Optimizing Make-ahead Chemotherapy Drug Policies at an Outpatient Infusion Center

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OUTLINE

- Motivation
- Model Description
- Probability of Wasting a Pre-mixed Drug
- Model Formulation
- Computation Experiments
- Conclusion/Future Work

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GOAL

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

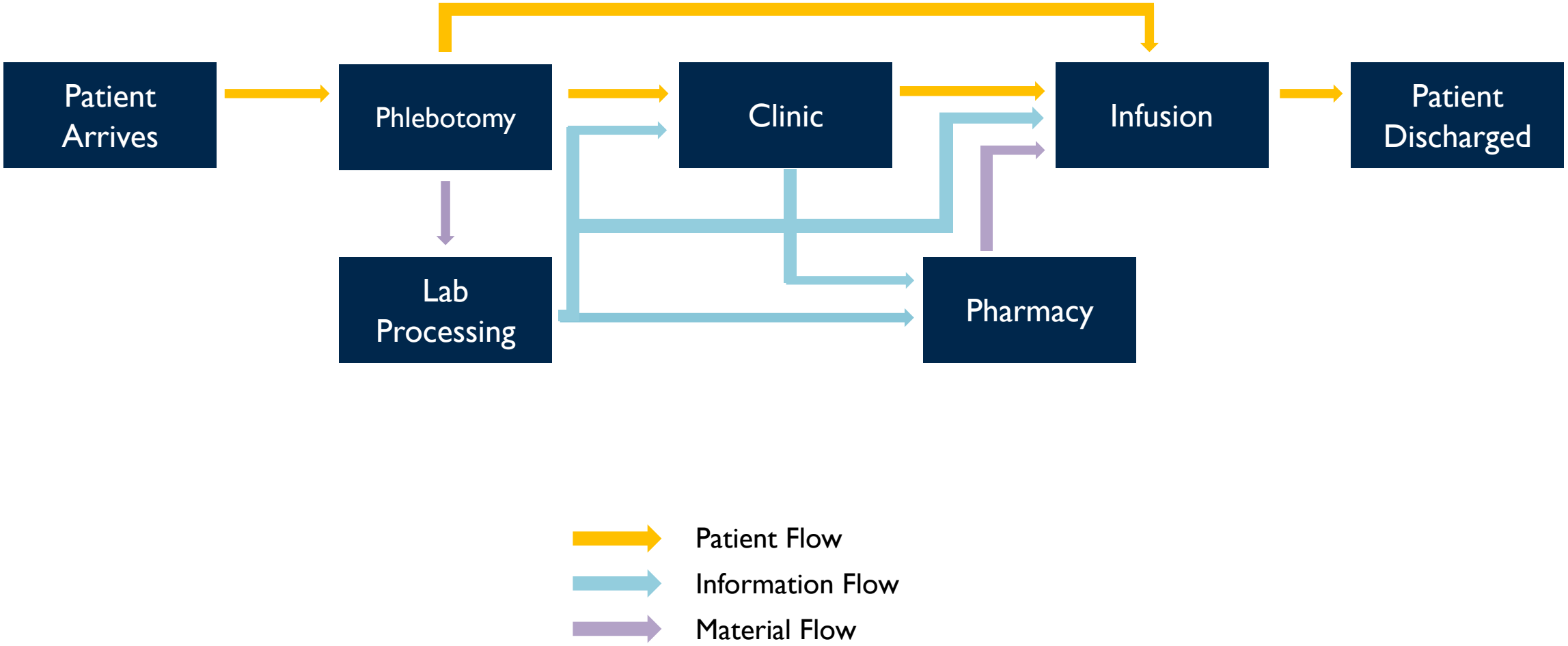
MOTIVATION

- Cancer
  - ~1.8 million new cases estimated in 2019
  - More than half require chemotherapy treatment
  - Variable infusion treatment times (30 min – 8 hr)

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

Source:
American Cancer Society (2019) http://www.cancer.org

OUTPATIENT INFUSION PATIENT FLOW



WHAT IS CHEMOTHERAPY?

- Typically require solutions to be made in pharmacy
  - Hang-by time – time after drug is made until it must be administered
- Used to
  - Control
  - Cure
  - Ease
- Variable doses correlate to patient weight
- Solution administered by IV over time (variable)
- Drugs vary in cost ($10-$20,000+)

PRE-MIXING CHEMOTHERAPY DRUGS

- Anytime a drug is mixed before a patient is deemed ready to receive it

- Factors to consider:
  - Last minute cancellation may lead to wasting pre-mixed drug
  - Storage safety protocol
  - Tradeoff between waste cost and reduced patient waiting time

PRE-MIXING CHEMOTHERAPY DRUGS

University of Michigan Rogel Cancer Center (UMRCC)

- Will only pre-mix drugs during a fixed window of 6am-8am

- Pre-mix based on a fixed list of drugs
  - Based on cost and common use

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

PRE-MIXING LITERATURE REVIEW

- Masselink, I. H., van der Mijden, T. L., Litvak, N., & Vanberkel, P. T. (2012). Preparation of chemotherapy drugs: Planning policy for reduced waiting times. *Omega, 40*(2), 181-187.

- Soh, T. I. P., Tan, Y. S., Hairom, Z., Ibrahim, M., Yao, Y., Wong, Y. P., ... & Tan, C. S. (2014). Improving wait times for elective chemotherapy through pre-preparation: a quality-improvement project at the National University Cancer Institute of Singapore. *Journal of oncology practice*, *11*(1), e89-e94.

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OPTIMIZATION MODEL DESCRIPTION

- Chemotherapy Pre-mix Integer Program with hang-by time (CPIP-HT)
  - Verification – performed by pharmacists
  - Compounding – done by technicians

- Objective
  - Maximize the difference between expected saved wait time and waste cost
  - Two-hour window to pre-mix

OPTIMIZATION MODEL ASSUMPTIONS

- All drugs' mixing times are deterministic
- Each patient is scheduled for only one drug
- Pharmacy task can be reduced to two steps
- Probability of deferral taken from BART

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PREDICTING PATIENT DEFERRALS

- Defining a patient *treatment deferral*
  - Patient arrives at the cancer center but is unable to receive their treatment (i.e. last minute cancellation)
  - Oncologist or nurse may deem them too ill for treatment after arrival
  - Unplanned treatment change
  - Social support

PREDICTING PATIENT DEFERRALS

- Prediction Model
  - Utilized patient specific data to predict their chance of deferral

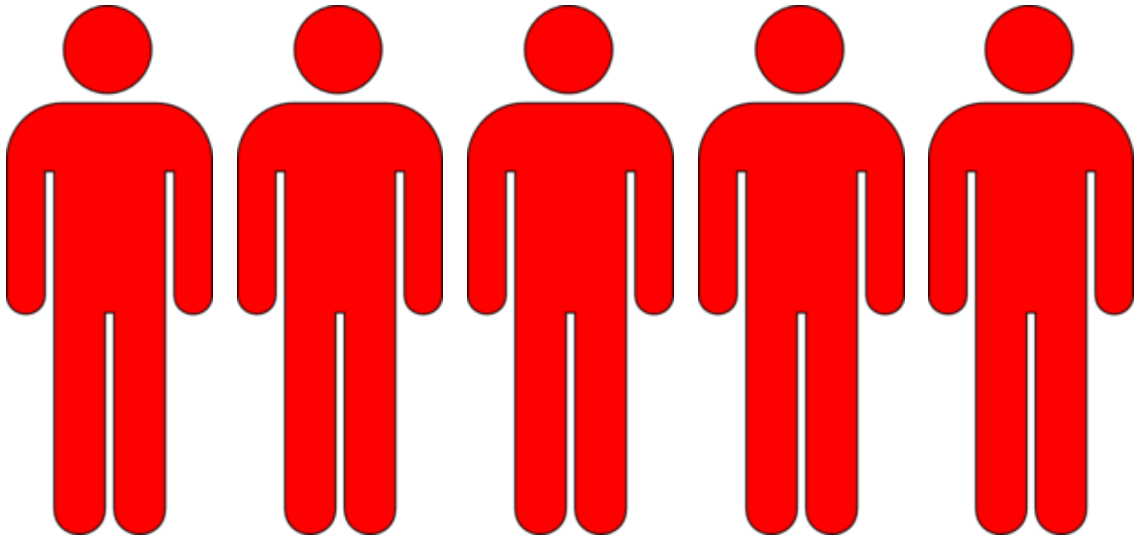
  - Richardson, D. B., Guikema, S. D., & Cohn, A. E. (2017). Predicting Patient Treatment Deferrals at an Outpatient Chemotherapy Infusion Center: A Statistical Approach. *JCO Clinical Cancer Informatics*, *1*, 1-8.

PROBABILITY OF WASTING A DRUG

Let S be defined as the set containing the probability of deferrals p_i for all i patients scheduled to receive the same drug. Given m total patients ($i \in m$)

$$S := \{p_1, p_2, \ldots, p_m\}$$

$$P(1) = \prod_{i \in S} p_i$$



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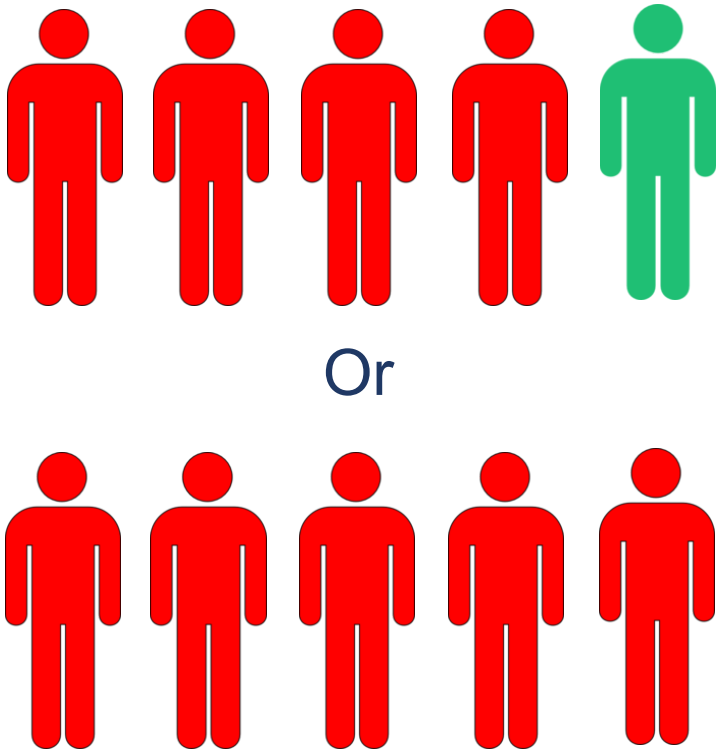
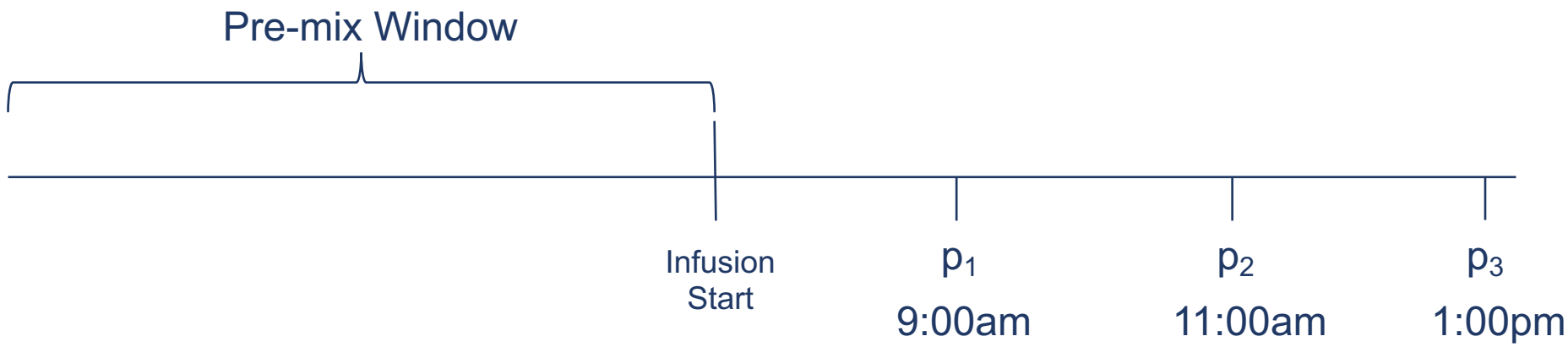
$$P(2) = \sum_{i \in S} \left[(1 - p_i) \prod_{j \in S \setminus \mathrm{i}} p_i \right] + P(1)$$



PROBABILITY OF WASTING A DRUG WITH HANG-BY TIME



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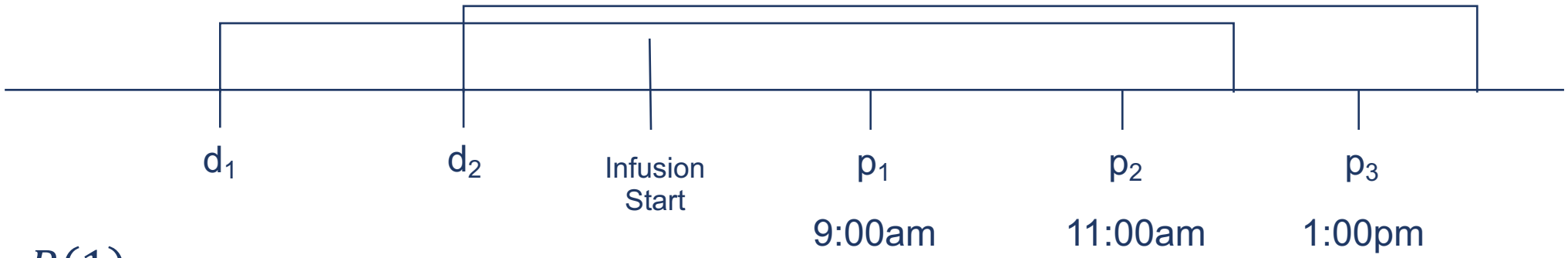

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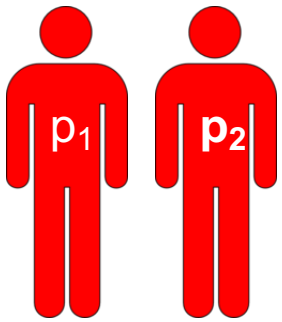

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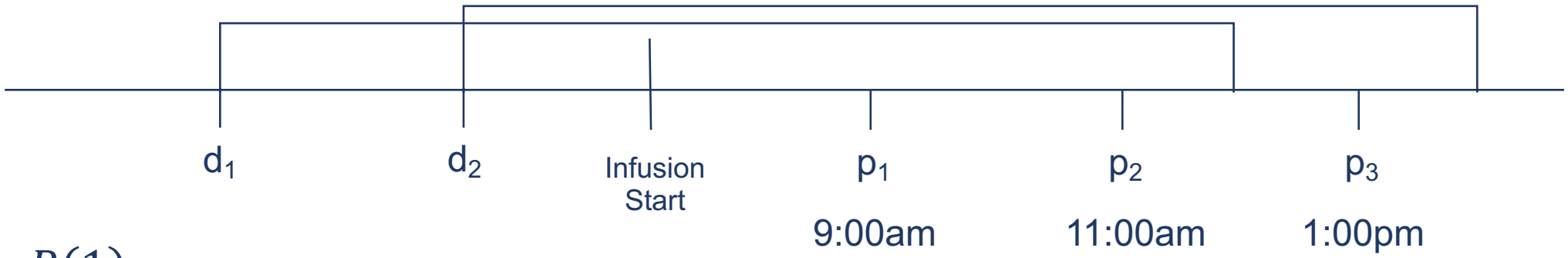

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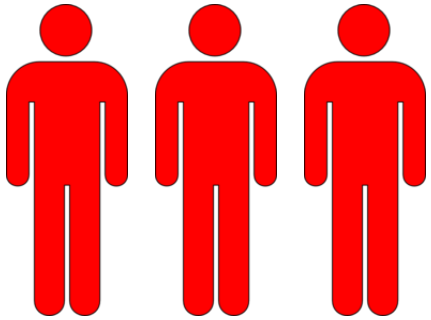

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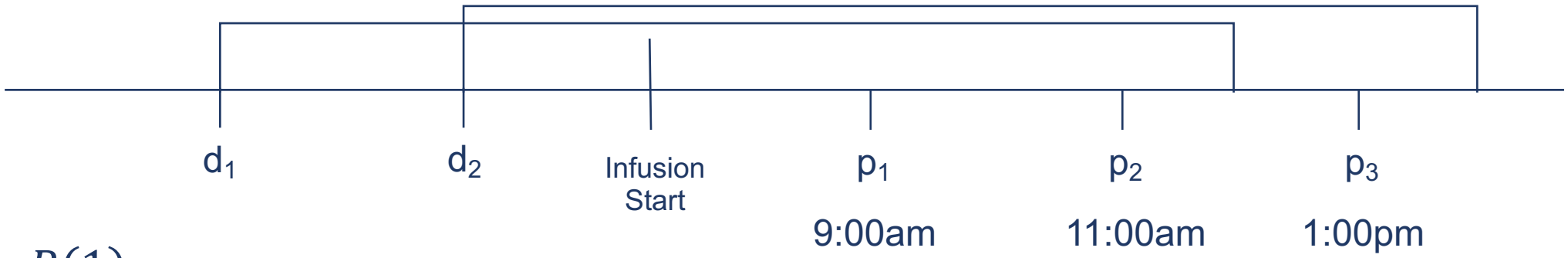
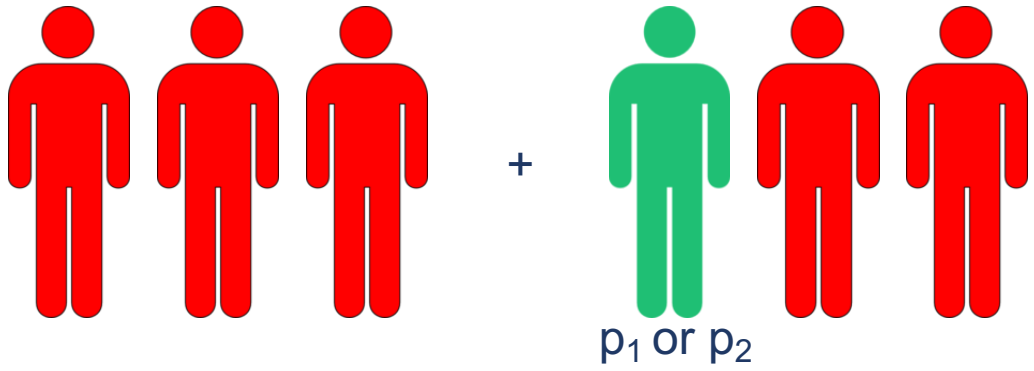


$$P(1) = p_1 p_2$$

$$P(2) = p_1 p_2 p_3 + (1 - p_1)\, p_2 p_3 + (1 - p_2) p_1 p_3 = p_3$$



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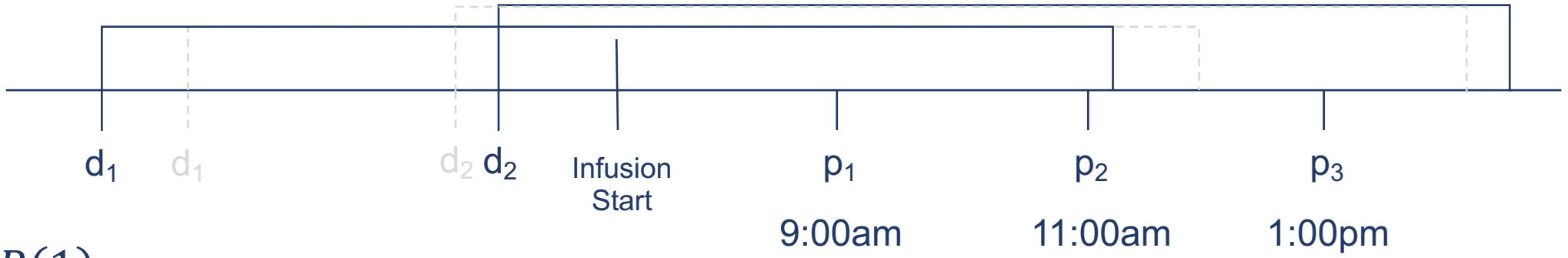

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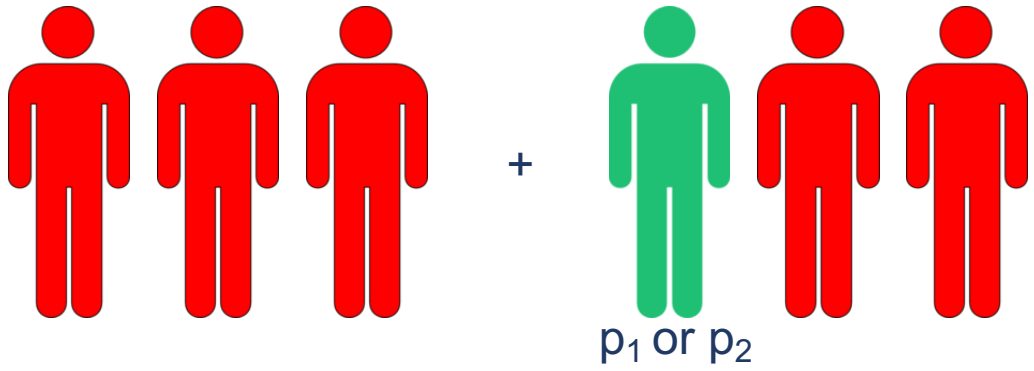

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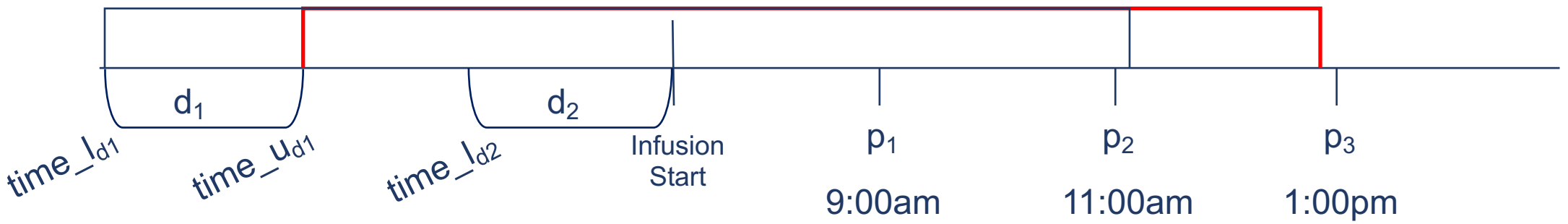

- We then use the upper and lower time bounds on each dose to make sure the drug is made both early and late enough to be viable for a pre-determined set of patients

PATIENT ELIGIBILITY VECTOR

- e_i^d is the i^{th} eligibility vector of drug $d \in D$ Now suppose we have 3 doses of a drug d

e_1^d = [0 0 0]

- zero doses of this drug were pre-mixed

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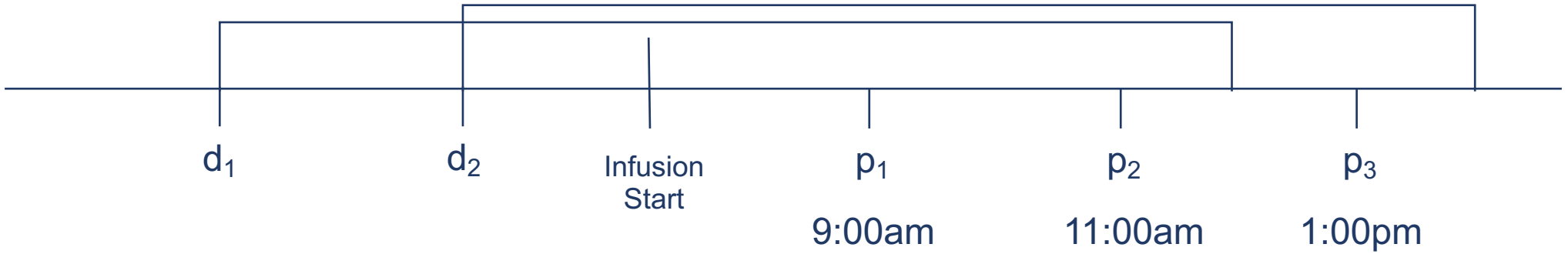

e_{10}^d = [2 3 0]

- the first dose will only be viable for the first two patients while the second will be viable for all three patients. The third dose is not pre-mixed

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OPTIMIZATION MODEL

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

$$E_i^d[\text{Waste Cost}] = c_d \sum_{n=1}^{m_d} P_d(n,i) \qquad E_i^d[\text{Saved Wait}] = \Delta_d \sum_{n=1}^{m_d} [1 - P_d(n,i)]$$

Parameters

Δ_d: the value of savings of drug $d \in D$ *(i.e., $(p_{d1}+p_{d2})$ *dollar value of patient waiting time*

c_d: the cost of drug d

p_{ds}: the time it takes to process drug d at stage s

m_d: the number of doses needed for each drug d

$P_d(n,i)$: probability of wasting the n does of drug d drug

Sets

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

E_d: set patient eligibility vectors for all $d \in D$

Variables

$$a_i^d = \begin{cases} 1 & \text{if we select patient eligibility vector } i \in E \text{ for drug } d \in D \\ 0 & \text{o. w.} \end{cases}$$

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

$$\boldsymbol{maximize} \sum_{d \in D} \sum_{i \in E} (E_i^d[\text{Saved Wait}] - E_i^d[\text{Waste Cost}]) a_i^d \,,$$

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OPTIMIZATION MODEL CONSTRAINTS

- Only can select one eligibility vector for each drug
- All doses indicated in vector must be made if eligibility vector is selected
- All doses must be made within the time bounds associated with the eligibility vector

OPTIMIZATION MODEL CONSTRAINTS (CONT.)

- Limited number of pharmacists for verification
- Limited number of techs for drug compounding
- No preemptions allowed
- Must complete drug once started

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COMPUTATIONAL EXPERIMENTS

- How large is our integer linear program (i.e., number of variables and constraints)?
- What is the computational time needed to generate inputs and solve the model?
- How granular should we discretize time and still maintain a quality solution?

COMPUTATIONAL EXPERIMENTS

- Time discretization cases: 5 min, 2 min, 1 min

- Scenarios
  1. At most one dose of a drug is scheduled
  2. 2-5 doses of a drug are scheduled
  3. 10 doses of each drug scheduled

Note: We run 10 instances of each scenario in each case with a 2 hour time limit as well as a 1% optimality gap

TIME DISCRETIZATION ANALYSIS

Scenario	Case	Number of Variables	Number of Constraints
1	5 min	11118	20930
	2 min	27048	114181
	1 min	53621	438066
2	5 min	11351	21207
	2 min	27358	115191
	1 min	54061	442966
3	5 min	1377780	21668
	2 min	1393749	118996
	1 min	1420388	457244

Scenarios

1. At most one dose of a drug is scheduled
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TIME DISCRETIZATION ANALYSIS

Scenario	Case	Median Load Time (sec)	Median Solve Time (sec)
1	5 min	2	6
	2 min	6	54
	1 min	20	3205
2	5 min	2	10
	2 min	6	460
	1 min	21	3195
3	5 min	6632	85
	2 min	6609	123
	1 min	6628	309

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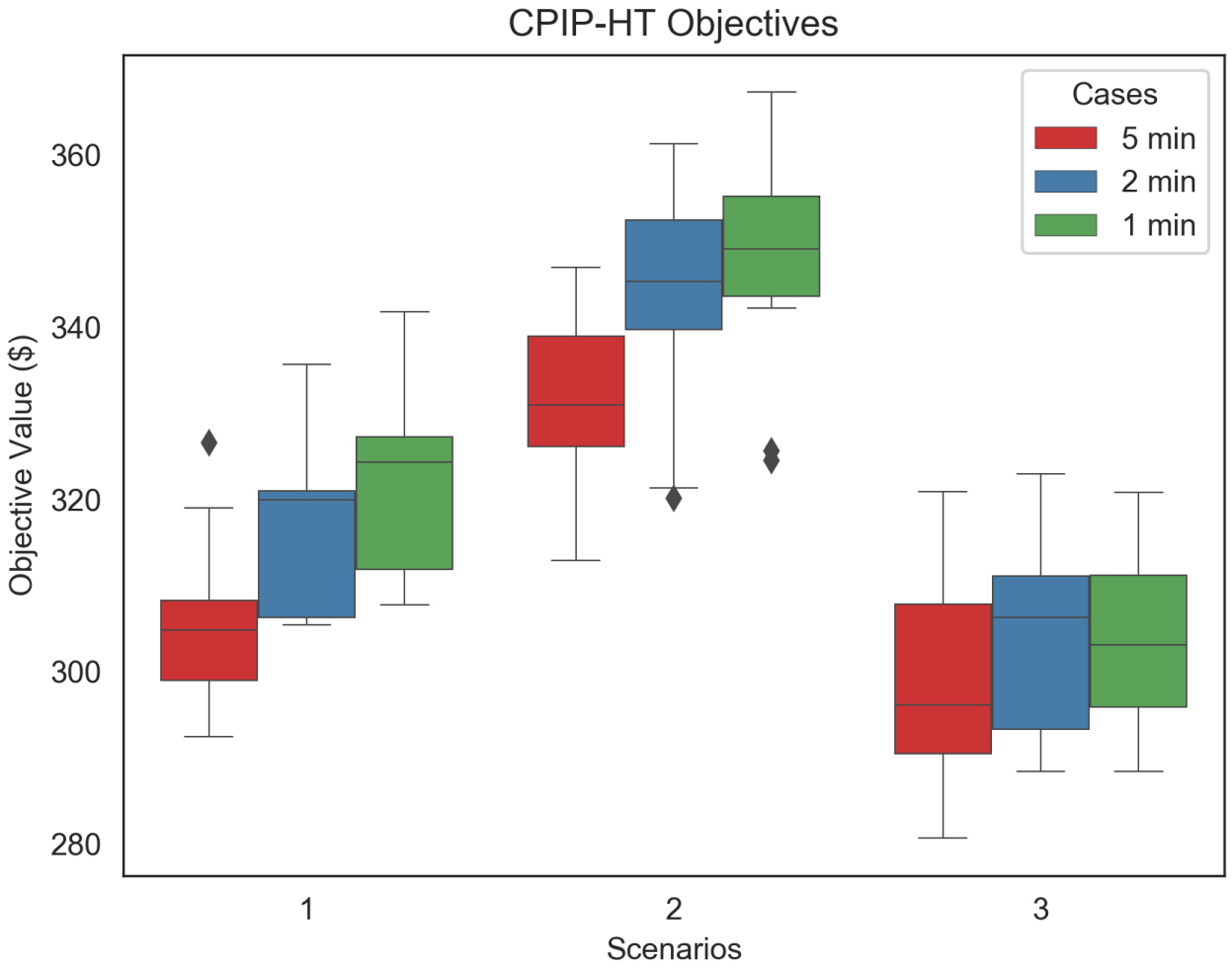
TIME DISCRETIZATION ANALYSIS



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COMPUTATIONAL EXPERIMENTS SUMMARY

- Determined discretizing time to 2 minutes was sufficient for our problem
- Problem size grows at factorial rate but is bounded in practice (i.e., never more than 10 doses of the same drug on a scheduled for a given day)
- Model formulations finds optimal solution providing a conservative estimate on patient wait time saved

CONCLUSIONS/FUTURE DIRECTIONS

- Developed a pre-mix optimization model utilizing the probabilities from the prediction model
- Address time dependencies and interdependences introduced by hang-by time
- Potential next steps include time dependent reward parameter

Thank you!

- Center for Healthcare Engineering and Patient Safety (CHEPS)
- CHEPS Chemo Team
  - Special thank you to Matt See for his hard work these past few years
- UMRCC Collaborators
- Rackham Merit Fellowship
- Bonder Foundation

COUNTING ELIGIBILITY VECTORS

- $Total\ number\ of\ vectors = \sum_{d \in D} \binom{2m_d}{m_d}$ where m_d is the total number of patients scheduled for drug d on a given day

- Given m_d = 2 for a single drug d, we might have the following vectors
  - [0 0], [1,0], [2,0], [1,1], [1,2], [2,2]
  - Total number of vectors = $\binom{4}{2}$ = 6

- However what if we have m_d = 10 then the total number of vectors = $\binom{20}{10} = 184{,}756$