher rate of employment, signifying that they were more functional. Surveillance bias: Extra attention in one group may have enhanced compliance and lead to early detection and correction of problems that would have lead to hospitalization. Approximately 50% of the time contacts with the family were in the home because they failed to attend clinic Information Bias: Frequent contact by healthcare providers with the patient may have influenced the outcomes of hospitalization or function, as the healthcare provider may have intervened with problems which might have led to hospitalization.	Significantly lower rate of hospital readmission and the mean hospital-free period for those who were readmitted was significantly longer in the experimental group clinical status and overall level of functioning in patients who were not readmitted were significantly better in experimental subjects 43.6% of the control group and 20.5% of the intervention group were non-compliant ($p < .01$)

Appendix 2

Ethics Committee Approval

HENRY FORD HEALTH SYSTEMS HUMAN RIGHTS COMMITTEE TRANSMITTAL FORM
(PLEASE TYPE OR NEATLY PRINT IN BLACK INK)

I. General Information

1. Project Title	Validation Study of Prescription Refill Indices as Measures of Compliance in Chronic Illness				
2. Principal Investigator (Name/Degree/Title)			Christine Cole Johnson, Ph.D., MPH Assoc. Director, Research		
Department	JFCC	Division		Phone/Page	874-6672
3. Contact Person (Name/Degree/Title)			Christine Cole Johnson, Ph.D., MPH Assoc. Director, Research		
Department	JFCC	Division		Phone/Page	874-6672
4. Grant Title & Project Director (if different)					
5. Sponsor/Funding Source (name of agency, company, NIH institute or internal committee that will fund/sponsor the research			Internal funds/McGill University		
6. Date Submitted to Funding Agency			N/A		
7. Multicenter study?	☐ Yes	☒ No	8. Proposed Project Period		8/1/99 - 7/31/00

9. Performance Site(s):	Detroit	Fairlane	Lakeside	Troy	West Bloomfield	☒ Other (specify):
	☐	☐	☐	☐	☐	Database Review

10. Research to be conducted:	Inpatient	Inpatient/Outpatient	Outpatient	☒ Other (specify):
	☐	☐	☐	Database Review

II. SIGNATURES

11. The undersigned accepts responsibility for assuring that the protocol will be conducted in adherence to all applicable FDA and HHS regulations and institutional Policies relative to the protection of the rights and welfare of human subjects.	Signature of Principal Investigator	Date
	Christine Cole Johnson	7/9/99

12. As Division Head (Where there are no divisions, Chairman of the Dept.), the undersigned has reviewed and supports the scientific merit of the attached protocol and its submission to the Human Rights Committee. The principal investigator is qualified to conduct the study and the resources necessary to perform the study are available.

Print or type Name of Div Head/Dept Chair/Med Dir	Signature	Date
Raymond Demers, M.D., MPH		7/9/99

DO NOT WRITE BELOW THIS LINE

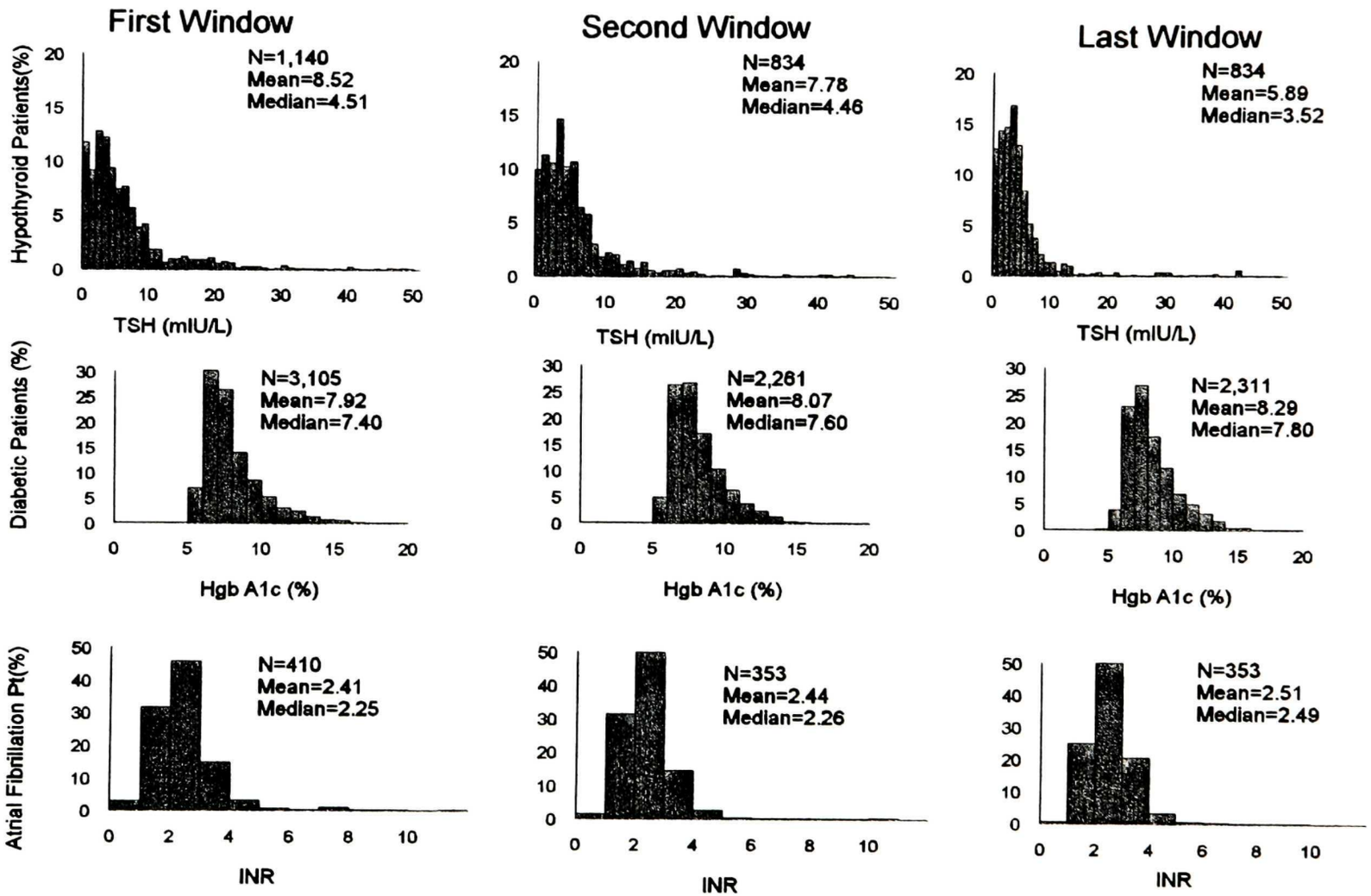
HRC APPROVAL STAMP	PROTOCOL APPROVAL (to be completed by Human Rights Committee)
Received by IRB JUL 13 1999 Approval Not Required RECEIVED JUL 9 1999	☐ Full Board Review ☐ Expedited Review ☑ Exempt Period of Approval 7-13-99 Exempt IRB Ref. #_____ Accession No._____

4/96 (f:\users\forms\hrc\newhrctf.wpd)

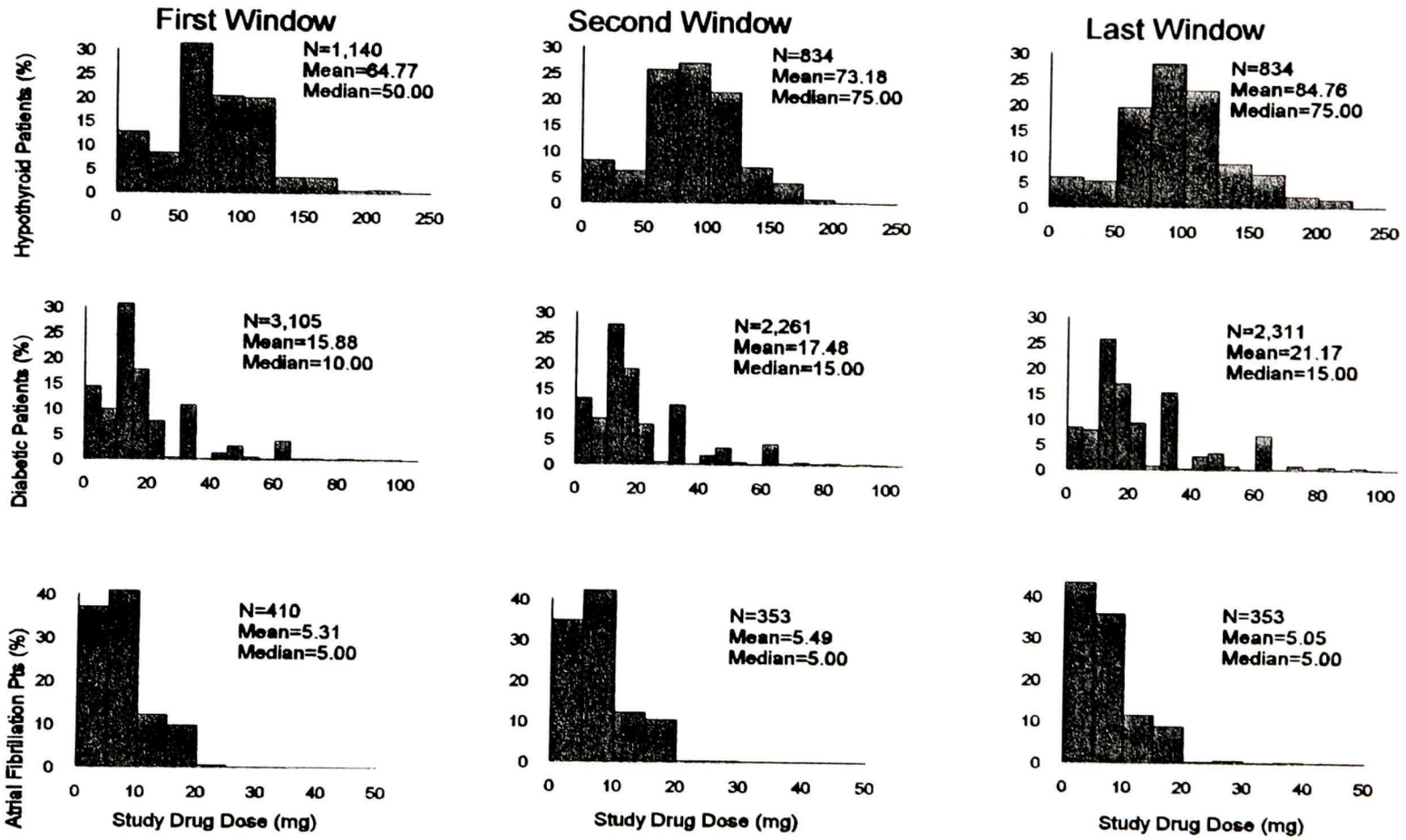
Appendix 3

Distribution Plots of Laboratory Tests, Drug Dose, and Compliance

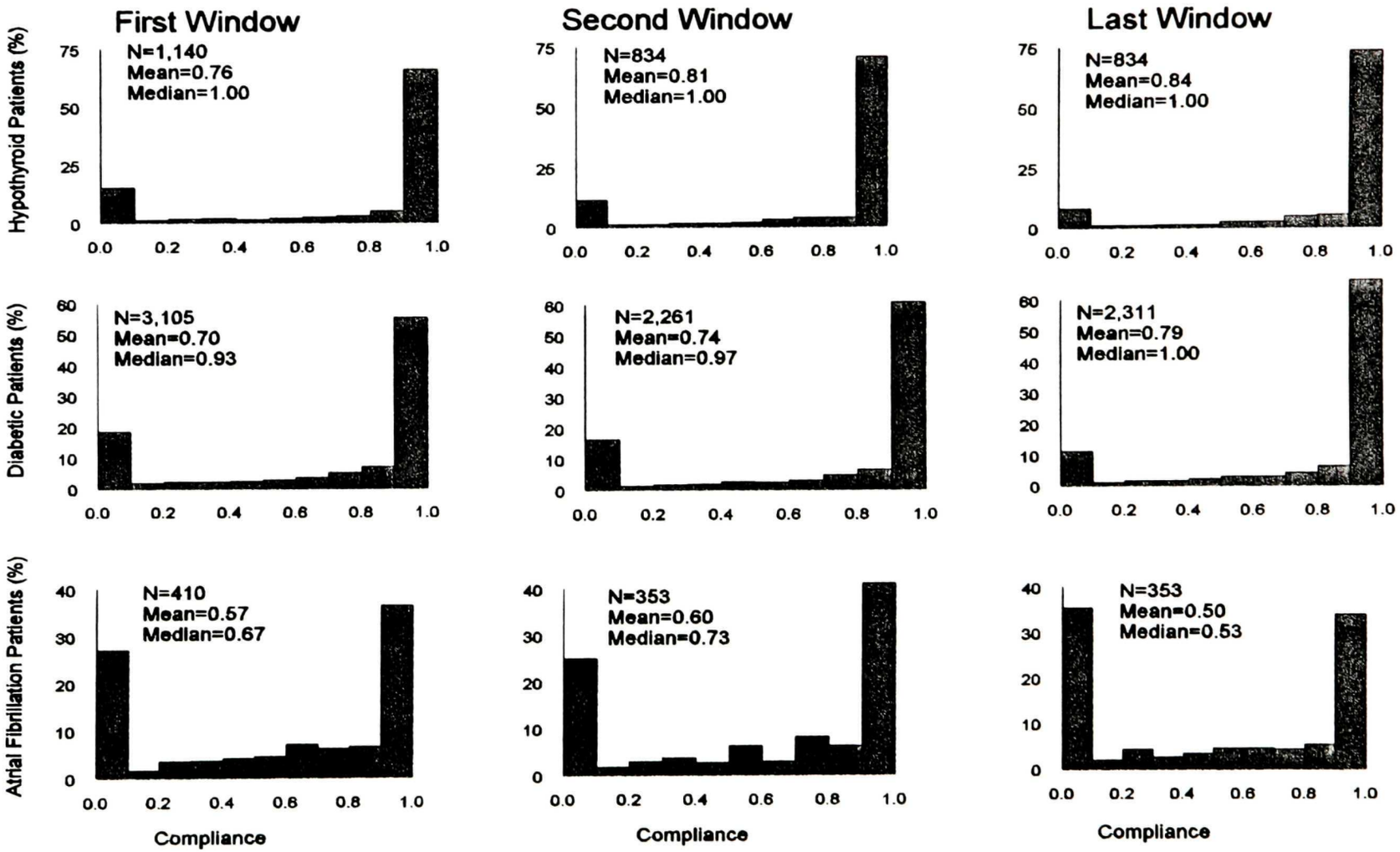
Appendix 3 - Figure 1 - Distribution of Laboratory Results



Appendix 3 - Figure 2 - Distribution of Dose of Study Drugs



Appendix 3 - Figure 3 - Distribution of Compliance



Appendix 4

Algorithm SAS Code

Appendix 4 Algorithm SAS Code
Atrial Fibrillation Example

```
      *SAS FILE IS Atrial Fib Time window.SAS* ;
/*************************************************************************/
/* F:\fairchild\real data\version8.sas   6-19-01                         */
/* PROCESSING LOGIC                                                      */
/* ---------------                                                       */
/* 1. Discard lab tests within three days of first test in               */
/*    a series.                                                          */
/*                                                                       */
/* 2. Remove observation pairs with same date and +/-                    */
/*    quantity.                                                          */
/*                                                                       */
/* 3. Collapse two Rx on the same day into one observation               */
/*    according to the following rules:                                  */
/*                                                                       */
/*    - Added if the sum of the doses = subsequent dose +/-              */
/*      a fuzz factor. (Dose adjustment factor)                          */
/*      (If the durations of the two doses are different,                */
/*      then the duration will be the longer of the two.)                */
/*    - If the two doses are different, then assume the                  */
/*      lower dose was taken first.                                      */
/*    - If the doses are the same, assume the second Rx is               */
/*      an early refill.                                                 */
/*                                                                       */
/* 4. Overlapping prescriptions will be considered an early              */
/*    refill if doses are the same regardless of the overlap             */
/*    interval. Extend the number of days of the second                  */
/*    prescription by the overlap.                                       */
/*                                                                      */
/* 5. Overlapping prescriptions                                          */
/*                                                                       */
/*    - will be added regardless of dose if:                             */
/*                                                                       */
/*    (PREVIOUS DOSE) + (CURRENT DOSE) = (NEXT DOSE) +/-                 */
/*     a fuzz factor                                                     */
/*                                                                       */
/*    - ELSE will be considered a dose switch if the doses               */
/*      are not the same.                                                */
/* ------------------------------------------------                      */
/* 05/25/01  Jim  Exclude lab tests after last dosing date.              */
/* 06/01/01  Jim  Account for "excess" days in duration calc,            */
/*           but keep "days" from original meds file for                 */
/*           rule 4b. (Rules attached to end of file)                    */
/* 06/19/01  Jim  Change Rule 4a,b: Use shorter number of days           */
/*           if two Rx on same day.                                      */
/*           Exclude labs after start of last Rx                         */
/*************************************************************************/

libname test 'c:\sas';
```

```
options ls=120 pageno=1 nocenter;

%let window=30;
%let dosefuzz=20;   * Fuzz factor for addition of doses (Rule 4a);
%let c=*;      * Print intermediate data sets for testing;
          * %let c=*  to comment out prints      ;
          * %let c=   to see the prints         ;
%macro subset;

  *if pid = '01323';


%mend subset;

%LET DRUG=
     (drugname= 'COUMADIN' or
     drugname ='WARFARIN SODIUM');


proc datasets library=work kill;

/* Selects only the appropriate lab tests and renames date variable*/

data lab;
     set test.ctylab (drop=testdesc order_dr);
    if testcode='INR' or testcode='DINRWB';
     if testcode in ('DTSH','TSH');
     %subset;
     IF Result NE . AND TESTDATE NE .;

    FORMAT testdate DATE9.;
    RENAME testdate=DATE;
    run;

  proc sort; by pid date;run;

&c proc print data=lab;
&c title original lab data;


/*------- BEGIN 06-26-00 MODIFICATION TO SELECT FIRST TEST IN A SERIES -------;
     This step discards immediate repetition of lab testing if the repeat lab
     is within 3 days of the first lab in a series   */

DATA LAB; SET LAB; BY PID;
  LASTDATE=LAG(DATE);

  *** DISCARD TESTS 3 OR FEWER DAYS FOLLOWING THE PREVIOUS TEST;

  IF NOT FIRST.PID AND DATE-LASTDATE LE 3 THEN DELETE;
  DROP LASTDATE; run;

&c proc print data=lab;
```

```
&c title lab data after discarding tests <= 3 days apart;

* ------- END 06-26-2000 FIRST TEST MODIFICATION ----------------------------;

/*------- BEGIN 06-12-01 MODIFICATION TO DELETE SUBSEQUENT TESTS ------------;
       DURING AN INTERVAL OF LENGCH &WINDOW                        -------;
     This step discards all tests after the first test during an interval
     equal to the window length -- prevents losing windows when tests are
     less than &WINDOW days apart.                                    */

data lab; set lab; by pid;
  retain tempdate;
  if first.pid then do;   * First lab test per patient;
    tempdate=date;        *  Save date            ;
    return;             *  Stop processing       ;
  end;
  if date-tempdate < &window
    then delete;        * Discard test and stop processing;
  tempdate=date;          * Save date as start of next inerval;
  drop tempdate;

* ------ END 06-12-01 MODIFICATION ----------------------------------------;

data keep;
  set test.T_keeper;by pid; *keeper file contains subjects with abn TFT prior to
                    begining synthyroid treatment;
  %subset;
  run;
&c proc print;
&c title T_keeper;

data lab;  *selects necessary lab for the Keeper patients;
  merge keep (in=a) lab ;by pid; *Repetitive lab in LT 3 days of first test is eliminated;
   if a; drop normalra high low normal_r;
     proc sort;by pid date; run;

&c proc print data=lab;
&c title lab data for keeper patients;

data dose;
  set test.Apprx;
      IF &DRUG;
      %subset;
      if serv_dt ne .; drop Index_dt;
   format serv_dt date9.;

proc sort;by pid serv_dt ;

&c proc print data=dose;
&c title original drug data;

* ---- BEGIN 06-19-01 MOD TO REMOVE LABS AFTER LAST Rx DATE -----;
```

```
DATA LASTDOSE (RENAME=(SERV_DT=LASTRX));
  SET DOSE; BY PID;
  IF LAST.PID;
  KEEP PID SERV_DT;

DATA LAB; MERGE LAB (IN=A) LASTDOSE; BY PID;
  IF A;
  IF N(DATE,LASTRX)=2 AND DATE > LASTRX THEN DELETE;
  DROP LASTRX;

&c proc print data=dose;
&c title original lab data after exluding tests after last Rx;

* ----- END 06-19-01 MOD TO REMOVE LABS AFTER LAST Rx DATE ------;

/* Caluclates tabs/day for all prescriptions  */

Data dose;
   set dose;
   RENAME serv_dt=Date;
   Retain DIN 0;  * ??? converts NDC_code character variable to numeric variable;
   Din=input(NDC_code, Best12.);
   days4b=days;              * Keep original value for rule 4b;
   if quantity=days then tabsQD=1;
   if quantity < days then do;
     excess=quantity-days;
     tabsQD=(quantity/days);
   end;
   if quantity > Days then do;
     excess=mod(quantity,days);
     if mod(tabsQD,0.5)=0 then excess=0;
     tabsQD=((quantity-excess)/days);
     days=days + int(excess/tabsQD);   * Add excess days (ignore partial day);
   end;                    *number of tablets per day;
   drop NDC_code;
run;
  proc sort;by din;run;

&c proc print data=dose;
&c title drug data after calculating tabs per day;

data firstdb;
  set test.first;
  Din=input(NDC_code, Best12.);
  keep din strength;
run;
  proc sort;by din;run;

/* Calculates dose for each prescription*/

data drug;
merge dose firstdb; by din;
   IF strength NE .;
```

```
  IF DAYS > 0 AND DATE NE .;
  dose=(tabsQD * strength);
  Rename Date=Start;
  drop tabsqd strength;
run;
proc sort;by pid start dose; run;

proc datasets library=work; delete dose firstdb;

&c  proc print data=drug;
&c  title dosing data set after merging with firstdb;
* ---- BEGIN 07-28-00 MOD TO REMOVE OBSERVATION PAIR IF NEGATIVE QUANTITY -----;

DATA MED; SET DRUG; BY PID;
  RETAIN FLAG 0;
  IF NOT LAST.PID THEN DO;
    OBSNUM=_N_+1;
    SET DRUG (KEEP=START DAYS QUANTITY RENAME=(START=NEXTDATE
            DAYS=NEXTDAYS QUANTITY=NEXTQ)) POINT=OBSNUM;
  END;
  IF QUANTITY = -(NEXTQ) AND QUANTITY NE . AND
    START=NEXTDATE THEN DO;
    FLAG=1;
    DELOBS=1;
  END;
  ELSE IF FLAG THEN DO;
    FLAG=0;
    DELOBS=1;
  END;
  IF DELOBS NE 1;
  DROP FLAG NEXTDAYS NEXTDATE NEXTQ DELOBS;

proc datasets library=work; delete drug;

&c proc print data=med;
&c title med after removing pairs with negative quantity;

* ---- END 07-28-2000 NEGATIVE QUANTITY MODIFICATION ------------------------;


* ----- BEGIN CODE TO PROCESS TWO PRESCRIPTIONS ON SAME DAY (Rule 4) ---------;

DATA MED;
 SET MED NOBS=NOBS; BY PID;       * Read current observation;
  RETAIN FLAG FLAG2 0;
  IF NOT LAST.PID THEN DO;
    OBSNUM=_N_+1;              * Read current +1 observation;
     SET MED (KEEP=DOSE START DAYS DAYS4B QUANTITY RENAME=(DOSE=NEXTDOSE
         START=NEXTDATE
             DAYS=NEXTDAYS DAYS4B=NEXT_4B QUANTITY=NEXTQ)) POINT=OBSNUM;

    IF _N_ LT NOBS-1 THEN DO;    * Read current +2 observation;
      OBSNUM = OBSNUM + 1;
```

```
      SET MED (KEEP=PID DOSE DAYS DAYS4B START
                          RENAME=(PID=NEXT2PID  DOSE=NEXT2DOS  DAYS=NEXT2DAY
        START=NEXT2DAT
              DAYS4B=NEXT2_4B))
          POINT=OBSNUM;
      IF PID = NEXT2PID AND
        ABS(NEXT2DOS - (DOSE + NEXTDOSE)) LE &DOSEFUZZ AND
        START = NEXTDATE
      THEN COMBINE=1;        * Rule 4a;
    END;

    IF _N_ LT NOBS-2 THEN DO;   * Read current +3 observation;
      OBSNUM = OBSNUM + 1;
      SET MED (KEEP=PID DOSE DAYS DAYS4B START
            RENAME=(PID=NEXT3PID DOSE=NEXT3DOS DAYS=NEXT3DAY
                DAYS4B=NEXT3_4B START=NEXT3DAT))
          POINT=OBSNUM;
      IF PID = NEXT3PID AND
        DOSE = NEXT2DOS AND
        DAYS4B = NEXT2_4B AND
        NEXTDOSE = NEXT3DOS AND
        NEXT_4B = NEXT3_4B AND
        START = NEXTDATE AND
        NEXT2DAT = NEXT3DAT
      THEN DO;
          COMBINE=2;        * Rule 4b;
          FLAG2 = 1;
      END;
    END;
  END;
  IF FLAG THEN DO;
    FLAG=0;
    RETURN;
  END;
*** Rule 4a ***;
  IF COMBINE = 1 AND NOT FLAG2 AND NOT LAST.PID THEN DO;
    FLAG = 1;
    DOSE= DOSE + NEXTDOSE;
*   DAYS = MAX(DAYS,NEXTDAYS);   * Original definition;
    DAYS = MIN(DAYS,NEXTDAYS);   * New definition (06/19/01);
    OUTPUT;
  END;
*** Rule 4b ***;
  ELSE IF COMBINE = 2 OR FLAG2 = 1 THEN DO;
    FLAG = 1;
    DOSE= DOSE + NEXTDOSE;
*   DAYS = MAX(DAYS,NEXTDAYS);   * Original definition;
    DAYS = MIN(DAYS,NEXTDAYS);   * New definition (06/19/01);
    OUTPUT;
    IF FLAG2 = 1 AND COMBINE NE 2 THEN FLAG2=0;
  END;
*** Rule 4c.2 ***;
    ELSE IF START=NEXTDATE AND DOSE=NEXTDOSE AND COMBINE NE 1 AND NOT
```

```
        LAST.PID THEN DO;
    FLAG = 1;
    DAYS = DAYS + NEXTDAYS;
    OUTPUT;
  END;
*** Rule 4c.1 ***;
   ELSE IF START=NEXTDATE AND DOSE NE NEXTDOSE AND COMBINE NE 1 AND NOT
        LAST.PID THEN DO;
    FLAG = 1;
    OUTPUT;
    DOSE = NEXTDOSE;
    START = NEXTDATE + DAYS;
    DAYS = NEXTDAYS;
    OUTPUT;
  END;
  ELSE OUTPUT;
  DROP FLAG FLAG2 NEXTDAYS NEXTDOSE NEXTDATE NEXTQ QUANTITY EXCESS DIN
     COMBINE NEXT2DOS NEXT2DAY NEXT3DOS NEXT3DAY NEXT2DAT NEXT3DAT
     NEXT2PID NEXT3PID;
run;

&c  proc print data=med;
&c  title med after processing two prescriptions on the same day;

* ---- END CODE TO PROCESS TWO PRESCRIPTIONS ON THE SAME DAY (Rule 4) -------;


* ---- BEGIN 07-29-00 MOD TO INCREASE DURATION OF RX IF EARLY REFILL --------;

PROC SORT; BY PID START DOSE;
RUN;

DATA MED; SET MED; BY PID;
  RETAIN FLAG XTRADAYS 0;
  STOP = START + (DAYS -1) + XTRADAYS;
  IF NOT LAST.PID THEN DO;
    OBSNUM=_N_+1;
       SET MED (KEEP=DOSE START RENAME=(DOSE=NEXTDOSE START=NEXTDATE))
        POINT=OBSNUM;
  END;
  IF DOSE=NEXTDOSE AND NEXTDATE <= STOP
     AND NOT LAST.PID THEN DO;
    FLAG=1;
    XTRADAYS = STOP - NEXTDATE +1;
    DAYS = NEXTDATE - START;
  END;
  ELSE IF FLAG=1 OR LAST.PID THEN DO;
    DAYS = DAYS + XTRADAYS;
    FLAG=0;
    XTRADAYS=0;
  END;
  IF DAYS LE 0 THEN DELETE;
  DROP XTRADAYS FLAG NEXTDATE NEXTDOSE STOP;
```

```
&c proc print data=med;
&c title med after increasing duration of RX if early refill;

* ----- END 07-29-00 RX DURATION MODIFICATION ------------------------------;


DATA MED (RENAME=(START=SDATE));
  SET MED;
  BY PID;

  EDATE = START + DAYS - 1;        * END DATE OF CURRENT RX;
  LASTDOSE = LAG(DOSE);            * DOSE OF PREVIOUS RX;
  LASTDAYS = LAG(DAYS);            * DURATION OF PREVIOUS RX;
  LASTDATE = LAG(START);           * DATE OF PREVIOUS RX;
  IF FIRST.PID THEN DO;
    LASTDOSE = .;   * IGNORE IF FIRST RX PER PID;
    LASTDAYS = .;
    LASTDATE = .;
  END;

  IF NOT LAST.PID THEN DO;         * READ NEXT RX;
    OBSNUM = _N_ + 1;
     SET MED (KEEP=DOSE START DAYS RENAME=(DOSE=NEXTDOSE START=NEXTSDAT
           DAYS=NEXTDAYS)) POINT=OBSNUM;
    NEXTEDAT = NEXTSDAT + NEXTDAYS - 1;  * END OF NEXT RX;
  END;

  IF EDATE - NEXTSDAT GE 0
    AND NOT LAST.PID THEN DO;          * CHECK FOR OVERLAP;
    OLAPDAYS = EDATE - NEXTSDAT + 1;     * DAYS OVERLAP OF NEXT RX;
    OVERLAP = 'Y';                   * SET OVERLAP FLAG;
  END;

  IF OVERLAP='Y' AND NOT LAST.PID THEN DO;  * DETERMINE OVERLAP ACTION;
    IF ABS(NEXTDOSE - (LASTDOSE + DOSE)) LE &DOSEFUZZ AND NOT FIRST.PID
                    THEN OACTION = 'A';  * ADD;
      ELSE IF NEXTDOSE NE DOSE THEN OACTION = 'S';  * SWITCH;
  END;
  FORMAT EDATE NEXTEDAT LASTDATE DATE9.;
  run;

&c proc print;
&c title medications intermediate analysis data set;
  run;

DATA MEDDAYS;     * Expand to one observation per date;
  SET MED; BY PID;

  IF OVERLAP NE 'Y' OR
    (OVERLAP='Y' AND OLAPDAYS LE 0 AND OACTION NE 'A')
      THEN DO;                   * NO OVERLAPPING RX;
    DO DATE = SDATE TO EDATE;
      OUTPUT;
```

```
  END;
 END;

 ELSE IF OVERLAP = 'Y' AND OACTION = 'A' THEN DO;  * OVERLAP - ADD RX;
   STOP1 = SDATE + (LASTDAYS - (SDATE - LASTDATE)) -1;
   STOP2 = NEXTSDAT -1;
   DO DATE = SDATE TO STOP2;
     OUTPUT;                    * CURRENT DOSE;
   END;
   DOSE = LASTDOSE;
   DO DATE = SDATE TO MIN(STOP1,STOP2);
     OUTPUT;      * WHATEVER IS LEFT OF LAST DOSE      ;
   END;          * (NOT LONGER THAN START OF NEXT DOSE);
 END;

 ELSE IF OVERLAP = 'Y' AND OACTION = 'S' THEN DO;  * OVERLAP - SWITCH RX;
   DO DATE = SDATE TO (NEXTSDAT - 1);
     OUTPUT;
   END;
 END;
 ELSE IF OVERLAP = 'Y' AND OACTION = ' ' THEN DO;  * OVERLAP - EARLY REFILL;
   DO DATE = SDATE TO (NEXTSDAT - 1);
     OUTPUT;
   END;
 END;
 KEEP PID DRUGNAME DOSE DATE;

Proc sort;by pid date;run;  /*  merge meds and lab data   */

DATA MEDDAYS; MERGE MEDDAYS (IN=MED) lab (IN=LAB);
 BY PID DATE;
 IF MED THEN MEDDAY=1;
 IF LAB THEN LABDAY=1;

*  Proc datasets library=work;

DATA SKIPDAYS; SET MEDDAYS; BY PID;
 IF NOT LAST.PID THEN DO;
   OBSNUM=_N_+1;
   SET MEDDAYS (KEEP=DATE RENAME=(DATE=NEXTDATE)) POINT=OBSNUM;
   SKIPDAYS=NEXTDATE-DATE-1;
   IF SKIPDAYS > 0 THEN DO;
     DO I=1 TO SKIPDAYS;
       DATE=DATE+1;
       OUTPUT;
     END;
   END;
 END;
 KEEP PID DATE;

* Interleave days with meds or lab tests and days without;

DATA MEDDAYS;
```

```
  SET MEDDAYS SKIPDAYS; BY PID DATE;
  RETAIN FIRSTDAT;
  IF FIRST.PID THEN FIRSTDAT=.;
  IF MEDDAY AND FIRSTDAT=. THEN FIRSTDAT=DATE;
  IF DATE < FIRSTDAT + 90
    OR FIRSTDAT = . THEN DELETE; * REMOVE 90 DAY DOSE ADJUSTMENT PERIOD;
  FORMAT FIRSTDAT DATE9.;
  DROP FIRSTDAT;

DATA MEDDAYS (RENAME=(TOTDOSE=DOSE));
  SET MEDDAYS; BY PID DATE;
  IF FIRST.DATE THEN TOTDOSE=0;
  TOTDOSE+DOSE;                * SUM TOTAL DOSE PER DAY;
  IF LAST.DATE THEN OUTPUT;
  DROP DOSE;
RUN;
&c proc print data=meddays;
&c title meddays after merging with labs and adding non-dosing days;
&c title2 after removing 90 day dose adjustment period;
&c title3 after summing total dose per day;
run;

DATA CHECKMED; SET MEDDAYS; BY PID;
  RETAIN START;
  LASTDOSE=LAG(DOSE);
  LASTDATE=LAG(DATE);
  IF FIRST.PID THEN DO;
    START=DATE;
  END;
  ELSE IF LAST.PID THEN DO;
    STOP=DATE;
    RXDOSE=DOSE;
    OUTPUT;
  END;
  ELSE DO;
    IF DOSE NE LASTDOSE THEN DO;
      STOP=LASTDATE;
      RXDOSE=LASTDOSE;
      OUTPUT;
      START=DATE;
    END;
  END;
  FORMAT STOP START DATE9.;
  KEEP PID START STOP RXDOSE;

PROC PRINT DATA=CHECKMED;
  TITLE FINAL DOSING INTERVALS AFTER CALCULATION;

Proc datasets library=work; delete skipdays;

* Assign windows prior to lab tests;

PROC SORT DATA=MEDDAYS; BY PID DESCENDING DATE;
```

```
DATA MEDDAYS; SET MEDDAYS; BY PID;
  RETAIN STARTWIN WINFLAG doseflag;
  IF FIRST.PID THEN DO;
    WINFLAG = 0;          * WINDOW FLAG (OFF);
    WINNUM = 0;           * COUNTER FOR WINDOWS;
    STARTWIN=.;           * STARTDATE FOR WINDOW;
    doseflag = 0;
  END;
  if dose > 0 then doseflag = 1;
  IF LABDAY and doseflag THEN DO;  * START NEW WINDOW;
    WINNUM + 1;
    STARTWIN=DATE;
    WINFLAG = 1;
  END;
  IF WINFLAG THEN DO;
    IF STARTWIN-DATE+1 LE &WINDOW THEN DO;  * IN;
      WIN=WINNUM;
      WINDAY=STARTWIN-DATE+1;
    END;
    ELSE WINFLAG = 0;                 * OUT;
  END;
  DROP STARTWIN WINFLAG WINNUM;

PROC SORT; BY PID DATE;

* Renumber windows, with earliest as number 1;


*-------- BEGIN 07-01-00 MODIFICATION TO RENUMBER WINDOWS ONLY FOR -------;
*-------- WINDOWS WHICH ARE OF FULL LENGTH                    -------;

DATA MEDDAYS; SET MEDDAYS (RENAME=(WIN=DWIN)); BY PID;
  RETAIN FLAG AWIN;
  LASTDWIN=LAG(DWIN);
  IF FIRST.PID THEN DO;
    FLAG=0;
    AWIN=0;
  END;
  IF WINDAY >= &WINDOW AND FLAG=0 THEN DO;  * Window is full length  ;
    FLAG=1;                       *  Set flag          ;
    AWIN+1;                       *  Increment window count;
  END;
  IF FLAG=1 THEN WIN=AWIN;              * If date in window, assign number ;
  IF WINDAY=1 THEN FLAG=0;              * Reset flag if 1st day of window  ;
  DROP FLAG AWIN DWIN LASTDWIN;

&c proc print data=meddays;
&c title meddays with windows numbered;

*-------- END 07-01-00 MODIFICATION ----------------------------------;


/*
```

```
PROC PRINT noobs; BY PID;var date days medday labday result win;run;
  TITLE PROCESSED DATA;
  TITLE2 WINDOW Day window preceding test LAB for medication DRUG;
*/

Proc sort;by pid win;run;

 DATA SUMDAYS; SET MEDDAYS (WHERE=(WIN NE .));

  BY PID WIN;
  LENGTH DRUG $ 30;
  RETAIN DRUG LASTDOSE winstart;
  IF FIRST.WIN THEN DO;
    WINDAYS=0;
    DRUGDAYS=0;
    SUMDOSE=0;
    DRUG=' ';
    LASTDOSE=.;
    WINSTART=DATE;
  END;
  WINDAYS+1;                    * COUNT DAYS PER WINDOW;
  IF MEDDAY THEN DRUGDAYS+1;        * COUNT MED DAYS PER WINDOW;
  IF DRUGNAME NE ' ' THEN DRUG=DRUGNAME;
  SUMDOSE + DOSE;                * ACCUMULATE DOSE PER WINDOW;
  IF DOSE > 0 THEN LASTDOSE=DOSE;

  IF LAST.WIN AND WINDAYS=&WINDOW THEN DO;  * WINDOW MUST BE COMPLETE;
    MRC=DRUGDAYS/&WINDOW;
    IF DRUGDAYS > 0 THEN
      MEANDOSE=SUMDOSE/DRUGDAYS;     * MEAN DOSE (based on days with drug);
    ELSE MEANDOSE=0;
    Winstop=date;
    OUTPUT;
  END;
  FORMAT WINSTART WINSTOP DATE7.;
  KEEP PID LASTDOSE MEANDOSE DRUG WIN WINDAYS DRUGDAYS MRC result
     WINSTART WINSTOP;

PROC PRINT NOOBS;
  TITLE SUM OF MED DAYS PER &WINDOW DAY WINDOW;
run;

proc sort out=c_keyvar;by pid DRUGDOSE DRUG RESULT WIN  MRC;run;

data count;set c_keyvar;by pid;
 if first.pid;
 proc print;run;
   title data count;

PROC FREQ; TABLES WIN DRUGDOSE RESULT MRC;RUN;

//*
```

Programming Rules Employed for Program Development:

Rule #1 Frequent Laboratory Testing Rule

Frequent testing rule: Frequent testing was defined as testing within 3 days of previous test: If a lag time of 3 or few days between laboratory testing was detected; the first test of the series was retained for use in the analysis and subsequent test were discarded.

Rules for Prescriptions That Overlap in Time (Early Prescription Dispensation)

There are at least 3 possible explanations why a patient filled a new prescription before the previous prescription ran out:

a. Switch - The dose was switched to the new prescription and the previous one was discontinued
b. Addition - The new prescription is intended to be taken in addition to the previous one. The dosages should be summed.
c. Early Refill - The dose is the same and the patient is getting a new supply before the previous prescription runs out.

Rule #2 Overlapping Prescriptions with Different Doses When the dose is different between two overlapping prescriptions, I will call it:

2a Addition if subsequent doses are the sum of the two or near the sum of the two (± 20 mg for levothyroine drugs and 5mg for warfarin an hypogylcemic drugs). Levothyroxine example :

50mg Rx----------
25 mg Rx----------
80mgRx----------80mg----------

The duration of the 50 mg dose will end with the Rx of 25 mg. The beginning of 75 mg will occur on the date of the second Rx for 25 mg. and end on the date of the Rx for 80 mg.

2b Switch if there is no evidence that it is an addition. The duration of the first prescription will end on the date that the second (switch) prescription starts.

50mg Rx----------
25 mg Rx---------- 25mg Rx----------

The duration of the 50 mg dose will end with the first Rx for 25 mg.

Rule #3 Overlapping Prescriptions with Same Dose
When the dose is the same for two overlapping prescriptions, I will call it:

3a: Addition if the subsequent Rx's are similar (the same 2 prescriptions prescribed together in the future) or a new (replacement) prescription that is the sum of the two doses (± 15 mg for levothyroxine and 5 mg for coumadin). The duration of the two prescriptions will be

calculated as follows:

50mg Rx#1[30days]
50mg Rx#2 [10-day overlap, out of 30 days supply]
100mg Rx#3 (3-day overlap/30

Duration are: 50mg dose - 20 days
100 mg dose- 40 days,10days for overlap of two 50mg Rx's plus 30 days for Rx#3.

3b Early refill if there is no evidence that the second prescription was intended to be an addition. The overlapping days will be added to the end of the second prescription. See example below:

rx1[30days]
rx2 [10days overlap, out of 30 days supply]

Rule #4 Two Prescriptions on the Same Day This is a special case of overlapping prescriptions. I will call it:

4a1. Addition if subsequent doses are the sum of the two or near the sum of the two doses.

50 mg Rx----------
50 mg Rx----------
100mg Rx----------

The duration will be equal to the longest number of days supply of the two prescriptions.

4b2. Addition if subsequent Rx date has exactly the same dose and duration and the pattern is repeated at the next Rx date.
50 mg Rx--------
25mg Rx----------
12mg Rx----------
25mg Rx--------
12mg Rx--------

4c. Sequential prescriptions if the subsequent doses do not suggest that the two prescriptions were intended to be additions (taken together). The duration of the two prescriptions will be the sum of the days of supply for the two prescriptions.

4c.1 If sequential prescriptions are different doses, it will be assumed that the prescription with the lowest dose was prescribed to be taken first and the higher dose second.

4c.2 If sequential prescriptions are the same dose, it will be assumed that the second prescription is an early refill.

The challenge to rule 4 is can one be certain that the 2 prescriptions on the same day were intended to be taken together (additive) or sequentially (either early refill or step-dosing). The problematic scenario (for the program) is instances were the pattern of large dose + small dose is repeated over time. See 4b

*//

Appendix 5

Multivariate Models and Parameter Estimates

Hypothyroid Patients

Multivariate Model and Parameter Estimates

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	3.4976	0.5002	2.5173	4.4779	6.99	<.0001
Compliance	-0.6874	0.0978	-0.8790	-0.4957	-7.03	<.0001
Dose*	-0.0088	0.0009	-0.0107	-0.0070	-9.54	<.0001
Age	-0.0026	0.0020	-0.0067	0.0014	-1.29	0.1959
Time	0.0048	0.0024	0.0000	0.0095	1.98	0.0482
Renal	0.0113	0.0758	-0.1372	0.1598	0.15	0.8812
Hepatic	-0.1461	0.1005	-0.3430	0.0509	-1.45	0.1462
Obesity	0.3932	0.1078	0.1820	0.6044	3.65	0.0003
Inc Drugs	0.0953	0.1057	-0.1120	0.3025	0.90	0.3676
Dec Drugs	0.1361	0.1435	-0.1450	0.4173	0.95	0.3427
Gender**	-0.3688	0.0721	-0.5102	-0.2274	-5.11	<.0001
Comp*dose	-0.0099	0.0018	-0.0134	-0.0064	-5.47	<.0001

* TSH decreases is expected with increases in compliance and dose

** Reference group: male=0

Diabetic Patients

Multivariate Model and Parameter Estimates

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	2.2656	0.0487	2.1702	2.3611	46.52	<.0001
Compliance*	-0.0660	0.0061	-0.0779	-0.0540	-10.83	<.0001
Dose	0.0008	0.0001	0.0005	0.0011	5.66	<.0001
Time	0.0038	0.0002	0.0034	0.0043	17.64	<.0001
Age	-0.0029	0.0003	-0.0034	-0.0024	-10.39	<.0001
Gender**	0.0143	0.0068	0.0009	0.0277	2.09	0.0363
Inc Drugs	-0.0088	0.0115	-0.0315	0.0138	-0.77	0.4441
Dec drugs	0.0004	0.0047	-0.0089	0.0097	0.08	0.9350
Renal	-0.0182	0.0115	-0.0406	0.0043	-1.59	0.1126
Hepatic	-0.0120	0.0101	-0.0317	0.0078	-1.19	0.2357
Obesity	-0.0014	0.0095	-0.0200	0.0172	-0.15	0.8824
Comp*time	-0.0013	0.0005	-0.0023	-0.0002	-2.41	0.0159
Time*dose	-0.0001	0.0000	-0.0001	-0.0000	-5.81	<.0001

* Hgb_{A1c} decrease is expected with high levels of compliance and dose

** Reference group: male=0

Atrial Fibrillation Patients

Multivariate Model and Parameter Estimates

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	0.8212	0.1223	0.5814	1.0609	6.71	<.0001
Compliance	0.0206	0.0158	-0.0104	0.0517	1.30	0.1932
Dose*	0.0022	0.0012	-0.0002	0.0046	1.84	0.0663
Time	0.0009	0.0007	-0.0004	0.0022	1.38	0.1664
Gender**	-0.0337	0.0154	-0.0639	-0.0035	-2.19	0.0286
Age	0.0009	0.0008	-0.0007	0.0025	1.09	0.2740
Renal	-0.0340	0.0067	-0.0471	-0.0209	-5.09	<.0001
Hepatic	-0.0048	0.0232	-0.0503	0.0408	-0.20	0.8377
Obesity	-0.0176	0.0365	-0.0891	0.0539	-0.48	0.6293
Inc Drugs	-0.0057	0.0123	-0.0298	0.0184	-0.47	0.6409
Dec Drugs	0.0175	0.0229	-0.0274	0.0623	0.76	0.4453

* INR increase is expected with high levels of compliance and dose
** Reference group: male=0