IMPROVING GLAUCOMA COMPLIANCE USING A LEAN SIX SIGMA DMAIC APPROACH.

by

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ABSTRACT

JOHANNA FICATIER. Improving glaucoma management and compliance using a Lean Six Sigma approach. (Under the direction of DR. ERTUNGA C. OZELKAN)

Compliance to the treatment is a major factor in the evolution of glaucoma. The purpose of this study is to identify the factors that result in non-compliance to glaucoma treatment.

More specifically, a Lean Six Sigma DMAIC (Define, Measure, Analyze, Improve, Control) methodology is applied to improve the follow-up process for Glaucoma patients in a Veterans Affairs (VA) Hospital in North Carolina, USA.

The main problem in the current control process appears to be the low compliance (i.e. adherence to prescribed medication). In order to improve glaucoma treatment compliance and thus patient care, past medical data are analyzed to identify influential factors for non-compliance. Some of the factors investigated include patient age, proximity to the treatment center, presence of a supportive unit, drug abuse history and past trauma record. As part of the Lean Six Sigma framework, a regression model is developed to be used as a decision-aid tool for the hospital and the medical doctors to detect and control compliance issues during the follow-up process.

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LIST OF ABBREVIATIONS

AAO:	American Academy of Ophthalmology
DMAIC:	Define Measure Analyze Improve Control
IOP:	Intra Ocular Pressure
NTG:	Normal Tension Glaucoma
OHT:	Ocular Hyper Tension
POAG:	Primary Open-Angle Glaucoma
VA:	Veterans Affairs
WHO:	World Health Organization

CHAPTER 1 : INTRODUCTION

With a global population growth, ageing population in developed countries, but also because of a degradation of lifestyle, we observe a significant shift of the healthcare focus from the healing of acute diseases to the management of chronic conditions. (World Health Organization (WHO), 2003; Magnuson, 2010). The long (generally lifetime) and overwhelming treatment necessary to control the chronic conditions lead to a new problem in chronic diseases management: the problem of non-compliance or non-adherence to the treatment (Neiheisel, Wheeler, & Roberts, 2014). Medication adherence for chronic diseases treatment reaches only 50% in developed countries, but is even lower in developing countries (World Health Organization (WHO), 2003; Bosworth et al., 2011)

Patient compliance or, as it is more widely-used: "medication adherence," is defined as whether the patient adheres to the medical instructions, including timing, dosage and application methods of medication. Persistence is defined as whether the patient collects the medication refill as prescribed (Waterman, Evans, Gray, Henson, & Harper, 2013). The most common way to measure persistence is by checking the patients' refills rate at the pharmacy and compare with the prescribed rate. However, persistence does not guarantee good adherence to the treatment as Friedman et al. (2007) proved. To measure adherence, some direct measurement methods exist: measurement of a bio-marker for a drug, measurement of concentration of a drug in blood or urine (Shi et al., 2010). However, those methods are expensive and onerous. Indirect methods to measure adherence include

but are not limited to: electronic monitoring and self-assessment (Shi et al., 2010). Unfortunately, those measurements are likely to be biased by the Hawthorne effect: the fact that people have a tendency to consciously or not change their behavior when they know they are being observed, as explained by Okeke et al., (2009).

Glaucoma is one very concerning chronic condition: according to the World Health Organization (WHO) (2014), Glaucoma is responsible for 2% of visual impairment worldwide. As for most chronic conditions, the patients affected by Glaucoma are increasing every year, with an estimation of 79.6 million by 2020 (Quigley & Broman, 2006). Moreover, in their meta-analysis of 56 articles, Cedrone et al. (2008) showed that the rate of non-diagnosed Glaucoma is extremely high worldwide.

In the United States, more than 3.6 million of people were affected by visual impairment or blindness in 2004, and the number of blind people is estimated to increase by 70% to 1.6 million by 2020, according to the Eye Diseases Prevalence Research Group (2004). Dr. Friedman and his research Group from the Wilmer Eye Institute studied in the Salisbury Eye Evaluation Project the effects of vision impairment on mobility and Quality of Life. The study, separated in 3 papers :Freeman et al. (2008), Ramulu et al. (2009), Friedman et al. (2011) showed that Visual Impairment very negatively affects mobility performance and quality of life.

In addition, the direct medical costs for the treatment of Glaucoma was calculated to reach $2.9 billion in 2004, representing 17.8% of the total costs of visual disorders treatment (Rein et al., 2006).

Glaucoma prevalence is influenced by various factors including but not limited to: age, gender, ethnicity, genetic predisposition, etc. Once it has been diagnosed the Intra-

Ocular Pressure (IOP) is the only proven modifiable factor for Glaucoma evolution (Barton, Hitchings & Budenz, 2013). Management of Glaucoma as recommended by the American Academy of Ophthalmology (AAO) (2010) consists in setting a target IOP (usually 25% lower than the IOP at diagnosis), and making sure that the patient's IOP remains stable within a certain range. Before having to turn to laser therapy or eye surgery, IOP control can be achieved by topical therapy, i.e. application of eye drops several times a day (Dreer, Girkin, & Mansberger, 2012).

In a study on 102 patients, Sleath et al. (2011) showed that a good adherence (measured and self-assessed) was associated with a better Visual Field compared with those for the non-adherent patients. Similarly, Rossi et al. (2011) showed that not only a good adherence rate had a statistically significantly effect on a stable Visual Field, but also that no other factor (socio-demographic) had a significant effect in the regression analysis. A good adherence to the initial treatment seems therefore critical to prevent the aggravation of Glaucoma conditions to blindness (Barton, Hitchings & Budenz, 2013).

However, the "Guidelines for Follow-up Glaucoma Status" as recommended by the American Academy of Ophthalmology (AAO) (2010) consist in guidelines for ophthalmic examination and follow-up intervals, but no compliance measurement/assessment is recommended. A similar tendency is found in the recommendations by the European Glaucoma society.

Unfortunately, Glaucoma is of no-exception from the other chronic diseases: a study of pharmacy claims on a large US healthcare database showed that nearly a half of the newly diagnosed Glaucoma patients interrupted their treatment within a year (Nordstrom, Friedman, Mozaffari, Quigley, & Walker, 2005).

There is therefore a need to understand the non-compliance behavior and to identify those different factors that affect it. Similarly, a follow-up care compliance assessment process would help to determine which actions should be taken in the case of identified non-adherence to the treatment more accurately. The problem addressed in this study can be summarized in the following research questions:

- What are the main factors influencing non-compliance behavior?
- How can non-compliance behavior be identified and assessed quantitatively?
- Which interventions (training, meetings, change of medication etc.) result in a significant improvement of compliance?
- Can a standard follow-up process be determined to replace the existing guidelines, now including compliance assessment?
- Can a predictive model be developed to predict future non-compliance risk among newly diagnosed patients?

After a review of the existing literature related to the glaucoma compliance research, detailed description of the methodology, we performed a data analysis before drawing conclusions, focusing on answering the research questions stated above.

Table 1: Definition of key terms

Term	Definition
Glaucoma	"Primary open-angle glaucoma is a progressive, chronic optic neuropathy in adults in which intraocular pressure (IOP) and other currently unknown factors contribute to damage and in which, in the absence of other identifiable causes, there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated with an anterior chamber angle that is open by gonioscopic appearance". (American Academy of Ophthalmology (AAO), 2010)
Compliance (Synonym: Adherence)	"The act of conforming to the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking. Therefore medication compliance may be defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen." Compliance is measured over a period of time and reported as a percentage" (Cramer et al., 2008) General differentiation in use: "patient compliance" or "medication adherence"
Persistence	"Persistence is the length of time between initiation and the last dose, which immediately precedes discontinuation" (Cramer et al., 2008; Vrijens et al., 2012)

CHAPTER 2 : LITERATURE REVIEW

In this section a literature review is provided related to glaucoma compliance related research. The literature review has been organized in the 3 following themes:

- Compliance and main factors
    - Socio-demographic factors
    - Non-intentional non-adherence
    - Intentional non-adherence and psychological factors
    - Difference in treatment: type, frequency, technique
- Electronic monitoring and reminder devices
- Practices and Interventions to improve compliance

2.1 Glaucoma Non-compliance and Main Factors

2.1.1 Socio-demographic and Psychological Factors

Some socio-demographic characteristics have been associated with medication adherence: for instance, older patients generally show lower adherence. An explanation, as (Banning, 2008) summarized in their literature review, is that co-morbidity is usually higher for the elderly, leading to difficulty in medication management but also lack of faith in the treatment. Sleath et al. (2011) also conducted an analysis to estimate the relation between ethnicity and non-compliance behavior. They concluded after their study that non-white patients were more likely to be non-adherent than whites, with Black patients particularly at risk. However, as Wheeler et al. (2014) pointed out in their comprehensive

review of factors influencing adherence, those demographic characteristics are very likely to be related to some other factors such as education, wealth, health literacy, etc.

Understanding the adherence behavior is therefore critical in order to determine the eventual interventions to improve adherence (Rees, Leong, Crowston, & Lamoureux, 2010).

Non-compliance to Glaucoma treatment can be intentional or unintentional (Rees et al., 2010). Self-reported adherence measurements paired with other measures of adherence (such as persistence measurement and electronic monitoring), can help differentiate between intentional and non-intentional non-compliance.

2.1.2 Non-intentional Non-adherence

In a meta-analysis of 41 articles for various chronic diseases, Shi et al. (2010) showed that self-reported adherence measurement was in average 14.9% higher than electronic monitoring measurements, supporting the assumption that non-compliance is generally non-intentional. The most frequently observed causes for non-intentional non-compliance are: lack of awareness of the importance of a regular treatment, or simply forgetting to apply the drops, especially when the treatment frequency is overwhelming (from 2 times/days). Indeed, unlike oral drugs where blisters or dosing boxes help to verify if the treatment has been taken as planned and take a corrective dose when an oversight is identified, visual control is not possible with the bottle of eye drops which are usually used for the Glaucoma treatment (Cate et al., 2009).

As a consequence, the simpler the treatment the better the compliance (Reardon, Kotak, & Schwartz, 2011). We can also observe that the duration of the treatment is usually associated with improved compliance (Reardon et al., 2011) as patients get to understand

better the treatment over time and include more efficiently the dose administrations in their daily routine.

2.1.3 Intentional Non-adherence and Psychological Factors

Intentional non-compliance can happen, mainly due to the lack of faith in the treatment. This can be due to misunderstanding or lack of understanding of the importance and efficiency of the treatment, or lack of faith in the physician (Stryker et al., 2010). In a study on 102 patients, Sleath et al. (2012) showed that visual field defect severity was associated with higher adherence. Despite a small sample size and the fact that adherence was measured by self-assessment, they concluded that patients who have started to experience vision loss are more motivated to follow the treatment in order to prevent further aggravation.

Wheeler et al. (2014) explained that adherence behavior is strongly influenced by psychosocial factors such as cultural beliefs, depression and lack of self-confidence, physical or cognitive impairment, as well as substance abuse and side effect in reaction to the medication. Moreover, based on a review of 8 articles they conclude that living alone, i.e. lack of support, can also be a strong factor influencing non-adherence. In a study on self-report assessment on Veterans patients, Sleath et al. (2009) also found that difficulties in drops application was a significant factor for non-adherence.

In their review of literature on medication adherence, Wheeler et al. (2014) found that, stronger than all the above psychological factors, financial limitation is the most important factor for interruption of treatment. Indeed, in their “Cost Analysis of Glaucoma Medications,” Rylander et al. (2008) showed that Glaucoma medication annual cost varies from $150.81 for β-Blockers (generic) to up to $873.98 in the case of the treatment of both

eyes, 3 times per day, using $\propto_2$-agonist . Moreover, they showed a general annual increase of Glaucoma medications price in their observation period from 2002 to 2006.

2.1.4 Treatment: Type, Frequency, Technique

Compliance in the case of Glaucoma is especially difficult to measure because it is not directly linked with amelioration of measurable conditions (Cate, Bhattacharya, Clark, Holland, & Broadway, 2013). Indeed, IOP being subject to diurnal variation, IOP measurement alone is not enough to assess the progression of the disease (American Academy of Ophthalmology (AAO), 2010; Rossi et al., 2011; Barton, Hitchings & Budenz, 2013). Therefore, measuring IOP alone does not give a good indication of evolution, and, consequently, of good compliance, which needs to be assessed by a separate method (Cate et al., 2012). Follow up evaluation, as defined by the American Academy of Ophthalmology (AAO, 2010), should include clinical examination with IOP measuring, but also optic nerve head (i.e. optic disc) and visual field assessment.

Moreover, and especially in the case of Glaucoma, another reason for the non-success of the initial treatment can be inefficient application (missing the eye with the drop), which is very hard to measure. In their study where they observed patient instillation method, Gupta et al. (2012) showed that only 8.5% of Glaucoma patients managed to instill the drop properly. Similarly Tatham, Sarodia, Gatrad, and Awan (2013) found that more than half (54.1%) of the 85 observed patients were identified by observers to have a poor instillation method although the mean assessed difficulty score was only 2.9 on a scale of 1-10. More concerning, they found that 11.4% patients totally missed the eye, resulting in a missed dose despite a compliant tentative.

Tatham et al. (2013) also showed that training on instillation method had a statistically significant effect on the quality of the instillation technique.

Therefore, as they pointed out in their conclusion, poor instillation technique has to be identified and differentiated from poor adherence in order to take the appropriate corrective action. For example, dosing aid devices exists for patients with dexterity disabilities (Cate et al., 2009). Failing to identify poor technique as a reason for treatment non-evolution could indeed lead the physician to prescribed unnecessary additional treatment, with the risk of adding costs and potential side effects. In a study, Sleath et al. (2012) developed a self-efficacy questionnaire which could be used by eye physicians to assess whether the instillation method needs to be verified.

2.2 Electronic Monitoring and Reminder Devices

For most chronic diseases, electronic reminders such as SMS, regular phone calls from the practitioner or nurse can appear to be a solution (Vervloet et al., 2012). In the case of Glaucoma the treatment being by instillation of eye drops, reminder devices such as the Travatan ™ Dosing Aid © not only measure whether the doses are taken as prescribed (making the Travatan ™ a favorite for adherence studies), but it also can be set up so as to generate a visual and audio reminder to the patient (Okeke et al., 2009).

Electronic reminders may therefore fix the problem of unintentional non-compliance by reminding the patient to take his drops at the prescribed intervals. However, in their study where they inspected whether the presence of such a monitoring device on the bottle would influence positively the patient compliance, Hermann et al. (2011) found that it has no significant effect. In other studies Vervloet et al., (2012) found that the efficiency of electronic reminders could not be proven effective on the long term (more

than 6 months). Indeed, in the case of chronic diseases such as Glaucoma, the treatment often has to be taken for a very long period of time, for the rest of the patient life in the case of Glaucoma, and we can expect the reminders to fall into a routine and its effects to soften after a certain time (Vervloet et al., 2012).

Considering also that electronic monitoring devices are usually expensive and non-covered by insurance (Shi et al., 2010), they are usually not used to improve compliance, their use being limited to specific experiments or studies.

Vervloet et al. (2012) suggested as future research to try to use electronic devices for monitoring and use reminders only when omission is measured, thus preventing the reminder itself to become part of the "routine". A potential solution could therefore be the development of monitoring & reminder devices (smartphone apps, etc.) but we also have to take into consideration that in the case of Glaucoma the patients are usually older adults, thus not very keen with technologies. Moreover further research needs to be done to draw further conclusion whether this solution is the cost-efficient or not.

2.3 Practices and Interventions to Improve Compliance

Possible interventions include education of the patient or his close family about the Glaucoma, the gravity of an aggravation and the importance of the treatment, training on the drop instillation, but also psychological support for the patient.

Among the interventions (reminders, education/training, simplification of medication treatment) tested in their study, Waterman et al. (2013) showed that education stood out to be the only significantly effective method and Gray et al. (2011) showed that a single intervention was not enough, but an individual patient follow up program had a significantly positive effect on the compliance.

Moreover, Gupta et al., (2012) proved in their observation of 70 patients that not only very few patients (8.5%) could instill the drop properly, but also that nearly as few (18.5%) had received explanations on the instillation method, pointing out the need for education on the instillation method as well.

There is therefore a need to develop a robust follow-up process of the patient, measuring compliance on a regular basis in order to take the appropriate actions when the compliance seems to fall to lower levels than presumed.

CHAPTER 3 : METHODOLOGY

3.1 Introduction: Lean Six Sigma

Lean six sigma (LSS) has its roots in the lean manufacturing principles introduced by Toyota (Chiarini, 2012) and the six sigma initiatives in Motorola (Pzydek and Keller, 2003).

Facing a need to change in order to survive in a highly competitive global environment, Toyota, inspired by Ford's introduction of "Mass Production" manufacturing methods, developed new tools aiming for better quality and higher production efficiency. Those methods, including but not limited to "Just-In-Time" (1937), "5S," "Kanban" (1950), etc., first became known as the "Toyota Production System" (TPS) and started to spread in the automotive industry (Chiarini, 2012). A first official translation of the TPS handbook was made in 1975. Womack, Jones and Roos (1990) introduced the term "Lean," generalizing the TPS methods to "Lean manufacturing".

In parallel, Bill Smith at Motorola developed in the late 80's "Six Sigma" as a quality management methodology (Pzydek and Keller, 2003). Those methods, refined by General Electric (GE) in the 90's, became widely adopted process improvement methods. Six Sigma methodology do not only overlap with the principles of Lean Manufacturing, these two concepts are complementary, Lean focusing on eliminating waste and improving efficiency, and Six Sigma focusing on minimizing variability and delivering products

within the customer's specification limits. The combination of both "Lean" and "Six Sigma," "Lean Six Sigma" methodology, is nowadays widely used (George, 2002).

In the late 90's, Lean Six Sigma methods started to be used in the Service industry, including Healthcare. Particularly, the Virginia Mason Medical Center in Seattle, WA, was in 2002 the First Health Care System to declare and adopt TPS as management system, with goals to improve quality of care and patient safety (Plsek, 2013).

3.2 Overview of DMAIC Approach

This study follows the well-known five-phased Lean Six Sigma methodology known as the DMAIC cycle, where DMAIC stands for Define, Measure, Analyze, Improve and Control as shown in Figure 1. More precisely, the DMAIC methodology consists of 1. Defining the goal of the improvement project, 2. Measuring the current system performance, 3. Analyzing the system in order to identify potential improvement areas, 4. Improving the system and 5. Controlling the sustainability of the changes in the new system (Pzydek and Keller, 2003).

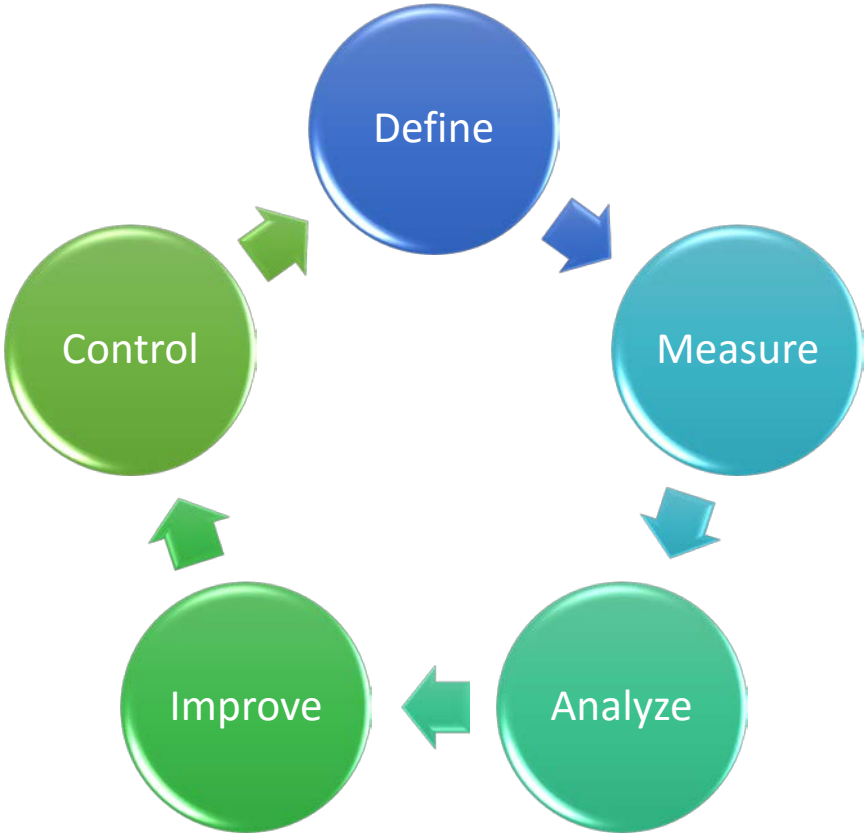

Figure 1: Lean Six Sigma DMAIC project cycle

Each step in the DMAIC cycle has a specific purpose and associated tools and techniques, which are adapted to our study as described in Figure 2:

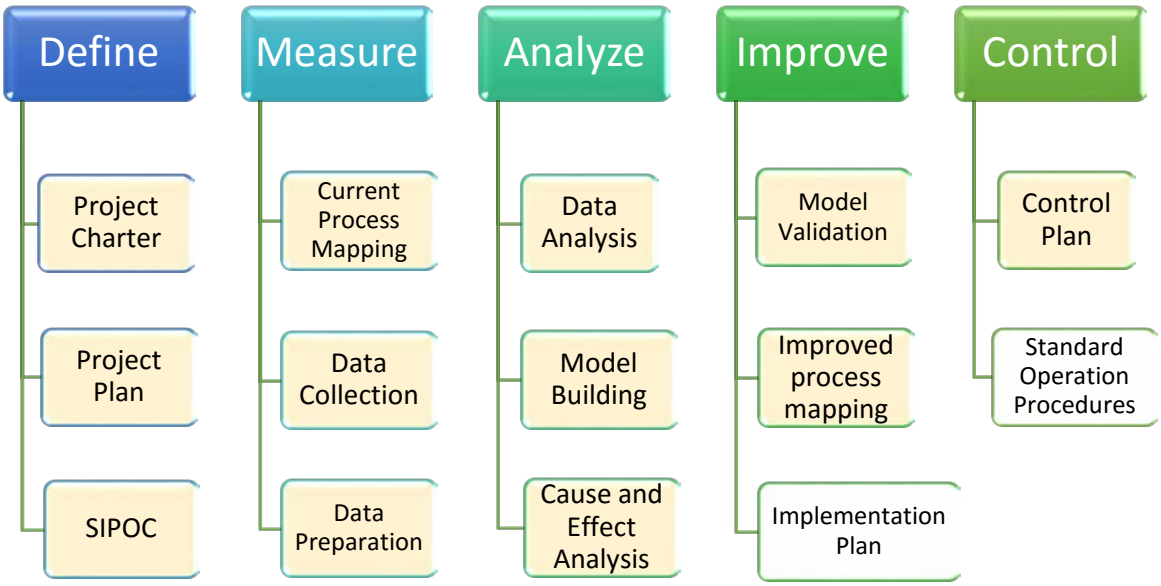

Figure 2: Lean Six Sigma DMAIC project Work Breakdown Structure (WBS)

3.2.1 Define Phase

The objective of the Define phase is to clearly define and quantify the objectives and scope of the project. This is a joint study between the VA hospital at Salisbury, NC and the University of North Carolina at Charlotte (UNC Charlotte). Lean Six Sigma tools such as Project Charter, Project Plan and SIPOC are to be developed in Define Phase.

3.2.2 Measure Phase

The goal of the Measure phase is to gather information about the current process and to gauge the current system performance. Various Lean Six Sigma tools (process mapping, SIPOC, charting, etc.), are used to visually and statistically summarize the glaucoma treatment process and the collected data.

Since Data Collection is an important part of the Measure phase, related methodologies are further described below.

3.2.2.1 Data Collection

In this section, we elaborate further on the data collection plan, data collection process, sampling method, sample size plan and data preparation.

- Data collection plan

The data variables can be classified into outputs and inputs.

- Outputs:

While the primary output to measure is Glaucoma Treatment Compliance, this measure needs to be defined. Some possible measures of compliance include refill rate ratio measurement or electronic monitoring. In this study we choose the Prescription Refill Rate as the compliance measure for practicality purposes since this data was readily available. Refill rate also seems to align with the literature which talks about Medication Possession Ratio (MPR) as a possible measure (Friedman et al., 2007). MPR is calculated as the ratio between the days of medication coverage based on the prescription refill picked up by the patient over the number of days in the observation period. Generally, a patient is considered compliant if the ratio is superior or equal to 80%, and non-compliant under (Cate et al., 2013). The output measure is summarized in Table 2.

Table 2: Output variable

Variable Coded Name	Variable Name	Operational Definition	Data Collection Method
refill	Refill Rate	Number of months refills were ordered over the total duration of observation	Retrospective Medical Chart Review

- Inputs:

We based our data collection plan on the literature review where we could identify some factors that might have a potential effect on the glaucoma treatment compliance. Although Ung et al. (2009) failed to prove that the association between medication adherence and follow-up visit adherence was significant, they point out that visit adherence can have a significant effect on disease progression. Moreover, since we believe it is also an indicator of patient behavior, in this study we decided to also collect the missed appointments records as factor for compliance

Input variables to be collected to measure the outcome are summarized in

Table 3. As shown in this table the 20 input variables can be grouped into socio-demographic, psychological, glaucoma record, and medical record categories.

Table 3: Input variables

	Data Category	Variable Coded Name	Variable Name	Operational Definition	Hypothesis	Data Collection Method
1	Socio-demographic	race	Race	White, black or other	Compliance is better for White	Retrospective Medical chart review
2		age	Age	Age in years	Compliance decreases with age	
3		married	Married	Marital Status	Compliance is better with presence of supportive third	
4		employ	Employed	Employment Status	Active people less compliant	
5		miles	Distance to Hospital	Distance to travel for Care at the Hospital	Compliance is worsen by distance	
6	Psychological	subabuse	Substance Abuse	Absence/presence of listed record of substance abuse	Any psychological disorder has a negative influence on compliance	
7		ptsd	PTSD	Absence/presence of Post-Traumatic Stress Disorder		
8		depress	Depression	Clinical Diagnosis of Depression		
9		mental	Mental Disorder	Diagnosis for other mental disorders: schizophrenia, bipolar disorder, or dementia		
10	Glaucoma record	duration	Duration	Number of months treated at VA for glaucoma	Compliance decreases with duration / severity of the disease	
11		missaptE	Missed Appointments Eye	Total number of missed appointments in Optometry for the past 2 years		
12		stage	Stage	Stage of Glaucoma		

Table 3: Input variables (continued)

	Data Category	Variable Coded Name	Variable Name	Operational Definition	Hypothesis	Data Collection Method
13	Glaucoma record	medchg	Medication Change	Number of times the glaucoma medications were added or changed during treatment	Numerous changes in medication can be a sign	Retrospective Medical chart review
14		gl meds	Glaucoma Medication	Total number of different prescribed glaucoma medications	Numerous treatment decrease compliance	
15		dr/day	Drops per Day	Total number of applications / day	Overwhelming treatment decreases compliance	
16	Medical record	#diag	Other Diagnosis	Total number of diagnosis listed for the patient	Co-morbidity leads to bad compliance	
17		missMD	Missed Medical Doctor Appointments	Total number of missed appointments in General Medicine for the past 2 years	Low medication compliance associated with low visit adherence	
18		totmed	Total Medication	Total number of prescribed medications	Numerous medications lead to bad compliance	
19		SC %	Service Connected Status	Percentage of service connected status (related to injury or income from VA)	Compliance decreases with disability level	
20		insur	Insurance Level	Level of insurance coverage (VA, Medicare, other)	Financial burden can influence bad compliance	

Attributes for each input variable are summarized in Table 4:

Table 4: Data collection plan

	Name of Measure	Input / Output	Type of Data	Level of measurement	categories
1	race	Input	Discrete	Nominal	Black, White, Other
2	age		Continuous	Scale	
3	married		Discrete	Nominal	Yes =1 / No =0
4	employ		Discrete	Nominal	Yes =1 / No =0
5	miles		Continuous	Scale	
6	subabuse		Discrete	Nominal	Yes =1 / No =0
7	ptsd		Discrete	Nominal	Yes =1 / No =0
8	depress		Discrete	Nominal	Yes =1 / No =0
9	mental		Discrete	Nominal	Yes =1 / No =0
10	duration		Continuous	Scale	
11	missaptE		Continuous	Scale	
12	stage		Discrete	Nominal	1, 2, 3
13	medchg		Continuous	Scale	
14	gl meds		Discrete	Scale	1, 2, 3
15	dr/day		Continuous	Scale	
16	#diag		Continuous	Scale	
17	missMD		Continuous	Scale	
18	totmed		Continuous	Scale	
19	SC %		Continuous	Scale	
20	insur		Discrete	Nominal	1, 2, 3
21	refill	Output	Continuous	Scale	

- Data collection process

The whole data collection and analysis process is summarized in a cross-functional flow chart displayed in Figure 3.

Data are collected by retrospective medical chart review. i.e. extraction of data of interest from the information already existing in the database when the study is initiated. Once collected the data are organized in excel spreadsheet and provided to the researchers.

- Inclusion criteria**:** Veterans patients diagnosed with Glaucoma, currently seen at a VA hospital in NC. Whereas some Veterans chose to receive all their care at a single VA Medical Center, other prefer to see their regular family Doctor for the regular care and come only to the VAMC or special care. Data selected this study include patients coming for follow-up visit at the VAMC at least 2 times per year.
- Exclusion criteria: "Sensitive" patients as defined by the VA policy, i.e. patients older than 88 years old or HIV patients are excluded from this study.

Data are filtered to exclude any "identifier" (such as name, social security number, telephone number and address) in order to ensure confidentiality of the data, before providing the data to the external researchers for statistical analysis.

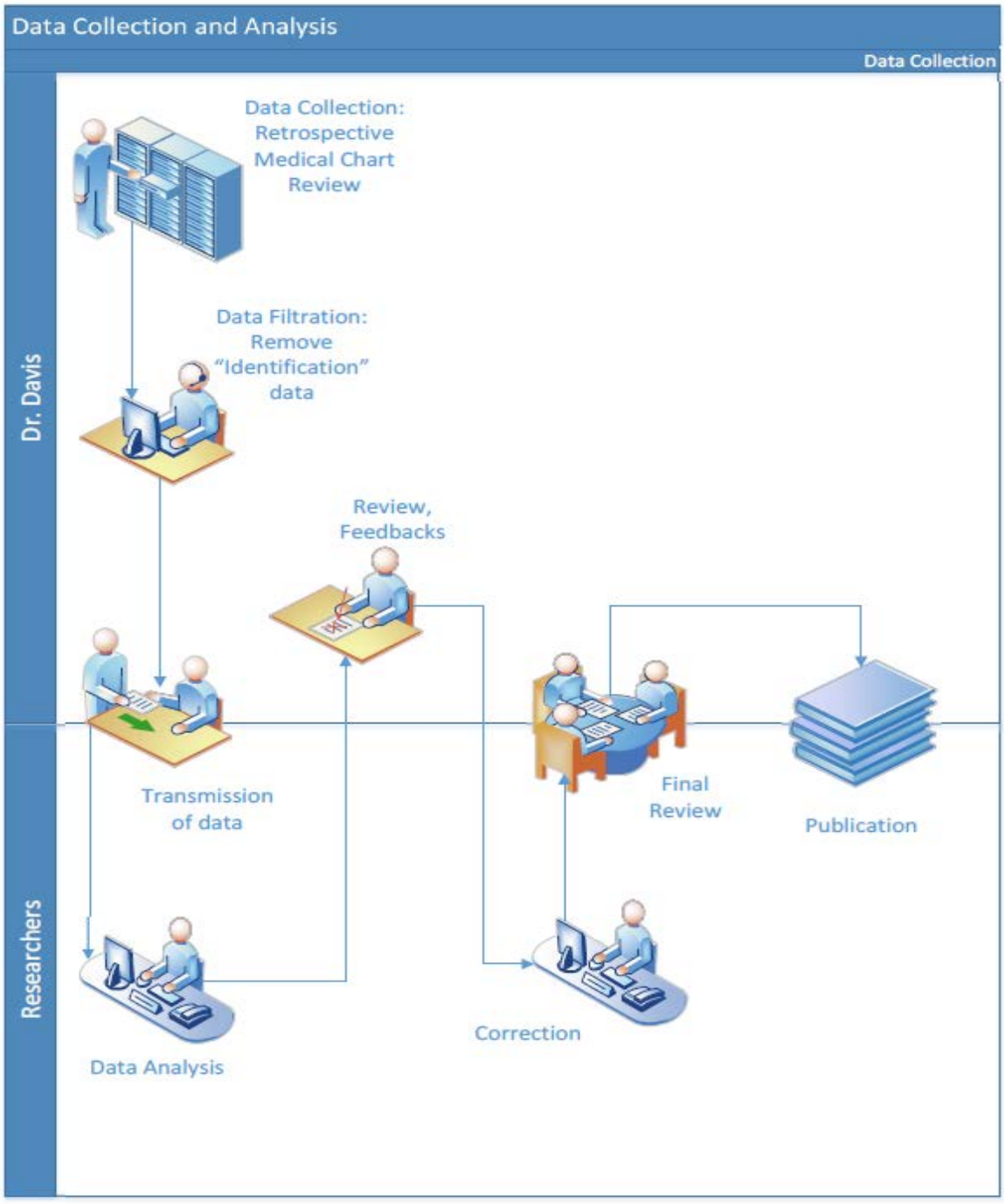

Figure 3: Data collection and analysis - cross-functional flow chart

- Sampling method

In this study we use a random split sampling method. randomization (Figure 4) which is an assumption used in many statistical methods ensures that the sample is representative of the entire population of the glaucoma patients. Split sampling refers to the separation of the data into two sets: calibration data and validation data. The calibration data is used to develop the predictive glaucoma treatment compliance model and the validation data is used to test the predictive capability of the developed model.

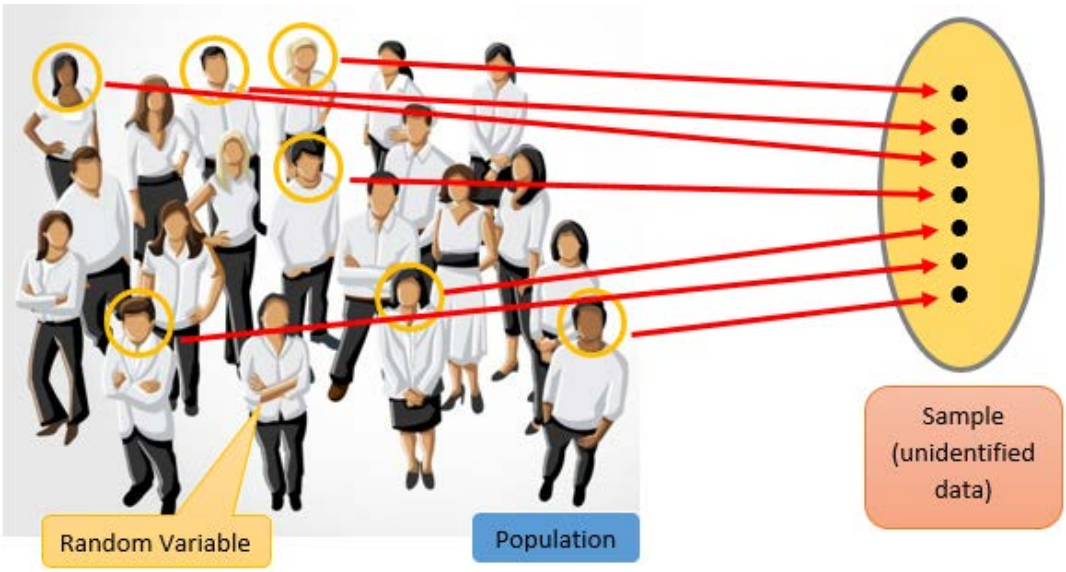

Figure 4: Simple random sampling method

- Sample size plan

Sample size is a critical element which can influence the accuracy of the results of the statistical analysis. Generally, the larger the sample size the more precise the estimation.

In this study, the data analysis consists in two steps: calibration (model building) and validation, and as indicated before for this purpose, we will use the method of Split Sampling to separate the data set into Calibration data and Validation data. To estimate the sample size, we need to consider these two sets of data.

For a multiple regression analysis Cohen and Cohen (1983) provided some guidelines for the identification of the required sample size. With the assumptions of a power level of 80% (0.80) and a significance level of 95% (alpha = 0.05), the minimum R^2 that the specified sample size will detect are summarized in Table 5:

Table 5: minimum R^2 for specified sample size

Sample Size	**Number of Independent Variables**			
	2	**5**	**10**	**20**
20	39	48	64	NA
50	19	23	29	42
100	10	12	15	21
250	4	5	6	8
500	3	4	5	9
1000	1	1	2	2

Adapted from: J. Cohen & P. Cohen (1983). Applied Multiple Regression/Correlation Analysis for the Behavioural Sciences. Hillsdale, NJ: Lawrence Erlbaum]

Considering we will reduce the number of factors to less than 20 independent variables, a sample size of 250 would give us an R Square value of less than 8, which is acceptable for our purpose. However, reducing the sample size to 100 would increase the significant R Square value to 21.

For a factor analysis, Verma (2012) recommends a sample size of 5-20 times the number of variables. For the initial 21 variables, a sample size of 250 would be more than 11 times the 21 variable, which is acceptable.

To confirm the sample size, we finally use the sample size calculation formula

$$n = \left(\frac{Z_{\alpha/2}S}{\Delta}\right)^2$$

With the sample size factors:

- n = minimum sample size
- $Z_{\propto/2}$ The corresponding Z value for acceptable risk level of α/2

  We take a statistical significance level (=Alpha level) of 0.05, i.e. a confidence level 95%. The corresponding Z value is 1.96.
- Δ the acceptable margin of error: we can tolerate a difference of 5%, i.e. 0.05 with a 90% chance (power: 0.9).
- s the estimation of the population standard deviation. Descriptive statistic of a preliminary sample gave us a standard deviation for compliance of 0.1757

Using the statistical analysis software Minitab Ver. 17 with the above parameters, we found that a minimum sample size of 130 was recommended.

Power and Sample Size

1-Sample Z Test

Testing mean = null (versus ≠ null)
Calculating power for mean = null + difference
α = 0.05 Assumed standard deviation = 0.1757

Difference	Sample Size	Target Power	Actual Power
0.05	130	0.9	0.900552

Figure 5: Minitab output for sample size estimation

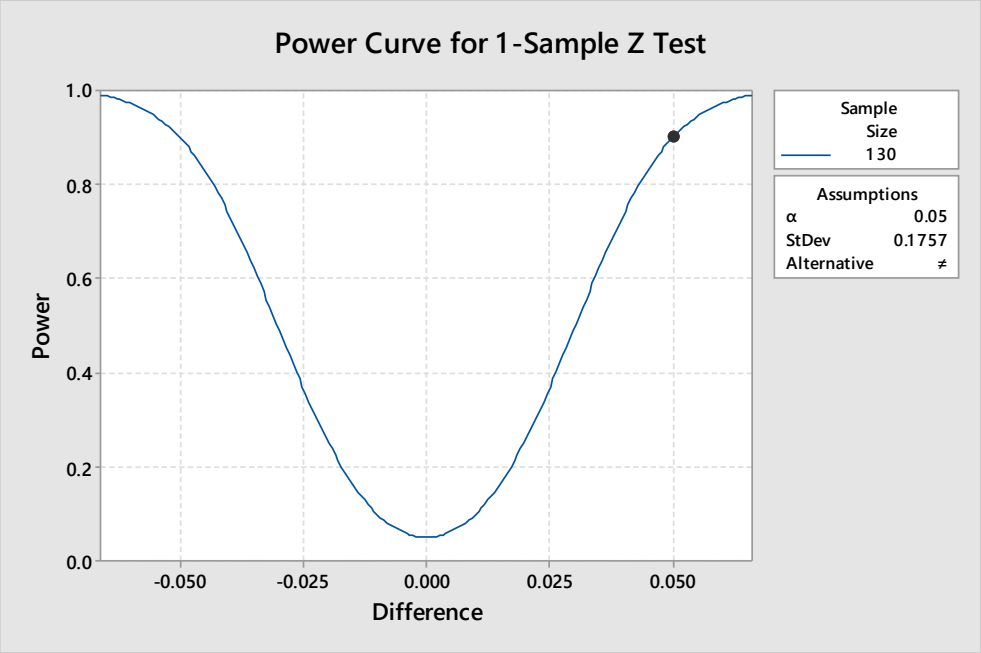

Figure 6: Minitab power curve

Since the data are split into 2 sets, it was concluded that a sample size of 250 (i.e. 200 for calibration and 50 for validation) would be large enough to obtain precise and accurate results in the analysis.

- Data preparation:

As indicated in the input and output data descriptions (Table 4), we do have categorical data to deal with. In order to utilize the categorical data to develop the glaucoma treatment compliance models, we need to do some data coding or data transformation. The coding is done using 1 and 0 values, which indicates that a condition exists versus not, respectively. Another consideration is related to the data scales. The non-categorical data such as age or number of medications have different order of scales. In order to avoid data scale bias, a data normalization procedure is also followed to bring the data to comparable scales of 0 to 1.

3.2.3 Analyze Phase

In the analyze phase, statistical methods such as 1) factor analysis and 2) multivariate step-wise regression analysis are used to identify the relationship between the input and output variables. This statistical relationship helps identifying the influential factors of glaucoma treatment compliance, and to validate the hypothesis about potential areas for improvement in the glaucoma treatment process.

- Factor analysis:

Factor analysis is a multivariate data analysis technique used to reduce the large number of correlated variables into a smaller number of uncorrelated (independent) variables, by classifying them into independent underlying “factors” (Verma, 2012). In the case of the glaucoma compliance problem we have 21 variables. Through the factor analysis, we are aiming to find the top “factors” that explain most of the variation in the data. Figure 7 shows an illustration of how the 21 possibly correlated variables are reduced into uncorrelated “factors” through the factor analysis.

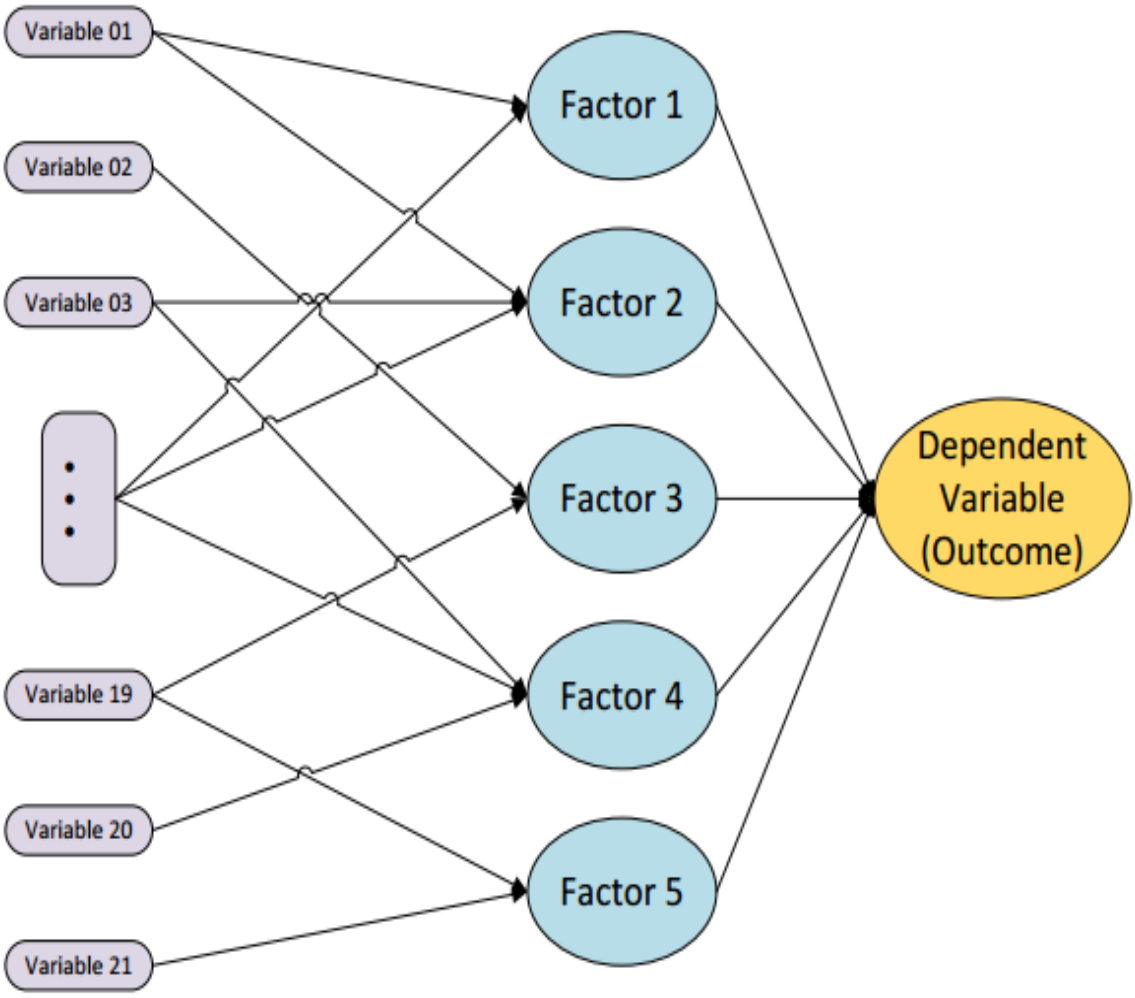

Figure 7: Factor analysis methodology

- Multivariate stepwise regression analysis:

Multiple step-wise regression analysis is a well-known statistical technique to build a mathematical relationship between the dependent (output) variables and those independent (input) variables. This relationship is summarized in a regression equation as illustrated in Figure 8.

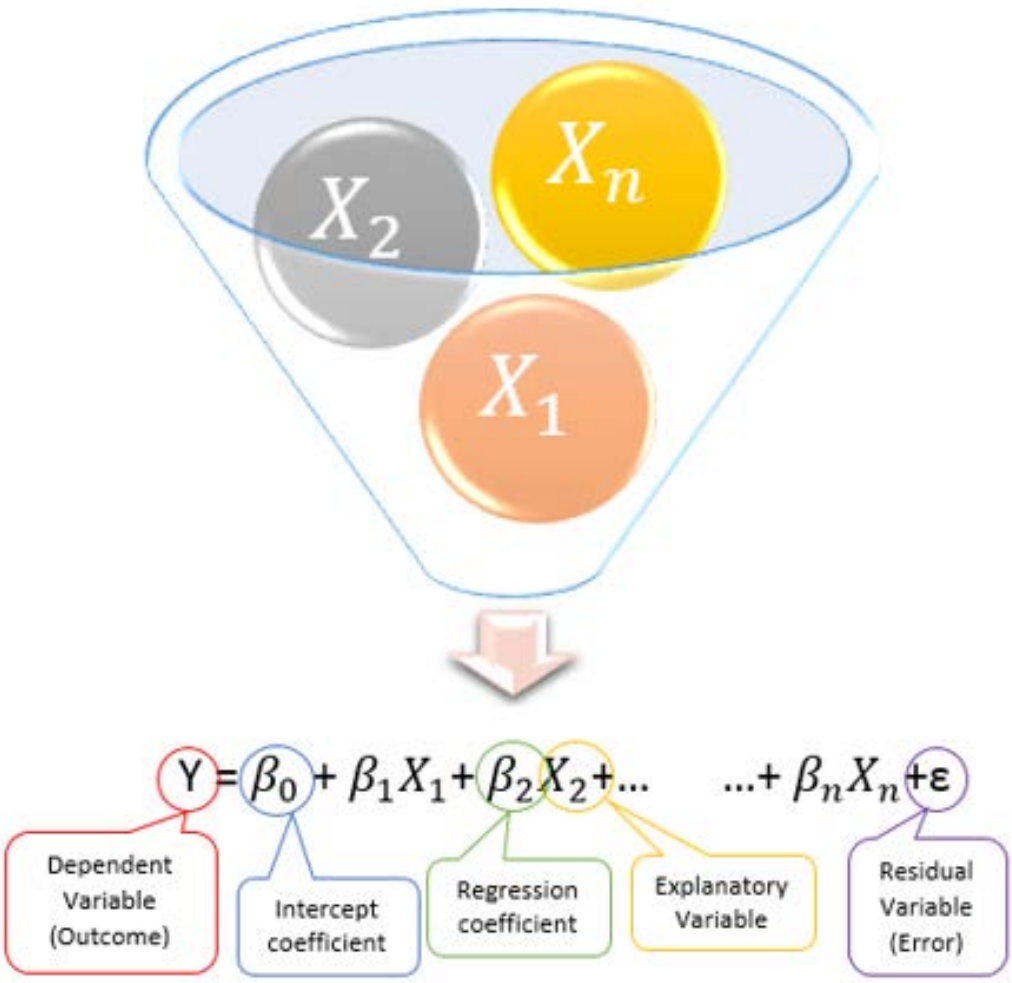

Figure 8: Regression analysis methodology

- Model building:

The model can then be used for prediction of future outcome based on the input variables. In our study, we particularly aim at using the results of the regression model to create a predictive model for the prediction of glaucoma treatment compliance as illustrated in Figure 9.

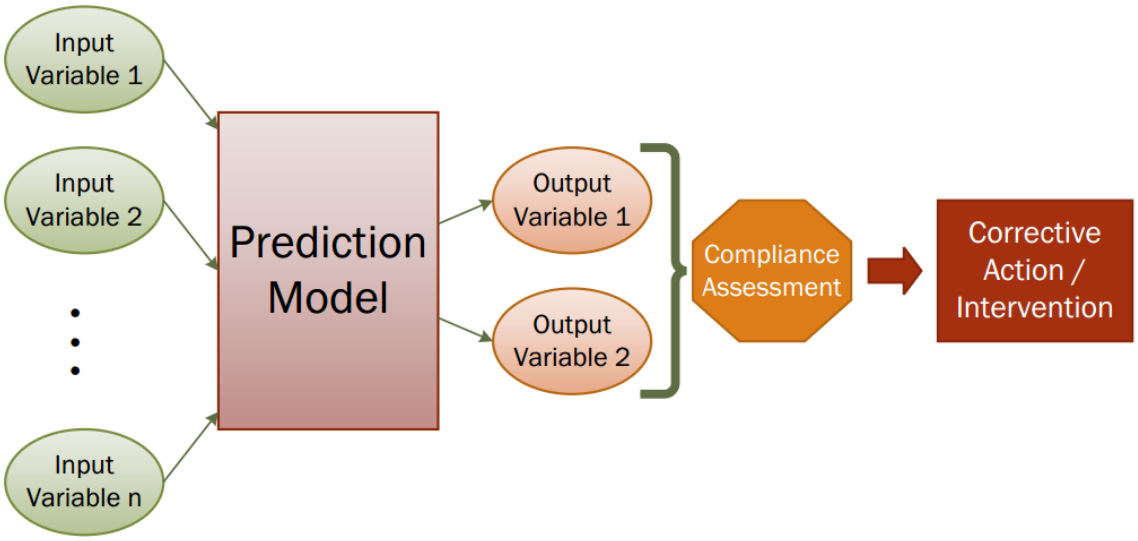

Figure 9: Predictive model and implementation

3.2.4 Improve Phase

In the improve phase, results and findings from the Analyze phase are used to improve the process. In our study it particularly consists in:

- Testing of the regression model using validation data.
- Development of the improved process
- Implementation plan

3.2.5 Control Phase

The last phase, control, is where actions are taken to ensure sustainability of the proposed improvements. In our study this will consist of a control plan.

CHAPTER 4 : APPLICATION – DEFINE PHASE

For the “Define” phase, the investigation team organized several meetings where they communicated about the project and its scope in order to determine the project charter as shown in Table 6. As indicated earlier, the goal has been determined as the identification and analysis of the influential factors for glaucoma non-compliance.

Table 6: Project charter

Project Description: The goal of this project is to improve the quality of care for Glaucoma patients, by improving the follow-up treatment process.
Problem Statement: In the current process, low compliance (adherence to prescribed medication) appears to be the most concerning problem. Influential factors for non-compliance need to be identified and analyzed.
Goal Statement: By identifying the influential factors the goal is to help the medical doctors to identify patient non-compliance to the glaucoma treatment and its root causes, and then to take the appropriate measures.
Scope In Scope: This study focuses on the two first research questions: • What are the main factors influencing non-compliance behavior? • How can non-compliance behavior be identified and assessed quantitatively?

Table 6: Project charter (continued)

Past data are collected from glaucoma patients' medical charts. A statistical analysis is performed to identify influential factors for glaucoma treatment compliance. Out of Scope: The last two research questions: • Which interventions (training, meetings, change of medication etc.) result in a significant improvement of compliance? • Can a standard follow-up process be determined to replace the existing guidelines, now including compliance assessment? As well as a real Scale Pilot study for testing of the process. Those are not addressed in this study but in further development of the project.
Assumptions: Data are collected and provided by VA Medical Center in Salisbury, NC
Constraints: Availability of data in different categories, time to collect data, timelines for VA internal approval processes, project period by the end of November, 2015.

4.1 SIPOC

A SIPOC diagram has been used to visually summarize the high level glaucoma follow-up care process (Figure 10). SIPOC stands for Supplier, Input, Process, Output, and Customer, which are the 5 columns of the diagram. The main input is the IOP measurement, which shows the progression and stage of glaucoma for a patient, which dictates the prescriptions and patient visitation intervals.

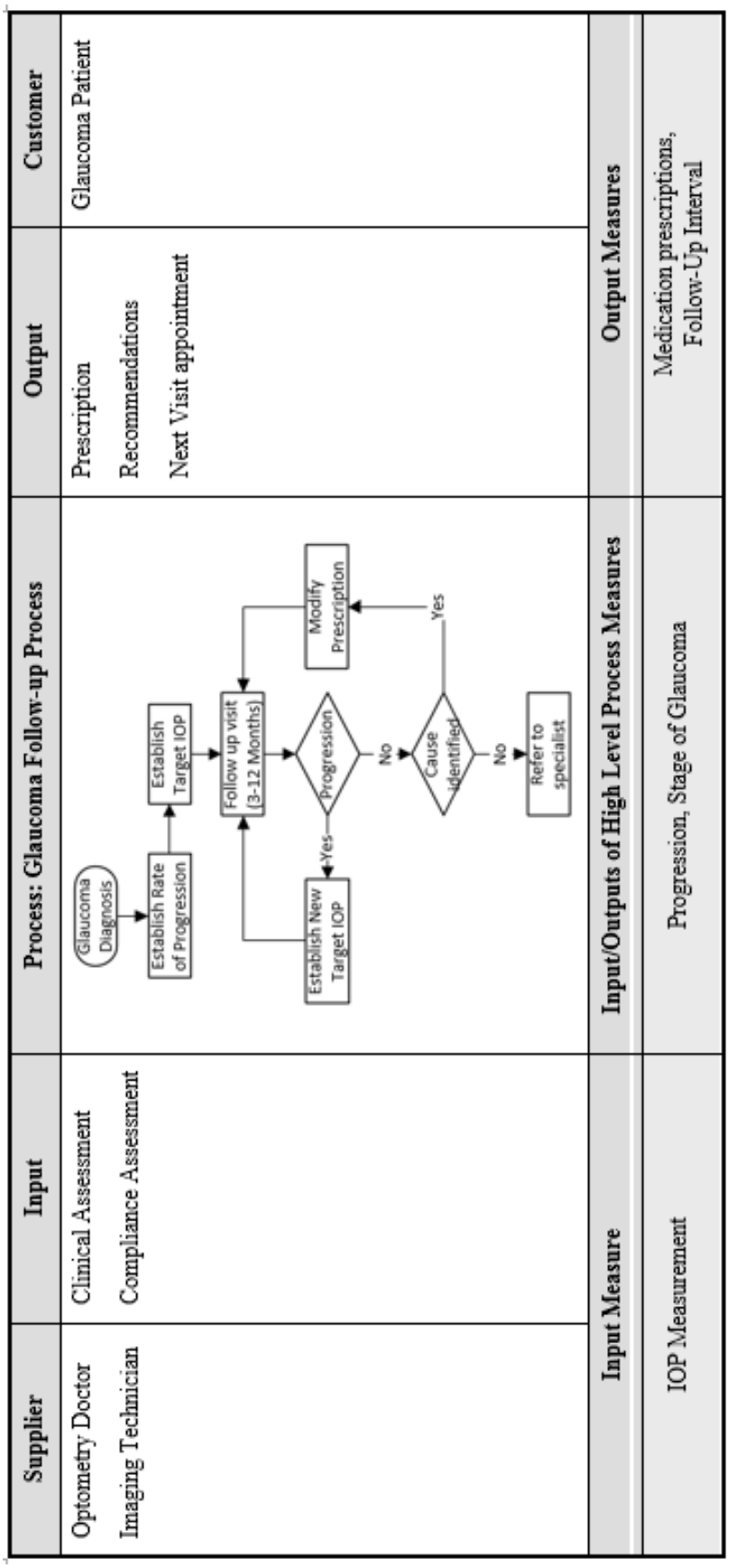

Figure 10: SIPOC

CHAPTER 5 : APPLICATION – MEASURE PHASE

The second step of the DMAIC process is Measure, where the emphasis is on understanding better the current process, before continuing with more precise analyze and improvements suggestions in the next phases. To understand better the process to improve, measurements and visual analysis of the current process are used, and data to be used in the analyze phase are collected.

5.1 Current Process Mapping

A process map is a graphical representation of the process flow, which helps to visually summarize the different individual steps of the current process as it is. In the Glaucoma patients follow up process, the optometry doctor works in close collaboration with the imaging technician, and the patients is also taking an active role by participating to the tests, answering follow-up questions, etc. A swim lane diagram was therefore chosen in order to visually distinguish the different actors of each sub-process.

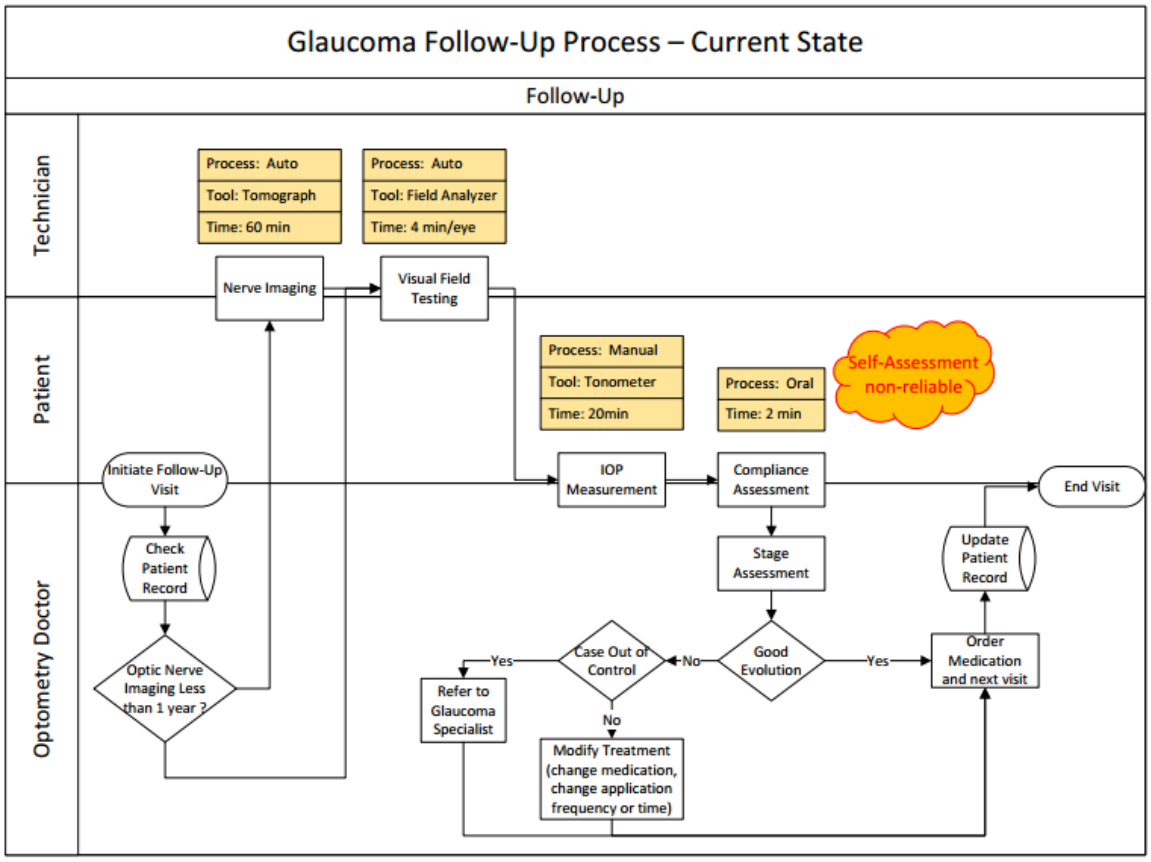

Figure 11: “As-is” glaucoma follow up process map

Before the data analysis where we analyze to which extend the problem is affecting the process, process mapping helps to visualize which areas/departments/steps are affected by the problem, and identify the bottlenecks and variation in the current process. Although this is the first step in identifying the future possible improvement opportunities, the current process map does not reflect those changes and shows the process as it is currently being used.

5.2 Data Collection

Data who describe well the problem should be collected. Since in this project data collection was started very early in the process, details on the data collection are described

in the methodology section. 250 data points were collected. A screen capture of the original data collection table is placed in the appendix A.

First of all, the response variable needs to be computed: it was defined in the methodology as the ratio between the days of medication coverage based on the prescription refill picked up by the patient over the number of days in the observation period, a new variable called “Refill Rate” is therefore computed.

CHAPTER 6 : APPLICATION – ANALYZE PHASE

6.1 Data Analysis

6.1.1 Exploratory Data Analysis

On the 250 data points collected, 133 patients were non-compliant, i.e. with a ratio between duration and refill rate lower than 80%. On this group of patients, 53.20% were non-compliant.

In order to have a better understanding of the data before actually performing the regression analysis, a graphical summary for each individual continuous variable was computed in Minitab. Those graphical summaries are attached in appendix B and the main characteristics are summarized in Table 7.

Table 7: Main characteristics of continuous data

Measure	Mean	Standard deviation	Outliers	Value of outliers
refill rate	0.76771	0.13365	None	
age	72.557	8.418	None	
miles	25.133	19.617	A115	65.4
			A218	66.3
			A112	67.5
			A245	69.5
			A210	71.2
			A215	73.1
			A1	75.12
			A63	80.1
			A109	80.8
			A49	86.9
			A145	97.1
			A118	105.7
			A54	114.5
duration	54.724	41.496	None	
missaptE	1.044	1.1966	None	
medchg	1.008	1.2057	None	
dr/day	2.132	1.2873	None	
#diag	10.800	3.477	A225	20
			A249	20
			A158	21
			A172	21
			A205	24
missMD	0.74	0.89195	A40	3
			A46	3
			A57	3
			A136	3
			A147	3
			A205	3
			A214	3
			A21	4
			A112	4
			A4	5
totmed	10.356	3.826	A229	21
			A249	22
SC %	30.6	38.214	None	

6.1.2 Preliminary Analysis

Before processing to the actual model building, we do some exploratory analysis on the raw data in order to assess the best model. Indeed, since we have many predictor variables for one response, some bias in the analysis may occur:

- Over-specified model: an over-complicated model with too many variables would create some noise and therefore have less precise estimate
- Under-specified model: oppositely, a model with too few predictor variables would be subject to bias and would not be able to accurately predict the variation.
- Multicollinearity: when some of the predictor variables are correlated to each other. Multicollinearity is our biggest concern since it would increase the variance of the coefficient estimates and therefore make the results more difficult to interpret but also make our model unstable.

Trying to graphically estimate the individual effect of each input variable on the response variable: refill rate, scatter plots are displayed for each continuous variable to explore the type of relationship to the output and attached in appendix C. One-way ANOVA is used to assess the individual effect of each categorical predictor factor. Interval plots are attached in appendix D and P values are summarized in Table 8.

Table 8: P values for ANOVA for each categorical variable

Variable	P Value
Race	0.206
married	0.982
employd	0.868
subabuse	0.295
ptsd	0.528
depress	0.166
mental	0.001
Stage	0.249
glmed	0.191
Insur	0.537

To have a more quantitative estimation of the effect of each predictor variable on the response variable, correlation coefficients are computed. Hypothesis stipulated in the data collection plan can then be verified and relations are summarized in Table 9.

Table 9: Individual correlations between variables and refill rate

Variable Coded Name	Correlation coefficient	P Value	Relation	Original Hypothesis	Hypothesis validated?
race	0.08	0.206	Very Weak positive	Compliance is better for White	Yes
age	-0.036	0.572	Very Weak negative	Compliance decreases with age	Yes
married	-0.001	0.982	Very Weak negative	Compliance is better with Presence of supportive third	No
employ	-0.011	0.868	Very Weak negative	Active people less compliant	Yes
miles	0.056	0.375	Very Weak positive	Compliance is worsen by distance	No

Table 9: Individual correlations between variables and refill rate (continued)

Variable Coded Name	Correlation coefficient	P Value	Relation	Original Hypothesis	Hypothesis validated?
subabuse	0.067	0.295	Very Weak positive	Any psychological disorder has a negative influence on compliance	No
ptsd	0.04	0.528	Very Weak positive		No
depress	-0.088	0.166	Very Weak negative		Yes
mental	-0.217	0.001	Weak Negative		Yes
duration	-0.24	0	Weak Negative	Compliance decreases with duration / severity of the disease	Yes
missaptE	-0.125	0.048	Very Weak Negative		Yes
stage	-0.098	0.123	Very Weak Negative		Yes
medchg	-0.171	0.007	Very Weak Negative	Numerous changes in medication can be a sign	Yes
gl meds	-0.079	0.211	Very Weak Negative	Numerous treatment decrease compliance	Yes
dr/day	-0.086	0.175	Very Weak Negative	Overwhelming treatment decreases compliance	Yes
#diag	-0.117	0.065	Very Weak Negative	Co-morbidity leads to bad compliance	Yes
missMD	-0.233	0	Weak Negative	Low medication compliance associated with low visit adherence	Yes
totmed	-0.043	0.497	Very Weak negative	Numerous medications lead to bad compliance	Yes
SC %	0.041	0.523	Very Weak positive	Compliance decreases with disability level	No
insur	0.049	0.438	Very Weak positive	Financial burden can influence bad compliance	Yes

In addition to correlation of each variable with the response variable, we also want to have an idea of the collinearity between the variables, so we computed the pairwise matrix for all the variables which can be found in appendix E.

Although some interesting observations could be made from those correlation coefficients, we don't want to make too early conclusions and we are interested in observing the whole set of data, since each variable may have a different effect when taken as the whole set.

6.1.3 Split Sampling:

A random list of 200 samples from the 250 was generated and used to split the data into 2 sets: 200 data points for the calibration and 50 for the validation of the model.

6.1.4 Model Selection

The very first step before the actual model building is to test different models with different parameters, in order to be able to assess and choose the model that fits the best our data.

It was mentioned in the methodology that we would perform normalization of the continuous data to bring them into a [0-100] scale. Several runs using normalized values and non-normalized values showed no difference in the results, and we therefore did not use the normalized data.

We choose the following parameters to be tested and compared:

- Factor analysis: as described in the methodology, performing a factor analysis can be a way to extract new independent factors from a set of variables highly correlated. In order to be able to assess the benefit of the factor analysis, we try with or without and compare.

- Type of stepwise regression model: (linear or non-linear). When performing a classical stepwise regression, we are making the assumption that the relation between the input variables and the output variable is a linear relation. To validate this assumption, we also decide to perform stepwise regression analysis including interaction terms and polynomial terms, and compare.
- Unusual observations. In our case we observe some unusual observations: points with leverage values or points with large residual. Although it is expected to have about 5% of the data being labeled as unusual observations, we want to assess their effect on the results and decide to compare the models when keeping those unusual observations, or after removing them.
- Transformation of the response variable. The graphical summary indicates that the data is not normally distributed (P value <0.005 for the Anderson-Darling Normality test). Moreover, this response variable “refill rate” is a calculated ratio between 2 other variables. One way to deal with non-normal response is to perform a Johnson Transformation, where the most accurate transformation function is selected from three families of functions in the Johnson system, which cover a wide variety of distributions by changing the parameters. Figure 12 shows details about the transformation: the best transformation and corresponding Z value, as well as the transformation function used. We can see that although the original data set was non-normal, the new transformed data follows a normal distribution with a P value of 0.161. Figure 13 shows the new distribution. We can observe that the range is not [0,1] anymore and the new distribution includes some negative values. To prevent confusion, the transformed response variable is called “new refill rate” and

used for the rest of the analysis. Normality of the response variable is not a requirement for regression analysis, with therefore decide to perform analysis with and without the transformation of the response variable and compare.

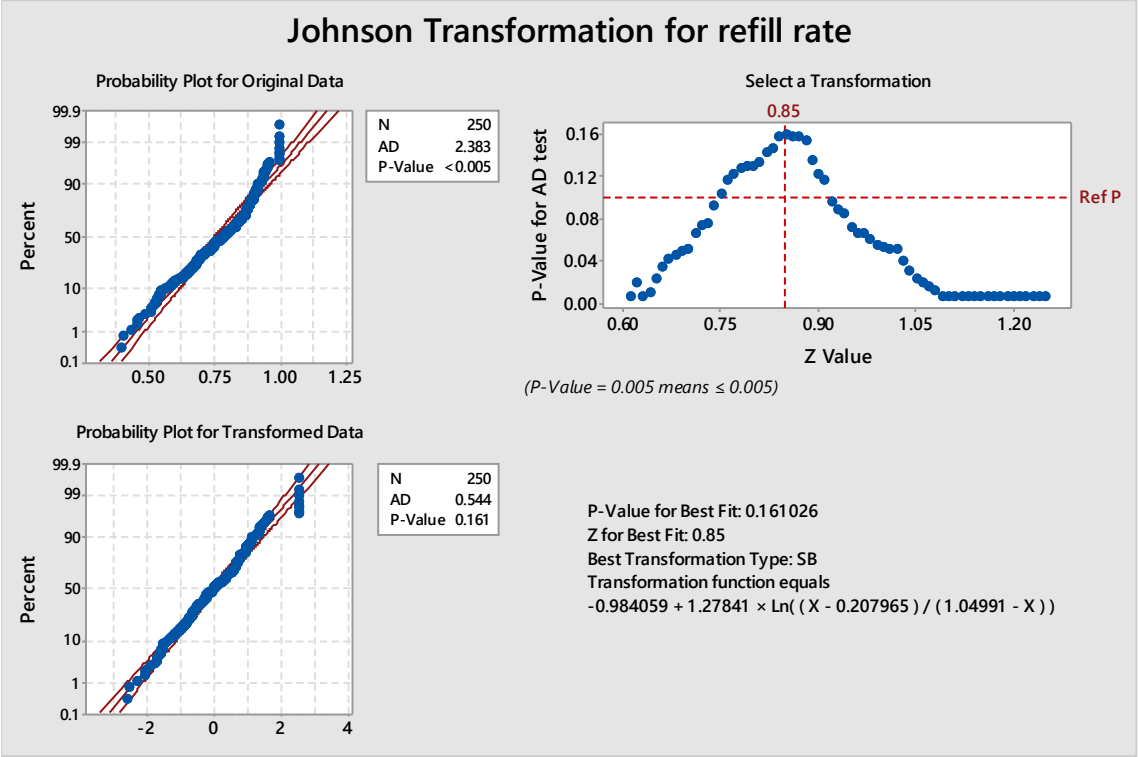

Figure 12 : Johnson transformation summary

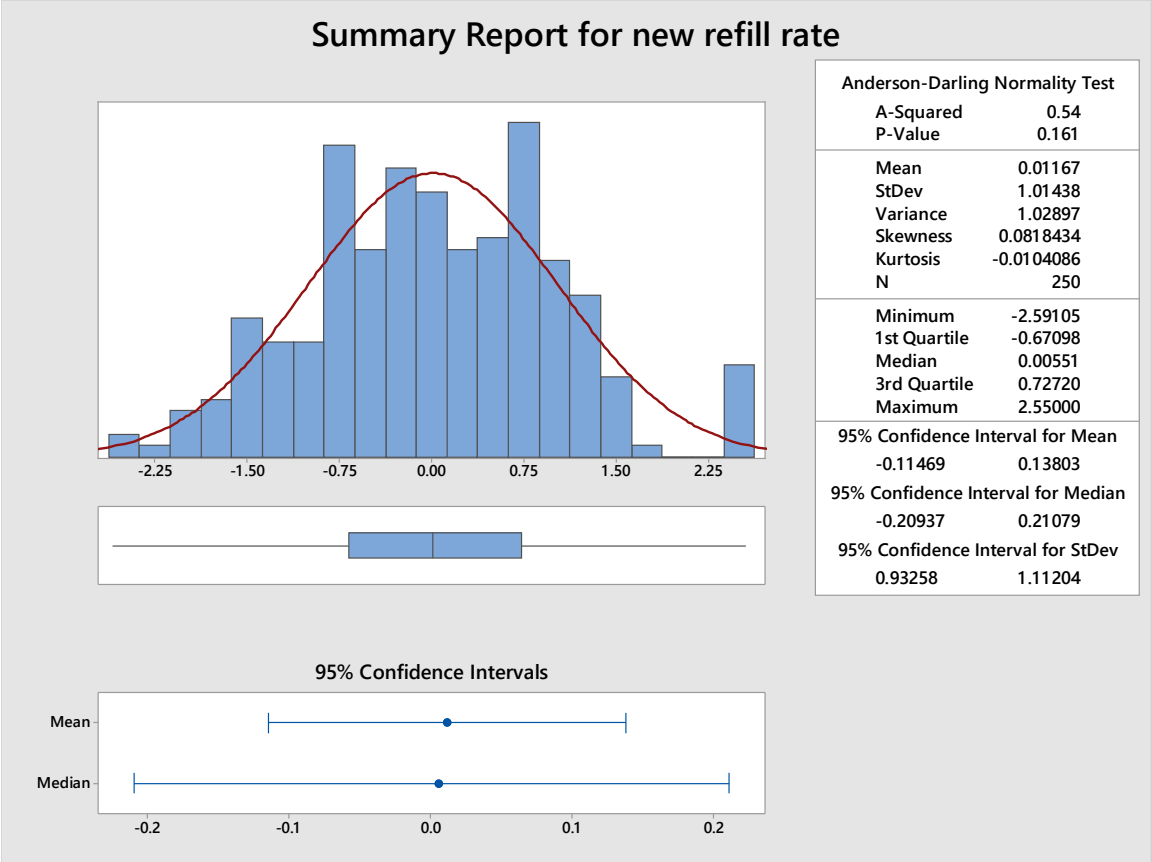

Figure 13: Graphical summary after Johnson transformation

- Replicates: we decide to perform 2 replicates of different sets of 200 data obtained from split sampling. We also perform analysis on the 250 original data points, to be used as an additional item for comparison.

  The measures chosen to compare those models are:

- For the calibration:
  - R2, the R Squared, showing how much of the variance in the response variable is explained by the model.
  - R2-adj, the adjusted R Square which has been adjusted according to the number of predictors in the model.

  - R2-pred, the predictive R square showing how much of the variance in the response variable the model has the capability to predict.

- For the validation:
  - R2, the coefficient of determination between the original and computed data values.
  - MSE, the Mean Square Error between the original and computed values, indicating the prediction accuracy of the model.

The results of the different runs and replicates are summarized in the tables in the following pages.

- UO stands for Unusual Observations: “keep” means that we kept the results of the stepwise regression with the unusual observations, “remove” means that we run additional steps, removing the unusual observations at each steps until we get none. The last column “# of UO” represents the number of unusual observations designated in the analysis.
- “transf” is for the transformation of the response variable, 0 indicating that the original data without transformation was used in the regression analysis, J indicating that the data after Johnson transformation was used.
- “terms” represents which kind of terms were included in the analysis, with L meaning only the linear terms, and NL meaning that the non-linear terms (polynomial and interactions terms) were also added to the analysis.
- * as R2 pred means that “some required terms are impossible to estimate"

Table 10: Summary for the models obtained with 250 data points

run	data set	UO	Factor Analysis	Transf	terms	R2	R2adj	R2pred	# of UO
R1	250	Keep	None	0	L	13.62%	12.57%	10.63%	20
R2					NL	83.44%	69.91%	*	8
R3				J	L	16.78%	14.73%	11.98%	22
R4					NL	99.31%	97.21%	92.95%	3
R5			FA	0	L	15.09%	12.99%	9.88%	15
R6					NL	100%	100%	100%	226
R7				J	L	16.41%	13.99%	10.84%	16
R8					NL	100%	100%	100%	226
R9		remove	None	0	L	32.55%	30.58%	27.13%	0
R10					NL	100%	100%	*	201
R11				J	L	27.91%	25.39%	21.87%	0
R12					NL	100%	100%	100%	227
R13			FA	0	L	47.18%	44.87%	41.60%	0
R14					NL	NA			
R15				J	L	40.62%	37.64%	34.06%	0
R16					NL	NA			

Table 11: Summary for the models obtained with 200 data points – Replicate 1

						Calibration				Validation	
run	data	UO	FA	Trans	terms	R2	R2adj	R2pred	# of UO	R2	MSE
R1	200 Replicate 1	Keep	None	0	L	13.49%	11.72%	9.05%	17	14.70%	0.0133
R2					NL	89.83%	83.55%	79.50%	8	7.85%	0.0577
R3				J	L	15.30%	13.12%	10.00%	11	16.77%	0.0127
R4					NL	59.53%	45.58%	*	10	0.00%	0.0352
R5			FA	0	L	13.90%	11.68%	8.41%	11	13.01%	0.0136
R6					NL	100%	100%	100%	168	NA	
R7				J	L	14.63%	12.43%	9.35%	11	13.77%	0.0132
R8					NL	100%	100%	100%	173	NA	
R9		remove	None	0	L	50.80%	46.56%	44.86%	0	13.84%	0.0143
R10					NL	100%	100%	*	153	NA	
R11				J	L	51.37%	48.17%	44.19%	0	15.22%	0.0136
R12					NL	100%	100%	99.37%	163	NA	
R13			FA	0	L	38.59%	35.69%	31.27%	0	15.05%	0.0139
R14					NL	NA					
R15				J	L	22.25%	18.55%	13.55%	0	11.63%	0.0136
R16					NL	NA					

Table 12: Summary for the models obtained with 200 data points – Replicate 2

						Calibration				Validation	
run	data	UO	FA	Transf	terms	R2	R2adj	R2pred	# of UO	R2	MSE
R1	200 Replicate 2	Keep	None	0	L	17.69%	15.57%	12.14%	15	6.37%	0.0170
R2					NL	96.48%	91.13%	80.87%	7	2.05%	0.0960
R3				J	L	18.60%	16.07%	12.22%	12	8.69%	0.0185
R4					NL	99.42%	97.50%	95.20%	5	0.04%	0.0724
R5			FA	0	L	17.83%	14.84%	10.34%	13	8.90%	0.0161
R6					NL	100%	100%	100%	170	NA	
R7				J	L	18.02%	15.04%	11.03%	15	10.44%	0.0177
R8					NL	100%	100%	100%	174	NA	
R9		remove	None	0	L	47.39%	44.13%	39.51%	0	10.48%	0.0213
R10					NL	100%	100%	100%	163	NA	
R11				J	L	41.73%	38.91%	35.28%	0	4.23%	0.0210
R12					NL	Impossible to estimate					
R13			FA	0	L	49.14%	46.19%	42.13%	0	7.90%	0.0214
R14					NL	NA					
R15				J	L	51.74%	49.02%	45.49%	0	3.14%	0.0219
R16					NL	NA					

The following observations can be made:

- Type of stepwise regression model: (linear or non-linear). Runs 6 and 8 seems to always give an extensive list of unusual observations from the first regression analysis. Those models have therefore to be eliminated. Since too many unusual observations are designated from the first try of the regression analysis, it was therefore not necessary to try the corresponding runs after removing the unusual observations: runs 14 and 16 are non-feasible. Runs 10 and 12 also presented a too numerous number of unusual observations in the next steps after we removed the first set of unusual observations, those 2 runs are eliminated as well. For the last 2 runs using the non-linear terms (runs 2 and 4), although the results of the calibration phase (R-Squared, predicted R-Square) are very good, the validation runs proves

that the models perform poorly to predict new data points. The high R square obtained in the calibration is uniquely thanks to a high number of predictors, and should not be interpreted as a good fit of the model. Runs 2, 4, 6, 8, 10, 12, 14 and 16 are therefore eliminated.

- Unusual observations: removing the unusual observations generally gives a better fit and predictability of the model.
- Factor analysis: factor analysis, when performed before a regression analysis using the linear terms only, generally helps to improve the model.
- Johnson transformation: when doing a regression analysis only, seems to improve the results, but not when using a factor analysis first.

In order to have a more precise estimate of the best model among the remainder (R1, R3, R5, R7, R9, R11, R13, R15), we perform 2 more additional replicates. The results are summarized in Table 13and Table 14.

Table 13: Summary for the models obtained with 200 data points – Replicate 3

					Calibration				**Validation**	
run	data	UO	FA	Transf	R2	R2adj	R2pred	# of UO	R2	MSE
R1	200 Replicate 3	Keep	None	0	18.68%	15.71%	11.65%	18	8.01%	0.0148
R3				J	19.13%	16.62%	13.00%	16	9.86%	0.0151
R5			FA	0	16.13%	13.17%	10.17%	13	7.69%	0.0144
R7				J	17.59%	15.03%	10.93%	14	7.94%	0.0153
R9		remove	None	0	57.51%	54.93%	51.07%	0	9.06%	0.0181
R11				J	36.27%	34.11%	31.02%	0	5.70%	0.0158
R13			FA	0	76.10%	73.71%	70.60%	0	5.60%	0.0185
R15				J	32.17%	29.29%	24.99%	0	4.87%	0.0166

Table 14: Summary for the models obtained with 200 data points – Replicate 4

					Calibration				Validation	
run	data	UO	FA	Transf	R2	R2adj	R2pred	# of UO	R2	MSE
R1	200 Replicate 4	Keep	None	0	15.42%	14.13%	11.80%	15	15.23%	0.0145
R3				J	16.44%	15.16%	13.09%	18	14.83%	0.0154
R5			FA	0	16.28%	14.12%	10.76%	13	13.89%	0.0147
R7				J	17.31%	15.18%	12.39%	15	13.82%	0.0155
R9		remove	None	0	43.63%	41.21%	37.68%	0	12.14%	0.0192
R11				J	18.66%	17.18%	14.63%	0	11.60%	0.0169
R13			FA	0	37.07%	34.60%	30.87%	0	15.69%	0.0184
R15				J	19.65%	17.27%	13.81%	0	19.55%	0.0154

The average results for each run (average of the values obtained for the 4 replicates) are computed and displayed in Table 15.

Table 15: Average results for the 4 replicates

run	**UO**	**FA**	**Transf**	**Calibration**		**Validation**	
				R2	**Rpred**	**R2**	**MSE**
R1	Keep	None	O	16.32%	14.28%	11.08%	0.01492
R3			J	17.37%	15.24%	12.54%	0.01543
R5		FA	O	16.04%	13.45%	10.87%	0.01470
R7			J	16.89%	14.42%	11.49%	0.01543
R9	remove	None	O	49.83%	46.71%	11.38%	0.01823
R11			J	37.01%	34.59%	9.19%	0.01683
R13		FA	O	50.23%	47.55%	11.06%	0.01805
R15			J	31.45%	28.53%	9.80%	0.01688

Runs R3 and R7, despite having the highest R squared for validation, present a relatively low R squared and predicted R squared for the calibration phase. R9 and R13, on the other hand present some satisfying results for both the calibration and validation phases. We therefore use runs R9 and R-13 to illustrate the model building. The actual

model building is described in the following pages and the validation is described in Chapter 7: Application – Improve Phase.

6.1.5 Calibration of Run R9

- Stepwise regression analysis

Variables are separated in the regression analysis input into “continuous factors” and “categorical factors”. We have used a stepwise regression analysis, where the least significant variables are gradually removed at each step. Value for the alpha to enter/remove variables is set to 0.15.

The model summary is displayed in Table 20.

Table 16: Model summary

S	R-SQ	R-SQ(ADJ)	R-SQ(PRED)
0.067482	50.80%	48.56%	44.86%

R square (R-SQ) or the coefficient of determination shows that model can explain 50.80% of the variance. R-SQ (PRED), the predictive R square shows that the model has the capability to predict 44.86% of the variance in the response variable. Analysis of variance (ANOVA) results are summarized in Table 17. The significance of the model (P-value for the regression) is 0, showing that the regression equation significantly accounts for the variability in the response variable.

Table 17: Analysis of Variance (ANOVA)

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	6	0.62054	0.103423	22.71	0
medchg	1	0.06835	0.068347	15.01	0
dr/day	1	0.03554	0.035537	7.8	0.006
missedMD	1	0.09113	0.091126	20.01	0
insur	1	0.02287	0.022869	5.02	0.027
employd	1	0.03052	0.030523	6.7	0.011
mental	1	0.26528	0.265281	58.26	0
Error	132	0.6011	0.004554		
Total	138	1.22163			

The coefficients for the significant factors are summarized in Table 18. The individual p values indicate the level of the effect of each factor to the response variable.

Table 18: Regression coefficients

Term	Coef	SE Coef	T-Value	P-Value	VIF
Constant	0.8463	0.0289	29.26	0	
medchg	-0.02307	0.00596	-3.87	0	1.48
dr/day	-0.01526	0.00546	-2.79	0.006	1.4
missedMD	-0.03476	0.00777	-4.47	0	1.06
insur	0.0239	0.0107	2.24	0.027	1.26
Employd 1	-0.0668	0.0258	-2.59	0.011	1.23
Mental 1	-0.1401	0.0184	-7.63	0	1.1

We can see that number of times the Glaucoma medication was changed, number of missed MD appointments and recorded mental disorder (other than PTSD or depression) are highly significant with a P value of 0. Number of drops per day, insurance level and employment status are also significant since they have P values smaller 0.05. All the variable except insurance level have negative coefficient, indicating that they are negatively related to compliance. Insurance level is the only variable related positively to

compliance. Those results seems to align with our previous hypothesis stated in the methodology section.

The obtained coefficients are then used in the regression equation which is summarized in Table 19.

Table 19: Regression equations

employd	mental	Regression equation
0	0	refill rate = 0.8463 - 0.02307 medchg - 0.01526 dr/day - 0.03476 missedMD + 0.0239 insur
0	1	refill rate = 0.7062 - 0.02307 medchg - 0.01526 dr/day - 0.03476 missedMD + 0.0239 insur
1	0	refill rate = 0.7795 - 0.02307 medchg - 0.01526 dr/day - 0.03476 missedMD + 0.0239 insur
1	1	refill rate = 0.6394 - 0.02307 medchg - 0.01526 dr/day - 0.03476 missedMD + 0.0239 insur

6.1.6 Calibration of Run R13

- Factor analysis

A factor analysis was performed in order to replace the 20 inter-related variables by 20 independent variables, and then to perform a regression analysis on those new variables. In order to simplify the factor structure, we chose to perform a Varimax rotation. In order to make the interpretation as easy as possible, the number of factors to extract is the number of input variables: 20.

Figure 14 below shows the scree plot of the eigenvalues for the 20 factors obtained as well as the cumulative variance explained. Although the Kaiser's rule would dictate to retain the factors with eigenvalue greater than 1 (Ledesma & Valero-Mora, 2007)., since the purpose of the factor analysis in this study was to obtain non-correlated and normalized

variables for the regression analysis, we chose to continue with the 20 factors, in order to retain 100% of the variance.

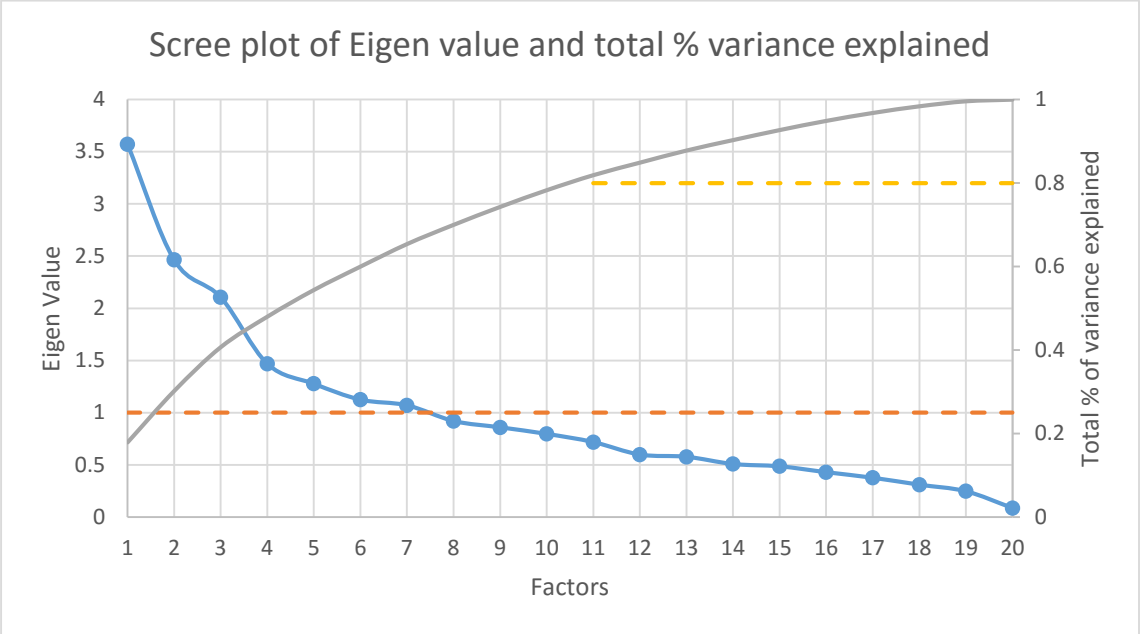

Figure 14: Eigen values and total variance explained

- Stepwise regression analysis

We have used a stepwise regression analysis, where the least significant variables are gradually removed at each step. Since the factor scores (computed in the factor analysis) are already in the form of normalized continuous data, there is no need to perform any transformation. The model summary is displayed in Table 20.

Table 20: Model summary

S	R-SQ	R-SQ(ADJ)	R-SQ(PRED)
0.0790155	37.07%	34.60%	30.87%

R square (R-SQ) or the coefficient of determination shows that model can explain 37.07% of the variance. R-SQ (PRED), the predictive R square shows that the model has the capability to predict 30.87% of the variance in the response variable. Analysis of variance (ANOVA) results are summarized in Table 21. The significance of the model (P-value for the regression) is 0, showing that the regression equation significantly accounts for the variability in the response variable.

Table 21: Analysis of Variance (ANOVA)

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	6	0.56262	0.09377	15.02	0
Factor2	1	0.14155	0.141545	22.67	0
Factor4	1	0.10063	0.100627	16.12	0
Factor6	1	0.04329	0.043289	6.93	0.009
Factor7	1	0.18456	0.184556	29.56	0
Factor9	1	0.06322	0.063221	10.13	0.002
Factor15	1	0.05978	0.059784	9.58	0.002
Error	153	0.95525	0.006243		
Total	159	1.51787			

The coefficients for the significant factors are summarized in Table 22. The individual p values indicate the level of the effect of each factor to the response variable. We can see that Factor 2, 4 and 7 are highly significant with a P value of 0. Factors 6, 9 and 15 have P values smaller 0.05. The obtained coefficients are then used in the following regression equation:

Refill Rate = 0.80625 + 0.03017 Factor2 + 0.02585 Factor4 + 0.01590 Factor6

- 0.03801 Factor7 - 0.02031 Factor9 - 0.02086 Factor15 (1)

Table 22: Regression coefficients

Term	Coef	SE Coef	T-Value	P-Value	VIF
Constant	0.80625	0.00629	128.19	0	
Factor2	0.03017	0.00634	4.76	0	1.02
Factor4	0.02585	0.00644	4.01	0	1.03
Factor6	0.0159	0.00604	2.63	0.009	1.04
Factor7	-0.03801	0.00699	-5.44	0	1.02
Factor9	-0.02031	0.00638	-3.18	0.002	1.02
Factor15	-0.02086	0.00674	-3.09	0.002	1.01

- Interpretation

The factor loadings (Table 23) obtained during the factor analysis are used to interpret the above results. While many factors contribute to the loadings of the identified factors, here we have set the loading threshold as 0.6 to differentiate the major factors.

Table 23: Rotated factor loadings (Varimax rotation)

Variable	Factor2	Factor4	Factor6	Factor7	Factor9	Factor15
race	0.008	0.004	0.01	-0.058	-0.036	0.071
age	-0.09	0.089	-0.068	-0.014	0.03	0.083
married	-0.037	0.007	0.012	-0.006	0.028	-0.044
employd	0.06	0.02	0.057	0	-0.063	-0.002
miles	-0.023	0.002	-0.025	0	0.107	-0.059
subabuse	0.04	-0.084	-0.066	0.024	-0.009	-0.082
ptsd	0.017	-0.189	0.051	0.022	-0.04	-0.924
depress	0.014	-0.965	-0.018	0.039	0.018	-0.166
mental	0.013	-0.017	-0.982	0.036	0.048	0.043
duration	-0.92	0.014	0.014	0.108	0.067	0.017
missaptE	-0.061	-0.017	-0.049	0.122	0.971	0.035
stage	-0.047	0.013	-0.037	0.029	0.102	0.054
medchg	-0.384	0.034	0.034	-0.041	0.079	0.013
gl meds	-0.113	-0.001	0.009	-0.005	0.054	0.032
dr/day	-0.133	-0.017	0.003	-0.023	0.028	0.017
No. diag	-0.097	-0.072	-0.086	0.027	-0.001	-0.065
missedMD	-0.085	-0.036	-0.036	0.983	0.118	-0.02
totmed	-0.014	-0.109	-0.103	0.054	0.047	-0.044
SC %	0.018	-0.118	0.009	0.036	-0.013	-0.257
insur	-0.074	0.041	0.082	0.034	0.039	0.016

As summarized in Table 24 , for each factor we obtained one loading variable. This analysis shows that the most influential factors of non-compliance are longer duration of glaucoma, depression, mental disorder, missed appointments for both the optometry department and the general medicine, and PTSD. It can be summarized by the following generic “y=f(x)” equation:

Compliance = f (Duration, Depression, Mental Disorder, Missed Appointments for the Eye, Missed MD Appointments, PTSD) (2)

Table 24: Factors interpretation summary

Factor	Loading Variable	relation
Factor2	Duration of Glaucoma	Negative
Factor4	Depression	Negative
Factor6	Mental Disorder (other than depression and PTSD)	Negative
Factor7	Missed Appointments (all departments)	Negative
Factor9	Missed Appointments (Optometry departments)	Negative
Factor15	PTSD	Positive

One finding that might look surprising is that we found a positive relation between PTSD and compliance, meaning that patients diagnosed with PTSD are more likely to have a higher compliance than the patients without diagnosis. This can be explained by the fact that those patients are generally given extra attention and additional care compared to the patient who don't present the disorder, and we can assume a supportive third supports them in their medication management, resulting in higher compliance.

6.1.7 Interpretation

In addition to develop prediction model, we were interested in identifying the influential factors for non-compliance in order to be able to target the sensitive patients. As we could see in the 2 runs chosen to illustrate the model building, different variables are significant in different models. Since we have developed 40 models above, we choose to observe the frequency to which a factor appears in the models. A summary of all the factors and their appearance in the various models is presented in Figure 15. Factors in green are the factors who were found to have a positive relation to the refill rate.

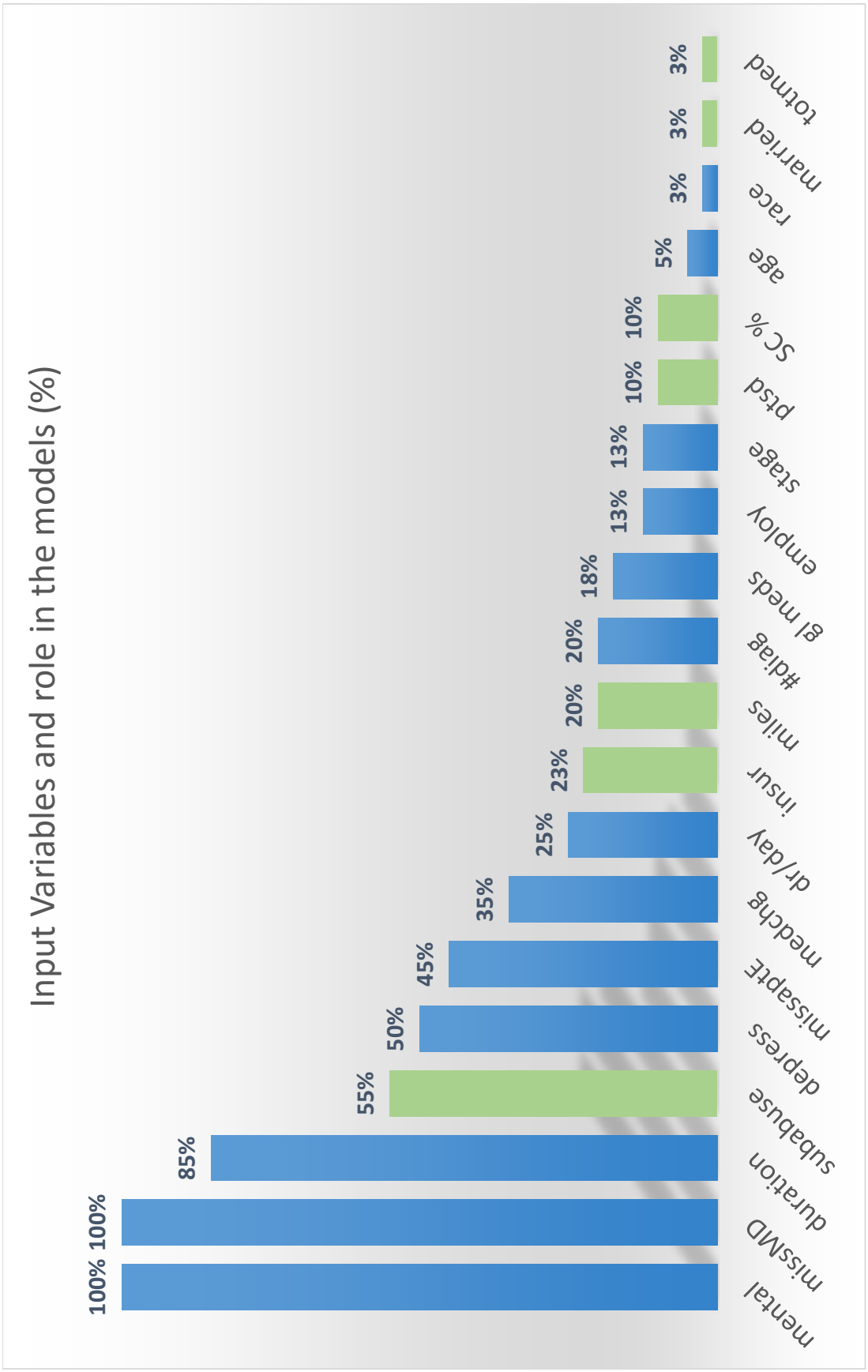

Figure 15: Input variables and role in the models (%)

We can see that mental disorder (other than PTSD and depression) as well as number missed MD appointments are significant factors in all the models (100%). Duration of Glaucoma was found significant in 85% of the models. Those findings can be used by the optometry physician to identify the patients with the higher risk of non-compliance and pay special attention to those patients.

In addition to PTSD and insurance level, explained above, we can see that recorded substance abuse, distance to the hospital, service connected status, and total medication also have a positive relation to the refill rate, which is contradictory to our initial hypothesis. For substance abuse, service connected status and total medication, the interpretation is similar than for PTSD: those patients are given extra attention, even help from a supportive third, which results in better compliance. For the distance to the hospital, this can be explained by the fact that patients living further, and we can presume, in a more remote area are more likely to order their medication right after their visit, making their refill rate higher than the patients living closer who don't make a routine of order their medication at each hospital visit.

6.2 Cause and Effect Diagram

A Cause and Effect Diagram (C&E Diagram) is used to visually organize and display the potential causes for the specific outcome we are trying to improve. Those potential causes are usually obtained through brainstorming and classified into 6Ms: Man, Machine, Materials, Methods, Measurements, Milieu (Environment). In this study we did not address "Machine" and limited to the 5 other Ms. The following diagram is therefore a summary of the potential causes influencing the non-compliance to Glaucoma medication.

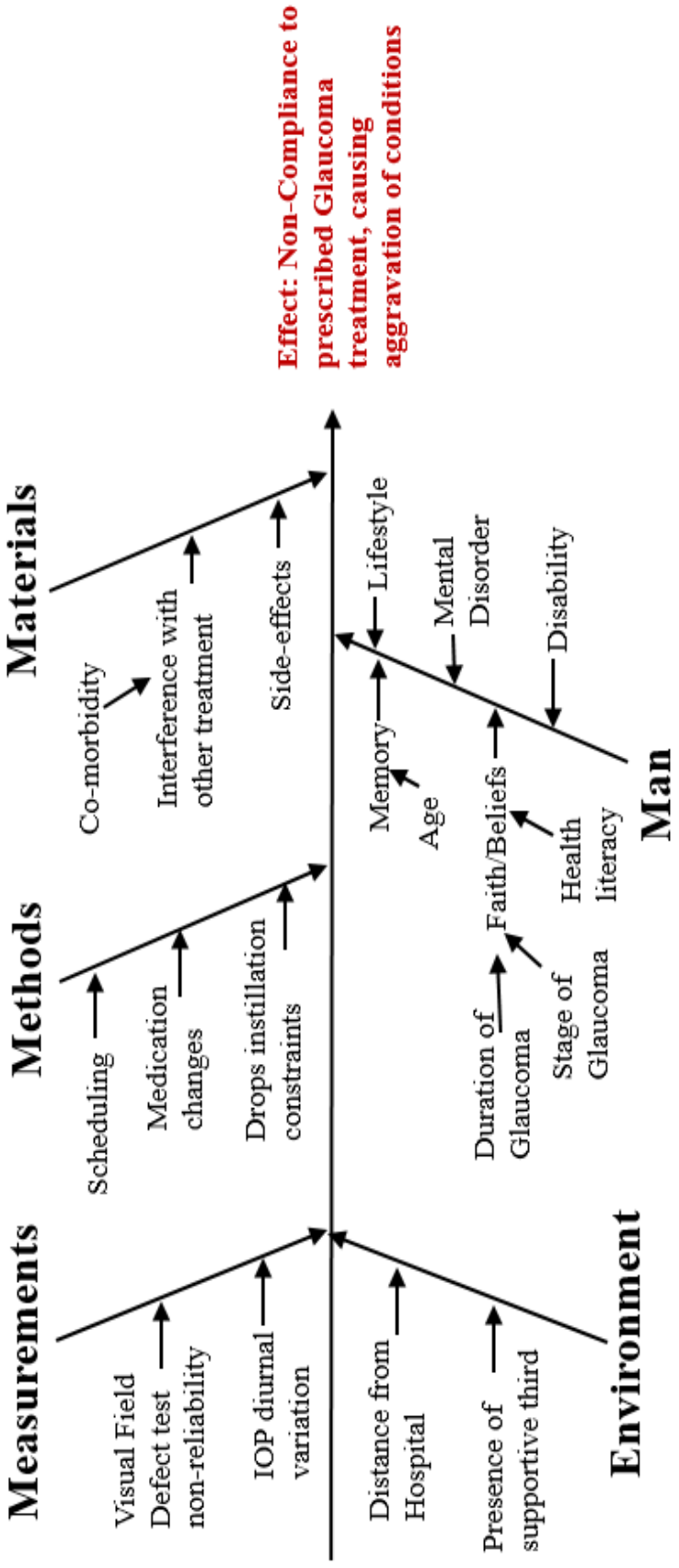

Figure 16: Cause and Effect (C&E) Diagram (also called Fishbone Diagram)

CHAPTER 7 : APPLICATION – IMPROVE PHASE

The goal of this project is using a lean six sigma approach to help an optometry physician to be able to quantitatively assess and predict the problem of non-compliance. In the Improve phase, a new follow-up process is developed and proposed, including compliance assessment in the model.

7.1 Model Validation

Before introducing the prediction model into the glaucoma follow-up care process, a validation step is performed. Using the remaining 50 data points randomly selected during the split sampling, the predictive power of the proposed model is tested. Figure 17 shows the comparison between the originally measured compliance with the predicted compliance by the regression model for the run R9, and Figure 18 for the run R13.

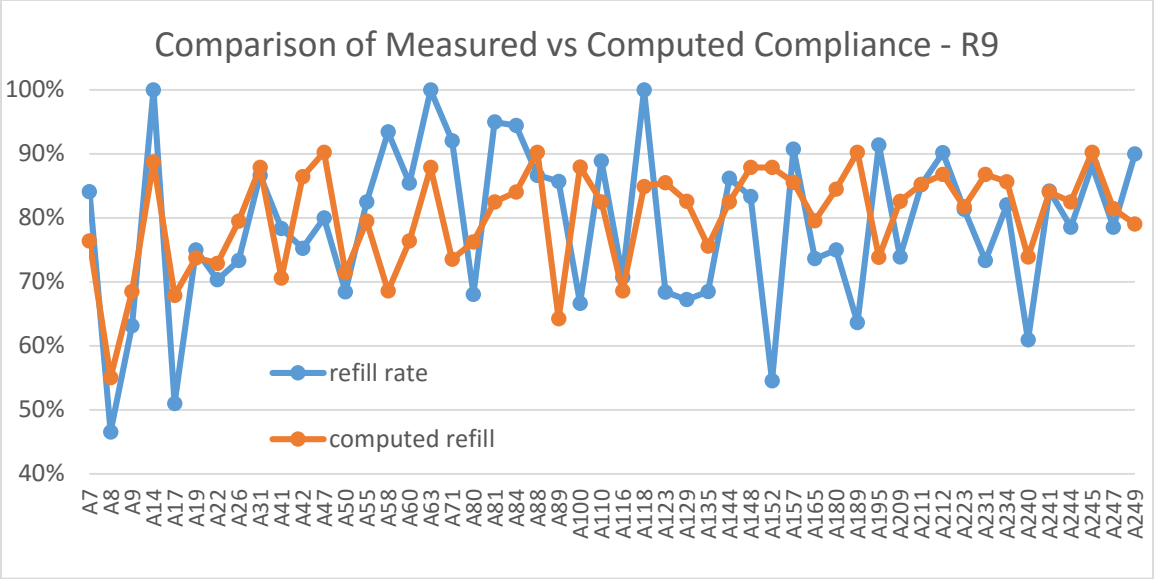

Figure 17: Graphical comparison of measured vs computed compliance – run 9

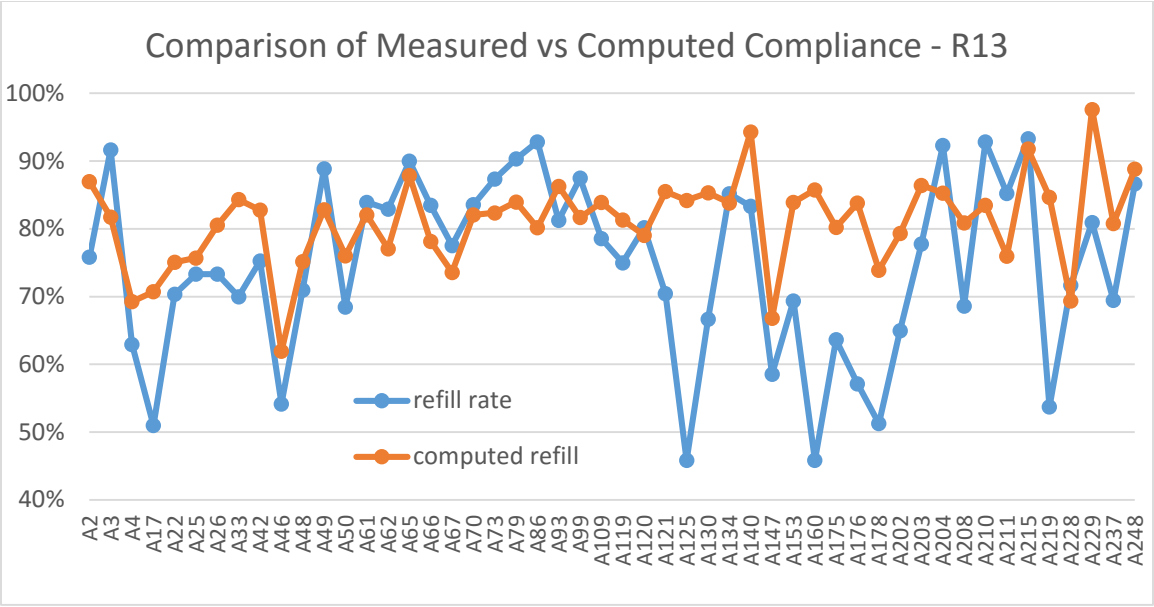

Figure 18: Graphical comparison of measured vs computed compliance – Run 13

Results indicate that the 50 validation data points follow a similar trend as the originally measured values. In addition to the graphical analysis, the following analysis were conducted:

- The mean squared error (MSE) is 0.0143 for R9 and 0.0184 for R13 indicating that the model has a good forecasting accuracy.
- The correlation coefficient between measured and computed compliance is 0.37 for R9 and 0.39 for R13 indicating a promising linear relation.

The above results show that the regression model developed in the calibration phase has the potential for the prediction and assessment of compliance, and thus inclusion into the patient follow-up care process.

7.2 Improved Process Mapping

During the Analyze phase, critical areas for improvement were identified: Measurement of compliance by self-assessment is not accurate. Based on the results of the analysis, a compliance index score can be developed for the improved follow up process. A future state process map is then designed, including the compliance prediction model.

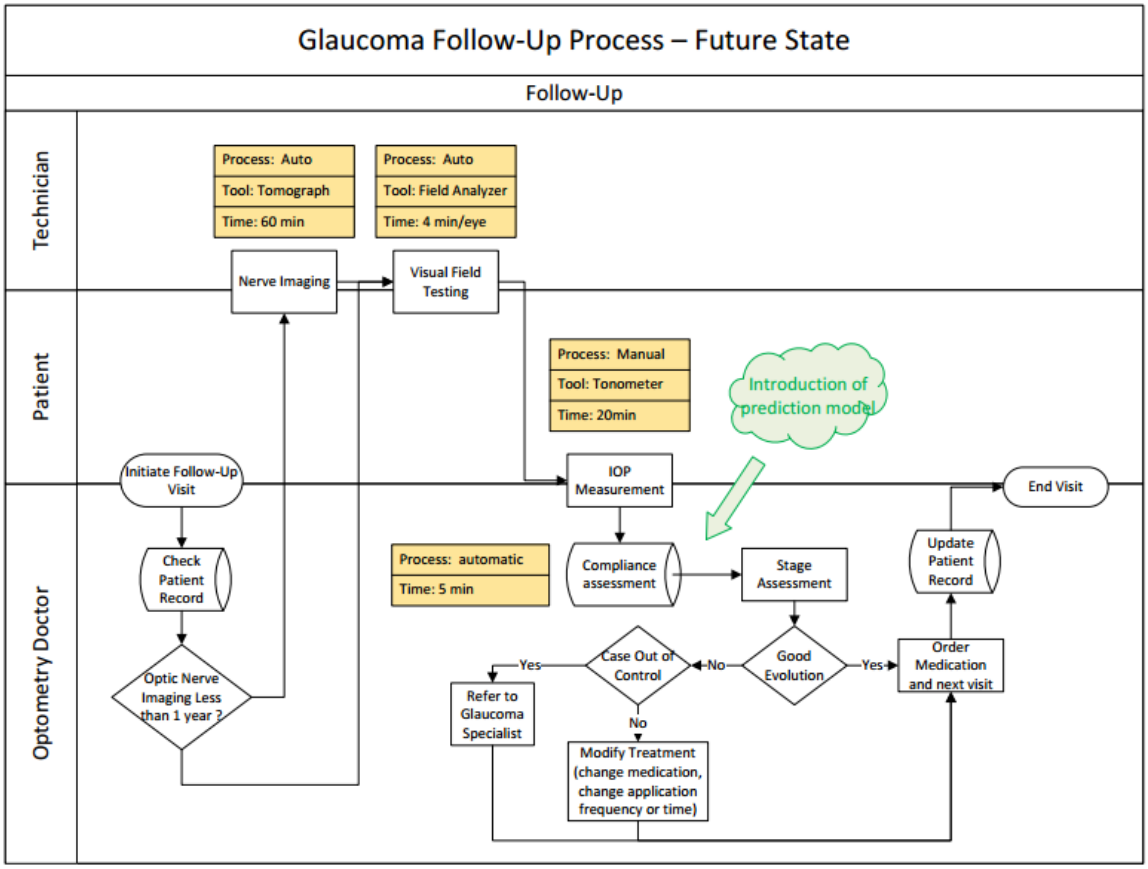

Figure 19: Future-state process map

CHAPTER 8 : APPLICATION – CONTROL PHASE

In the Control phase, changes as well as improved methodologies will be documented to ensure sustainability of the change. In this project, the main improvement is the introduction of the predictive model into the glaucoma follow-up care process.

8.1 Control Plan

The control plan acts as the guide for the stakeholder of the improved process. Adapted for this study, it is a thorough summary of the control actions to assess the non-compliance behavior, with enough details to ensure clear understanding by all the doctors.

Table 25: Control plan

Control Subject	Subject Goal	Frequency of Measure	Criteria for Decision	Action / Responsible Party	Analysis Method
Glaucoma Patient non-compliance	Compliance higher than 80%	Every patient, in case of non-satisfying Clinical results	Compliance lower than 80%	Refer to the Glaucoma Specialist	Compliance assessment using the compliance prediction model

CHAPTER 9 : DISCUSSIONS - CONCLUSION

Glaucoma is a very concerning chronic disease, and glaucoma patients are increasing worldwide. Glaucoma needs to be treated timely in order to avoid its ultimate complication: blindness. The most commonly chosen treatment method: by daily drop applications can help to slow down or stop glaucoma evolution only if the treatment is taken rigorously. Non-compliance behavior, i.e. the patient not following the doctor instructions in terms of treatment, dosage, timing, etc., is therefore the most important concern for the optometry doctors. In order to enable the Optometry doctor to take the appropriate action, and thus to provide better care to the patient, non-compliance behavior needs to be identified and quantified.

In this study, we have applied a lean six sigma DMAIC framework to analyze the underlying factors for glaucoma treatment compliance analytically. A predictive model was developed using regression analysis coupled with factor analysis. The major findings can be summarized as follows:

- The main factors influencing non-compliance behavior have been identified as recorded mental disorder, recorded missed MD appointments, Duration of Glaucoma, recorded substance abuse and depression. These influential factors can serve as preliminary indicators for the optometry physicians to identify the patients with higher risk of non-compliance.

- Split sampling approach showed that the proposed prediction model can be used as a tool to quantitatively assess the non-compliance, and can be used by the Optometry physician to predict non-compliance simply by using the medical record of the patients.

While the results of the study are encouraging, there are a few limitations and related future work, which will be discussed next:

The subjects of this study were veteran patients from a VA hospital in NC, USA. Since it is known that the specific cohort of Veterans have a higher risk of depression, mental disorder and a higher occurrence of disability, the findings of this study have to be taken with great care if generalized to a non-veteran population. On the other hand, although those results might not be generalized as-is to a general hospital and to other regions, the methodology used in this study can be used and followed to adjust to the observed population.

The measure of compliance used in this study was the refill rate, ratio calculated by the number of months refills were ordered over the total duration of observation. This measure can be biased by the 2 following cases:

- Since we extracted data from the VA database system, the information we have concern the visits and the refills made at a VA medical center. However, some patients may see other care providers, and fill their prescription at other pharmacies. For those patients, even if they were compliant the refill rate we measured would appear as being low.
- Pick-up of a prescription does not guarantee a proper use of the medication. For example, patients living far or having transportation limitations may pick up

their medication after each visit and stock their medication at home. For those patients, even if they were non-compliant, the refill rate we measured would appear as being satisfying.

The regression analysis performed on 40 different models gives some consistent results, but we also observed some variation between the replicates when using the split sampling method. Future research including a bigger sample size should enable a more robust analysis.

Regarding the statistical analysis method, the following limitations were observed:

- The factor analysis rotation method chosen was Varimax, which is an orthogonal rotation method. Performing an oblique rotation where factors are allowed to be correlated could have been an interesting alternative, which could not be performed with the statistical analysis software chosen for this study, but could be done in future research using other software.
- We choose in this study to perform the Johnson transformation on the response variable: “refill rate” and compare with the non-transformed data. Future research might include other transformations of the response variable (e.g. logit transformation). Similarly, beta regression or logistic regression method might be an interesting alternative analysis method to test in further analysis.

In addition, the future research will address the following two research questions.

- Which interventions (training, meetings, change of medication etc.) result in a significant improvement of compliance?

- Can a standard follow-up process be determined to replace the existing guidelines, now including compliance assessment?

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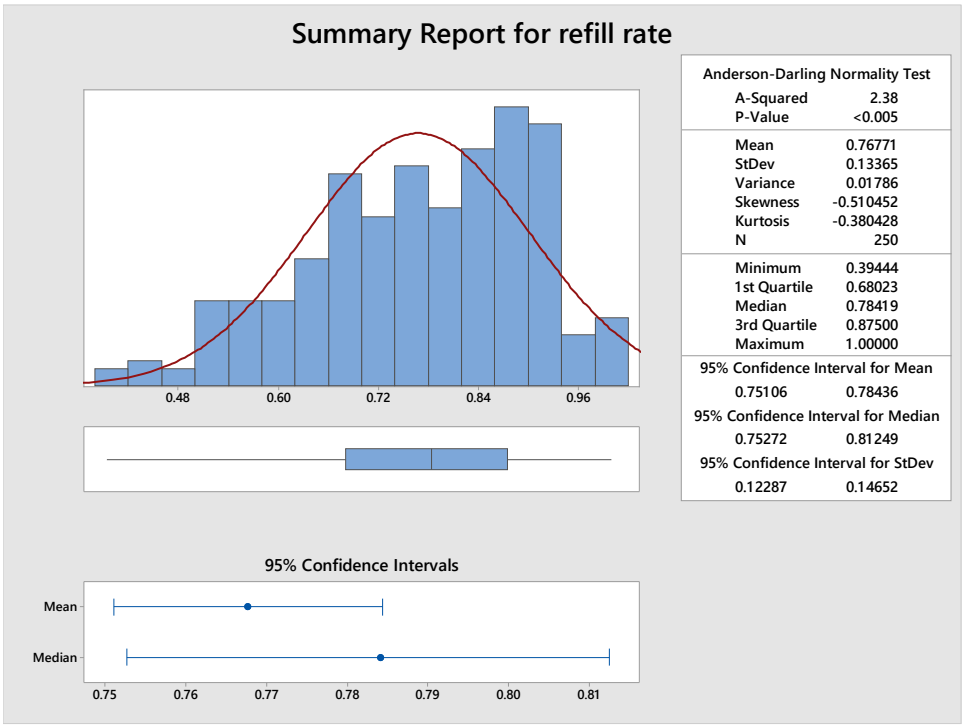
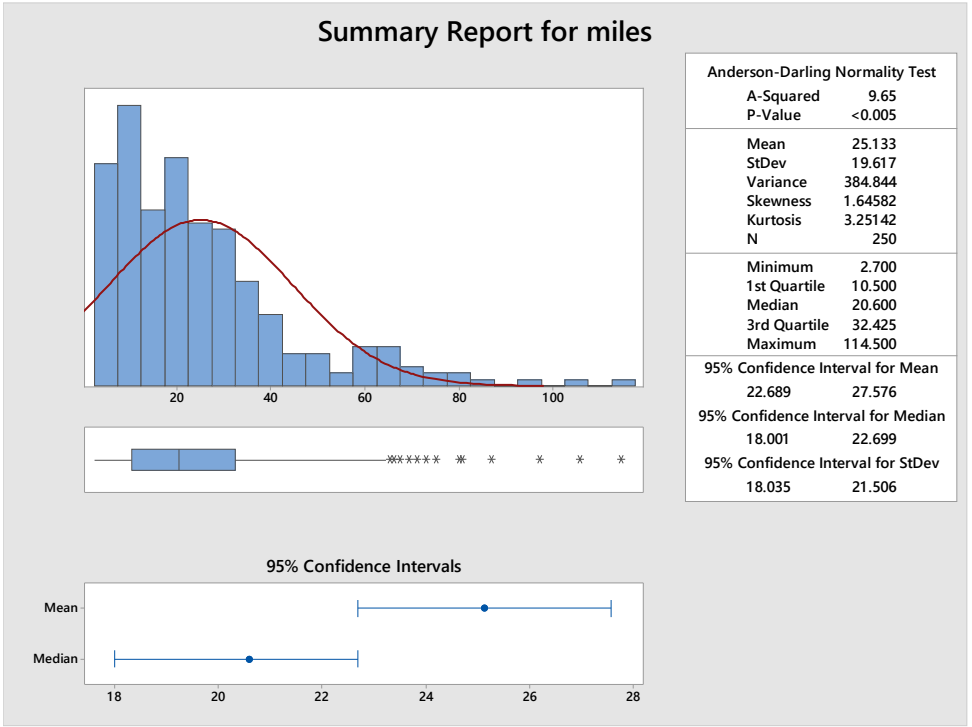
APPENDIX A : DATA COLLECTION SAMPLE

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y
1	ID	homzip	tr zip	miles	race	subabuse	ptsd	depress	mental	totmed	missaptE	#diag	employd	duration	refill	married	medchg	hi IOP	gl meds	dr/day	SC %	age	stage	insure	missMD
2	A1	286	28144	75.12	w	0	1	1	0	11	2	12	0	31	24	1	0		1	1	90	72.5	2	2	0
3	A2	280	28144	20.95	w	0	1	0	0	8	1	13	0	120	91	1	3		1	1	10	78	1	3	0
4	A3	281	28144	35.2	w	0	0	0	0	13	0	14	0	48	44	1	0		1	1	50	74.1	1	3	1
5	A4	282	28213	6.51	b	0	1	1	0	18	1	12	0	27	17	0	0		1	1	0	66.8	1	3	5
6	A5	282	28213	12.8	b	0	0	0	0	10	1	14	0	85	58	1	1		2	3	20	72.1	3	1	1
7	A6	273	27103	31	w	0	0	0	0	11	0	14	0	122	87	1	4		2	3	0	75.1	2	3	1
8	A7	271	27103	8.3	w	0	0	0	0	8	4	12	0	63	53	1	3		1	1	0	81.6	2	3	2
9	A8	270	27103	36.11	w	0	0	1	1	7	0	11	0	58	27	1	4		3	5	70	70.5	3	2	1
10	A9	274	27103	29	b	0	0	1	1	11	4	11	0	19	12	1	1		2	3	0	66.3	1	2	0
11	A10	280	28144	36	b	0	0	0	1	8	3	8	0	62	40	0	2		2	3	0	78	3	2	0
12	A11	272	28144	48.4	b	0	0	0	0	6	2	10	0	10	9	1	0		1	1	0	69.5	3	3	1
13	A12	282	28144	42.3	b	0	0	1	0	14	1	12	0	180	71	0	3		1	1	60	75.5	2	2	1
14	A13	273	28144	61.9	w	0	1	1	0	12	3	14	0	132	116	0	3		3	5	60	74.2	3	2	0
15	A14	281	28213	21.7	w	0	0	1	0	9	1	5	0	8	8	1	0		1	2	50	64.3	1	3	0
16	A15	282	28213	11.4	w	0	0	0	0	10	3	10	0	36	33	1	1		3	6	90	72.4	3	2	2
17	A16	286	28144	27.4	w	0	0	0	0	11	0	8	0	141	74	1	4		1	1	10	78.8	2	3	1
18	A17	272	27103	24.5	w	0	0	0	0	9	2	13	0	151	77	0	3		3	5	80	68.3	3	2	2
19	A18	280	28213	29.5	w	0	0	1	1	15	0	12	0	96	73	1	0		1	1	0	70.7	2	3	1
20	A19	271	27103	10.5	b	0	0	0	0	10	3	15	0	84	63	1	3		3	5	0	82.5	3	3	1
21	A20	271	27103	11.5	w	0	0	0	0	8	2	15	0	130	72	1	3		3	4	0	79.5	3	3	1
22	A21	281	28144	61.6	b	0	0	0	0	9	0	7	1	12	8	0	0		1	1	0	62.2	1	2	4
23	A22	280	28144	39.5	b	0	0	0	0	12	3	11	0	118	83	1	3		2	4	100	76.5	3	2	1
24	A23	280	28144	13.7	w	0	0	0	1	14	0	15	0	24	13	1	0		1	1	0	74.8	1	3	1
25	A24	280	28144	62.2	b	0	0	1	0	10	3	11	0	10	9	0	0		2	2	20	82.5	3	2	2
26	A25	286	27103	51	w	0	1	1	0	15	3	10	0	30	22	0	0		1	1	80	67.8	1	2	2

APPENDIX B : INDIVIDUALS GRAPHICAL SUMMARIES





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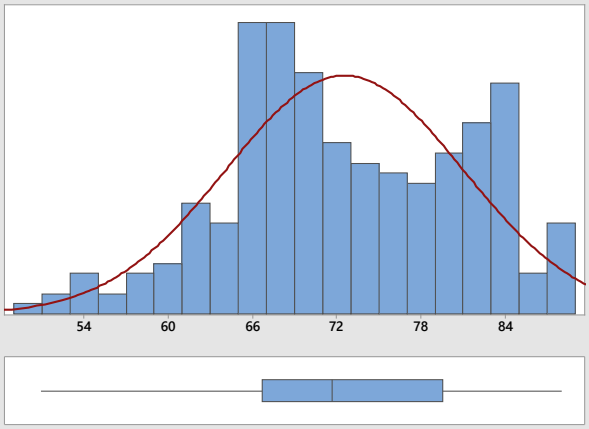
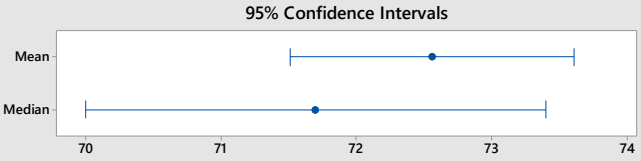


Anderson-Darling Normality Test	
A-Squared	1.95
P-Value	<0.005
Mean	72.557
StDev	8.418
Variance	70.868
Skewness	-0.115136
Kurtosis	-0.597740
N	250
Minimum	50.900
1st Quartile	66.700
Median	71.700
3rd Quartile	79.525
Maximum	88.000
95% Confidence Interval for Mean	
71.509	73.606
95% Confidence Interval for Median	
70.000	73.399
95% Confidence Interval for StDev	
7.739	9.229



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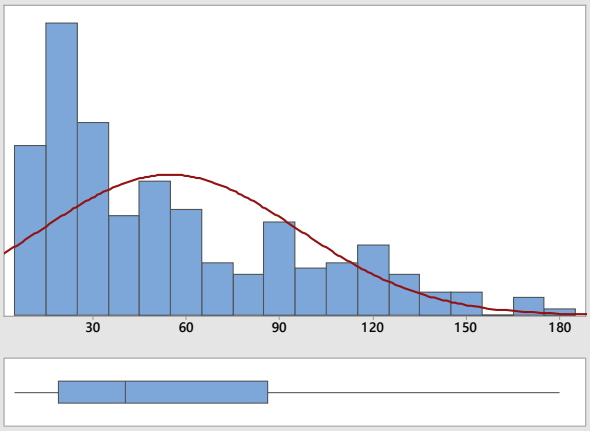
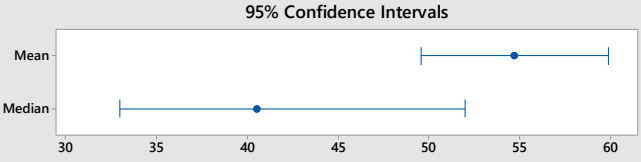


Anderson-Darling Normality Test	
A-Squared	9.05
P-Value	<0.005
Mean	54.724
StDev	41.496
Variance	1721.920
Skewness	0.903633
Kurtosis	-0.140166
N	250
Minimum	5.000
1st Quartile	19.000
Median	40.500
3rd Quartile	86.250
Maximum	180.000
95% Confidence Interval for Mean	
49.555	59.893
95% Confidence Interval for Median	
33.006	51.994
95% Confidence Interval for StDev	
38.150	45.491



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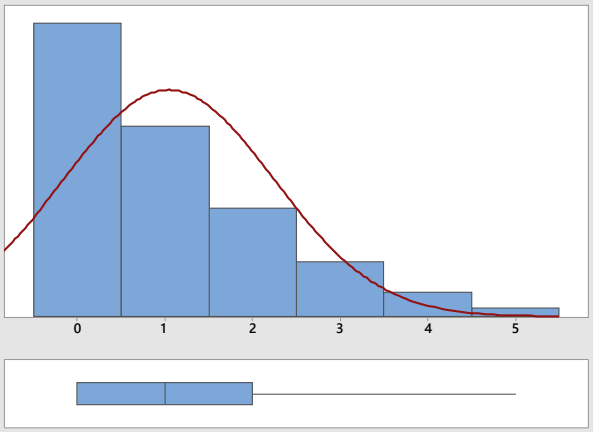
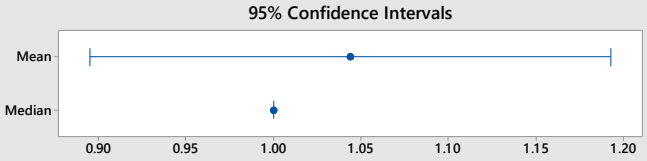


Anderson-Darling Normality Test	
A-Squared	17.19
P-Value	<0.005
Mean	1.0440
StDev	1.1966
Variance	1.4318
Skewness	1.13406
Kurtosis	0.72908
N	250
Minimum	0.0000
1st Quartile	0.0000
Median	1.0000
3rd Quartile	2.0000
Maximum	5.0000
95% Confidence Interval for Mean	
0.8949	1.1931
95% Confidence Interval for Median	
1.0000	1.0000
95% Confidence Interval for StDev	
1.1001	1.3118



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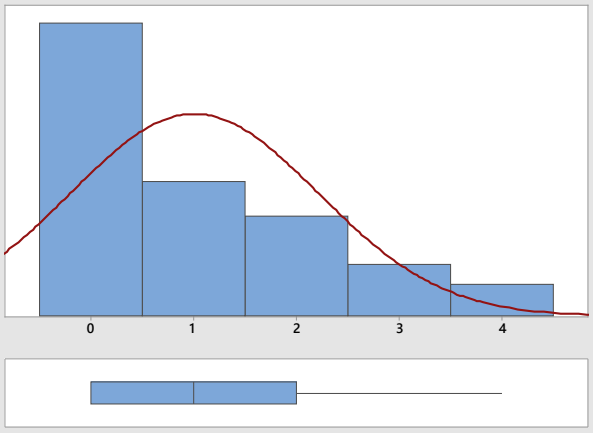
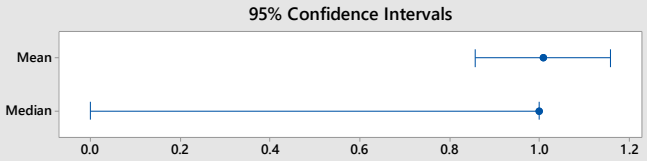


Anderson-Darling Normality Test	
A-Squared	20.08
P-Value	<0.005
Mean	1.0080
StDev	1.2057
Variance	1.4538
Skewness	0.996198
Kurtosis	-0.046332
N	250
Minimum	0.0000
1st Quartile	0.0000
Median	1.0000
3rd Quartile	2.0000
Maximum	4.0000
95% Confidence Interval for Mean	
0.8578	1.1582
95% Confidence Interval for Median	
0.0000	1.0000
95% Confidence Interval for StDev	
1.1085	1.3218



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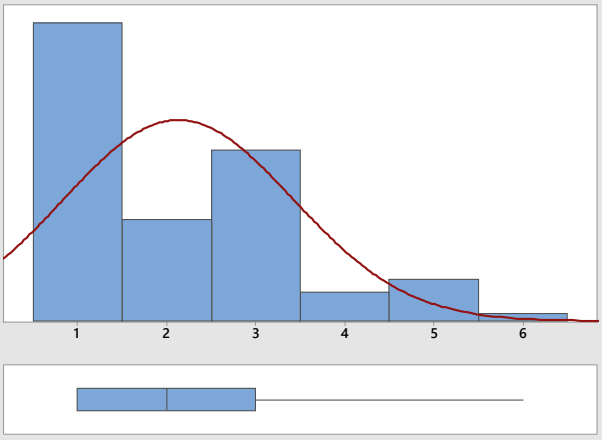
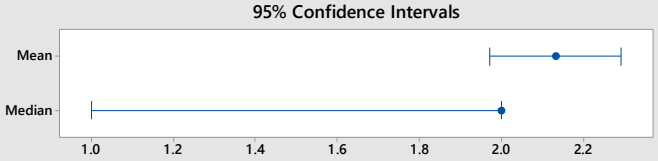


Anderson-Darling Normality Test	
A-Squared	18.43
P-Value	<0.005
Mean	2.1320
StDev	1.2873
Variance	1.6572
Skewness	0.946980
Kurtosis	0.130751
N	250
Minimum	1.0000
1st Quartile	1.0000
Median	2.0000
3rd Quartile	3.0000
Maximum	6.0000
95% Confidence Interval for Mean	
1.9716	2.2924
95% Confidence Interval for Median	
1.0000	2.0000
95% Confidence Interval for StDev	
1.1835	1.4113



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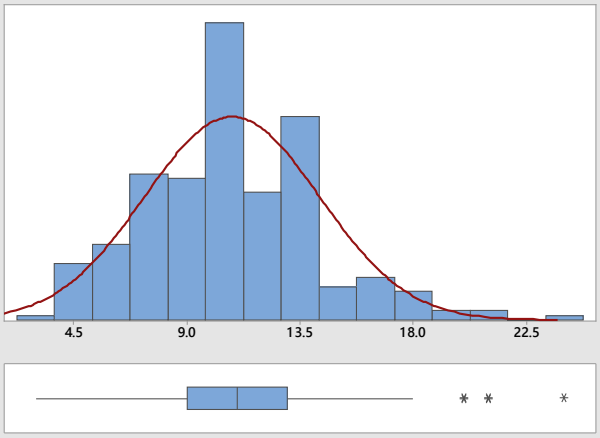
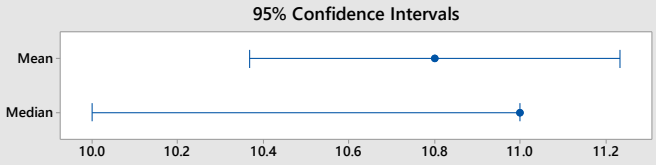
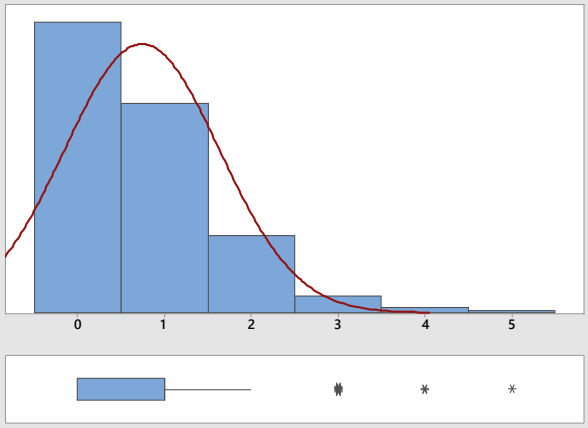


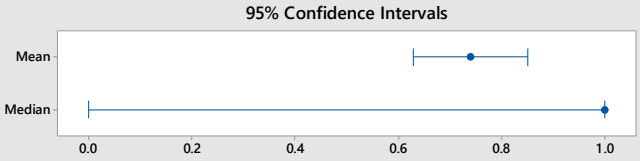
Anderson-Darling Normality Test	
A-Squared	1.61
P-Value	<0.005
Mean	10.800
StDev	3.477
Variance	12.088
Skewness	0.503972
Kurtosis	0.702482
N	250
Minimum	3.000
1st Quartile	9.000
Median	11.000
3rd Quartile	13.000
Maximum	24.000
95% Confidence Interval for Mean	
10.367	11.233
95% Confidence Interval for Median	
10.000	11.000
95% Confidence Interval for StDev	
3.196	3.812



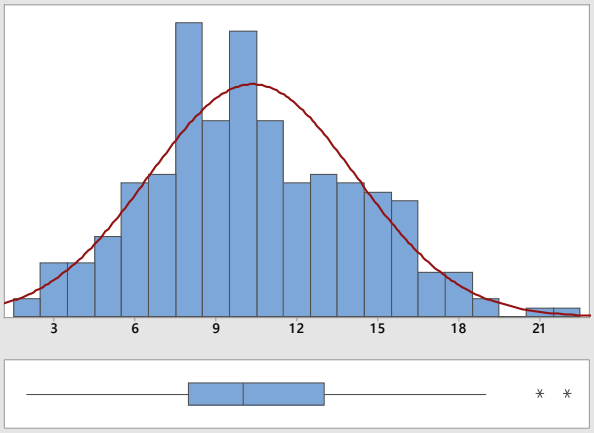
Summary Report for missedMD



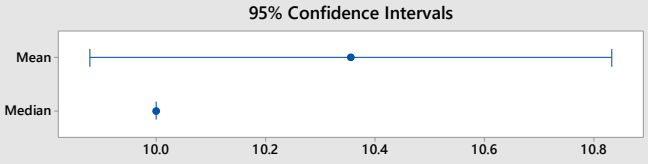
Anderson-Darling Normality Test	
A-Squared	21.37
P-Value	<0.005
Mean	0.74000
StDev	0.89195
Variance	0.79558
Skewness	1.39154
Kurtosis	2.52193
N	250
Minimum	0.00000
1st Quartile	0.00000
Median	1.00000
3rd Quartile	1.00000
Maximum	5.00000
95% Confidence Interval for Mean	
0.62889	0.85111
95% Confidence Interval for Median	
0.00000	1.00000
95% Confidence Interval for StDev	
0.82002	0.97783

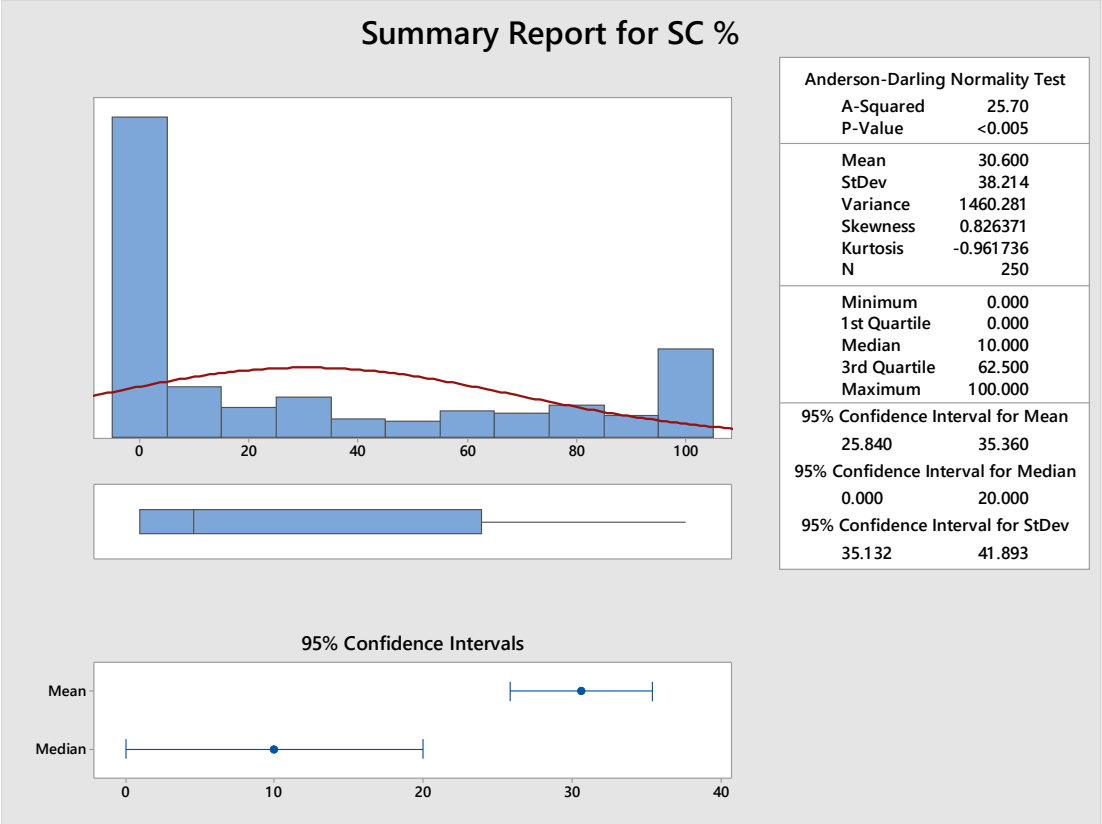


Summary Report for totmed

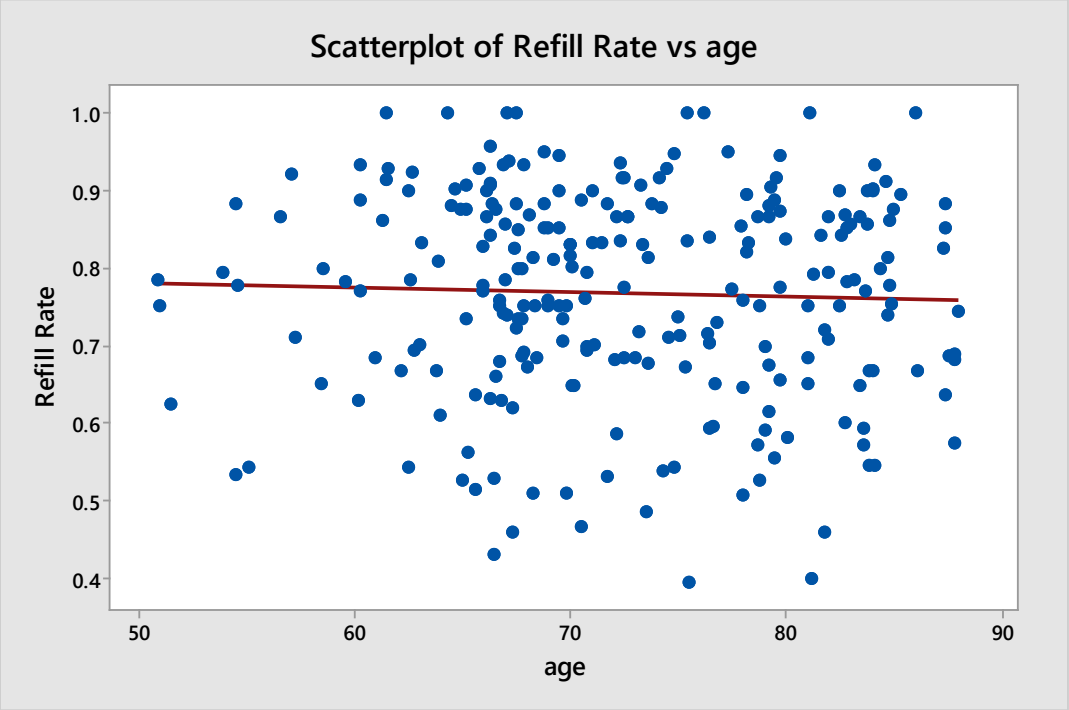


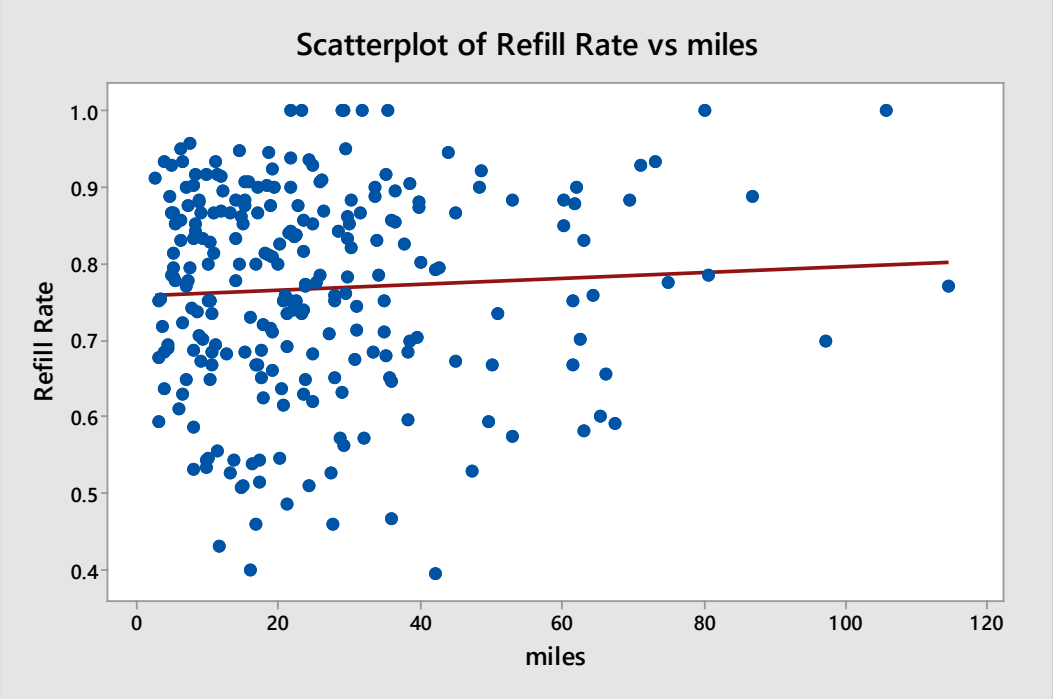
Anderson-Darling Normality Test	
A-Squared	1.50
P-Value	<0.005
Mean	10.356
StDev	3.826
Variance	14.640
Skewness	0.274536
Kurtosis	-0.243961
N	250
Minimum	2.000
1st Quartile	8.000
Median	10.000
3rd Quartile	13.000
Maximum	22.000
95% Confidence Interval for Mean	
9.879	10.833
95% Confidence Interval for Median	
10.000	10.000
95% Confidence Interval for StDev	
3.518	4.195

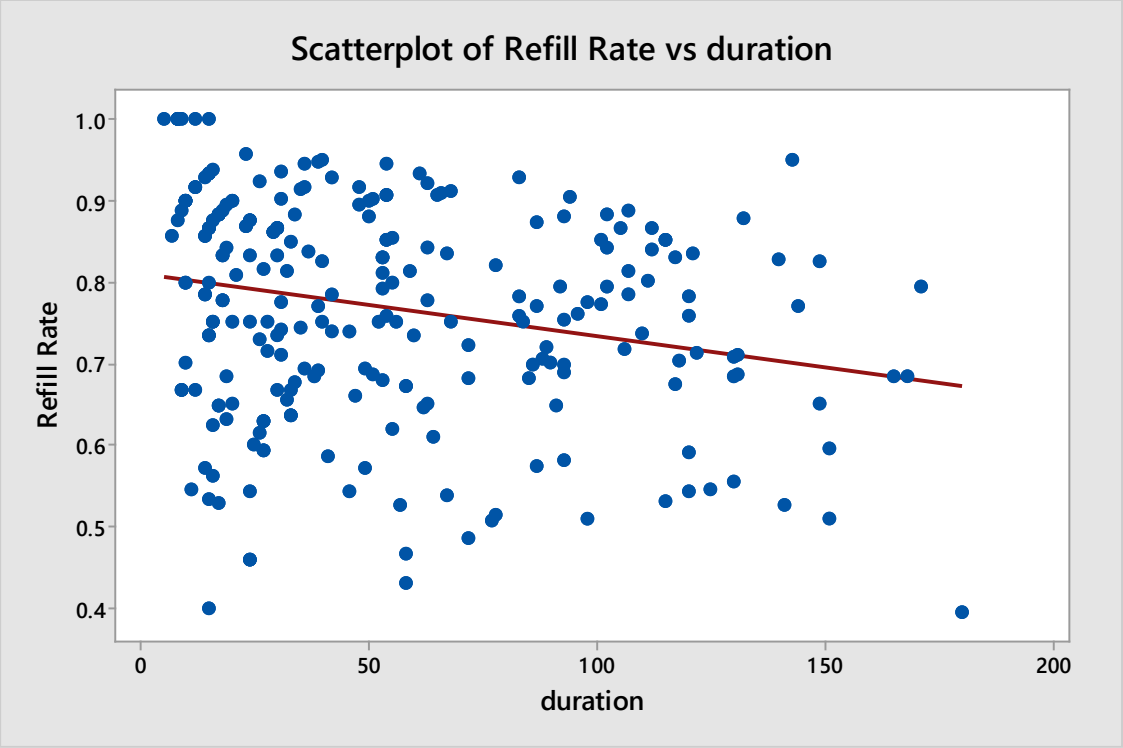


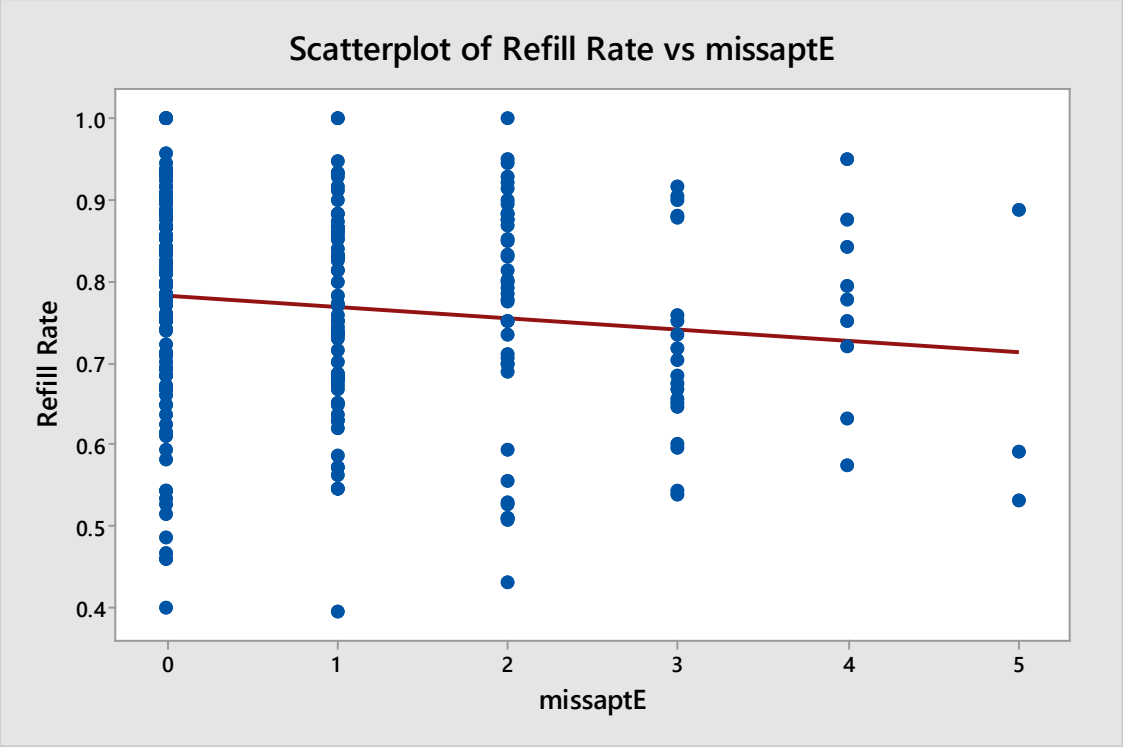

Summary Report for SC %
Anderson-Darling Normality Test
A-Squared 25.70
P-Value <0.005
Mean 30.600
StDev 38.214
Variance 1460.281
Skewness 0.826371
Kurtosis -0.961736
N 250
Minimum 0.000
1st Quartile 0.000
Median 10.000
3rd Quartile 62.500
Maximum 100.000
95% Confidence Interval for Mean
25.840 35.360
95% Confidence Interval for Median
0.000 20.000
95% Confidence Interval for StDev
35.132 41.893
0
20
40
60
80
100
95% Confidence Intervals
Mean
Median
0
10
20
30
40

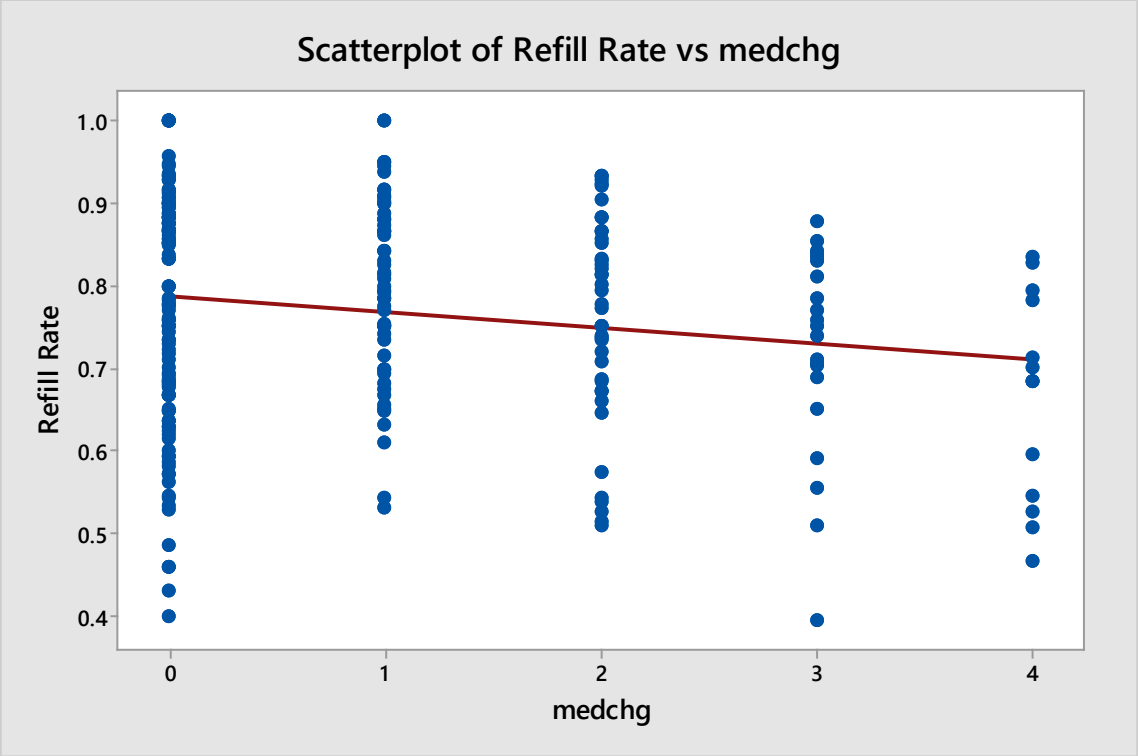
APPENDIX C : INDIVIDUAL SCATTER PLOTS FOR CONTINUOUS DATA

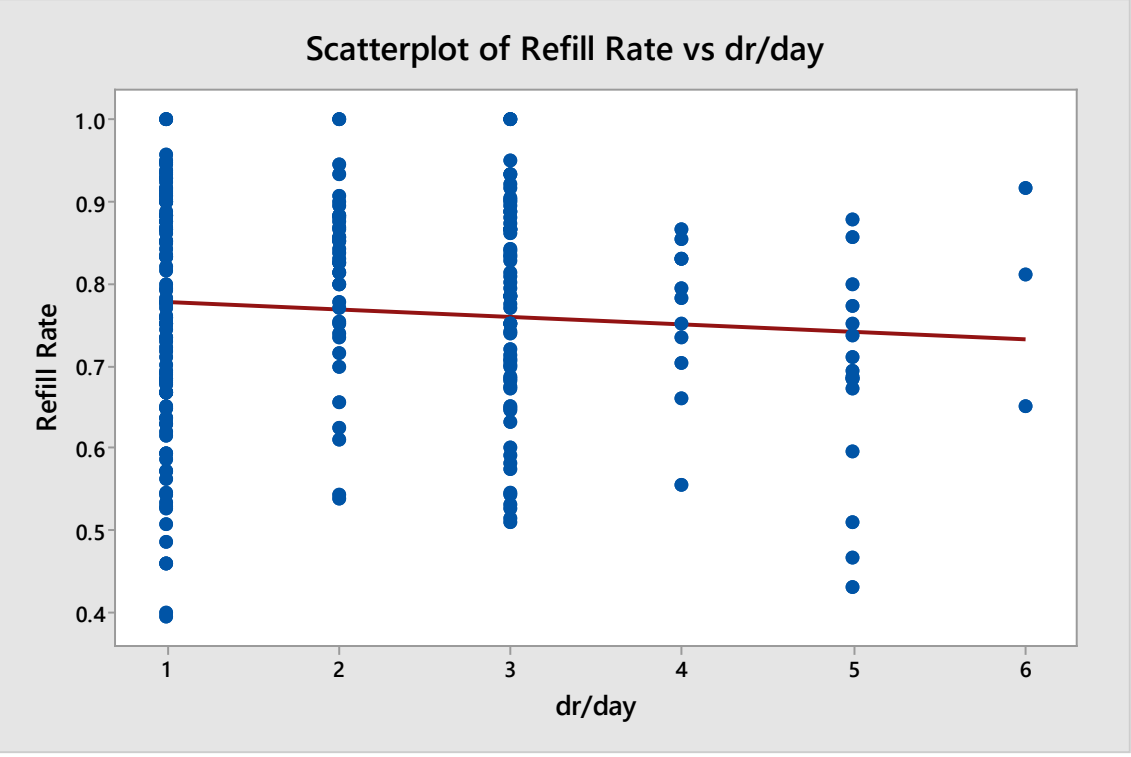


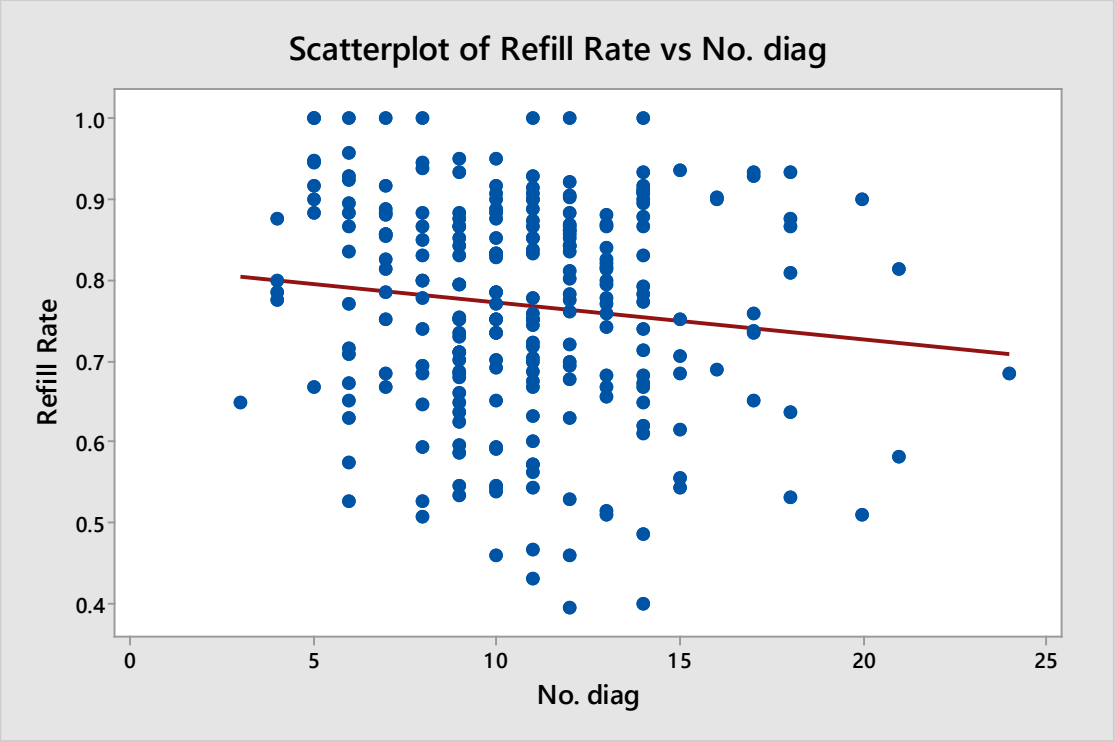


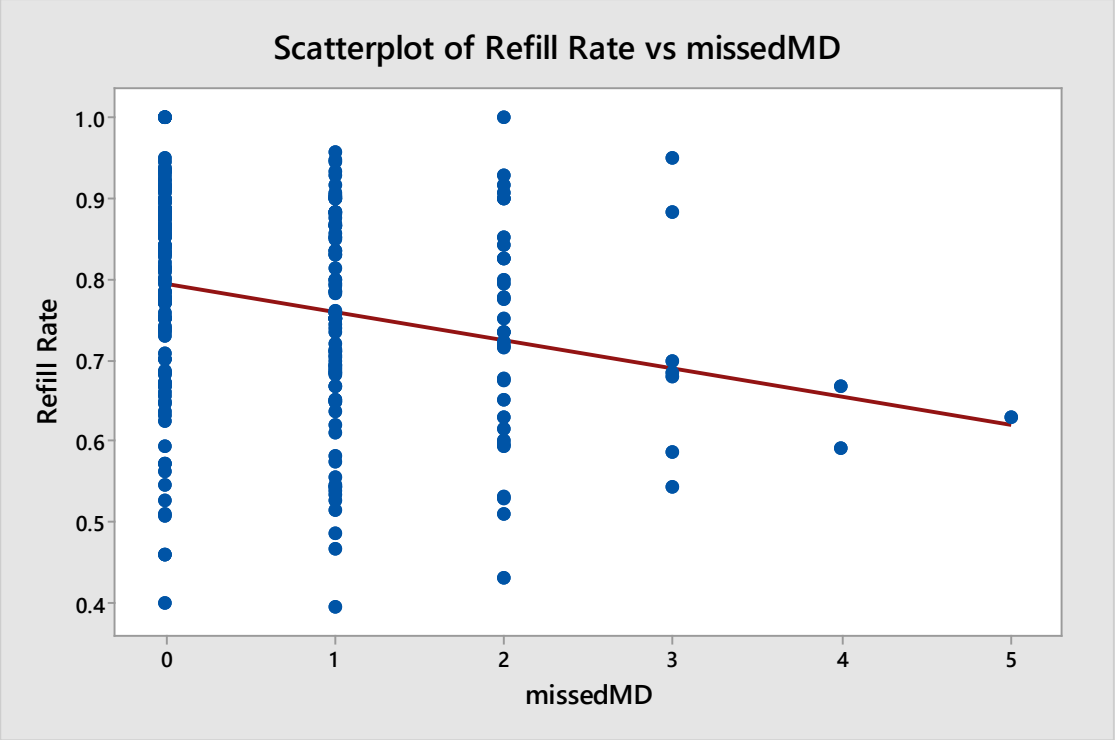

Scatterplot of Refill Rate vs duration
Refill Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
50
100
150
200
duration

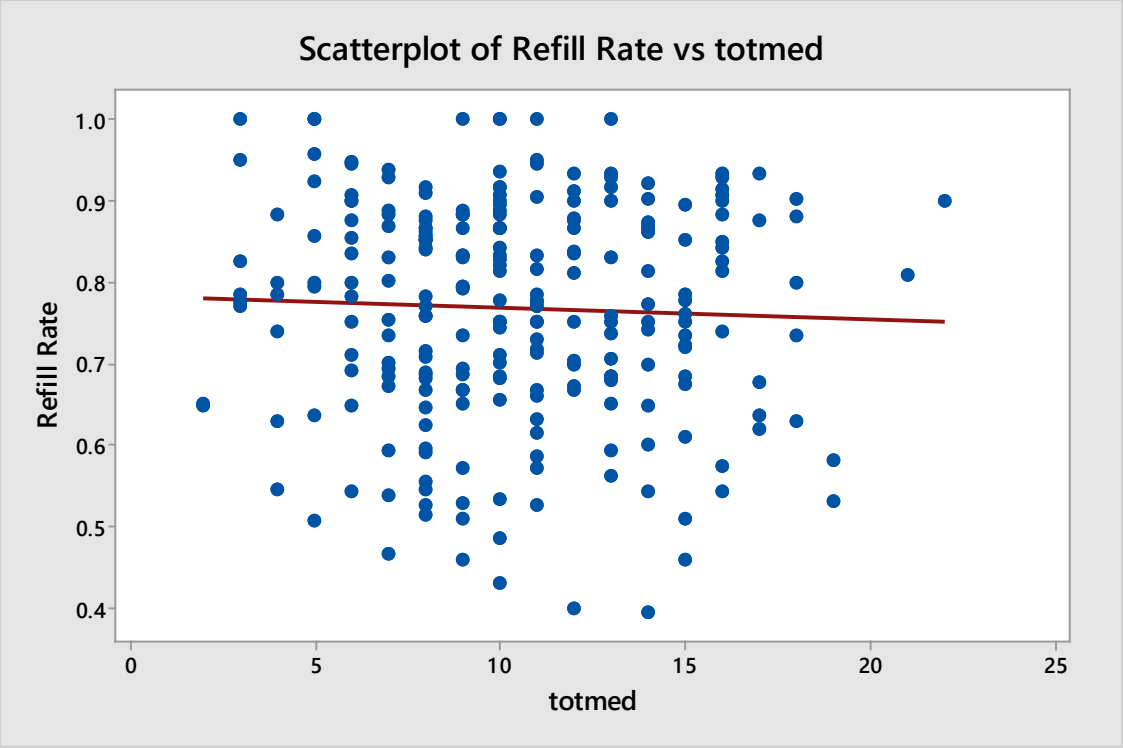

Scatterplot of Refill Rate vs missaptE
Refill Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
1
2
3
4
5
missaptE

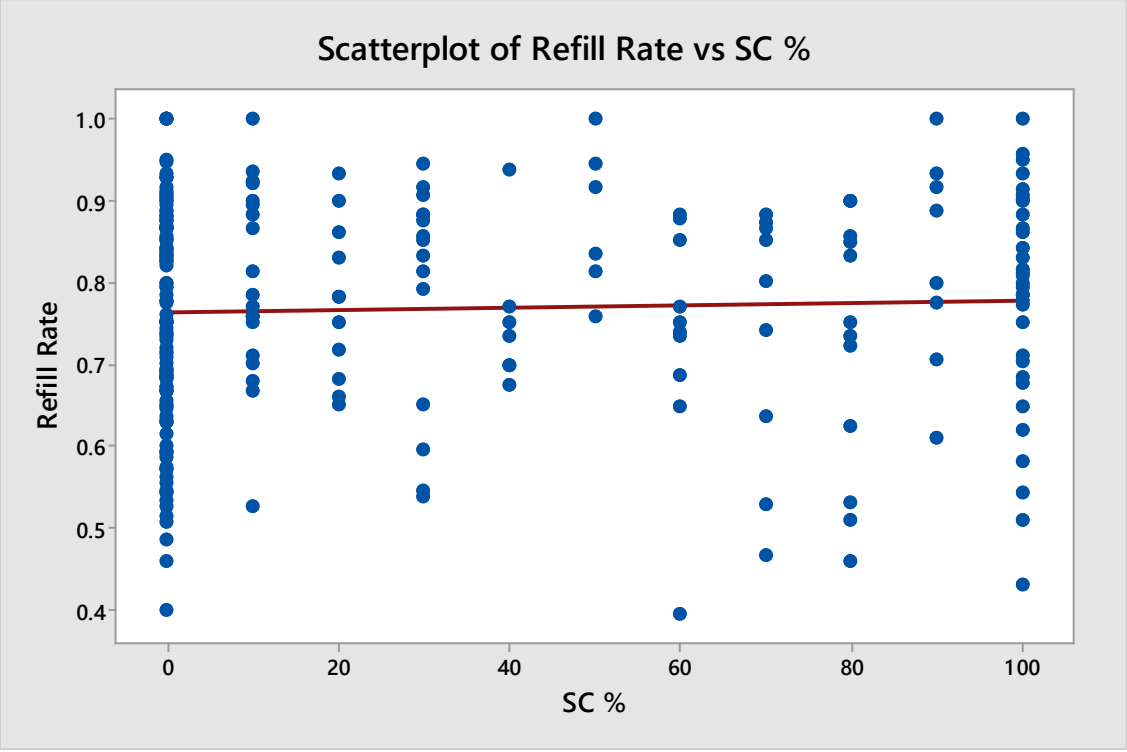

Scatterplot of Refill Rate vs medchg
Refill Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
1
2
3
4
medchg


Scatterplot of Refill Rate vs dr/day
Refill Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
1
2
3
4
5
6
dr/day

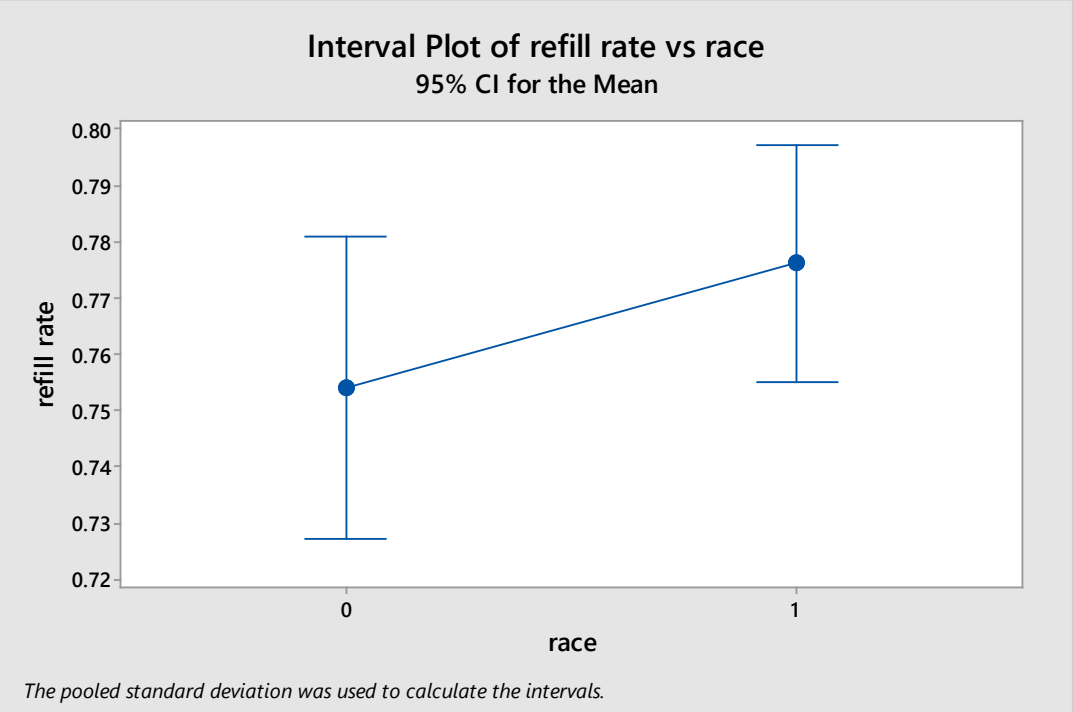

Scatterplot of Refill Rate vs No. diag
Refill Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
5
10
15
20
25
No. diag

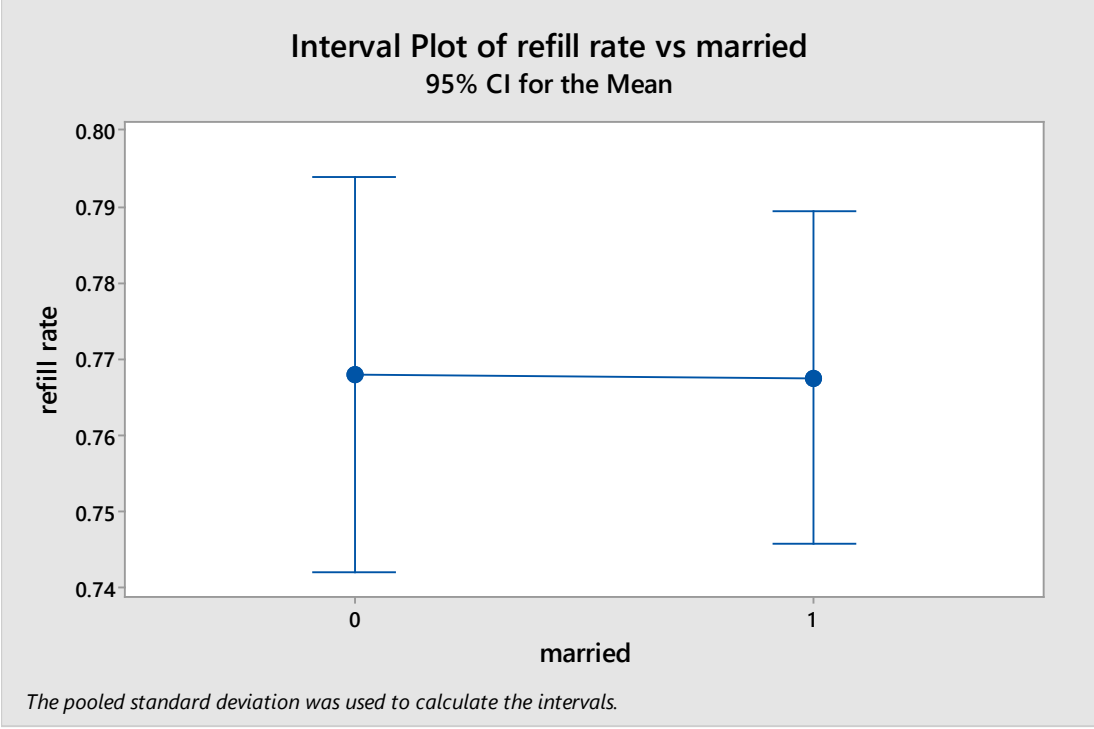

Scatterplot of Refill Rate vs missedMD
Refill Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
1
2
3
4
5
missedMD


Scatterplot of Refill Rate vs totmed
Refill Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
5
10
15
20
25
totmed

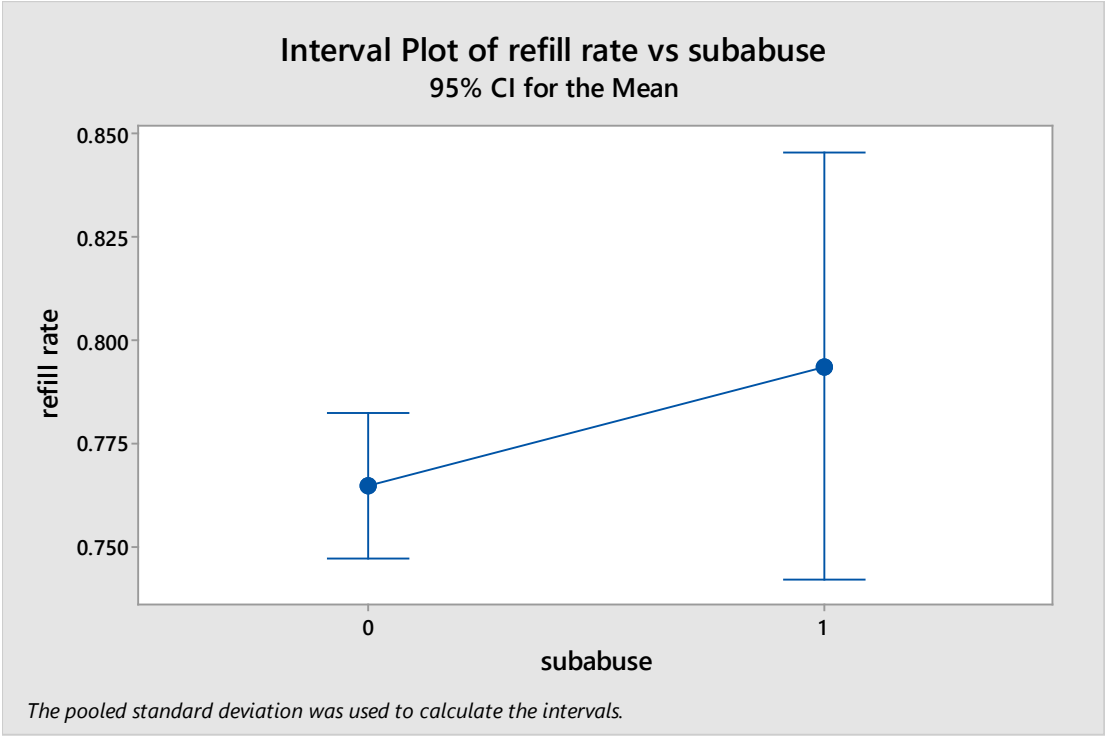

Scatterplot of Refill Rate vs SC %
Refill Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
20
40
60
80
100
SC %

APPENDIX D : INDIVIDUALS INTERVAL PLOTS FOR CATEGORICAL DATA

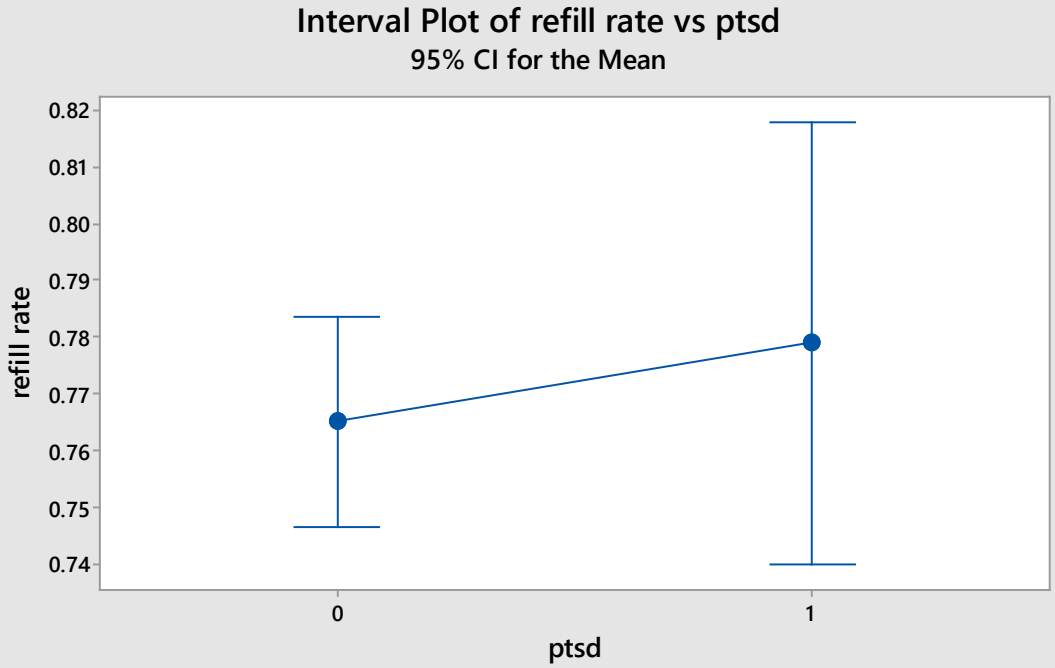




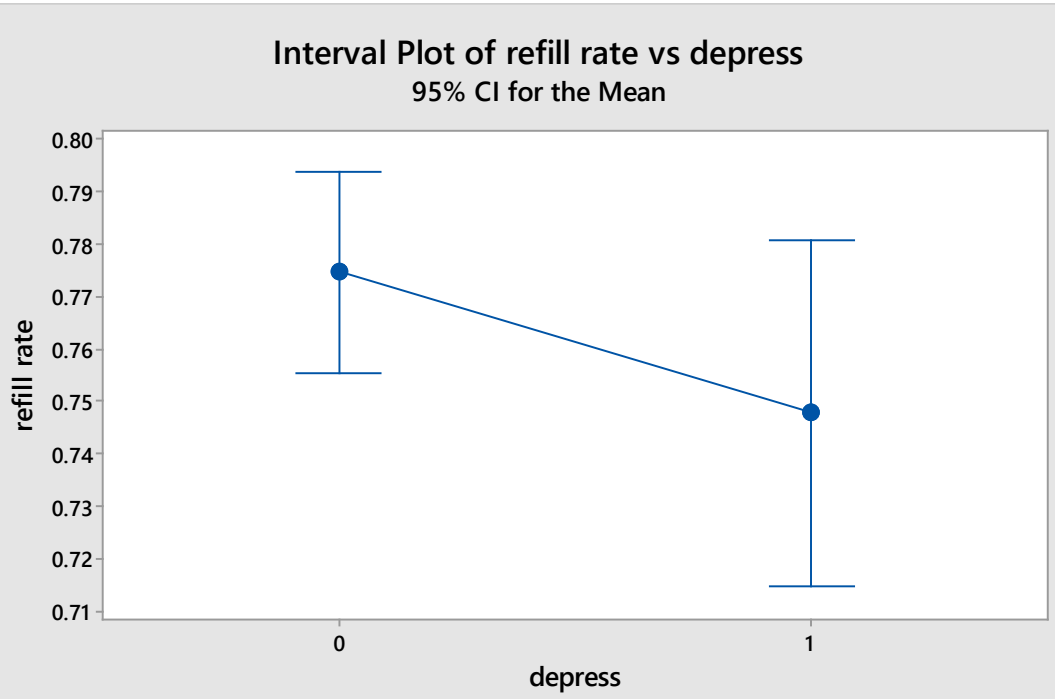
The pooled standard deviation was used to calculate the intervals.



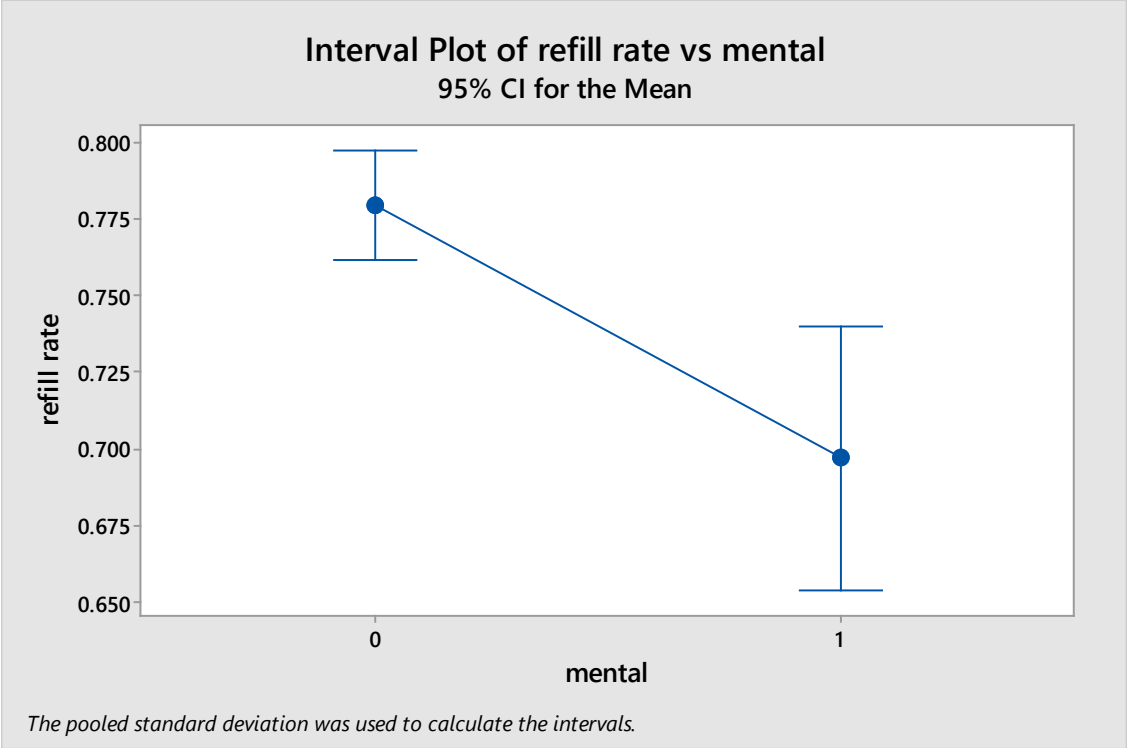
The pooled standard deviation was used to calculate the intervals.



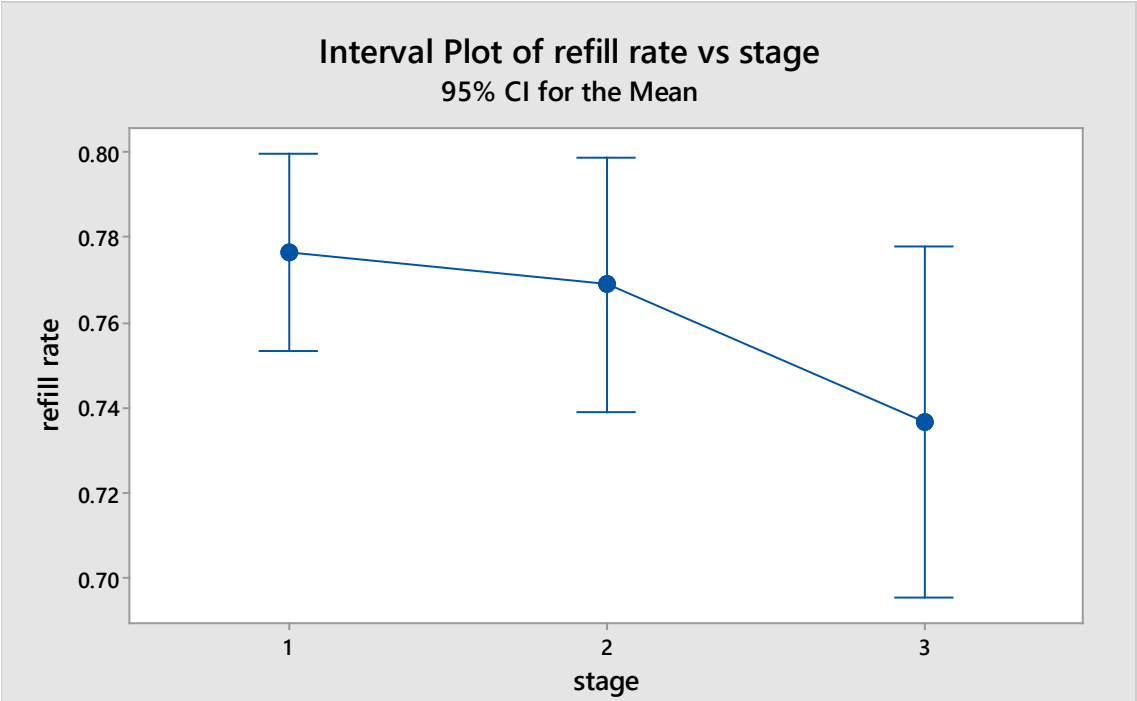
The pooled standard deviation was used to calculate the intervals.



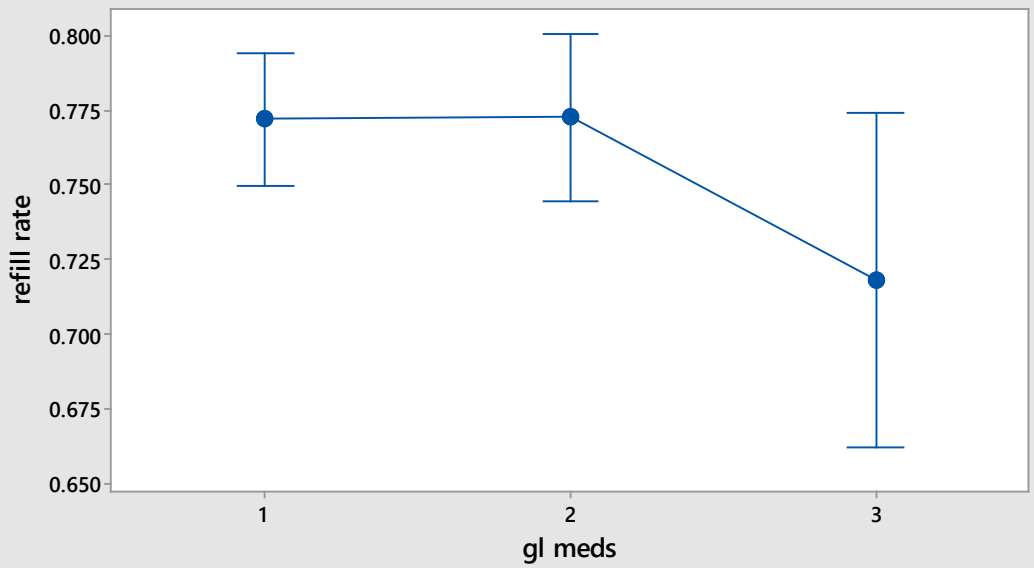
The pooled standard deviation was used to calculate the intervals.



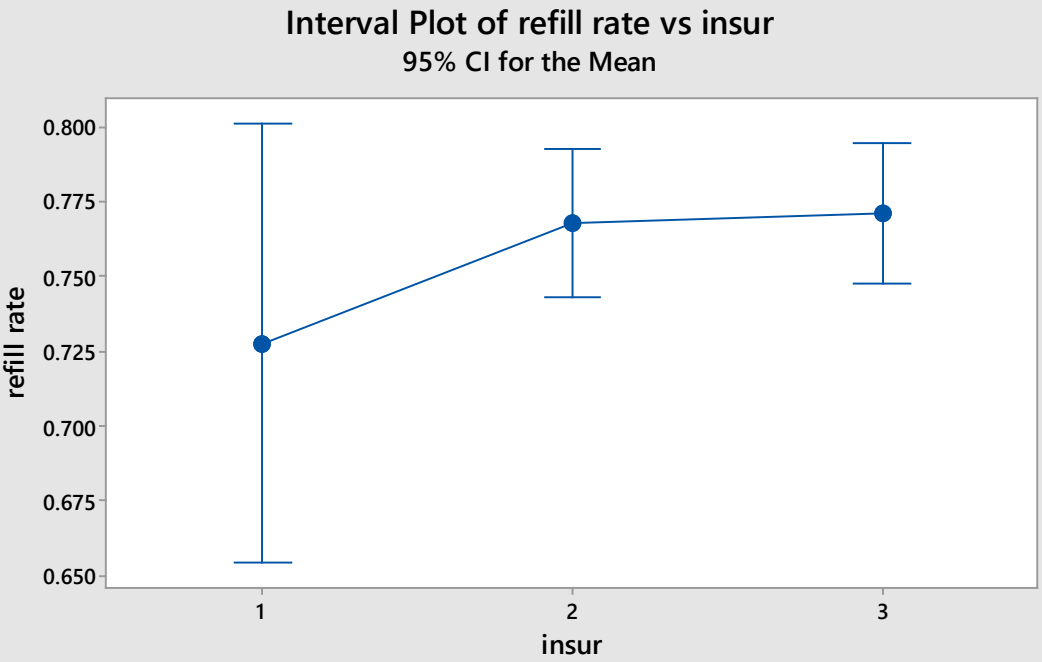
The pooled standard deviation was used to calculate the intervals.



The pooled standard deviation was used to calculate the intervals.



The pooled standard deviation was used to calculate the intervals.



The pooled standard deviation was used to calculate the intervals.

APPENDIX E : PAIRWISE CORRELATION MATRIX

	refill rate	race	age	married	employd	miles	subabuse	ptsd	depress	mental	duration	missaptE	stage	medchg	gl meds	dr/ day	No. diag	missedMD	totmed	SC %
race	0.08																			
	0.206																			
age	-0.036	0.244																		
	0.572	0																		
married	-0.001	0.031	0.029																	
	0.982	0.624	0.645																	
employd	-0.011	-0.086	-0.466	-0.097																
	0.868	0.173	0	0.125																
miles	0.056	0.154	0.018	-0.142	-0.023															
	0.375	0.015	0.772	0.024	0.722															
subabuse	0.067	-0.219	-0.284	-0.061	0.051	-0.078														
	0.295	0	0	0.337	0.425	0.219														
ptsd	0.04	-0.16	-0.228	0.104	0.02	0.103	0.21													
	0.528	0.011	0	0.101	0.757	0.106	0.001													
depress	-0.088	-0.051	-0.184	0.007	-0.03	0.001	0.19	0.384												
	0.166	0.426	0.004	0.914	0.638	0.986	0.002	0												
mental	-0.217	-0.031	0.118	-0.027	-0.118	0.046	0.122	-0.077	0.047											
	0.001	0.626	0.062	0.671	0.063	0.472	0.055	0.224	0.464											
duration	-0.24	-0.017	0.229	0.115	-0.177	0.043	-0.135	-0.053	-0.03	-0.013										
	0	0.787	0	0.071	0.005	0.498	0.033	0.4	0.632	0.839										
missaptE	-0.125	-0.068	0.094	0.058	-0.15	0.206	-0.034	-0.069	0.032	0.109	0.179									
	0.048	0.286	0.136	0.361	0.018	0.001	0.587	0.275	0.613	0.086	0.005									
stage	-0.098	-0.157	0.176	0.043	-0.165	-0.069	-0.081	-0.13	-0.036	0.06	0.21	0.215								
	0.123	0.013	0.005	0.502	0.009	0.28	0.2	0.039	0.568	0.342	0.001	0.001								
medchg	-0.171	-0.043	0.132	0.127	-0.14	-0.019	-0.144	-0.072	-0.065	-0.06	0.643	0.175	0.399							
	0.007	0.501	0.036	0.045	0.027	0.761	0.023	0.258	0.307	0.349	0	0.005	0							
gl meds	-0.079	-0.124	0.169	0.092	-0.14	-0.039	-0.195	-0.1	-0.011	-0.018	0.369	0.15	0.579	0.56						
	0.211	0.05	0.007	0.147	0.027	0.534	0.002	0.116	0.861	0.782	0	0.018	0	0						
dr/day	-0.086	-0.125	0.126	0.137	-0.112	-0.031	-0.178	-0.057	0.018	-0.016	0.381	0.124	0.549	0.569	0.905					
	0.175	0.049	0.046	0.031	0.078	0.627	0.005	0.371	0.775	0.807	0	0.05	0	0	0					
No. diag	-0.117	-0.007	0.121	0.237	-0.11	-0.073	-0.063	0.152	0.169	0.175	0.201	0.025	-0.035	0.025	-0.006	0.009				
	0.065	0.911	0.057	0	0.084	0.253	0.318	0.016	0.008	0.006	0.001	0.691	0.577	0.691	0.92	0.892				
missedMD	-0.233	-0.118	-0.021	0.002	-0.018	0.01	0.055	0.058	0.089	0.081	0.185	0.244	0.052	-0.028	-0.012	-0.026	0.078			
	0	0.063	0.741	0.975	0.777	0.878	0.384	0.365	0.161	0.2	0.003	0	0.416	0.66	0.855	0.683	0.221			
totmed	-0.043	-0.061	0.096	0.104	-0.169	-0.014	-0.004	0.153	0.236	0.209	0.057	0.093	-0.105	-0.091	-0.092	-0.041	0.586	0.124		
	0.497	0.338	0.13	0.102	0.007	0.821	0.946	0.015	0	0.001	0.365	0.142	0.097	0.151	0.149	0.515	0	0.051		
SC %	0.041	-0.145	-0.258	0.213	-0.056	-0.031	0.153	0.528	0.289	-0.006	-0.024	-0.017	0.001	-0.016	0.04	0.123	0.167	0.079	0.293	
	0.523	0.021	0	0.001	0.378	0.623	0.016	0	0	0.919	0.704	0.786	0.993	0.804	0.525	0.052	0.008	0.214	0	
insur	0.049	0.295	0.396	0.271	-0.317	0.001	-0.233	-0.077	-0.099	-0.134	0.208	0.097	0.081	0.163	0.139	0.133	0.086	0.052	0.036	-0.116
	0.438	0	0	0	0	0.99	0	0.224	0.117	0.034	0.001	0.127	0.202	0.01	0.028	0.035	0.175	0.413	0.569	0.066