MICHIGAN ENGINEERING
UNIVERSITY OF MICHIGAN

Determining an Optimal Schedule for Pre-Mixing Chemotherapy Drugs

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Outline

- Background
  - General Patient Flow
  - Define Pre-mix
  - Goal
  - Motivation
  - Literature
- Problem Description
  - Probabilities of wasting drugs
  - Static Model
- Future Steps

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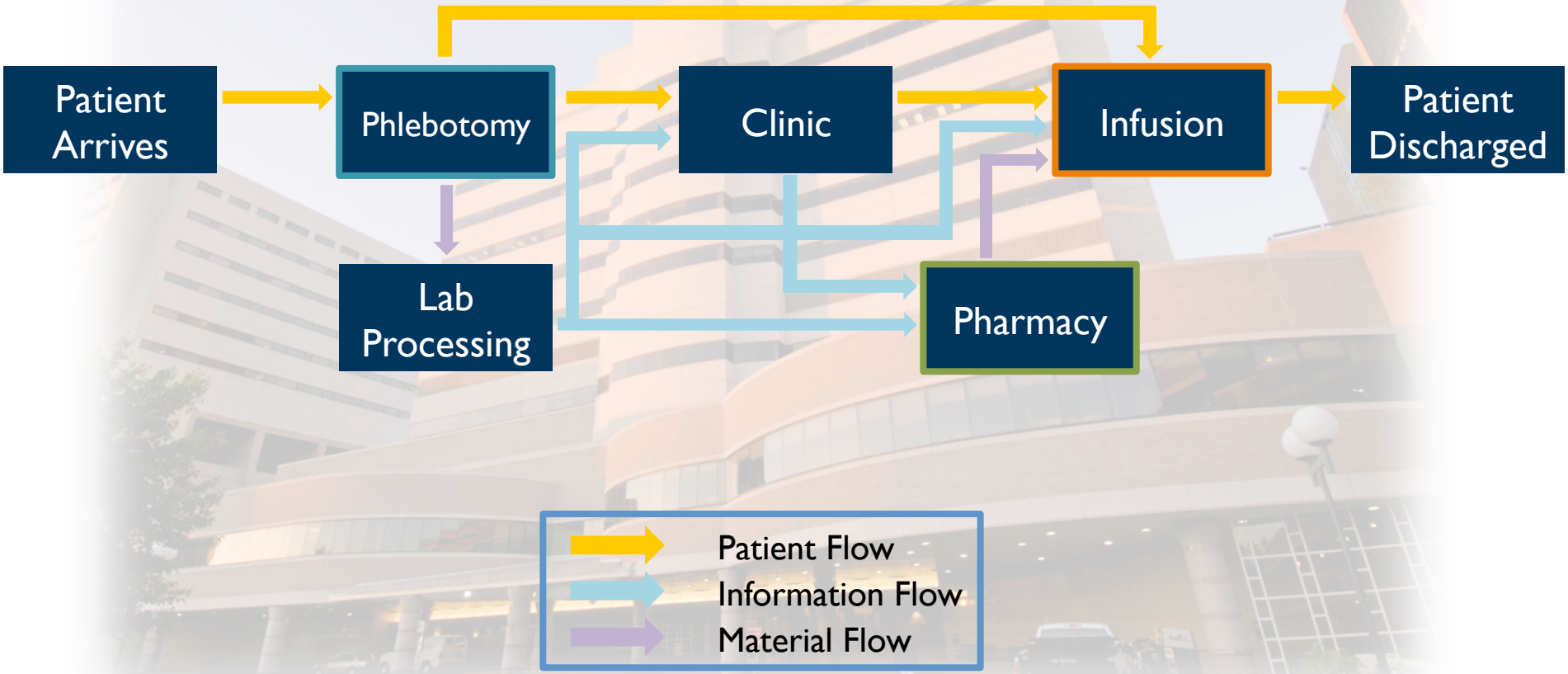
Infusion Overview



What is Pre-mix ?

- Anytime you mix a drug before a patient is deemed ready to receive it
  - Generally you don't pre-mix drugs due to risk in wastage cost
  - Consider the trade off between waste cost and reduced patient waiting time

UMCCC Current Pre-mix Policy

- Will only mix drugs during a fixed window of time before patients arrive
  - 6am-8am
- Have a fixed list of drugs they are willing to mix
  - Based on cost and common use

Goal

- Reduce patient waiting times

- Best case without pre-mix
  - Patient will wait duration of mixing drug (~30-60 min)

"This is the pre-pre-pre-waiting room, sir. You have 3 other waiting rooms to wait in before you see the doctor...if it isn't too late in the day."

Motivation

- Cancer
  - Second leading cause of death in the U.S.
  - ~1.6 million estimated cases in 2015
  - More than half require chemotherapy treatment

- Infusion centers
  - Increased outpatient demand leads to undesirable outcomes such as:
    - Increased patient waiting times
    - Overworked staff

Current Literature

- Pre-mixing does prove to have positive outcomes
  - *Masselink, I., Mijden, T., Litvak, N., & Vanberkel, P. (2011). Preparation of chemotherapy drugs: Planning policy for reduced waiting times.*
- Cost associated with patient wait in cancer care
  - *Yabroff, K. Robin, et al. "Patient time costs associated with cancer care." Journal of the National Cancer Institute 99.1 (2007): 14-23.*
- Deciding when to mix Chemo drugs
  - *Mazier, Alexandre, Jean-Charles Billaut, and Jean-François Tournamille. "Scheduling preparation of doses for a chemotherapy service." Annals of Operations Research 178.1 (2010): 145-154.*

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Key Terms

- Hang-by time: the time duration that a drug has until it must be administered to patient.

- Deferral: Patient is too ill to receive treatment

- No show: Patient missed appointment without calling in

Description of Problem (Static)

- We will also consider having a fixed window for pre-mix

- Assumptions
  - All drugs will last for all patients scheduled that day (most last 12 hours)
  - Only make L drugs at a time
  - All drugs take 30 minutes to make

Probability of Wasting a Drug

- We first say all patients have a probability of p to defer/no show on any given day. Assume we have m_d patients scheduled to receive the same drug d on a given day. We want the probability of wasting each dose we decide to premix.

Probability of Wasting a Drug

- We first say all patients have a probability of p to defer/no show on any given day. Assume we have m_d patients scheduled to receive the same drug d on a given day. We want the probability of wasting each dose we decide to premix.
- Let m_d=4

$$Prob(\text{Wasting } 1^{st} \text{ dose}) = p^4$$

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<u>General</u>

$$Prob(\text{Wasting nth dose}) = \sum_{i=1}^{n} \binom{m_d}{m_d - i + 1} p^{m_d - i + 1}(1-p)^{i-1}$$

Probability of Wasting a Drug (Cont.)

- The previous formulation considers all patients to have equal probability of deferral. However this could depend on
  - age
  - sex
  - treatment
  - type of cancer
  - etc.

Probability of Wasting a Drug (Cont.)

- Let's now consider the probability of wasting a particular dose given patient i has a probability of deferral/no show p_i
- Let's define a new set S_d which is the total number of patients scheduled to receive drug d for the day. $S_d=\{1,2,\ldots,m_d\}$

Probability of Wasting a Drug (Cont.)

- Let's now consider the probability of wasting a particular dose given patient i has a probability of deferral/no show $p_{i.}$
- Let's define a new set S_d which is the total number of patients scheduled to receive drug d for the day. $S_d=\{1,2,\ldots,m_d\}$.

$$Prob(\text{Wasting } 1^{st} \text{ dose}) = \prod_{i \in S_d} p_i$$

Probability of Wasting a Drug (Cont.)

- Let's now consider the probability of wasting a particular dose given patient i has a probability of deferral/no show $p_{i.}$
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$$Prob(\text{Wasting } 1^{st} \text{ dose}) = \prod_{i \in S_d} p_i$$

$$Prob(\text{Wasting } 2^{nd} \text{ dose}) = \sum_{i \in S_d} \left[(1 - p_i) \prod_{j \in S_d \setminus i} (p_j) \right] + \prod_{i \in S_d} p_i$$

Probability of Wasting a Drug (Cont.)

- Let's now consider the probability of wasting a particular dose given patient i has a probability of deferral/no show p_i.
- Let's define a new set S_d which is the total number of patients scheduled to receive drug d for the day. $S_d=\{1,2,\ldots,m_d\}$.

$$Prob(\text{Wasting } 1^{st} \text{ dose}) = \prod_{i \in S_d} p_i$$

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$$Prob(\text{Wasting } 3^{rd} \text{ dose}) = \sum_{i \in S_d} \sum_{j \in S_d \setminus i} \left[(1-p_i)(1-p_j) \prod_{k \in S_d \setminus \{i,j\}} p_k\right] + \sum_{i \in S_d} \left[(1-p_i) \prod_{j \in S_d \setminus i} (p_j)\right] + \prod_{i \in S_d} p_i$$

Probability of Wasting a Drug (Cont.)

- Currently receiving/analyzing data to determine how to best categorize patients

- Current model will only vary the probability of deferral by drug, not by patient type

Model Description

Sets

- D: set of drugs d (e.g. 50 mg of Taxotere)
- T: set of time units (each being 30 min)

Variables

$$x_{nt}^{d} = \begin{cases} 1 & \text{if we mix the nth dose of drug } d \text{ at time } t \\ 0 & \text{o.w.} \end{cases}$$

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

Objective

- We first define our Expected Waste cost of a drug with the following:

$$E_n^d[waste\ cost] = \sum_{w=1}^{n} c_d P_d(w)$$

- Then we maximize the difference between Projected Savings and Expected Waste

$$\text{maximize} \sum_d \sum_n \sum_t (\Delta_d - E_n^d[waste\ cost]) * x_{nt}^d$$

<u>Parameters</u>

- Δ_d: the reward/savings for mixing drug d
- T: the total time units for the premix period
- c_d: the cost of drug d
- $n[d]$: the number of doses needed for each drug based on the scheduled patients
- M: very large number

Constraints

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

Relate our auxiliary variable to the decision variable

Parameters

- Δ_d: the reward/savings for mixing drug d
- T: the total time units for the premix period
- c_d: the cost of drug d
- $n[d]$: the number of doses needed for each drug based on the scheduled patients
- M: very large number

Constraints

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

$$y_n^d \leq y_{n+1}^d \qquad \forall d, n = 1..n[d] - 1 \qquad (2)$$

Must make the first dose before making 2nd,3rd,...

Parameters

- Δ_d: the reward/savings for mixing drug d
- T: the total time units for the premix period
- c_d: the cost of drug d
- $n[d]$: the number of doses needed for each drug based on the scheduled patients
- M: very large number

Constraints

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

$$y_n^d \leq y_{n+1}^d \qquad \forall d, n = 1..n[d] - 1 \qquad (2)$$

$$\sum_t t x_{nt}^d \leq \sum_t t x_{n+1t}^d + M * y_{n+1} \qquad \forall n, d \qquad (3)$$

Dose ordering

Parameters

- Δ_d: the reward/savings for mixing drug d
- T: the total time units for the premix period
- c_d: the cost of drug d
- $n[d]$: the number of doses needed for each drug based on the scheduled patients
- M: very large number

Constraints

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

$$y_n^d \leq y_{n+1}^d \qquad \forall d, n = 1..n[d] - 1 \qquad (2)$$

$$\sum_t t x_{nt}^d \leq \sum_t t x_{n+1t}^d + M * y_{n+1} \qquad \forall n, d \qquad (3)$$

$$\sum_d \sum_n x_{nt}^d \leq L \qquad \forall t \qquad (4)$$

Only make L at a time

<u>Parameters</u>

- Δ_d: the reward/savings for mixing drug d
- T: the total time units for the premix period
- c_d: the cost of drug d
- $n[d]$: the number of doses needed for each drug based on the scheduled patients
- M: very large number

Constraints

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

$$y_n^d \leq y_{n+1}^d \qquad \forall d, n = 1..n[d] - 1 \qquad (2)$$

$$\sum_t t x_{nt}^d \leq \sum_t t x_{n+1t}^d + M * y_{n+1} \qquad \forall n, d \qquad (3)$$

$$\sum_d \sum_n x_{nt}^d \leq L \qquad \forall t \qquad (4)$$

$$\sum_t x_{nt}^d \leq 1 \qquad \forall n, d \qquad (5)$$

Can only make the nth dose of a drug once

Parameters

- Δ_d: the reward/savings for mixing drug d
- T: the total time units for the premix period
- c_d: the cost of drug d
- $n[d]$: the number of doses needed for each drug based on the scheduled patients
- M: very large number

Example

- Suppose we have patients scheduled to receive 15 different drugs.
- Each takes 30 min to make

Drug	Hang by	Price	Currently pre-mixed	Treatment for
Carboplatin	12 hrs	2.52	Yes	Cancer of the ovaries, head, and neck
Paclitaxel	12 hrs	4.10	Yes	Cancer in the lungs, ovary, or breast
Cyclophosphamide	12 hrs	879.00	Yes	Leukemia and lymphomas, and nephrotic syndrome
Folotyn	12 hrs	4637.21	No	T-cell lymphoma
Adcetris	12 hrs	6516.00	No	Treats Hodgkin's lymphoma and systemic anaplastic large cell lymphoma

Example Scenarios

	Scenario 1
Reward	1 for all drugs
# of Doses	2 for each drug
$P_d(n)$	p=.25 for all drugs

Example Scenarios

	Scenario 1	Scenario 2
Reward	1 for all drugs	11.67 for all drugs
# of Doses	2 for each drug	2 for each drug
$P_d(n)$	p=.25 for all drugs	p=.25 for all drugs

Example Scenarios

	Scenario 1	Scenario 2	Scenario 3
Reward	1 for all drugs	11.67 for all drugs	11.67 for all drugs
# of Doses	2 for each drug	2 for each drug	2 for each drug
$P_d(n)$	p=.25 for all drugs	p=.25 for all drugs	inverse to cost of drug ranging from .02 to .30

Example Scenarios

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Reward	1 for all drugs	11.67 for all drugs	11.67 for all drugs	11.67 for all drugs
# of Doses	2 for each drug	2 for each drug	2 for each drug	1-2 lower cost 3-5 higher cost
$P_d(n)$	p=.25 for all drugs	p=.25 for all drugs	inverse to cost of drug ranging from .02 to .30	p=.25 for all drugs

Example Scenarios

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Reward	1 for all drugs	11.67 for all drugs	11.67 for all drugs	11.67 for all drugs	11.67 for all drugs
# of Doses	2 for each drug	2 for each drug	2 for each drug	1-2 lower cost 3-5 higher cost	1-2 lower cost 3-5 higher cost
$P_d(n)$	p=.25 for all drugs	p=.25 for all drugs	inverse to cost of drug ranging from .02 to .30	p=.25 for all drugs	inverse to cost of drug ranging from .02 to .30

Results

Drugs	Cost
A	$1.61
B	$2.52
C	$4.10
D	$6.80
E	$16.56
F	$83.40
G	$91.54
H	$155.56
I	$367.02
J	$698.60
K	$879.00
L	$1,158.84
M	$2,389.39
N	$4,637.21
O	$6,516.00
TOTAL	—

Results

Drugs	Cost	Scen. 1
A	$1.61	2
B	$2.52	1
C	$4.10	1
D	$6.80	1
E	$16.56	—
F	$83.40	—
G	$91.54	—
H	$155.56	—
I	$367.02	—
J	$698.60	—
K	$879.00	—
L	$1,158.84	—
M	$2,389.39	—
N	$4,637.21	—
O	$6,516.00	—
TOTAL	—	5

Results

Drugs	Cost	Scen. 1	Scen. 2
A	$1.61	2	2
B	$2.52	1	2
C	$4.10	1	2
D	$6.80	1	1
E	$16.56	—	1
F	$83.40	—	—
G	$91.54	—	—
H	$155.56	—	—
I	$367.02	—	—
J	$698.60	—	—
K	$879.00	—	—
L	$1,158.84	—	—
M	$2,389.39	—	—
N	$4,637.21	—	—
O	$6,516.00	—	—
TOTAL	—	5	8

Results

Drugs	Cost	Scen. 1	Scen. 2	Scen. 3
A	$1.61	2	2	2
B	$2.52	1	2	2
C	$4.10	1	2	2
D	$6.80	1	1	1
E	$16.56	—	1	1
F	$83.40	—	—	—
G	$91.54	—	—	—
H	$155.56	—	—	—
I	$367.02	—	—	—
J	$698.60	—	—	—
K	$879.00	—	—	—
L	$1,158.84	—	—	—
M	$2,389.39	—	—	—
N	$4,637.21	—	—	—
O	$6,516.00	—	—	—
TOTAL	—	5	8	8

Results

Drugs	Cost	Scen. 1	Scen. 2	Scen. 3	Scen. 4
A	$1.61	2	2	2	2
B	$2.52	1	2	2	2
C	$4.10	1	2	2	1
D	$6.80	1	1	1	1
E	$16.56	—	1	1	1
F	$83.40	—	—	—	—
G	$91.54	—	—	—	—
H	$155.56	—	—	—	—
I	$367.02	—	—	—	—
J	$698.60	—	—	—	—
K	$879.00	—	—	—	1
L	$1,158.84	—	—	—	—
M	$2,389.39	—	—	—	—
N	$4,637.21	—	—	—	—
O	$6,516.00	—	—	—	—
TOTAL	—	5	8	8	8

Results

Drugs	Cost	Scen. 1	Scen. 2	Scen. 3	Scen. 4	Scen. 5
A	$1.61	2	2	2	2	—
B	$2.52	1	2	2	2	1
C	$4.10	1	2	2	1	—
D	$6.80	1	1	1	1	1
E	$16.56	—	1	1	1	—
F	$83.40	—	—	—	—	—
G	$91.54	—	—	—	—	—
H	$155.56	—	—	—	—	—
I	$367.02	—	—	—	—	—
J	$698.60	—	—	—	—	1
K	$879.00	—	—	—	1	2
L	$1,158.84	—	—	—	—	1
M	$2,389.39	—	—	—	—	—
N	$4,637.21	—	—	—	—	—
O	$6,516.00	—	—	—	—	2
TOTAL	—	5	8	8	8	8

Results

Drugs	Cost	Scen. 1	Scen. 2	Scen. 3	Scen. 4	Scen. 5
A	$1.61	2	2	2	2	—
B	$2.52	1	2	2	2	1
C	$4.10	1	2	2	1	—
D	$6.80	1	1	1	1	1
E	$16.56	—	1	1	1	—
F	$83.40	—	—	—	—	—
G	$91.54	—	—	—	—	—
H	$155.56	—	—	—	—	—
I	$367.02	—	—	—	—	—
J	$698.60	—	—	—	—	1
K	$879.00	—	—	—	1	2
L	$1,158.84	—	—	—	—	1
M	$2,389.39	—	—	—	—	—
N	$4,637.21	—	—	—	—	—
O	$6,516.00	—	—	—	—	2
TOTAL	—	5	8	8	8	8

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Next Steps

- <u>Static Model</u>
  - Consider
    - Hang-by time for various drugs
    - Preparation time for various drugs
  - Continue working with data collection to run logistical regression
    - How to categorize various types of patients
- <u>Dynamic Model</u>
  - Goal: To find an optimal drug-mixing schedule throughout the day and update as we observe patient deferrals

Thank You!

Contacts

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CHEPS

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Appendix

- States – 3-dimensional
  - t: Time of day we are making the decision
  - O: List of orders for patients scheduled that day
  - S: Inventory of premixed drugs
- Actions
  - Mix a certain drug or not mix at $A = \{o \in O, \emptyset\}$
- Stages
  - [0,T] in 15 min intervals
- Rewards
  - Expected reward of mixing drug o at time t

Appendix

Replace with updated version

$$v(t, O, S) = \max_{o \in O} \{R(o,t) + p(o)v(t', O \backslash o, S \cup \{o\}) + (1 - p(o))v(t', O \backslash o, S)\}$$

where:

$p(o)$ is the probability of deferral of patient receiving order o

$R(o,t)$ is the expected reward of preparing order o at time t

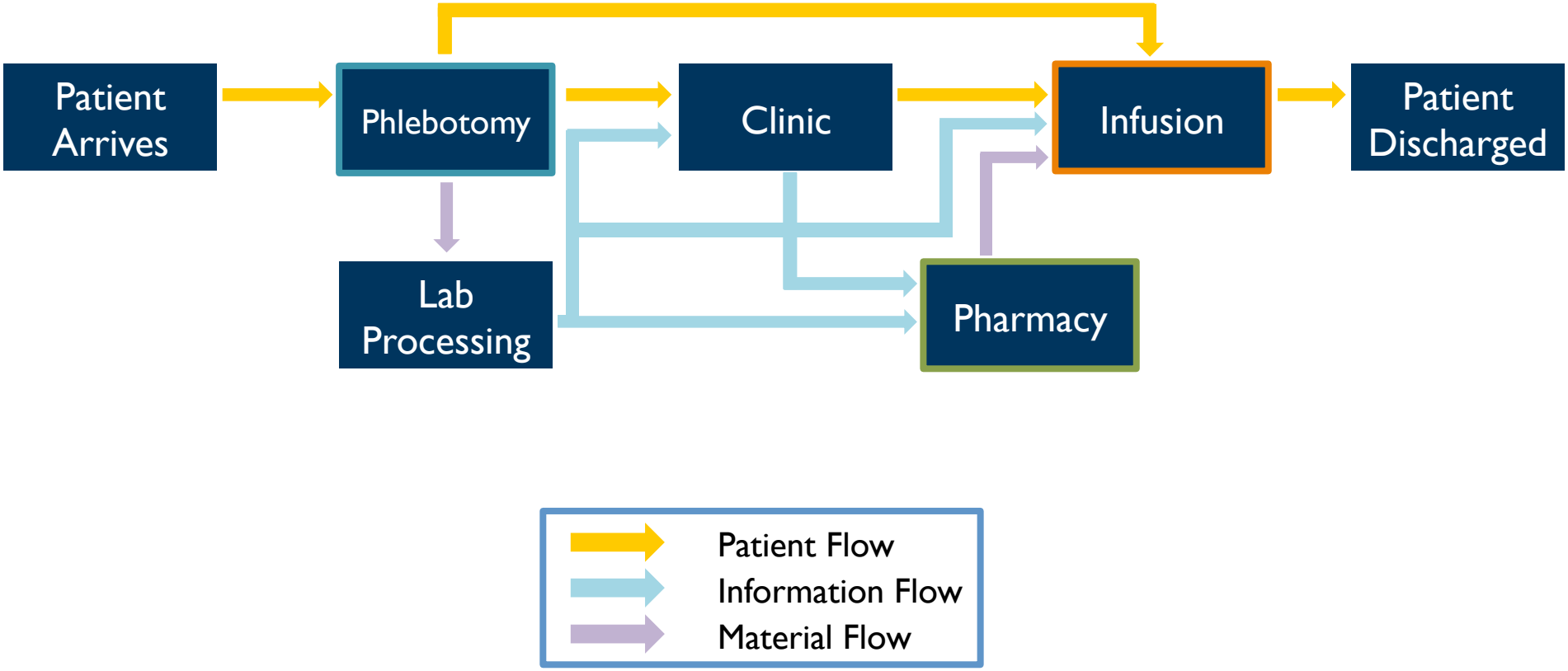
$v(t', O', S')$ is the expected reward after we prepared order o.

Work started by Sarah Bach Jeremy Casting

Appendix

- For $|O|$ moderately low
  - Use backward induction
- For $|O|$ otherwise
  - State space blows up!
  - Approximate Dynamic programming

Infusion Overview



Appendix

<u>Scenario 1</u>
Objective Value = 3.36
E[Waste] = 1.64

<u>Scenario 3</u>
Objective Value = 87.82
E[Waste] = 5.575

<u>Scenario 3</u>
Objective Value = 87.7
E[Waste] = 5.70

<u>Scenario 4</u>
Objective Value = 88.74
E[Waste] = 4.66025

<u>Scenario 5</u>
Objective Value = 92.23
E[Waste] = 1.17