

AN OPTIMIZING METHOD FOR DRUG FORMULARY DECISIONS

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ABSTRACT

This study investigates the optimization of formulary decisions concerning reimbursement for therapeutic options. A procedure is identified to facilitate formulary decision making and guide healthcare policy toward achieving optimal therapeutic objectives while incorporating the needs and preferences of both patients and their healthcare providers.

A reimbursement policy based on a combination of multi-attribute utility methods and goal programming is introduced to maximize HIV antiretroviral drug therapy under limited recourses. The methodology used in this study provides a general framework for identifying an optimal formulary selection for pharmacotherapy aimed at optimizing health outcomes through reimbursement policies.

INTRODUCTION

During the last decade, Canadian provincial drug benefit plan cost increases have averaged 18% per year while private sector drug plans have been reporting cost increases averaging 15% annually, far in excess of changes in the consumer price-index.^{1,2} The greatest challenge of the next decade for drug benefit plans will be making the best use of limited available resources to attain the highest quality healthcare for the lowest cost.³ In the struggle to control the rapidly escalating costs of drug benefit plans, Canadian drug plan sponsors have increasingly been forced to implement a variety of cost-control measures in administering and designing drug benefit plans. One principal method of controlling drug benefit plan costs has been the implementation of restricted formularies. Restricted formularies are essentially lists of pharmaceutical products that a given health benefit plan will choose to reimburse plan enrollees for the treatment of specific conditions based on their therapeutic value and cost.^{4,5}

The major points of contention concerning the implementation of formularies relate to their impact on the quality of patient care and total healthcare costs.⁶ Some advocate that the organizing principle of a drug formulary is to “maximize cost-effectiveness and benefits by excluding more expensive agents when possible, without compromising patient care.”⁷ However, an examination of the literature reveals that the implementation of these restrictive policies has often resulted in paradoxical consequences. While costs associated with the drug plan may in fact decline, unintended negative effects on the achievement of optimal patient health outcomes, as well as increased total health care costs and increased stakeholder dissatisfaction often result.⁸

Such problems most often are the result of using inadequate decision criteria to support formulary decisions by largely ignoring the benefit profiles of competing drug therapies.^{9,10} A recurrent theme in the literature is the emphasis which benefit consultants for the government and third party payers place on minimizing drug plan costs.¹¹ This focus on drug cost often causes formulary decision-makers to eliminate or not list costly new drug therapies, irrespective of the long-term benefits they provide. Comparative evaluations of alternate drug therapies that consider drug benefits must be incorporated into formulary decisions to ensure wise spending of healthcare dollars.¹²

This study necessitates that a decision framework be developed and tailored to the specific complexities inherent in a particular therapeutic/disease scenario. For the purposes of this study, the antiretroviral drug therapy class used in managing HIV infection has been selected. The HIV antiretroviral drug therapy class provides an interesting case for the study and evaluation of the proposed formulary design framework. However, it is thought that the general approach in developing the formulary decision framework could be adapted and applied to similar therapeutic areas.

THE DECISION PROBLEM

The problem addressed in this study relates to the identification of an optimal formulary reimbursement policy to maximize health-outcomes with respect to the antiretroviral treatment of HIV infection. The population consists of asymptomatic, treatment naive patients whose viral loads are in excess of 10,000 copies per mL and whose CD4+ counts range between 200-500 cells per mm³. The optimal policy being sought is one that will best satisfy the concurrent achievement of multiple therapeutic goals listed in table 1.

These objectives have been repeatedly cited in the peer review literature and are widely recognized as critical determinants of long-term success in the treatment of HIV infection^{13,14,15}.

Table 1: Antiretroviral Treatment Formulary Goals / Decision Attributes
1 Achieve durable suppression of HIV replication
2 Prevent or delay disease progression
3 Minimize antiretroviral drug related adverse effects
4 Maximize ease of use of an antiretroviral regimen
5 Minimize the potential of developing resistance to antiretroviral therapy
6 Treat HIV infection according to most recent evidence-based peer-review antiretroviral treatment guidelines
7 Maximize the number of therapeutic options available in case of therapeutic failure

In seeking to satisfy these goals, ten therapeutic decision options were considered. In this particular therapeutic area, the antiretroviral therapeutic decision option or entity is defined as a combination of multiple antiretroviral agents. This is due to relatively recent research, which has found mono-antiretroviral therapy inadequate to achieve therapeutic goals and sustained clinical benefit.

The antiretroviral therapeutic combinations being evaluated for inclusion in a hypothetical formulary were identified through market research.¹⁶ These specified combinations which are currently accepted by treatment guidelines are displayed in table 2.

Table 2: Most Commonly Used Antiretroviral Drug Combination by Market Share				
rank	Combination	mkt rank	combination	mkt share

1	d4T+3TC+Ind	14%	6	3TC+d4T	4%
2	AZT+3TC+Ind	12%	7	d4T+3TC+Saq	3%
3	AZT+3TC	10%	8	d4T+3TC+Rit+Saq	2%
4	AZT+3TC+Saq	8%	9	AZT+3TC+Rit	2%
5	d4T+3TC+Rit	6%	10	d4T + ddI + Ind	2%

Source: ISIS Research. (1997). Treatment of HIV Disease in Canada: Phase IX. August, pp.9,13.

Therapeutic combinations considered for inclusion into this model were limited to antiretroviral medications approved by the Canadian Health Protection Branch for sale at the time this study was conducted. The protease inhibitor, nelfinavir, as well as an entire new class of medications called non-nucleoside-reverse-transcriptase inhibitors including nevirapine, delavirdine, and efavirin were eliminated from consideration as they were not licensed and therefore not eligible for formulary acceptance.

All therapeutic decision options under consideration for inclusion in the hypothetical formulary can be evaluated in accordance with the goals listed in Table 1 and with regard to the decision attributes shown in table 3.

Table 3: Antiretroviral Therapeutic Decision Attributes
1. HIV viral load suppression
2. Prevention or delay of disease progression
3. Drug-related adverse effects
4. Ease of use
5. Resistance
6. Level of support of recent treatment guidelines
7. Downstream therapeutic options in case of treatment failure.

While antiretroviral therapy can undoubtedly be characterized by numerous other attributes, they were not relevant to the formulary decision problem under study and were therefore excluded from the decision problem. This resulted in a parsimonious and focused formulary decision model. A number of potentially relevant attributes were also excluded from consideration in the decision problem due to the fact that there was not enough clear scientific evidence to adequately support their inclusion at the time the study was conducted. Prime among these is the cross-resistance between protease inhibitors within a combination. This was eliminated as a distinct attribute due to the fact that the relationship between genotypic resistance, in-vitro phenotypic resistance findings, and clinical significance regarding the sequencing of protease inhibitors is still unclear and much debated.^{17,18}

In addition to therapeutic objectives, therapeutic constraints were also included in the decision problem to ensure certain objectives achieve at least the minimum level considered acceptable to patients and/or healthcare professionals.

METHODOLOGY

Weighted goal-programming was selected as an overall decision analysis framework due to its ability to set specific targets for the defined goals. This target setting

defines the minimal or maximal standard or level of a given objective that must be achieved to best satisfy a therapeutic objective. Because of the multiple and sometimes conflicting objectives, the weighted-goal programming model was formulated to minimize deviation from the series of defined goals (table 1) which were prioritized through the incorporation of penalties and deviation variables. The objective function is shown below.

$$\text{MIN} \quad \sum_{j=1}^6 \sum_{i=1}^7 \alpha_{ij} n_{ij}$$

Where α_{ij} = the penalty coefficient related to the underachievement deviational variable n , for goal i , and patient j .

The decision attributes (table 3) and factors were measured using the multiattribute utility (MAUT) methods^{19,20}.

Each of the ten decision options (table 2) under consideration were subsequently reviewed and assessed with respect to the defined therapeutic objectives (decision attributes) and factors. The formulation was completed by incorporating of patient and healthcare professional preferences. These preferences were captured through a literature review as well as development and administration of comprehensive questionnaires.

An analysis of the data suggested a high degree of consistency between healthcare professional respondents, and the presence of significant variation between patient respondents with respect to:

- 1.) The relative importance and desirability of achieving various treatment objectives.
- 2.) The valuation of each attribute and/or factor levels.
- 3.) The minimum acceptable levels of each relevant attribute and/or factor.

In order to assess the impact of the observed variation on the generation of an optimal solution, four goal-programming models were constructed. Each model was based on the assignment of various weights to individual and group preferences of patients and health care professionals. The four scenarios evaluated are as follows:

- 1.) Equal weighing of individual patient preferences (patients only)
- 2.) Averaged patient preferences (patients only)
- 3.) Averaged healthcare professional preferences (healthcare professionals only)
- 4.) Combined and equal weighted patient and healthcare professional preferences and linear value functions

In order to determine which, if any, of the decision models were “valid”, each of the four formulations were adapted, modeled and solved as a multi-attribute utility (MAUT) decision problem. Each resulting MAUT solution yielded a rank order for the ten alternative therapeutic decision options being evaluated. Decision constraints included in the goal programming formulations were applied manually to the rank ordered decision options generated by each of the four models. Through this process we were able to:

- 1.) Assess the impact of inter-patient variability with regard to therapeutic objectives, strength of preferences and their impact on the selection of optimal treatment.
- 2.) Determine the appropriate level of preference aggregation for patients (i.e. by individual patient, patient type, or aggregated population)
- 3.) Identify differences with regard to therapeutic objectives and strength of preferences between patients and healthcare professionals
- 4.) Determine the appropriate level of preference aggregation weighting between patients and healthcare professionals (i.e. 70/30%, 50/50%, 30/70%)

In structuring this decision problem model to derive meaningful and valid solutions, weighted-goal programming required that a scaling and normalizing procedure be applied to the goals prior to solving any of the aforementioned formulations. If left unadjusted, the incommensurable nature of the goals in this problem would result in the introduction of an artificial bias that was not reflective of the actual decision maker preferences.

In this case, utilizing the scaling method demonstrated by Romero²¹, each goal incorporated in the proposed goal programming decision problem was normalized to a maximum optimal level set at 100 with the coefficients of the integer decision variables adjusted accordingly. Since each goal was set to the maximum level, which is impossible to surpass, only negative or underachievement deviational variables were incorporated in each goal programming model.

The constraints introduced into the formulation to ensure minimal acceptable target levels for each of the stated therapeutic goals were expressed in terms of the following variables:

X_{jk} = the patient j , put on therapeutic combination k , $k = 1$ to 10 ,

g_{ij} = the goal i , for patient j ,

c_{ij} = the therapeutic constraint representing a minimal acceptable level of care to be satisfied by goal i , for patient j ,

and t_{ij} = the target for goal i , for patient j .

The overall model structure for the basic formulation is shown below.

Treatment Combination k	Antiretroviral Combination Contribution to Goal Achievement										negative variable n_g	goal (g) target level	Penalty Weights
	1	2	3	4	5	6	7	8	9	10			
Goal g / Constraint c	X_{j1}	X_{j2}	X_{j3}	X_{j4}	X_{j5}	X_{j6}	X_{j7}	X_{j8}	X_{j9}	X_{j10}			
g_{1j}											$+ n_{1j}$	$= t_{1j}$	
g_{2j}											$+ n_{2j}$	$= t_{2j}$	
g_{3j}											$+ n_{3j}$	$= t_{3j}$	
g_{4j}											$+ n_{4j}$	$= t_{4j}$	
g_{5j}											$+ n_{5j}$	$= t_{5j}$	
g_{6j}											$+ n_{6j}$	$= t_{6j}$	
g_{7j}											$+ n_{7j}$	$= t_{7j}$	
c_{1j}													\geq min. acceptable level
c_{2j}													\geq min. acceptable level
c_{3j}													\geq min. acceptable level
c_{4j}													\geq min. acceptable level
c_{5j}													\geq min. acceptable level
c_{6j}													\geq min. acceptable level
c_{7j}													\geq min. acceptable level

Each goal-programming model was subsequently solved as an integer goal-programming problem using LINDO to identify the optimal selection of antiretroviral combinations without cost constraints. Corresponding MAUT analyses were also carried out. Because MAUT does not handle decision constraints, the analysis first consisted of ranking the decision alternatives based on the relevant decision-maker preferences. Once the rank ordering was complete, the ability of each regimen to satisfy the minimal acceptable level of care constraints was determined manually.

A comparison of the goal programming solutions to the MAUT solutions revealed inconsistent selections between 3 of the 4 formulations. The first model, based on individual preferences and linear value functions, proved to be the only congruent model based on its accuracy in selecting optimal therapy which addressed inter-patient variation. When compared against the six individual patient MAUT analyses determining the optimal treatment selection for the population. The complete formulation for this model is displayed in Appendix 1.

The findings of this analysis permitted the selection of an appropriate weighted goal programming formulary decision model that yielded a unique optimal, and thus Pareto-efficient solution. The level of resources required to achieve the optimal solution was then calculated using monthly drug acquisition costs for each of the therapeutic combinations under consideration.

RESULTS

Four goal programming models were developed to study the decision problem. These four models were based on individual patient preferences, aggregated patient preferences, aggregated healthcare professional preferences, and combined patient and healthcare preferences. The results of the four models are summarized in table 4.

Given the differences identified in the various optimal solutions generated, this study found that variations in preferences observed between healthcare professionals and patients were significant enough to shift the optimal solution. The optimal solution generated using the goal programming model based on the preferences at the individual level was found to be most reflective of the actual decision-makers values and preferences. This solution was equivalent or congruent to the selections generated by conducting an individualized MAUT decision analysis for each of the patients using manually applied decision constraints.

This optimal solution or identified reimbursement policy specifically assigned 3 patients to the therapeutic combination d4T + 3TC + Indinavir, and 3 patients to the combination AZT + 3TC + Indinavir. This selection is consistent with the market research study results conducted by ISIS Canada which identified these selections as the two therapeutic combinations with the largest shares of the antiretroviral therapy market. In addition, four of the six participants had actually been initiated on either of these two therapeutic combinations. The same therapies were selected for three of these four patients, indicating that the methods used to capture and determine the values and preferences of individual patients were fairly consistent with their actual treatment decisions.

Table 4. Four Model Comparison of Goal Programming vs. MAUT as an Overall Formulary Drug Selection Decision Framework.				
	Individual Patients	Aggregated Patients	Aggregated Healthcare Professionals	Combined Healthcare Professionals and Patients (50%/50%)
Goal Programming Optimal Therapeutic Selection	Combo1: patients 3,5,6 Combo 2: patients 1,2,4	Combo1: 5 patients Combo 3: 1 patient	Combo 2: 5 patients Combo 6: 1 patient	Combo1: 5 patients Combo 3: 1 patient

MAUT Optimal Therapeutic Selection	Combo1: patients 3,5,6 Combo 2: patients 1,2,4	Combo1: all patients	Combo 2: all patients	Combo1: all patients
GP Solution Evaluation	Optimal Selection	3 patients receive suboptimal care, 2 patients placed on therapy not best satisfying needs, and 1 patient placed on inadequate therapy	3 patients receive suboptimal care, 2 patients placed on therapy not best satisfying needs, and 1 patient placed on inadequate therapy	3 patients receive suboptimal care, 2 patients placed on therapy not best satisfying needs, and 1 patient placed on inadequate therapy
MAUT Solution Evaluation	Optimal Selection	3 patients receive suboptimal care. 3 patients placed on therapy not best satisfying needs.	3 patients receive suboptimal care. 3 patients placed on therapy not best satisfying needs.	3 patients receive suboptimal care. 3 patients placed on therapy not best satisfying needs.
Congruence	✓	✗	✗	✗

The previous section was concerned with identifying the most appropriate formulary reimbursement model and its corresponding optimal solution. The solution identified assigned three patients to the therapeutic combination d4T + 3TC + Indinavir, whereas the other three patients were assigned to AZT + 3TC + Indinavir. Given that each combination has a per/patient monthly drug acquisition cost of \$1004.19 and \$1158.09 respectively, the total calculated financial resources required to provide this optimal formulary therapeutic selection for those six patients is \$6486.84 per month. The level of financial resources required by the optimal solutions derived through the four models are displayed in Table 5.

Table 5: Four Model Comparison of Monthly Drug Acquisition Costs Required for a Six Patient Formulary.				
	Individual Patients	Aggregated Patients	Aggregated Healthcare Professionals	Combined Healthcare Professionals and Patients (50%/50%)

Goal Programming Optimal Therapeutic Selection	Combo1: patients 3,5,6 Combo 2: patients 1,2,4	Combo1: 5 patients Combo 3: 1 patient	Combo 2: 5 patients Combo 6: 1 patients	Combo1: 5 patients Combo 3: 1 patient
MAUT Optimal Therapeutic Selection	Combo1: patients 3,5,6 Combo 2: patients 1,2,4	Combo1: all patients	Combo 2: all patients	Combo1: all patients
Monthly Drug Acquisition Financial Resources Required for six patients - GP	\$6,486.84	\$5,694.25	\$6,309.85	\$5,694.25
Monthly Drug Acquisition Financial Resources Required for six patients - MAUT	\$6,486.84	\$6,025.14	\$6,948.54	\$6,025.14

However the level of financial resources does little to explain the level of therapeutic objectives satisfied by this optimal solution for each of the six patients. Table 6 summarizes the level of each therapeutic objective satisfied and the level of tradeoffs made for each patient by the identified optimal solution. However, these values reflect the values of individual patients and cannot be compared directly between patients.

Table 6: Level of Therapeutic Objectives Satisfied Each of Six Patients

100%-Nij	Patient 1 Combo 2	Patient 2 Combo 2	Patient 3 Combo 1	Patient 4 Combo 2	Patient 5 Combo 1	Patient 6 Combo 1
Goal 1	76.2%	77.88%	72.5%	49.69%	74.05%	60.04%
Goal 2	100%	100%	100%	100%	100%	100%
Goal 3	57.42%	50.81%	94.81%	60.48%	90.09%	66.06%
Goal 4	43.55%	9.9%	46.03%	49.52%	50.82%	38.27%
Goal 5	100%	100%	100%	100%	100%	100%
Goal 6	100%	100%	n/a	100%	97%	75%
Goal 7	50%	98%	100%	10%	67%	10%

SUGGESTIONS FOR FUTURE RESEARCH

The principal limitation identified in utilizing multiattribute utility measurement in combination with goal-programming stems from the significant level of heterogeneity in respondent preferences regarding the various treatment attributes. Given the limited scope of the small study sample, it is impossible to reliably comment on the population characteristics. However, if the significant level of variation exhibited in this case study reflects the nature of a population to which this type of analysis may be applied in the future, it is suggested that efforts be directed at modeling the population as a series of subgroups, within which individuals share similar attitudes and preferences in regard to

distinct therapeutic objectives and decision attributes. While it is unrealistic to suggest that each and every patient within a population should be interviewed and the magnitude of their objectives and preferences identified, sampling techniques can be applied to identify these distinct patient subgroups who share preferences and would select the same therapies on the basis of those preferences.

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Appendix 1: GOAL PROGRAMMING FORMULATION BASED ON INDIVIDUAL PATIENT LEVEL PREFERENCES AND LINEAR VALUE FUNCTIONS

Variable Definition:

Let α_{ij} = the penalty coefficient related to the underachievement deviational variable n , for goal i , and patient j .

Where patient $j = 1$ to 6 , where j = the patient number identifier
Where the goal $i = 1$ to 7 , where i = the goal number identifier

Let g_{ij} = the goal i , for patient j .

Let X_{jk} = the patient j , put on therapeutic combination k .

Where therapeutic combination $k = 1$ to 10

Let n_{ij} = the % underachievement of goal i , for patient j .

Let c_{ij} = the therapeutic constraint representing a minimal acceptable level of care to be satisfied by goal i , for patient j

$$\begin{aligned} \text{MIN} \quad & 10 \text{ N11} + 100 \text{ N12} + \quad \text{N13} + 10 \text{ N14} + 99 \text{ N15} + 90 \text{ N16} + \\ & 10 \text{ N21} + 100 \text{ N22} + 100 \text{ N23} + 100 \text{ N24} + 100 \text{ N25} + 100 \text{ N26} + \\ & \quad \quad \quad 75 \text{ N32} + \quad \text{N33} + \quad \text{N34} + 100 \text{ N35} + 90 \text{ N36} + \\ & \quad \quad \quad \text{N41} + 20 \text{ N42} + \quad \text{N43} + \quad \quad \quad 98 \text{ N45} + \quad \text{N46} + \\ & 10 \text{ N51} + \quad \text{N52} + 100 \text{ N53} + 10 \text{ N54} + 90 \text{ N55} + 10 \text{ N56} + \\ & 5 \text{ N61} + 40 \text{ N62} + \quad \quad \quad \text{N64} + 100 \text{ N65} + 50 \text{ N66} + \\ & 3 \text{ N71} + 40 \text{ N72} + 3 \text{ N73} + \quad \text{N74} + \quad \text{N75} + 80 \text{ N76} \end{aligned}$$

SUBJECT TO

$$\begin{aligned} \text{G11)} \quad & 76 \text{ X11} + 76.2 \text{ X12} + 1.2 \text{ X13} + 7 \text{ X14} + 76 \text{ X15} + 4.6 \text{ X16} \\ & + 7.8 \text{ X17} + 100 \text{ X18} + 75.4 \text{ X19} + 76 \text{ X110} + \text{N11} = 100 \end{aligned}$$

$$\begin{aligned} \text{G12)} \quad & 77.55 \text{ X21} + 77.88 \text{ X22} + 1.32 \text{ X23} + 11.55 \text{ X24} + 77.55 \text{ X25} \\ & + 7.59 \text{ X26} + 12.21 \text{ X27} + 99 \text{ X28} + 76.56 \text{ X29} + 77.55 \text{ X210} + \text{N12} \\ & = 100 \end{aligned}$$

$$\begin{aligned} \text{G13)} \quad & 72.5 \text{ X31} + 72.5 \text{ X32} + 2 \text{ X33} + \text{X34} + 72.5 \text{ X35} + \text{X36} + 2 \text{ X37} \\ & + 100 \text{ X38} + 72.5 \text{ X39} + 72.5 \text{ X310} + \text{N13} = 100 \end{aligned}$$

$$\begin{aligned} \text{G14)} \quad & 49.69 \text{ X41} + 49.69 \text{ X42} + 2.7 \text{ X43} + 3.87 \text{ X44} + 49.6 \text{ X45} \\ & + 2.79 \text{ X46} + 5.67 \text{ X47} + 100 \text{ X48} + 49.33 \text{ X49} + 49.6 \text{ X410} + \text{N14} \\ & = 100 \end{aligned}$$

$$\begin{aligned} \text{G15)} \quad & 74.05 \text{ X51} + 74.06 \text{ X52} + 1.93 \text{ X53} + 1.32 \text{ X54} + 74.05 \text{ X55} \\ & + 1.2 \text{ X56} + 2.26 \text{ X57} + 100 \text{ X58} + 74.02 \text{ X59} + 74.05 \text{ X510} + \text{N15} \\ & = 100 \end{aligned}$$

$$\begin{aligned} \text{G16)} \quad & 60.4 \text{ X61} + 60.73 \text{ X62} + 1.99 \text{ X63} + 11.56 \text{ X64} + 60.4 \text{ X65} \\ & + 70.6 \text{ X66} + 12.88 \text{ X67} + 100 \text{ X68} + 59.41 \text{ X69} + 60.4 \text{ X610} + \text{N16} \\ & = 100 \end{aligned}$$

$$\begin{aligned} \text{G21)} \quad & 100 \text{ X11} + 100 \text{ X12} + 50 \text{ X13} + 100 \text{ X14} + 100 \text{ X15} + 50 \text{ X16} \\ & + 100 \text{ X17} + 100 \text{ X18} + 100 \text{ X19} + 100 \text{ X110} + \text{N21} = 100 \end{aligned}$$

$$\begin{aligned} \text{G22)} \quad & 100 \text{ X21} + 100 \text{ X22} + 2 \text{ X23} + 100 \text{ X24} + 100 \text{ X25} + 2 \text{ X26} + 100 \text{ X27} \\ & + 100 \text{ X28} + 100 \text{ X29} + 100 \text{ X210} + \text{N22} = 100 \end{aligned}$$

$$\text{G23)} \quad 100 \text{ X31} + 100 \text{ X32} + 20 \text{ X33} + 100 \text{ X34} + 100 \text{ X35} + 20 \text{ X36}$$

$+ 100 X37 + 100 X38 + 100 X39 + 100 X310 + N23 = 100$
 G24) $100 X41 + 100 X42 + 50 X43 + 100 X44 + 100 X45 + 50 X46$
 $+ 100 X47 + 100 X48 + 100 X49 + 100 X410 + N24 = 100$
 G25) $100 X51 + 100 X52 + 90 X53 + 100 X54 + 100 X55 + 90 X56$
 $+ 100 X57 + 100 X58 + 100 X59 + 100 X510 + N25 = 100$
 G26) $100 X61 + 100 X62 + 50 X63 + 100 X64 + 100 X65 + 50 X66$
 $+ 100 X67 + 100 X68 + 100 X69 + 100 X610 + N26 = 100$
 G31) $87.17 X11 + 57.42 X12 + 77.39 X13 + 92.32 X14 + 1.32 X15$
 $+ 70.25 X16 + 100 X17 + 23.05 X18 + 12.07 X19 + 19.76 X110 + N31$
 $= 100$
 G32) $77.74 X21 + 50.81 X22 + 90.55 X23 + 74.59 X24 + 34.96 X25$
 $+ 100 X26 + 78.07 X27 + 12.05 X28 + 14.65 X29 + 1.95 X210 + N32 = 100$
 G33) $94.8 X31 + 49.27 X32 + 100 X33 + 68.47 X34 + 0.68 X35$
 $+ 93.22 X36 + 76.95 X37 + 23.73 X38 + 11.86 X39 + 20.11 X310 + N33 = 100$
 G34) $56.43 X41 + 60.48 X42 + 100 X43 + 69.98 X44 + 0.2 X45$
 $+ 90.26 X46 + 78.01 X47 + 40.16 X48 + 11.04 X49 + 21.18 X410 + N34 = 100$
 G35) $90.09 X51 + 68.97 X52 + 100 X53 + 70.26 X54 + 38.15 X55$
 $+ 55.71 X56 + 79.31 X57 + 13.79 X59 + 16.81 X510 + N35 = 100$
 G36) $66.06 X61 + 22.76 X62 + 100 X63 + 70.73 X64 + 0.2 X65 + 94 X66$
 $+ 79 X67 + 29.78 X68 + 10.87 X69 + 26.42 X610 + N36 = 100$
 G41) $72.78 X11 + 43.55 X12 + 81.67 X13 + 24.65 X14 + 75.62 X15$
 $+ 100 X16 + 60.65 X17 + 66.63 X18 + 39.64 X19 + 53.02 X110 + N41 = 100$
 G42) $21.1 X21 + 9.9 X22 + 100 X23 + 55.24 X24 + 37.23 X25$
 $+ 55.76 X26 + 26.23 X27 + 37.05 X28 + 51.44 X29 + 17.38 X210 + N42 = 100$
 G43) $46.03 X31 + 41.78 X32 + 94.75 X33 + 37.19 X34 + 38.53 X35$
 $+ 99 X36 + 59.56 X37 + 38.95 X38 + 0.28 X39 + 43.9 X310 + N43 = 100$
 G44) $60.14 X41 + 49.52 X42 + 92.47 X43 + 28.04 X44 + 54.7 X45$
 $+ 100 X46 + 51.19 X47 + 54.7 X48 + 15.93 X49 + 26.55 X410 + N44 = 100$
 G45) $50.82 X51 + 51.86 X52 + 100 X53 + 49.03 X54 + 79.59 X55$
 $+ 82.68 X56 + 23 X57 + 75.88 X58 + 55.67 X59 + 20.99 X510 + N45 = 100$
 G46) $38.27 X61 + 34.01 X62 + 100 X63 + 31.94 X64 + 70.67 X65$
 $+ 93.33 X66 + 38.87 X67 + 47.47 X68 + 50.67 X69 + 34.93 X610 + N46 = 100$
 G51) $100 X11 + 100 X12 + 100 X15 + 100 X18 + 100 X19 + 100 X110 + N51 = 100$
 G52) $100 X21 + 100 X22 + 100 X25 + 100 X28 + 100 X29 + 100 X210 + N52 = 100$
 G53) $100 X31 + 100 X32 + 100 X35 + 100 X38 + 100 X39 + 100 X310 + N53 = 100$
 G54) $100 X41 + 100 X42 + 100 X45 + 100 X48 + 100 X49 + 100 X410 + N54 = 100$
 G55) $100 X51 + 100 X52 + 100 X55 + 100 X58 + 100 X59 + 100 X510 + 100 N55 = 100$
 G56) $100 X61 + 100 X62 + 100 X65 + 100 X68 + 100 X69 + 100 X610 + N56 = 100$
 G61) $77 X11 + 100 X12 + 11 X13 + 9 X14 + 77 X15 + 7 X16 + 50 X17 + 66 X18 + 100 X19 +$
 $100 X110 + N61 = 100$
 G62) $75 X21 + 100 X22 + 38 X23 + X24 + 75 X25 + 13 X26 + 25 X27$
 $+ 75 X28 + 100 X29 + 100 X210 + N62 = 100$
 G64) $55 X41 + 100 X42 + 6 X43 + X44 + 55 X45 + 5 X46 + 50 X47$
 $+ 52 X48 + 100 X49 + 100 X410 + N64 = 100$
 G65) $97 X51 + 100 X52 + 50 X53 + X54 + 97 X55 + 25 X56 + 26 X57$
 $+ 95 X58 + 100 X59 + 100 X510 + N65 = 100$
 G66) $75 X61 + 100 X62 + 13 X63 + X64 + 75 X65 + 13 X66 + 50 X67$
 $+ 63 X68 + 100 X69 + 100 X610 + N66 = 100$
 G71) $50 X11 + 50 X12 + 100 X13 + 50 X14 + 50 X15 + 100 X16 + 50 X17$
 $+ 10 X18 + 50 X19 + 50 X110 + N71 = 100$
 G72) $98 X21 + 98 X22 + 100 X23 + 98 X24 + 98 X25 + 100 X26 + 98 X27$
 $+ X28 + 98 X29 + 98 X210 + N72 = 100$

G73) $100 X31 + 100 X32 + 100 X33 + 100 X34 + 100 X35 + 100 X36 + 100 X37 + 100 X39 + X310 + N73 = 100$

G74) $10 X41 + 10 X42 + 100 X43 + 10 X44 + 10 X45 + 100 X46 + 10 X47 + 10 X49 + 10 X410 + N74 = 100$

G75) $67 X51 + 67 X52 + 100 X53 + 67 X54 + 67 X55 + 100 X56 + 67 X57 + 33 X58 + 67 X59 + 67 X510 + N75 = 100$

G76) $10 X61 + 10 X62 + 100 X63 + 10 X64 + 10 X65 + 100 X66 + 10 X67 + X68 + 10 X69 + 10 X610 + N76 = 100$

C11) $76 X11 + 76.2 X12 + 1.2 X13 + 7 X14 + 76 X15 + 4.6 X16 + 7.8 X17 + 100 X18 + 75.4 X19 + 76 X110 \geq 38$

C12) $77.55 X21 + 77.88 X22 + 1.32 X23 + 11.55 X24 + 77.55 X25 + 7.59 X26 + 12.21 X27 + 99 X28 + 76.56 X29 + 77.55 X210 \geq 61.71$

C13) $72.5 X31 + 72.5 X32 + 2 X33 + X34 + 72.5 X35 + X36 + 2 X37 + 100 X38 + 72.5 X39 + 72.5 X310 \geq 0.51$

C14) $49.69 X41 + 49.69 X42 + 2.7 X43 + 3.87 X44 + 49.6 X45 + 2.79 X46 + 5.67 X47 + 100 X48 + 49.33 X49 + 49.6 X410 \geq 48.6$

C15) $74.05 X51 + 74.06 X52 + 1.93 X53 + 1.32 X54 + 74.05 X55 + 1.2 X56 + 2.26 X57 + 100 X58 + 74.02 X59 + 74.05 X510 \geq 0.8$

C16) $60.4 X61 + 60.73 X62 + 1.99 X63 + 11.56 X64 + 60.4 X65 + 7.6 X66 + 12.88 X67 + 100 X68 + 59.41 X69 + 60.4 X610 \geq 36.234$

C21) $100 X11 + 100 X12 + 50 X13 + 100 X14 + 100 X15 + 50 X16 + 100 X17 + 100 X18 + 100 X19 + 100 X110 \geq 50$

C24) $100 X41 + 100 X42 + 50 X43 + 100 X44 + 100 X45 + 50 X46 + 100 X47 + 100 X48 + 100 X49 + 100 X410 \geq 50$

C25) $100 X51 + 100 X52 + 90 X53 + 100 X54 + 100 X55 + 90 X56 + 100 X57 + 100 X58 + 100 X59 + 100 X510 \geq 90$

C26) $100 X61 + 100 X62 + 50 X63 + 100 X64 + 100 X65 + 100 X66 + 50 X67 + 100 X68 + 100 X69 + 100 X610 \geq 50$

C31) $86.17 X11 + 57.52 X12 + 77.39 X13 + 92.32 X14 + 1.32 X15 + 70.25 X16 + 100 X17 + 23.05 X18 + 12.07 X19 + 19.76 X110 \geq 0$

C32) $77.74 X21 + 50.81 X22 + 90.55 X23 + 74.59 X24 + 34.96 X25 + 100 X26 + 78.07 X27 + 12.05 X28 + 14.66 X29 + 1.95 X210 \geq 27.8$

C33) $94.8 X31 + 49.27 X32 + 100 X33 + 68.47 X34 + 0.68 X35 + 93.22 X36 + 76.95 X37 + 23.73 X38 + 11.68 X39 + 20.11 X310 \geq 6.99$

C34) $56.43 X41 + 60.24 X42 + 100 X43 + 69.98 X44 + 0.2 X45 + 90.26 X46 + 78.01 X47 + 40.16 X48 + 11.04 X49 + 21.18 X410 \geq 60$

C35) $90.09 X51 + 68.97 X52 + 100 X53 + 70.26 X54 + 38.15 X55 + 55.71 X56 + 79.31 X57 + 13.79 X59 + 16.81 X510 \geq 64$

C36) $60.06 X61 + 22.76 X62 + 100 X63 + 70.73 X64 + 0.2 X65 + 94 X66 + 79 X67 + 29.78 X68 + 10.87 X69 + 24.62 X610 \geq 14.65$

C41) $72.78 X11 + 43.55 X12 + 81.87 X13 + 24.56 X14 + 75.62 X15 + 100 X16 + 60.65 X17 + 66.63 X18 + 39.64 X19 + 53.02 X110 \geq 3.8$

C42) $21.1 X21 + 9.9 X22 + 100 X23 + 55.24 X24 + 37.23 X25 + 55.76 X26 + 26.23 X27 + 37.05 X28 + 51.44 X29 + 17.38 X210 \geq 0$

C43) $46.03 X31 + 41.78 X32 + 94.75 X33 + 37.19 X34 + 38.53 X35 + 99 X36 + 59.56 X37 + 38.95 X38 + 0.28 X39 + 43.9 X310 \geq 0$

C44) $60.14 X41 + 49.52 X42 + 92.47 X43 + 28.04 X44 + 54.7 X45 + 100 X46 + 51.19 X47 + 54.7 X48 + 15.93 X49 + 26.55 X410 \geq 37.5$

C45) $50.82 X51 + 51.86 X52 + 100 X53 + 49.03 X54 + 79.59 X55 + 82.68 X56 + 23 X57 + 75.88 X58 + 55.67 X59 + 20.99 X510 \geq 2.36$

C46) $38.27 X_{61} + 34.01 X_{62} + 100 X_{63} + 31.94 X_{64} + 70.67 X_{65} + 93.33 X_{66} + 38.87 X_{67} + 47.47 X_{68} + 50.67 X_{69} + 34.93 X_{610} \geq 26.25$
C51) $100 X_{11} + 100 X_{12} + 100 X_{15} + 100 X_{18} + 100 X_{19} + 100 X_{110} \geq 50$
C53) $100 X_{31} + 100 X_{32} + 100 X_{35} + 100 X_{38} + 100 X_{39} + 100 X_{310} \geq 0$
C54) $100 X_{41} + 100 X_{42} + 100 X_{45} + 100 X_{48} + 100 X_{49} + 100 X_{410} \geq 50$
C55) $100 X_{51} + 100 X_{52} + 100 X_{55} + 100 X_{58} + 100 X_{59} + 100 X_{510} \geq 50$
C56) $100 X_{61} + 100 X_{62} + 100 X_{65} + 100 X_{68} + 100 X_{69} + 100 X_{610} \geq 0$
C61) $77 X_{11} + 100 X_{12} + 11 X_{13} + 9 X_{14} + 77 X_{15} + 7 X_{16} + 50 X_{17} + 66 X_{18} + 100 X_{19} + 100 X_{110} \geq 76$
C62) $75 X_{21} + 100 X_{22} + 38 X_{23} + X_{24} + 75 X_{25} + 13 X_{26} + 25 X_{27} + 75 X_{28} + 100 X_{29} + 100 X_{210} \geq 91$
C64) $55 X_{41} + 100 X_{42} + 6 X_{43} + X_{44} + 55 X_{45} + 5 X_{46} + 50 X_{47} + 52 X_{48} + 100 X_{49} + 100 X_{410} \geq 50$
C66) $75 X_{61} + 100 X_{62} + 13 X_{63} + X_{64} + 75 X_{65} + 13 X_{66} + 50 X_{67} + 63 X_{68} + 100 X_{69} + 100 X_{610} \geq 75$
C71) $50 X_{11} + 50 X_{12} + 100 X_{13} + 50 X_{14} + 50 X_{15} + 100 X_{16} + 50 X_{17} + 10 X_{18} + 50 X_{19} + 50 X_{110} \geq 50$
C72) $98 X_{21} + 98 X_{22} + 100 X_{23} + 98 X_{24} + 98 X_{25} + 100 X_{26} + 98 X_{27} + X_{28} + 98 X_{29} + 98 X_{210} \geq 98$
C74) $10 X_{41} + 10 X_{42} + 100 X_{43} + 10 X_{44} + 10 X_{45} + 100 X_{46} + 10 X_{47} + 10 X_{49} + 10 X_{410} \geq 10$
C75) $67 X_{51} + 67 X_{52} + 100 X_{53} + 67 X_{54} + 67 X_{55} + 100 X_{56} + 67 X_{57} + 33 X_{58} + 67 X_{59} + 67 X_{510} \geq 67$
C76) $10 X_{61} + 10 X_{62} + 100 X_{63} + 10 X_{64} + 10 X_{65} + 100 X_{66} + 10 X_{67} + X_{68} + 10 X_{69} + 10 X_{610} \geq 10$
C81) $47.56 X_{11} + 44.6 X_{12} + 92.13 X_{13} + 67.52 X_{14} + 96.16 X_{16} + 60.74 X_{17} + 1.74 X_{18} + 4.71 X_{19} + 12.36 X_{110} \geq 42.75$
C82) $48.11 X_{21} + 48.07 X_{22} + 99.98 X_{23} + 79.65 X_{24} + 94.51 X_{26} + 74.06 X_{27} + 2.57 X_{29} + 14.43 X_{210} + 2 X_{28} \geq 46.39$
C83) $52.13 X_{31} + 51.7 X_{32} + 98.88 X_{33} + 79.97 X_{34} + 88.72 X_{36} + 68.35 X_{37} + 5.1 X_{38} + 5.52 X_{39} + 21.18 X_{310} \geq 47.15$
C84) $52.13 X_{41} + 51.7 X_{42} + 98.88 X_{43} + 79.97 X_{44} + 88.72 X_{46} + 68.35 X_{47} + 5.1 X_{48} + 5.52 X_{49} + 21.18 X_{410} \geq 47.15$
C85) $44.73 X_{51} + 42 X_{52} + 93.75 X_{53} + 68.66 X_{54} + 100 X_{57} + 66.31 X_{58} + 2.35 X_{59} + 7.8 X_{510} \geq 42$
C86) $48.48 X_{61} + 48.48 X_{62} + 100 X_{63} + 79.96 X_{64} + 93.8 X_{66} + 73.81 X_{67} + 2.8 X_{68} + 2.8 X_{69} + 15.15 X_{610} \geq 46.53$
N1) $X_{11} + X_{12} + X_{13} + X_{14} + X_{15} + X_{16} + X_{17} + X_{18} + X_{19} + X_{110} = 1$
N2) $X_{21} + X_{22} + X_{23} + X_{24} + X_{25} + X_{26} + X_{27} + X_{28} + X_{29} + X_{210} = 1$
N3) $X_{31} + X_{32} + X_{33} + X_{34} + X_{35} + X_{36} + X_{37} + X_{38} + X_{39} + X_{310} = 1$
N4) $X_{41} + X_{42} + X_{43} + X_{44} + X_{45} + X_{46} + X_{47} + X_{48} + X_{49} + X_{410} = 1$
N5) $X_{51} + X_{52} + X_{53} + X_{54} + X_{55} + X_{56} + X_{57} + X_{58} + X_{59} + X_{510} = 1$
N6) $X_{61} + X_{62} + X_{63} + X_{64} + X_{65} + X_{66} + X_{67} + X_{68} + X_{69} + X_{610} = 1$