Improving Make-ahead Chemotherapy Drug Policies in the Outpatient Infusion Center Pharmacy

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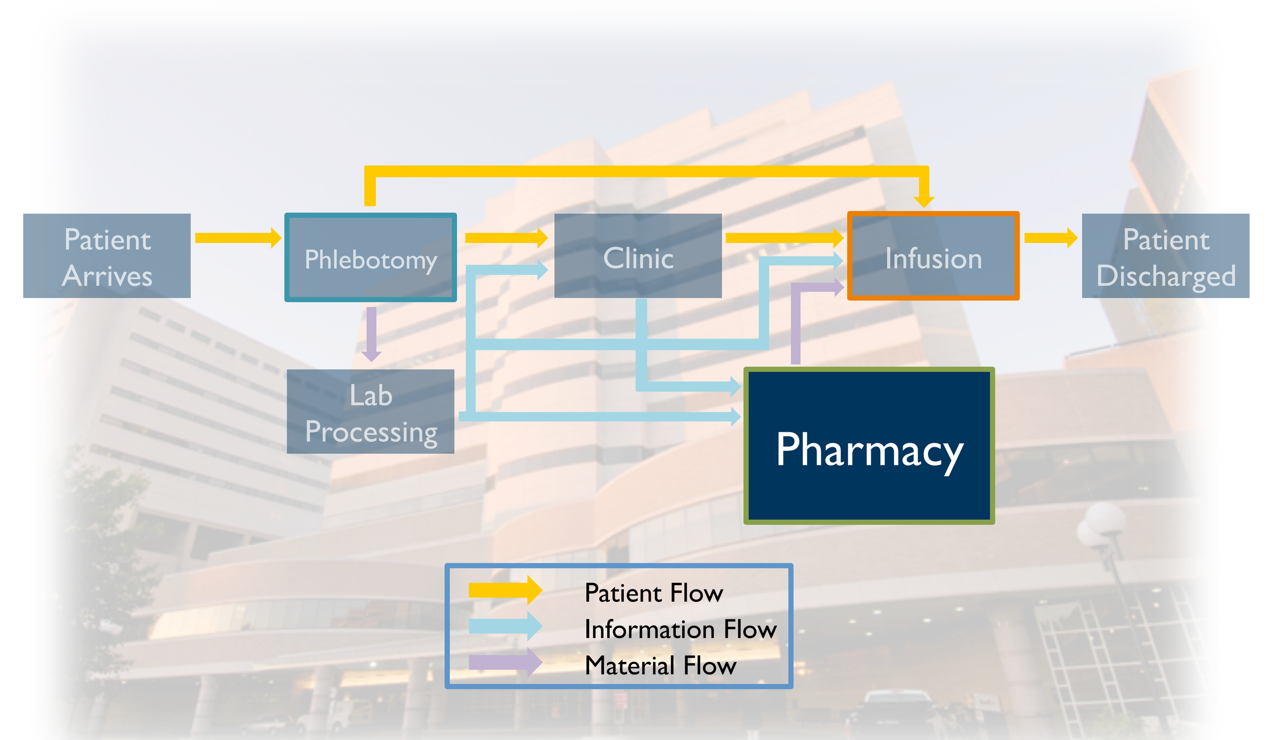
INTRODUCTION

Key Goal: Reduce patient waiting time by mixing chemotherapy drugs before patients arrive in the system or at earlier stages in the process

Motivation

- Cancer
  - Second leading cause of death in the U.S.
  - ~1.7 million estimated cases in 2017
  - More than half require chemotherapy treatment
- Infusion centers
  - Increased outpatient demand leads to undesirable outcomes such as:
    - Increased patient waiting times
    - Overworked staff



Dissertation Summary

We focus on optimizing drug preparation at the pharmacy to reduce patient delays. Drugs can be prepared the morning before patients arrive to prevent the patient from waiting the additional time needed to prepare their prescribed drugs in addition to any other wait time occurred during peak pharmacy hours. However, patients scheduled for outpatient chemotherapy infusion sometimes may need to cancel at the last minute even after arriving for their appointment (i.e. patient may be deemed too ill to receive treatment). This results in the health system incurring waste cost if the drug was made ahead since the drugs are patient specific and have a short shelf life. Infusion centers must implement policies to balance this potential waste cost with the time savings for their patients and staff.

This dissertation focuses on methods and strategies to improve the process flow of chemotherapy infusion outpatients by optimizing pharmacy make-ahead policies. We propose using three different methods which build upon each other. First we develop a predictive model which utilizes patient-specific data to estimate the probability that a patient will defer or not show for treatment on a given day. Next we utilize these probabilities in an integer programming model. This multi-criteria optimization model prioritizes which and how many drugs to make ahead given a fixed window of time. This is done with the dual objectives of reducing the expected waste cost as well as the expected patient waiting time. Lastly, we utilize simulation to better quantify the impact of our proposed policies. Each method utilizes electronic medical record data from the University of Michigan Rogel Cancer Center (UMRCC) but can be generalized for any cancer center.

What is Pre-mix?

- Anytime the pharmacy mixes a drug before a patient is deemed ready to receive it
- Generally, pharmacies do not pre-mix drugs due to risk in wastage cost
- Consider the trade off between waste cost and reduced patient waiting time

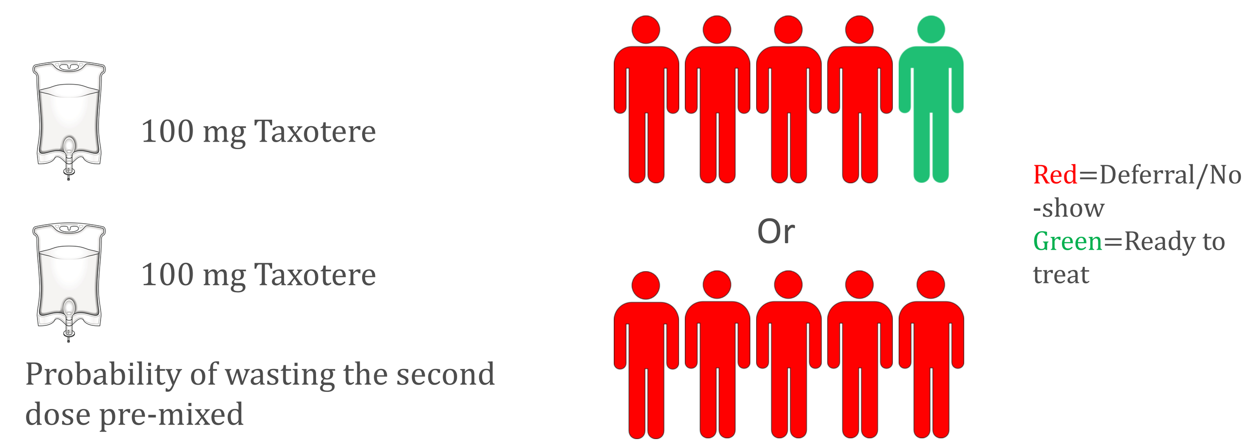
UMRCC Current Pre-mix Policy

- Will only pre-mix drugs from 6 am-7:30 am (before patients arrive)
- Will only pre-mix drugs from a fixed list (based on cost and pharmacist-ascribed "common use")

We expand this by considering patient probability of deferral and the number of patients scheduled for a particular drug.

1. PREDICTION

Suppose we have five patients scheduled to receive 100 mg of Taxotere on a given day. If the first patient defers/no-shows we then can give their drug to the second and so on. Therefore to waste one dose, all patients must defer or not show.



Methods

Tested Model	Description
Logistic Regression Model	Popular binary classification model that predicts the probability of your response using the logistic function
Classification and Regression Trees (CART)	Decision tree model that uses a binary partition recursion algorithm
Bagged CART	Bootstrap aggregation of multiple CART models
Random Forrest	Similar to Bagged CART, except only using a subset of variables for each tree
Multivariate Adaptive Regression Splines (MARS)	A non-parametric method which uses basis function transformations and regresses adaptively on transformed data
Bayesian Additive Regression Trees (BART)	A CART ensemble model, using Bayesian priors, that sums over the prediction of each tree
Neural Networks	Non-linear model based on the human neural network.

Table 1: Methods tested for prediction model

Data Summary

- University of Michigan Comprehensive Cancer Center Data from 2015
- N=28,919
- 3,522 total patients in sample
- 3,055 deferrals

(a)

Variables	Mean	St. Dev.	Min	Max
Len (min)	195.6	133.2	30	780
Age (years)	59	13.6	16	95
Total Prev. Cancel.	.8	1.4	0	21
Days since Last Cancel.	27.3	59.5	0	504
Tot. Prev. Visits	8.4	9.2	0	83
Days since Last Visit	15.3	23.3	0	448
BMI (kg/m^2)	27.9	6.8	12.7	78.7

(b)

Cat. Variables	Levels
Status (Response)	2
Sex	2
Race	8
Ethnicity	4
Marital Status	8
Treatment Protocol	51
Region	10

Table 2: (a) contains all tested numeric variables while Table (b) represents all categorical variables. We note that there were over 200 treatment protocols. However in order to fit a model we needed to reduce the number of categories based on frequency.

Results

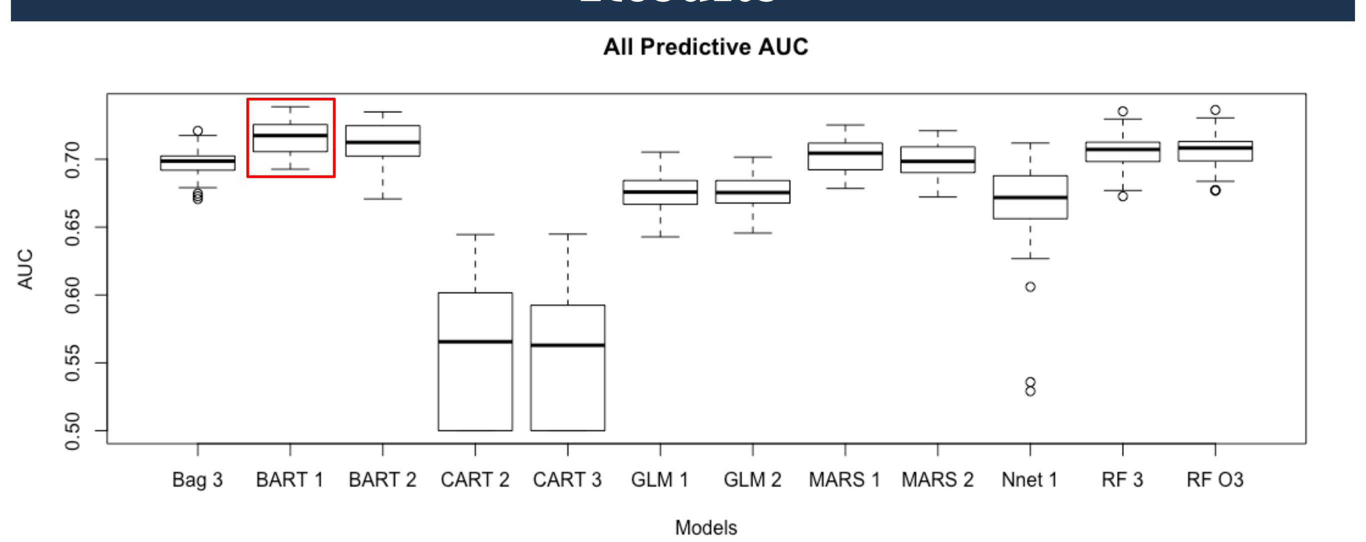


Figure 1: Box plots illustrate the predictive AUC and Brier Score respectively from 50 repeated hold out trials

Based on our performance metrics, we chose BART 1 as our final model. If we set a threshold at probability 0.75, we were able to correctly predict 21% of deferrals/no shows and 93% of completed appointments with an overall prediction accuracy of 84%.

2. OPTIMIZATION

We consider having a fixed window for pre-mix (2 hours) and want to determine which drugs to mix in order to maximize expected saved wait time and minimize expected waste cost. This expectation is determined from the probabilities discussed in Chapter 1.

Assumptions

- All drugs will last for all patients scheduled that day (most last 12 hours)
- All drugs' mixing times are deterministic
- Each patient is scheduled for only one drug

Model

Sets

D: set of drugs d (e.g. 50 mg of Taxotere)

Variables

$$x_{nts}^{d} = \begin{cases} 1 & \text{if mixing the } n\text{th dose of drug } d \text{ at time } t \text{ at stage } s \\ 0 & \text{o.w.} \end{cases}$$

$$y_{n}^{d} = \begin{cases} 1 & \text{if we don't mix the } n\text{th dose of drug } d \\ 0 & \text{o.w.} \end{cases}$$

$$z_{nts}^{d} = \begin{cases} 1 & \text{if mixing the } n\text{th dose of drug } d \text{ at time } t \text{ at stage } s \\ 0 & \text{o.w.} \end{cases}$$

Parameters

- Δ_d: the reward or savings for mixing drug d
- T: the total time units for the pre-mix period
- c_d: the cost of drug d
- p_{ds}: the time it takes to process drug d at stage s
- N_d: the number of doses needed for each drug d
- C_s: pre-mix capacity for stage s
- M: a very large number
- $P_d(n)$: probability of wasting the n does of drug d drug

Objective

Maximize the difference between our expected saved wait time and waste cost

$$E_n^d[\text{Waste Cost}] = c_d P_d(n) \qquad E_n^d[\text{Saved Wait}] = p_d \Delta_d [1 - P_d(n)]$$

$$\boldsymbol{max} \sum_d \sum_n \sum_t \left(E_n^d[\text{Saved Wait}] - E_n^d[\text{Waste Cost}]\right) * x_{nt1}^d$$

$$\sum_t x_{nts}^d + y_n^d = 1 \qquad \forall d, n, s \quad (1)$$

$$\sum_t z_{nts}^d + p_{ds} * y_n^d = p_{ds} \qquad \forall d, n, s \quad (2)$$

$$y_n^d \leq y_{n+1}^d \qquad \forall d, n = 1, \ldots, N_d - 1 \quad (3)$$

$$\sum_t t x_{nt1}^d \leq \sum_t t x_{(n+1)t1}^d + M * y_{n+1}^d \qquad \forall d, n = 1, \ldots, N_d - 1 \quad (4)$$

$$\sum_d \sum_n z_{nts}^d \leq C_s \qquad \forall t \quad (5)$$

$$x_{nt}^d \leq z_{n(t+i)\,s}^d \qquad \forall d, n, t = 1 \ldots (T - p_d + 1), i = 0 \ldots (p_d - 1) \quad (6)$$

$$\sum_t t x_{nt1}^d + p_{d1} - 1 \leq T \qquad \forall d, n \quad (7)$$

$$\sum_t (t + p_{d1}) x_{nt1}^d \leq \sum_t (t + p_{d1}) x_{nt1}^d \qquad \forall d, n \quad (8)$$

Constraints

(1) Either pick a time to start a drug or do not make it at all
(2) Drug must be completed if mixed
(3) If you do not make the n[th] dose you cannot make the (n+1)[th] dose
(4) Must make doses in order
(5) Can only make C drugs at a time
(6) No preemptions allowed
(7) Cannot start a drug unless there is enough time
(8) Drug must go through stage 1 before stage 2

Future Work

- Evaluate the optimization model using the simulation and compare with the "rule of thumb" policies
- Generate results for the various perspectives (patient, hospital, insurance company, etc.)
- Relax assumption patient only receive a single drug

3. SIMULATION

UMRCC Pharmacy has a goal to keep the drug order turnaround-time (TAT) under 1 hour for each patient. However, current TAT can be as much as 2 hours. Our focus is to improve the drug order TAT in the pharmacy and in turn reduce the overall time in the system for patients.

We propose various pre-mix policies ranging in risk tolerance to be tested through discrete-event simulation while considering the trade off of saved wait time vs. waste cost if a patient defers.

Methods

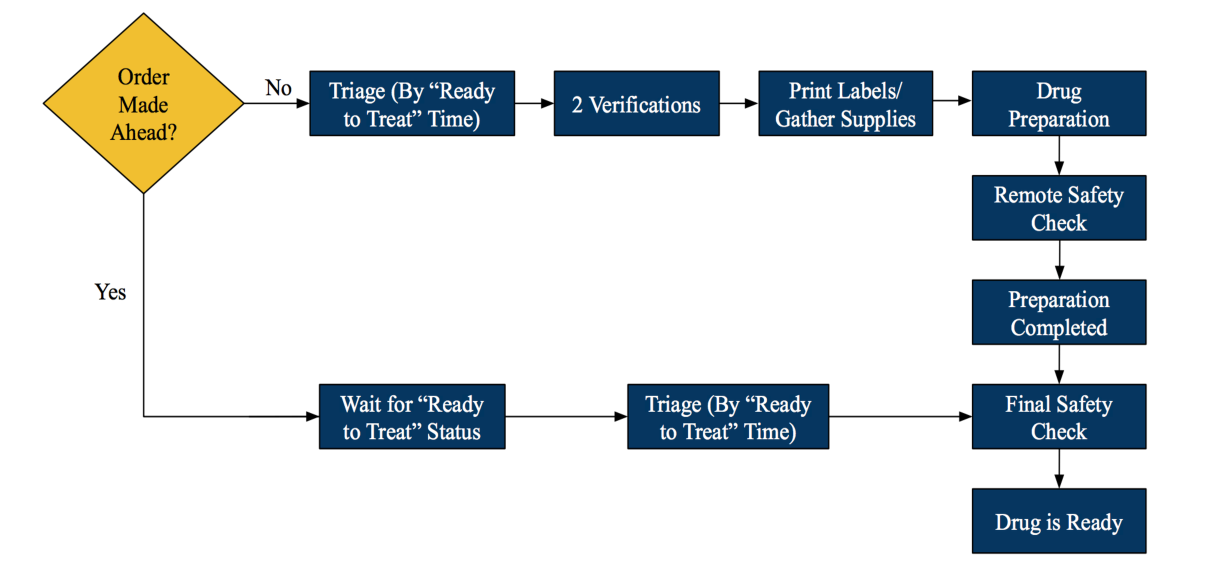


Figure 2: Pharmacy simulation process flow for chemotherapy infusion drug orders

- We assume that all pre-mixed orders will not expire before they are administered if the patient appointment is at noon or before
- We assume a single arrival stream of patients
- We assume a single drug order for each patient with a drug compounding probability of failure of 5%.
- There is also a chance for pre-mixed orders to be wasted if a patient defers or does not show.
- Simulation was done using the *Simpy* module in Python. The results below were obtained through 20 replications of a Monday-Friday at UMRCC

Results

Drug Order Time in System and Wasted Drug Results

Days	Metrics (mins)	No Pre-mix	Scenarios 1	2	3
1	Average	52.79	30.70	26.64	26.17
	CI	(49.51, 56.07)	(29.53, 31.87)	(26.23, 27.05)	(25.65, 26.68)
2	Average	85.63	46.60	41.73	38.19
	CI	(80.79, 90.46)	(44.43, 48.8)	(39.21, 44.25)	(36.19, 40.19)
3	Average	58.04	35.44	37.69	27.47
	CI	(54.74, 61.34)	(33.65, 37.22)	(34.87, 40.51)	(26.59, 28.35)
4	Average	38.10	24.78	22.82	22.43
	CI	(36.3, 39.89)	(24.18, 25.37)	(22.35, 23.33)	(22.06, 22.81)
5	Average	47.86	28.32	25.73	25.70
	CI	(44.95, 50.78)	(27.53, 29.09)	(25.27, 26.19)	(24.71, 26.7)
Avg of Avg # of Drugs Wasted		0	2.81	3.13	2.32

Table 2: Here we have the results for the drug order time in system. Scenario 1 pre-mixes the first 20 drugs for patients with a probability of deferral/no-show of .1 or lower. Scenario 2 disregards the probability of deferral/no-show and pre-mixes drugs for patients scheduled between 9am-12pm proportionally spaced out in each hour block based on the number of appointment in that block. Scenario 3 combines both ideas from Scenarios 1 and 2.

Future Work

- Use to justify the expected saved wait time by following recommendations taken from the static pre-mix model solution from Chapter 2
- Test various policies for mixing chemotherapy drugs throughout the day

Acknowledgments

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