Two-Stage Stochastic Programming for Interdisciplinary Pain Management

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Abstract

This research proposes a two-stage stochastic programming (2SP) method to optimize a treatment procedure for interdisciplinary pain management. The 2SP model incorporates non-convex nonlinear mixed integer constraints, which are constructed based on data from a real pain management program. A piecewise linear approximation method is derived to approximate the non-convex nonlinear constraints in the 2SP model. Consequently, an equivalent mixed integer linear programming (MILP) model is formulated and then solved quickly using a commercial branch-and-bound solver. A comparison of the policies generated by the MILP model with the policies generated by the original nonlinear 2SP model shows that given limited CPU time, the policies generated by MILP model outperform those of the original nonlinear 2SP model.

Keywords— Two-Stage Stochastic Programming, Pain Management, Regression, Linear Approximation, MILP, MINLP

1 Introduction

Chronic pain is a major public health problem in the United States. It's reported that about 100 million adult Americans were affected by chronic pain with an annual cost of $560 - $635 billion dollars (Pizzo & Clark, 2011). Conventional anti-nociceptive interventions for chronic pain, such as opioid medication and surgery, may lack long-term benefits, and many patients do not achieve satisfactory relief with single-drug or even combination therapies (Bolay & Moskowitz, 2002; Gatchel, McGeary, McGeary, & Lippe, 2014). As pain research and clinical practice has been developed

significantly in the past several decades, it was realized that pain is a multidimensional problem that involves sensory, emotional, and behavioral factors (Hardy, 1997; Serpell & Basler, 2008). Consequently, pain management, which uses an interdisciplinary approach to deal specifically with the management of chronic pain and help patients improve the quality of their life, is developing substantially (Wikipedia.org, 2016; Spanswick & Main, 2000).

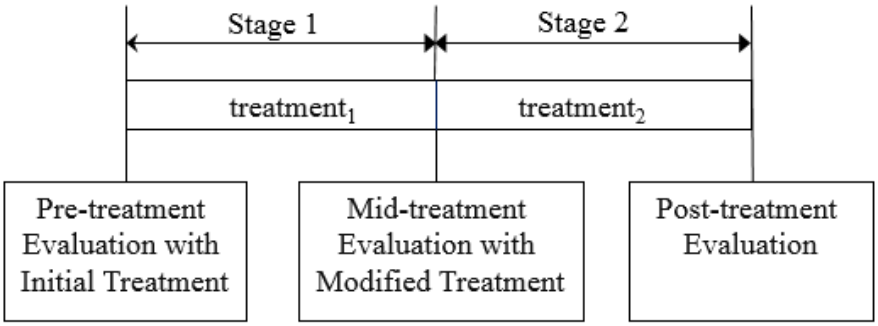


Figure 1 Two-stage Interdisciplinary Pain Management Program (Lin et al., 2014)

The Eugene McDermott Center for Pain Management at the University of Texas Southwestern Medical Center (the Center) conducts a two-stage pain management program for patients who are suffering from chronic pain. The procedure of the program is depicted in Figure 1. Prior to treatment for a patient, a *pre-treatment* evaluation is conducted. During pre-treatment evaluation, a patients information, such as age, gender, pain duration, medical history, and current pain outcome, is recorded. Based upon this information, stage-one treatment is determined for the patient. At the midpoint of the program, a *mid-treatment* evaluation is conducted to evaluate the patients pain outcome after having stage-one treatment. Based upon the results of the mid-treatment evaluation, stage-two treatment is prescribed. A final *post-treatment* evaluation, which is regarded as the completion of the program, is conducted to measure the patients final pain outcome.

The contribution of this research is a method to find an optimal treatment strategy that simultaneously minimizes a penalty for the expected pain outcome and treatment cost for individual patients. Two-stage stochastic programming is proposed to optimize the treatment procedure. The pain outcome at mid-treatment evaluation and post-treatment evaluation are predicted by system prediction functions, which are constructed based on the empirical data from the Center. These prediction functions that behave as constraints in the 2SP model are non-convex mixed-integer

nonlinear with continuous random variables, which result in a two-stage stochastic non-convex constrained problem. The traditional approach of solving the stochastic problem is approximating the continuous random variables by a finite discrete set. Then the equivalent deterministic non-convex mixed integer nonlinear program (MINLP) is given. This paper proposes an approach to solve the two-stage stochastic programming problem as follows: approximate the non-convex nonlinear constraints by high-fidelity piece-wise linear functions. Thus the non-convex MINLP is converted into a mixed integer linear programming program (MILP), which can be globally optimized by a commercial branch-and-bound solver.

The remainder of this paper is organized as follows: Section 2 provides the literature review on adaptive treatment strategies for pain management and an overview of multi-stage stochastic programming. Section 3 describes the two-stage stochastic model formulation and the linear approximation to the quadratic terms. The model description is given in section 3.1. Approximating non-convex quadratic functions by piecewise linear functions, the objective function, treatment interaction restrictions, and the extensive form of the linear approximation model are introduced in section 3.2. Section 4.1 describes the system prediction models and also the significant predictors in the model. Section 4.2 studies on the parameters of the 2SP model. Section 4.3 includes the analysis of the treatment usage in the linear approximated 2SP model optimization results. Section 4.3.1 compares the post-treatment pain outcome of the MILP 2SP model with that of the observed dataset. Section 4.4 compares the policies generated by the non-convex MINLP model with the policies generated by the approximated MILP.

2 Review of Adaptive Treatment Strategies

2.1 Adaptive Treatment Strategies

An adaptive treatment strategy (ATS) is a sequential treatment that requires adaptive changes in the duration, doses, or type of treatment over time depending on a patients ongoing response to past treatments. As a result of individual response heterogeneity, reoccurrence of symptoms, and more intensive or longer-term treatments may increase the possibility of intolerable side effects, ATS is a promising alternative to fixed treatment strategies in the treatment of chronic disorders (Pineau, Bellemare, Rush, Ghizaru, & Murphy, 2007; Murphy, Oslin, Rush, & Zhu, 2007) for three

reasons: (1) Patients' needs for treatments are heterogeneous; for example, some patients respond well to medication alone, whereas other patients may require additional talk-therapy to respond well. In this situation, the treatment type should vary across patients. (2) Patients' responses to certain treatements are heterogeneous; some patients respond better to a high dosage of treatment, while others respond better to a low dosage of treatment. Some will respond better to long periods of treatment rather than shorter periods. (3) Side effects can be avoided by identifying the not-functional component for particular patient (Murphy & McKay, 2004). Based on the reasons mentioned above, adaptive treatment strategies are emerging as a new approach for the treatment and long-term management of chronic, re-occurring disorders such as alcoholism, smoking cessation, cocaine abuse, depression, and hypertension (Murphy, 2005; Breslin et al., 1998; Brooner & Kidorf, 2002; Glasgow, Engel, & D'Lugoff, 1989; Kreuter & Strecher, 1996; Lavori, Dawson, & Rush, 2000; Unützer et al., 2001).

The estimation of the effects of each type of treatment is affected by whether the data is from randomized experimental studies or from observational studies. Data that is collected from the randomized clinical trials is ideal and can be used to make valid inferences about the causal effects of treatments on the outcome of interest. However, observational data in sequential treatment is not ideal because of the complex relationship between the time-dependent treatments and related variables, such as patient characteristics. In addition, the treatment variables at a previous stage can influence patient variables at the current stage, which will in turn influence the treatments at the following stage (Murphy, 2005). Such mutual interactions will lead to bias in estimating the true effect of treatments on the outcomes. This problem is commonly referred to as endogeneity or time-dependent confounding (Robins, 1999;Little & Rubin, 2000; MOODIE, PLATT, & KRAMER, 2009). In this paper, concerns about endogeneity are mitigated based upon methods described in Leboulluec (2013).

2.2 Algorithms for Constructing Adaptive Treatment Strategies

ATS includes a set of decisions that recommend how the treatment level and type should change depending on a patients ongoing responses to past treatments. Decisions occur at different points in time so that constructing adaptive treatment strategies can be regarded as a problem with multiple-stages of observations and actions. In addition, decisions at each stage should be taken

without full information about how random events will occur, such as the patients heterogeneity in response to treatments. As a result, this type of problem usually can be modeled using stochastic dynamic programming or multi-stage stochastic programming, which are related approaches used to model optimization problems under uncertainty for which a sequence of decisions can be taken in successive stages

The most relevant related research to this research is Lin et al. (2014), who employed approximate dynamic programming (DP) for optimal treatment strategies for patients. The approximate DP approach he used was based on the assumption of continuous state space; however, in this practical problem, state variables are mixed with integer variables. However, DP problems can usually be formulated as multi-stage stochastic programming problems, (Ahmed, 2010; Shapiro & Philpott, 2007; Birge & Louveaux, 1997; Sherali & Zhu, 2009). Consequently this research uses multi-stage stochastic programming.

The most widely applied and studied stochastic programming models are two-stage stochastic linear programs, although solution algorithms used for two-stage stochastic programs can be and have been extended to multi-stage stochastic programs. The uncertainty in the stochastic programming problem is often represented by random variables that are assumed to have a known distribution. A meaningful approximation of the distribution of continuous random variable by a discrete distribution often requires many scenarios. With the scenarios increasing, the size of the equivalent deterministic linear problems will increase rapidly, along with the computational time. Thus, seeking a good scenario generation method, which is able to get near optimal solutions by using a reasonable number of realizations, is significantly important. Frequently used scenario generation methods are sampling, statistical approaches, simulation, and other hybrid methods (Mitra & Domenica, 2010; Mitra, n.d.).

3 Two-Stage Stochastic Programming Model

3.1 General Formulation

The objective of the ATS method developed here is to find an optimal strategy that could minimize cost associated with treatments in stage 1 and 2, as well as a penalty on the expected final pain outcome, which also should satisfy the following conditions: drug dosage limitations, treatment

interaction restrictions, and outcome and state transition modeling constraints. Thus, the two-stage stochastic programming (2SP) model can be formulated as equation (1). Different from traditional two-stage stochastic programming problems, the model in this research has a second random variable ε_2

$$\min P\Big(E(Y_2(\varepsilon_1,\varepsilon_2))\Big) + \rho\Big(C(x_1) + E(C(x_2))\Big) \tag{1a}$$

$$\text{subject to: } Y_1(\varepsilon_1) = h_1(s_1, x_1, \varepsilon_1) \tag{1b}$$

$$Y_2(\varepsilon_1,\varepsilon_2) = h_2(s_2(\varepsilon_1), x_2(\varepsilon_1), \varepsilon_2) \tag{1c}$$

$$x_1^i x_1^j = 0, \quad x_2^i(\varepsilon_1) x_2^j(\varepsilon_1) = 0 \qquad \forall (x^i, x^j) \in \Lambda \tag{1d}$$

$$s_2(\varepsilon_1) = \Big[s_1, x_1, Y_1(\varepsilon_1)\Big] \tag{1e}$$

$$x_1 \in \Gamma_1, x_2(\varepsilon_1) \in \Gamma_2 \tag{1f}$$

In the objective function (1a), $P()$ is the penalty function on the expected final pain outcome, and $C()$ is the treatment cost function. The parameters ρ is a coefficient that balances treatment cost and the penalty on expected final pain outcome. In addition, s_1 is a constant vector of the patients state variables at the beginning of stage 1, which could include the patients entire medical history, s_2 is the vector of state variables at the beginning of stage 2, x_t is the vector of treatment decisions, Γ_t is the set of feasible treatment decisions, x_t^i is the dose or usage of treatment i in stage t, Λ is a set of treatment interaction restrictions, function h_t updates the patients pain outcome at the end of each stage, random vector ε_t represents the uncertainty in the system prediction models. Constraints (1b) and (1c) are pain outcome prediction functions at the mid-treatment evaluation point and the post-treatment evaluation point respectively. Constraint set (1d) includes the treatment interaction restrictions, which hence forth will be modeled as special order set constraints of type I (SOSI) and can be implemented directly in commercial branch-and-bound solvers like CPLEX. Constraint set (1e) shows the elements included in s_2. Constraint set (1f) includes the bounds and appropriate integer restrictions on treatment decision variables. According to Lin et al. (2014), constraint (1c) has quadratic terms as well as nonconvexity.

A linear approximation method is proposed in this research to approximate the non-convex constraint with piecewise linear function. Then the stochastic programming model can be solved

quickly by a mature branch-and-bound solver such as CPLEX. In addition, the solution of the approximation model is compared with the solution from original nonconvex model found by the non-convex nonlinear solver COUENNE. Results show that in limited time, the approximation method can in fact find better treatment strategies.

3.2 Linear Approximation Method

Quadratic terms in constraint (1c) are classified into three types as follows, (1) a binary variable interacts with a continuous variable, (2) a binary variable interacts with a binary variable, and (3) a continuous variable interacts with a continuous variable. The linear formulation for the interactions of types (1) and (2) are straightforward and given in constraint set (2) in which $x_{ij} = x_i x_j$.

$$\begin{array}{cc} \text{type 1:} & \text{type 2:} \\ l_j x_i \le x_{ij} \le u_j x_i, & x_{ij} \le x_k, \forall k = i, j \\ x_j - u_j(1 - x_i) \le x_{ij} \le x_j - l_j(1 - x_i), & x_{ij} \ge x_i + x_j - 1. \end{array} \tag{2}$$

This research has proposed a refitting regression model method with piecewise linear terms in place of type (3) quadratic term. If x_i and x_j are continuous variables with bounds $[l_i, u_i]$ and $[l_j, u_j]$, respectively, then the first order Taylor series approximation can be written as equation (3):

$$x_i x_j \approx -x_i^0 x_j^0 + x_j^0 x_i + x_i^0 x_j \tag{3}$$

where (x_i^0, x_j^0) is a selected point around which the approximation lies. Let $\bar{x}_i = \frac{l_i + u_i}{2}$ and $\bar{x}_j = \frac{l_j + u_j}{2}$ be the midpoints of the feasible space, and consider dividing the dividing the original region, $[l_i, u_i] \times [l_j, u_j]$, into 4 equal sub-regions $[l_i, \bar{x}_i] \times [l_j, \bar{x}_j]$, $[l_i, \bar{x}_i] \times [\bar{x}_j, u_j]$, $[\bar{x}_i, u_i] \times [l_j, \bar{x}_j]$, and $[\bar{x}_i, u_i] \times [\bar{x}_j, u_j]$. Consider two binary variables $\hat{x}_i$ and $\hat{x}_j$, which indicate that the variables are above their midpoints and defined by equation (4):

$$\hat{x}_k = \begin{cases} 1, & \text{if } x_k > \bar{x}_1 \\ 0, & \text{otherwise,} \end{cases} \qquad \forall k = i, j \tag{4}$$

The variables x_k and $\hat{x}_k$ can be linked by constraint set (5).

$$\frac{x_k - \bar{x}_k}{u_k - l_k} + \varepsilon \;\leq\; \hat{x}_k \;\leq\; 2\frac{x_k - l}{u_k - l_k}, \qquad \forall k = i, j. \tag{5}$$

The midpoint of the sub-region to which x is in can be expressed by equation set (6).

$$x_k^0 = \hat{x}_k \; \frac{u_k + \bar{x}_k}{2} + (1 - \hat{x}_k) \; \frac{l_k + \bar{x}_k}{2}, \qquad \forall k = i, j. \tag{6}$$

Substituting (6)into (3), equation (7) is derived.

$$\begin{aligned} x_i x_j \approx & -\frac{l_i + \bar{x}_i}{2}\frac{l_j + \bar{x}_j}{2} + \frac{l_j + \bar{x}_j}{2}x_i + \frac{l_i + \bar{x}_i}{2}x_j - \frac{u_i - l_i}{2}\frac{u_j - l_j}{2}\hat{x}_i\hat{x}_j \\ & - \frac{u_i - l_i}{2}\frac{l_j + \bar{x}_j}{2}\hat{x}_i - \frac{u_j - l_j}{2}\frac{l_i + \bar{x}_i}{2}\hat{x}_j + \frac{u_j - l_j}{2}\hat{x}_j x_i + \frac{u_i - l_i}{2}\hat{x}_i x_j \end{aligned} \tag{7}$$

In equation (7), the 7 terms x_i, x_j, $\hat{x}_i\hat{x}_j$, $\hat{x}_i$, $\hat{x}_j$, $\hat{x}_j x_i$, and $\hat{x}_i x_j$ are considered new features that may replace the quadratic term $x_i x_j$. Though the features $\hat{x}_i\hat{x}_j$, $\hat{x}_j x_i$, are $\hat{x}_i x_j$ are quadratic, they can be formulated as linear terms with additional linear constraints as described in constraints (2). In other words, a type (3) quadratic term can be approximated by 7 linear terms. Based on this approximation, a refit method is proposed for approximating type (3) quadratic terms in section 3.3.

3.3 Refitting Continuous Variable Interaction Terms

We only need to focus on the type (3) interaction terms since type (1) and type (2) quadratic terms can be linearized. For convenience, they are denoted by a linear term, therefore the original outcome and state transition model h, denoted as model 1 with m type (3) quadratic terms, can be described as equation (8)

$$Y = \beta_0 + \sum_{i=1}^{n} \beta_i x_i + \sum_{i=n+1}^{n+m} \beta_i (x_u x_{v(v \neq u)}) + \epsilon^1 \tag{8}$$

The procedure of refitting the model 1 is shown as follows, and the refit model denoted as model 2.

- Step 1: Remove the quadratic term away from model 1 to get equation (9) and calculate the

residual ϵ' from (9)

$$Y = \beta_0 + \sum_{i=1}^{n} \beta_i x_i + \epsilon' \tag{9}$$

- Step 2: Use ϵ' as a response variable to fit a linear regression model on linear predictors derived from (7) for the m type (3) quadratic terms using stepwise regression to get equation (10):

$$\epsilon' = \alpha_0 + \sum_{j=1}^{n'} \alpha_j x'_j + \epsilon^2 \tag{10}$$

- Step 3: Combine constant and linear terms in equations (8) and (10) to obtain Model 2 as shown in equation (11):

$$Y = \beta_0 + \alpha_0 + \sum_{i=1}^{n} \beta_i x_i + \sum_{j=1}^{n'} \alpha_j x'_j + \epsilon^2 \tag{11}$$

3.4 Revised Two-Stage Stochastic Programming Formulation

By using the aforementioned refit linear reformulation method, the nonconvex constraints are approximated by piecewise linear functions. Consequently, the 2SP model can be approximated by a piecewise linear model. By discretizing the continuous random variables ε_1 and ε_2 in 2SP, the deterministic equivalent is an MILP model, denoted as L2SP. Consider sampling each random variable ε_1 and ε_2 to n times to obtain discrete sample sets Ξ_1^n and Ξ_2^n. The MILP model of L2SP is shown as in equation (12). Constraint set (12a) is equivalent to (1b), representing the prediction model of the pain outcome at the mid-treatment evaluation point $Y_1(\omega_1)$. Constraint set (12b) represents the prediction model for the pain outcome measure at the post-treatment evaluation point, which is the piecewise linear approximation of constraint (1c). In (12b), the variable vector $x_L(\omega_1)$ represents in the linearized variables introduced to replace the quadratic interaction terms described in section 3.2. Constraint (12c) includes linear constraints that link the linearized variables $x_L(\omega_1)$ with the second-stage state and treatment variables with coefficient matrices B_x^2, B_s^2, and B_L^2, and vector d, as in constraints (2) and (5). Constraints (12d—12f) are the discretization of constraints (1d—1f), respectively. β_i^1 is the coefficient vector for predictors of the pain outcome at the mid-treatment evaluation point, β_i^2 is the coefficient vector for predictors of the approximated pain outcome model at the post-treatment evaluation point. Constraint set (12g) include appropriate restrictions on

the linearized variables. The rest of the notations are same as in 2SP (1) .

$$\min P\Big(\sum_{\omega_1\in\Xi_1^n}\sum_{\omega_2\in\Xi_2^n} Y_2(\omega_1,\omega_2))\Big) + \rho\Big(C(x_1) + \sum_{\omega_1\in\Xi_1^n} E(C(x_2(\omega_1)))\Big)$$

$$\text{subject to: } Y_1(\omega_1) = \beta_0^1 + \beta_1^1 x_1 + \beta_2^1 s_1 + s_1^T \beta_3^1 x_1 + \omega_1 \qquad \omega_1 \in \Xi_1^n \tag{12a}$$

$$Y_2(\omega_1,\omega_2) = \beta_0^2 + \beta_1^2 x_2(\omega_1) + \beta_2^2 s_2(\omega_1) + \beta_3^2 x_L(\omega_1) + \omega_2 \qquad \omega_1 \in \Xi_1^n, \omega_2 \in \Xi_2^n \tag{12b}$$

$$B_x^2 x_2(\omega_1) + B_s^2 s_2(\omega_1) + B_L^2 x_L(\omega_1) \le d \qquad \omega_1 \in \Xi_1^n \tag{12c}$$

$$x_1^i x_1^j = 0,\ x_2^i(\varepsilon_1) x_2^j(\varepsilon_2) = 0 \qquad \forall (i,j) \in \Lambda, \omega_1 \in \Xi_1^n \tag{12d}$$

$$s_2(\omega_1) = \Big[s_1, x_1, Y_1(\omega_1)\Big] \qquad \omega_1 \in \Xi_1^n \tag{12e}$$

$$x_1 \in \Gamma_1,\ x_2(\omega_1) \in \Gamma_2 \qquad \omega_1 \in \Xi_1^n \tag{12f}$$

$$x_L(\omega_1) \in \Gamma_L \qquad \omega_1 \in \Xi_1^n \tag{12g}$$

4 Case Study

The dataset from the Center has 294 patients. 235 of them are in a training dataset and the remaining 59 patients are in a testing dataset. This research uses Oswestry Pain Disability Questionnaire (OSW) pain outcome measure to model the problem. OSW score ranges from 0 to 50, and the score is classified into five levels. For a total score of 0-10, no treatment is necessary; 11-20 indicates mild disability and conservative treatment is recommended; 21-30 indicates severe disability and detailed investigation is required; 31-40 indicates crippling disability and severe Intervention is required; 41-50 indicates bed bound (Europeanmedicaltourist.com, 2016).

4.1 Outcome and State Transition Models

Stepwise variable selection criteria is used to predict pain outcome at the mid-treatment evaluation point, which is denoted as mid_OSW, and post-treatment evaluation point, which is denoted as Post_OSW. According to Lin et al. (2014) , the best subset of predicators at stage t are from state variables s_t, decision variables x_t, and two way interaction terms from all state variables with all decision variables. Least squares regression is employed to predict Mid_OSW, while weighted least squares regression is employed for the Post_OSW prediction model to mitigate endogeneity

concerns. Specifically, weights to mitigate endogeneity issues were from Leboulluec (2013). The Mid_OSW model in this research is given in (13).

$$\begin{aligned} Mid\_OSW = {} & 7.63651 + 0.57965 \times Pre\_OSW - 2.61561 \times StdProcGr11\_1 \times Stdage \\ & - 2.17391 \times StdRxGr3\_1 \times Stdonset + 1.03057 \times StdRxGr6\_1 \\ & \times Stdmarital\_2 - 2.83417 \times StdRxGr7\_1 \times Stdduration - 1.14044 \\ & \times StdRxGr7\_1 \times StdProcGr10\_0 + \varepsilon_1. \end{aligned} \tag{13}$$

The prefix $Stdx$ stands for standardized variable x. All interaction terms are standardized and centralized by $Stdx = \frac{x-(u+l)/2}{(u-l)/2}$, where u and l denote the upper bound and lower bound of x respectively.

The original selected Post_OSW model consists of two continuous (or integer) variable interaction terms. After linearly approximating quadratic terms by the refit method described in section 3.3, the linear refit Post_OSW model is derived. The residual analysis results of both original Post_OSW and refit Post_OSW model are given in Appendix B. Residual analysis results provided in Appendix C show that the refit model are as accurate as the original model and do not violate least squares modeling assumptions.

Equation (13) shows that muscle relaxants (RxGr4_1), other medicines (RxGr8_1), injections (ProcGr1_1), and block procedures (ProcGr2_1) are not selected as predictors of Mid_OSW. Tramadol (RxGr1_2), muscle relaxants (RxGr4_2), antidepressants (RxGr5_2), and tranquilizers (RxGr6_2) are not selected as predictors in the Post_OSW model. Muscle relaxants are the only treatment that is not selected as a significant predictor in either stage.

4.1.1 Penalty Function for Pain Outcome and Treatment Cost Function

Objective function (1a) of 2SP (1) is based upon that in Lin et al. (2014) and is summarized in this section. Objective function (1a) is comprised of two parts: a pain outcome penalty function and a treatment cost function. The pain outcome penalty function penalizes the expected value of the Oswestry Pain Disability Questionnaire (OSW) pain outcome measure. From a patients perspective, each of subsequent level is significantly worse than lower levels, so this research uses a five-piece

nondecreasing piecewise linear penalty function. OSW scores less than or equal to 10 are regarded as normal, so no penalty is applied. Along with the increase in disability level, the penalty on the expected pain outcome increases for each unit increase in final pain outcome score. In other words, the slope (α) for each piece has the following relationship: $\alpha_5 > \alpha_4 > \alpha_3 > \alpha_2 > \alpha_1 > \alpha_0 = 0$. The determination of the slope refers to the penalty function in Lin et al. (2014).

The purpose of treatment cost function is to place a higher cost on more treatment (either medications or surgery) in order to control the medication usage. Nondecreasing piecewise linear functions are also used to represent the treatment cost function. Two different types of treatments have been used in this research. Procedural treatments are binary, while pharmaceutical treatments are two-level and three-level discrete integer. Different piecewise linear function are used for each type of treatment variable, and the slopes of these functions are similarly from Lin et al. (2014).

4.2 Study of Parameters of L2SP Model

The L2SP model in this research contains two continuous random variables that follow normal distributions. This research employs the approach of approximating the continuous random variable with a discrete set obtained by random Monte Carlo sampling from its distribution, and then optimizes the equivalent deterministic problem. Whether or not the support set can closely approximate the normal distribution affects the quality of an optimal solution. The approximation accuracy can be improved by increasing sample size. However, as sample size increases, the size of the equivalent deterministic problem will increase quickly, which in turn increases computational time to solve L2SP. As a result, determining an appropriate sample size is very important for the L2SP problem. In addition, an appropriate treatment coefficient ρ is also very important to L2SP. If the value of ρ is too large, L2SP will recommend no treatment to patients because of the large cost of treatments. By contrast, with a value too small of ρ, the model would recommend too much treatment for only a little decrease in pain outcome.

The determination of Monte Carlo sample size and treatment coefficient are described in detail in this section. All procedures are coded in the C programming language, and the IBM ILOG CPLEX Callable library is used to solve L2SP. Experiments in this research are all executed on a desktop with eight processors at 2.67 GHz and 16 GB of memory. The program terminates at the following conditions: (1) either the elapsed time of the optimization routine reaches to six minutes

or (2) a relative tolerance on the gap between the best integer objective and the objective of the best node remaining are within 0.01.

4.2.1 Treatment Coefficient ρ

Different from traditional 2SP problems, there are two random variables, one at each stage in this research. Though the sample size for each random variable at each stage can be different, the same sample size n in each stage. In order to find an appropriate treatment coefficient ρ, we fix the Monte Carlo sample size at 50 for each stage with treatment interaction restriction constraints relaxed. Experiments are done with ρ equal to 0.1, 0.3, 0.5, and 0.7 separately. The average results for the 235 patients in training dataset is in Table 1. The table shows how the treatment cost decreases alongside an increase in treatment coefficient. Decreases in treatment cost means less treatment for patients. Meanwhile, the final pain outcome increases alongside an increase in treatment coefficient ρ. An OSW measure below or equal to 10 is considered a satisfactory pain outcome by the Center. As a result, 0.1 is selected for the treatment coefficient in this research; all experiments in the following sections are based on ρ equal to 0.1.

Table 1 Average Treatment Cost and Final Pain Outcome at Different ρ Value

Treatment coefficient ρ	$\rho = 0.1$	$\rho = 0.3$	$\rho = 0.5$	$\rho = 0.7$
Average Treatment Cost for Training Dataset	29.98	23.88	17.23	6.85
Average Final Pain Outcome for Training Dataset	10.12	10.81	12.43	15.88

4.2.2 Sample Size and Evaluation Procedure

In this section, a treatment evaluation procedure is developed in section 4.2.2.1, and the determination of sample size n is given in section 4.2.2.1 and section 4.2.2.2

4.2.2.1 Evaluation Procedure A much larger number of scenarios are used to evaluate the first-stage treatment policy generated by L2SP. Let $x^*_{1(n)}$ be the characteristic vector of a first-stage treatment policy generated from L2SP with n scenarios in each stage. In the evaluation procedure, L2SP is solved with more scenarios m in each stage and the vector of first stage decision variables are set to equal to the policy under evaluation. The mathematical model of *L2SP evaluator* is shown in equation (14). The objective in evaluator is regarded as the "real/true" objective achieved by

the policy.

$$\min P\Big(\sum_{\omega_1\in\Xi_1^m}\sum_{\omega_2\in\Xi_2^m} Y_2(\omega_1,\omega_2))\Big) + \rho\Big(C(x_1) + \sum_{\omega_1\in\Xi_1^m} E(C(x_2(\omega_1)))\Big)$$

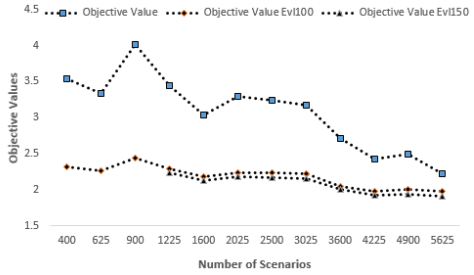
$$\text{subject to: (12a)—(12g)}, \qquad \forall\omega_1\in\Xi_1^m, \forall\omega_2\in\Xi_2^m$$

$$x_1 = x^*_{1(n)} \tag{14a}$$

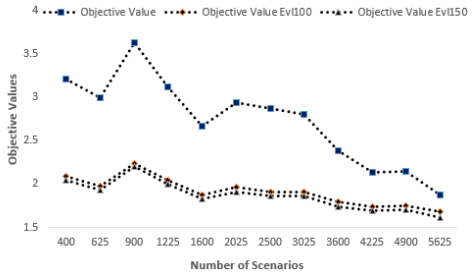
In this research, experiments are done using L2SP with $m = 100$ and $m = 150$.

4.2.2.2 Determination of Sample Size An appropriate sample size n is important. If n is too small, then L2SP cannot represent the 2SP model very well. If n is too large, the size of the problem will increase so that L2SP becomes intractable.

Given policy $x^*_{1(n)}$, the objective value of the L2SP evaluator with sample size of m is denoted as $f(x^*_{m(n)})$. An appropriate n is the number where $f(x^*_{m(n)})$ begins to level off along with the increase in n. We conduct experiments for training and testing datasets by generating first-stage



(a) Training Dataset



(b) Testing Dataset

Figure 2 Average Optimal Objectives in Different Scenarios across Different Evaluators for Patients

treatment policies using L2SP with sample sizes of n at 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70 and 75, and evaluate the generated policies with evaluation sample size of $m = 100$ and $m = 150$ separately. The averaged optimal objectives for both training and testing datasets are shown in Figures 2a and 2b. The dotted line with square markers represent the objective of L2SP with the different sample sizes n, while the diamond and triangle markers represent the evaluations of the corresponding first-stage treatment policies with $m = 100$ and $m = 150$. These two figures clearly demonstrate two points. One, the L2SP evaluator with 10,000 ($m^2 = 100^2$) scenarios is as good as the evaluator with 22,500 ($m^2 = 150^2$) scenarios, since the objective values in different evaluators

are very close to each other for different scenarios. Two, the objectives of two evaluators are both stabilized at sample size $n = 65$ (65^2 scenarios). As a result, the sample size for a good policy generator is $n = 65$.

4.3 Treatment Usage Analysis

In this section, we analyze the use of types of treatments from L2SP. The usage frequency for a first-stage treatment i is calculated by counting the number of times $x^{i*}_{1(n)}$ is positive for all 294 patients. Second-stage treatments are recourse actions based upon patient outcomes. Consequently, the usage frequency of second-stage treatment i is calculated by the number of times $x^i_2(\omega_1)$ is positive in the L2SP evaluation of $x^{i*}_{1(n)}$ averaged over $m = 100$ scenarios and summed over all 294 patients. The usage frequencies of treatment in the first and second stages among different sample sizes of n of L2SP are shown in Table 2. First-stage treatments end with _1, while second-stage treatments are denoted with _2. According to the L2SP results, the most frequently used type of treatment in the first stage is NSAIDS (RxGr2_1). It is estimated that this medicine has been applied to 82% of patients. The usage of procedure treatment cognitive behavioral therapy (CBT) (ProcGr9_1) varies a lot in different scenarios. Note that tramadol (RxGr1_1) is selected as a significant predictor in the prediction model, but it is never recommended for any patient by L2SP. This is likely because tramadol (RxGr1) has treatment interaction constraints with a lot of other types of treatments such as RxGr3, RxGr4, RxGr6, RxGr7, RxGr8, and ProcGr1 (see appendix A treatment interaction table 5). Consequently, if tramadol (RxGr1) is selected, none of these other treatments can be selected in the same stage.

In the observed dataset from the Center, the most frequently used treatment in the first stage is CBT (ProcGr9_1) as shown in the right column in Table 2, and the second most frequently used is physical therapy (ProcGr10_1). It is estimated that they are used by 75% and 71% patients, respectively. Many more types of treatment have been used by patients in the observed data than in the L2SP solutions.

From Table 2, the three most frequently used types of treatments from the L2SP solutions are NSAIDS (RxGr2_2), sleeping pills (RxGr7_2) and block procedures (ProcGr2_2) in second stage. The frequency in using block procedure has a wide variation in different scenarios. Worth mentioning is that stimulation procedure (ProcGr4_2) and physical therapy (ProcGr10_2) are seldom

Table 2 Usage Frequency of Treatment in Observations and Different Scenarios

Treatment	frequency for different scenarios in evaluator with m = 100												observed treatment frequency
	sample size (n)												
	20	25	30	35	40	45	50	55	60	65	70	75	
RxGr1_1	0	0	0	0	0	0	0	0	0	0	0	0	44
RxGr2_1	249	248	252	249	248	248	248	248	245	242	243	237	97
RxGr3_1	13	15	16	14	15	14	15	16	11	10	12	12	88
RxGr4_1	0	0	0	0	0	0	0	0	0	0	0	0	86
RxGr5_1	23	23	25	24	22	24	24	23	22	21	21	18	96
RxGr6_1	3	3	4	3	2	2	2	2	3	3	3	3	41
RxGr7_1	11	11	17	10	11	12	10	12	9	6	6	7	34
RxGr8_1	0	0	0	0	0	0	0	0	0	0	0	0	12
ProcGr1_1	0	0	0	0	0	0	0	0	0	0	0	0	67
ProcGr2_1	0	0	0	0	0	0	0	0	0	0	0	0	4
ProcGr4_1	11	10	15	11	9	10	10	10	8	7	5	5	19
ProcGr9_1	85	77	105	82	65	74	72	69	41	31	31	19	222
ProcGr10_1	11	11	14	11	10	11	11	11	7	5	7	6	209
ProcGr11_1	23	21	27	23	17	21	20	19	16	13	11	9	27
RxGr1_2	0	0	0	0	0	0	0	0	0	0	0	0	45
RxGr2_2	32	32	30	32	33	33	33	34	35	35	34	34	83
RxGr3_2	6	6	5	6	7	7	7	7	8	9	9	12	48
RxGr4_2	0	0	0	0	0	0	0	0	0	0	0	0	78
RxGr5_2	0	0	0	0	0	0	0	0	0	0	0	0	84
RxGr6_2	0	0	0	0	0	0	0	0	0	0	0	0	38
RxGr7_2	46	46	43	46	47	46	46	46	49	50	51	54	33
RxGr8_2	0	0	0	0	0	0	0	0	0	0	0	1	9
ProcGr1_2	26	27	25	26	27	26	27	26	27	27	27	27	64
ProcGr2_2	38	44	27	40	56	46	48	50	71	80	80	94	6
ProcGr4_2	0	0	0	0	0	0	0	0	0	0	0	0	26
ProcGr9_2	1	1	1	1	1	1	1	1	1	1	2	2	173
ProcGr10_2	0	0	0	0	0	0	0	0	0	0	0	0	157

used though they are selected as predictors in the transition and outcome model. Compared to the first stage, the usage frequency of CBT (RxGr9_2) is reduced in second stage. Since L2SP with $n = 75$ is regarded as an appropriate sample size, the treatment solution is compared with observed dataset. In the observed dataset, the most frequently used treatment is CBT (ProcGr9_2), and then physical therapy (ProcGr10_2), which is similar to the treatment usage in the first stage. The block procedure treatment (RxGr2_2) is the least frequently used treatment in the observed data. However, it is recommended much more frequently by L2SP. Many more types of treatment have been used by patients in the observed data than those recommended by L2SP in the second stage, which may be due to treatment interaction restrictions.

From Table 2, we can draw the conclusions that: (1) In both stages, many more types of treatment have been used in the observed data than in the L2SP results. (2) In the observed data, frequently used types of treatment in the first stage are similar as those in the second stage. However, there is a difference in the types of treatments used between the stages in the L2SP results. (3) CBT (ProcGr9_2) and physical therapy (ProcGr10_2) are more frequently used at the Center than suggested by L2SP. By contrast, NSAIDs (RxGr2_1) should be used more often than it used in the observed dataset.

4.3.1 Final Pain Outcome Comparison between MILP Model and Observed Data

To compare the final pain outcomes in the L2SP results with those in the observed data, an odds ratio analysis is employed. Patients that have a pre-treatment evaluation outcome within the normal/low range do not require treatment, and as a result, these *normal* patients are excluded from the comparison. Consequently, the effects of the L2SP treatments are compared only for patients that require treatment. As mentioned in section 4.2.2.2, optimal objective values evaluated by both evaluators are stabilized when the sample size for each stage increased to 65. Thus, a sample size 65 for each stage with 4225 scenarios is used as a first-stage treatment policy generator. Given the policy, the optimal final pain outcome is evaluated in the L2SP evaluator with $m = 100$. The results are compared with the observed final pain outcome in the original dataset.

According to the observed dataset, the odds of patients who require treatment (initial level of pain above normal) become normal after treatment is estimated by the proportion of the number of normal patients to the number of *above normal* patients, which referred to as the *observed odds*. Similarly the odds that patients become normal after treated by the L2SP policy are referred to as the *optimization odds* and is estimated by the following steps: (1) for each patient s, the probability that his/her final pain outcome is normal is denoted as p_s, which can be estimated by counting the fraction of scenarios resulting in $Post\_OSW \leq 10$. (2) The count of normal patients in optimization model is $N(opt\_normal) = \sum_{s \in S} p_s$, where S is the set of patients with an above normal initial level of pain. (3) The optimization odds can be estimated by the proportion $N(opt\_normal)/(|S| - N(opt\_normal))$.

The number of patients with a normal initial pain level is 24, so 270 patients require treatment. The expected number of normal patients from L2SP and the number of normal patients from the

observed dataset are given in a 2×2 contingency table shown in Table 3. The *observed odds* is estimated by the proportion of normal patients to above normal patients in the final evaluation, which are 51/219, and the optimization odds are 154.15/115.85. The estimated odds ratio of the optimization odds to the observed odds is 5.7. We can interpret this to mean that the treatment policy generated by L2SP is 5.7 times more likely to achieve the normal level.

Table 3 2×2 Contingency Table

Final pain outcome	Number of Normal Patients	Number of above Normal Patients
Optimization Model	154.15	115.85
Observed Dataset	51	219

4.4 Comparison of Linear Approximation 2SP Model and Nonconvex 2SP Model

An alternative approach to solve model (12) is to solve its deterministic model by a non-convex nonlinear solver such as COUENNE and BARON directly. The deterministic MINLP model, denoted as NL2SP, is be described in (15).

$$\min P\Big(\sum_{\omega_1 \in \Xi_1^m} \sum_{\omega_2 \in \Xi_2^m} Y_2(\omega_1, \omega_2))\Big) + \rho\Big(C(x_1) + \sum_{\omega_1 \in \Xi_1^m} E(C(x_2(\omega_1)))\Big)$$

$$\text{subject to: (12a),(12d)– (12f)}$$

$$Y_2(\omega_1, \omega_2) = \beta_0^2 + \beta_1^2 x_2(\omega_1) + \beta_2^2 s_2(\omega_1) + s_2^T(\omega_1)\beta_3^2 x_2(\omega_1) + \omega_2 \quad \omega_1 \in \Xi_1^n, \omega_2 \in \Xi_2^n \quad (15a)$$

In this research, we use the AMPL modeling language to model NL2SP, and then, use COUENNE as a non-convex MINLP solver. The previous section shows that the L2SP model with $n = 65$ is a good policy generator and could represent the 2SP model. However, AMPL/COUENNE cannot find a first stage in 90 minutes for NL2SP with sample sizes of n at 65, 50 and 40 for each stage. Thus, a smaller sample size of $n = 20$ is used to obtain a policy from NL2SP. Even with n reduced to 20, we set the maximum elapsed real time of 15 minutes for COUENNE, because it cannot find a solution within 6 minutes.

In order to compare the quality of treatment policies generated by L2SP (equation(12)) with NL2SP (equation(15)), the policy generated by L2SP with sample size of 20 (denoted as policy 1) and NL2SP with sample size of $n = 20$ (denoted as policy 2) are cross evaluated by two different

evaluators separately. The two evaluators are called as evaluator 1 and 2 separately, which are described in detail as follows.

Evaluator 1 is defined as similar to the L2SP evaluator described in section 4.2.2.1, except that the objective is to minimize the expected penalty on the pain outcome as well as the treatment cost instead of minimizing the penalty on the expected pain outcome with the treatment cost. The mathematical model of evaluator 1 is described in equation (16), in which the objective is multiplied the number of scenarios of pain outcome at post-treatment evaluation point to improve the computational precision and time. Evaluator 1 is solved by CPLEX.

$$\begin{aligned} &\min \Big(\sum_{\omega_1 \in \Xi_1^m} \sum_{\omega_2 \in \Xi_2^m} P(Y_2(\omega_1, \omega_2))) + \rho\Big(C(x_1) + \sum_{\omega_1 \in \Xi_1^m} E(C(x_2(\omega_1)))\Big)\Big) m^2 \\ &\text{subject to: (12a)—(12g), (14a)}, \qquad \forall \omega_1 \in \Xi_1^m, \forall \omega_2 \in \Xi_2^m \end{aligned} \tag{16}$$

Evaluator 2 is very similar to evaluator 1 except the pain outcome at the post-treatment evaluation point is the original non-convex quadratic models instead of the piecewise linear approximation model. The mathematical model of evaluator 2 is described in equation (17), which is solved by COUENNE.

$$\begin{aligned} &\min \Big(\sum_{\omega_1 \in \Xi_1^m} \sum_{\omega_2 \in \Xi_2^m} P(Y_2(\omega_1, \omega_2))) + \rho\Big(C(x_1) + \sum_{\omega_1 \in \Xi_1^m} E(C(x_2(\omega_1)))\Big)\Big) m^2 \\ &\text{subject to: (12a),(12d)– (12f), (14a), (15a)} \end{aligned} \tag{17}$$

Both evaluators 1 and 2 are used with sample size of $m = 100$. The cross evaluation result for policy 1 and policy 2 in evaluator 1 and 2 is summarized in Table 4. A student's t-test is employed to compare the objective values of the two solutions across different evaluators. The t-test is only done for patients that has an initial pain outcome above 10. The null hypothesis for this test is that there is no difference between the objective values achieved by these two policies; the alternative hypothesis is that the objective value achieved by policy 2 is greater than the objective value achieved by policy 1 for both evaluators. From the t-test summary shown in Table 4, we see that the null hypothesis is rejected at a significance level of 0.01 in both cases.

Table 4 Paired T-test ($\alpha = 0.01$) for Objective Values of MILP and MINLP Model

Paired Value	Objectives achieved by policy 2 − Objectives achieved by policy 1	Objectives achieved by policy 2 − Objectives achieved by policy 1
Evaluator	Evaluator 1	Evaluator 2
Mean	2036.2	683.0
Std Error	4311.7	2830.4
DF	269	269
tvalue (pvalue)	7.76 (< .0001)	3.97 (<0.0001)

In Table 4, both evaluators show that L2SP is better than NL2SP with respect to the quality of solutions and the computational time for two reasons: (1) policy 1 is found by L2SP in 6 minutes while policy 2 is found by NL2SP in 15 minutes; (2) the paired t-test shows that the objective value achieved by policy 1 is better (smaller) than the objective value achieved by policy 2.

4.4.1 Treatment Usage Comparison

The comparison of treatment usage in the first stage between L2SP and NL2SP is shown in Figure 3, which indicates that the most frequently used types of treatment in the first stage for both L2SP and NL2SP are NSAIDs and CBT. CBT is used relatively more frequently in NL2SP solutions than in L2SP solutions. However, the overall treatment selections including types of treatment and frequency of usage found by L2SP and NL2SP are quite similar.

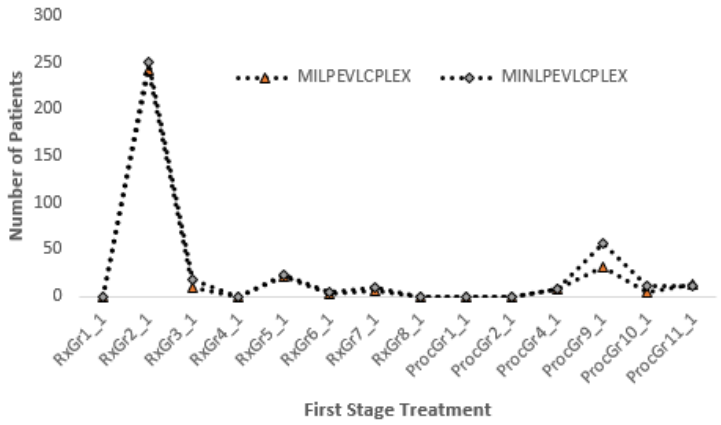


Figure 3 First-stage treatment Usage Comparison between MILP and MINLP

The treatment usage in second stage is shown in Figure 4. The dotted line with triangle markers (MINLPEVLCPLEX) and square markers (MINLPEVLCOUENNE) show the types of treatment used in second stage found by L2SP and NL2SP evaluators, respectively, given first-stage treatment policies generated by NL2SP. The diamond markers line (MILPEVLCPLEX) and asterisk markers line (MILPEVLCOUENNE) show the types of treatment used in second stage found by L2SP and NL2SP evaluators, given first-stage treatment policies generated by L2SP. The types of treatment as the recourse for a given policy are the same according to the same evaluator. However, the frequency of the usage in each type of treatment is different using the L2SP evaluator. By contrast, the frequency of the usage in each type of treatment is the same using the NL2SP evaluator. One of the reasons might be that the NL2SP evaluator only provides a best known solution instead of an optimal for many patients within elapsed time limit of 15 minutes.

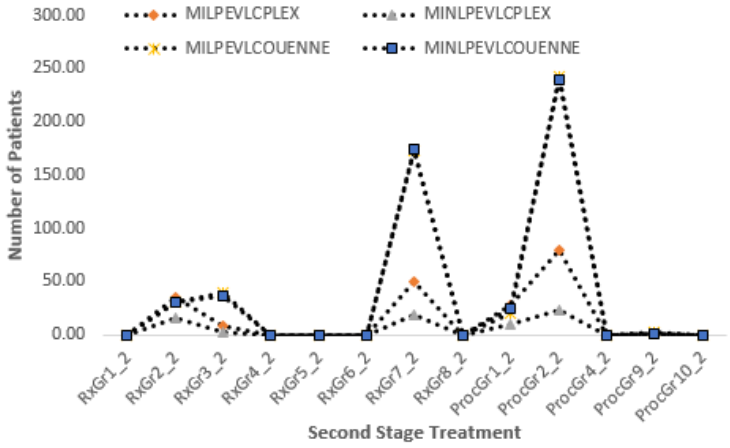


Figure 4 Second-stage treatment Usage Found by CPLEX Evaluator

In section 4.4, the solutions of L2SP and NL2SP are compared, and results show that the types of treatment recommended in the first stage by both L2SP and NL2SP are very similar. However, L2SP solved by CPLEX found in significantly less computational time than those of NL2SP solved by COUENNE.

5 Conclusions and Future Work

This research has developed a two-stage stochastic model to find optimal adaptive treatment strategies for a pain management program in UT Southwestern Medical Center, which incorporates pain outcome prediction models as constraints. However, the prediction model of the pain outcome at the post-treatment evaluation point is non-convex and nonlinear, which results in a non-linear non-convex deterministic model. A refit method is proposed to approximate the non-convex function by a piecewise linear function. As a result, a piecewise linear approximation MILP model is derived to approximate the original non-convex MINLP model. The policy generated by the piecewise linear approximation model is compared with the policy generated by solving the original non-convex model directly. Results show that the policy generated by the linear approximation MILP model is better than that of the MINLP model, because the policy generated by the MILP model within 6 minutes could achieve a lower objective value than the policy generated by MINLP model within 15 minutes.

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Appendices

Appendix A

Table 5 Treatment Interaction Table

Interaction Level	Two Interaction Treatments
Mild interaction	(RxGr1, RxGr3), (RxGr4, RxGr6), (RxGr4, RxGr7), (RxGr5, RxGr7), (RxGr5, ProcGr1), (RxGr5, ProcGr2), and (RxGr6, RxGr7)
Moderate Interaction	(RxGr1, RxGr4), (RxGr1, RxGr5), (RxGr1, RxGr6), (RxGr1, RxGr7), (RxGr1, RxGr8), (RxGr1, ProcGr1), (RxGr2, RxGr6), (RxGr2, RxGr8), (RxGr2, ProcGr1), (RxGr2, ProcGr2), (RxGr3, RxGr4), (RxGr3, RxGr5), (RxGr3, RxGr6), (RxGr4, RxGr8), (RxGr5, RxGr8), (RxGr7, RxGr8), (RxGr8, ProcGr1), and (RxGr8, ProcGr2)
Severe Interaction	(RxGr3, RxGr8), and (RxGr5, RxGr6)

Appendix B

Original Post_OSW model with two continuous interaction terms

$$\begin{aligned}
Post_OSW = {} & 6.81751 + 0.52798 \times mid_OSW 0.62507 \times StdProcGr4_1 \times Stdphydx20 + \\
& 0.41484 \times StdProcGr4_1_{S}tdmarital_1 + 1.14851 \times StdProcGr9_1 \times Stdmarital_1 + \\
& 1.75686 \times StdProcGr10_1_{S}tdpre_PDA - 1.01393 \times StdProcGr10_1 \times StdProcGr10_0 + \\
& 0.92568 \times StdRxGr1_1 \times StdRxGr2_0 - 0.62882 \times StdRxGr3_1 \times StdProcGr1_0 - \\
& 1.34039 \times StdRxGr5_1 \times Stdmarital_1 - 1.58767 \times StdRxGr6_1 \times Stdphydx3 - \\
& 0.30342 \times StdRxGr7_1 \times Stdphydx11 + 2.83819 \times StdProcGr1_2 * StdRxGr2_1 + \\
& 2.41501 \times StdProcGr1_2 \times Stdrace_1 + 1.33629 \times StdProcGr1_2 \times StdProcGr4_0 + \\
& 2.50013 \times StdProcGr2_2 \times Stdrace_2 - 1.67265 \times StdProcGr4_2 \times StdRxGr1_1 - \\
& 0.6863 \times StdProcGr9_2 \times StdRxGr6_1 - 0.15207 \times StdProcGr10_2 \times Stdmarital_2 \\
& -0.96831 \times StdRxGr2_2 \times StdProcGr4_1 + 0.19288 \times StdRxGr2_2 \times Stdpastdx4 \\
& -2.09052 \times StdRxGr2_2 \times Stdpastdx7 + 2.62666 \times StdRxGr2_2 \times StdRxGr4_0 - \\
& 1.12054 \times StdRxGr3_2 \times Stdmarital_4 - 2.69533 \times StdRxGr7_2 \times Stdmid_OSW + \\
& 0.28598 \times StdRxGr7_2 \times StdRxGr7_0 + 0.87232 \times StdRxGr8_2 \times Stdmarital_4 + \epsilon_2
\end{aligned} \tag{18}$$

Refitting the quadratic terms, the linear approximation model of Post_OSW with standardized

interaction form is shown as follows:

$$
\begin{aligned}
Post\_OSW = 6.30693 + 0.52798 \times mid\_OSW 0.62507 \times StdProcGr4\_1\_Stdphydx20 + \\
0.41484 \times StdProcGr4\_1\_Stdmarital\_1 + 1.14851 \times StdProcGr9\_1\_Stdmarital\_1 + \\
1.75686 \times StdProcGr10\_1\_Stdpre\_PDA - 1.01393 \times StdProcGr10\_1\_StdProcGr10\_0 + \\
0.92568 \times StdRxGr1\_1\_StdRxGr2\_0 - 0.62882 \times StdRxGr3\_1\_StdProcGr1\_0 - \\
1.34039 \times StdRxGr5\_1\_Stdmarital\_1 - 1.58767 \times StdRxGr6\_1\_Stdphydx3 - \\
0.30342 \times StdRxGr7\_1\_Stdphydx11 + 2.83819 \times StdProcGr1\_2\_StdRxGr2\_1 + \\
2.41501 \times StdProcGr1\_2\_Stdrace\_1 + 1.33629 \times StdProcGr1\_2\_StdProcGr4\_0 + \\
2.50013 \times StdProcGr2\_2\_Stdrace\_2 - 1.67265 \times StdProcGr4\_2\_StdRxGr1\_1 - \\
0.6863 \times StdProcGr9\_2\_StdRxGr6\_1 - 0.15207 \times StdProcGr10\_2\_Stdmarital\_2 - \\
0.96831 \times StdRxGr2\_2\_StdProcGr4\_1 + 0.19288 \times StdRxGr2\_2\_Stdpastdx4 - \\
2.09052 \times StdRxGr2\_2\_Stdpastdx7 + 2.62666 \times StdRxGr2\_2\_StdRxGr4\_0 - \\
1.12054 \times StdRxGr3\_2\_Stdmarital\_4 + 0.28598 \times StdRxGr7\_2\_StdRxGr7\_0 + \\
0.87232 \times StdRxGr8\_2\_Stdmarital\_4 + 2.61529 \times Stdmid\_OSW \\
-1.87207 \times StdRxGr7\_2\_IStdmid\_OSW + \epsilon_2;
\end{aligned}
\tag{19}
$$

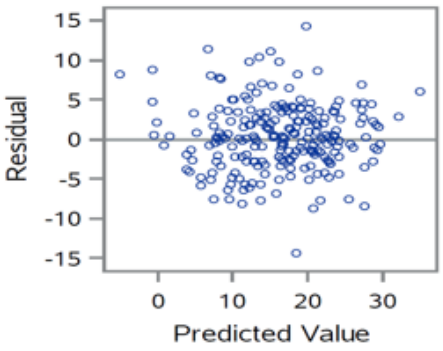
Appendix C

The residual plots and normality plots of Post_OSW and refit Post_OSW models for the training and testing datasets are included in Appendix B. From the residual plots for both training and testing datasets, we can see that residuals in refit model are distributed very similar to those of the original model. Moreover, the normality plots show that residuals in the original and the refit models both follow normal distributions.

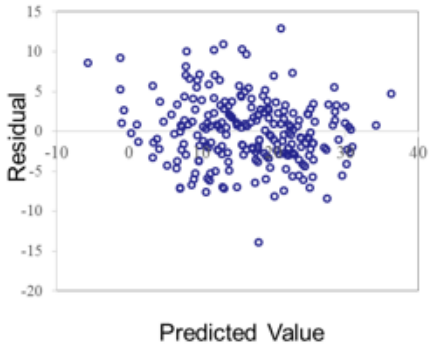
(a) Post_OSW model

(b) Refit Post_OSW model

Figure 5 Normality Plots for Testing Dataset

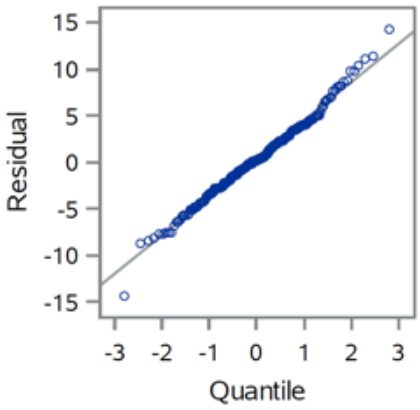


(a) Post_OSW model

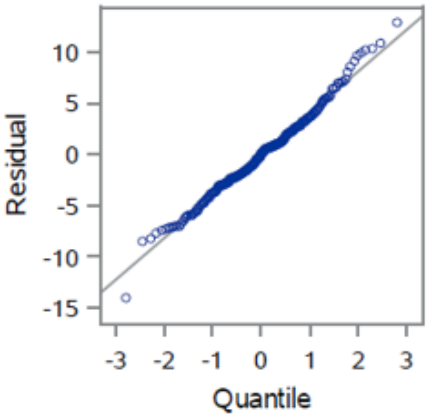


(b) Refit Post_OSW model

Figure 6 Resiual Plots for Training Dataset

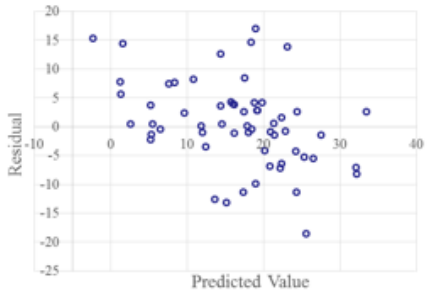


(a) Post_OSW model



(b) Refit Post_OSW model

Figure 7 Normality Plots for Training Dataset



(a) Post_OSW model

(b) Refit Post_OSW model

Figure 8 Residual Plots for Testing Dataset