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Capacity Planning for Networks of Stem-cell Donation Centres under Uncertainty

E. Gökalp

Warwick Manufacturing Department, The University of Warwick, Coventry, CV4 7AL, UK.

N. Gülpınar, X. V. Doan

Warwick Business School, The University of Warwick, Coventry, CV4 7AL, UK.

Abstract

Stem-cell transplantation is the last chance for patients of various blood-related diseases. Stem-cell donation centres admit patients in need of a stem-cell transplant and search for a perfect match between the patients and donors. The search process is time-consuming and requires expensive advanced equipments, in particular for DNA typing. In this paper, we are concerned with a capacity planning problem in a network of stem-cell donation centres. The underlying optimization model integrates the operations for a donor search and aims to maximize the number of transplantations. A scenario-based stochastic programming approach is introduced to investigate the effect of the demand and service time variabilities into the capacity planning problem. We consider the maximum possible waiting time during the search process to obtain robust solutions against uncertainties. For this purpose, we approximate the maximum waiting time in the advanced blood testing with a robust queuing approach. The computational experiments are designed to illustrate the performance of the capacity planning model.

Keywords: Health-care modelling, capacity planning, donation centres, stochastic programming.

Email address: Nalan.Gulpinar@wbs.ac.uk (N. Gülpınar)

1. Introduction

Stem-cell transplantation is the infusion or injection of healthy stem-cells to replace diseased or damaged ones (Fruchtman, 2003). This type of transplantation is crucial for the treatment of several blood and immune system illnesses including leukemia. Healthy stem-cells are collected directly from donors' hip bones or separated from donors' blood samples. The collection process normally does not cause any harm to donors, which makes it possible for a large donor database for stem-cells donation to be created. Potential donors can register to be included in the donor database and patients requiring stem-cell transplants have the option of conducting a search for matching cells among these potential donors. The stem-cell donor search process usually follows the same standards set by World Marrow Donation Agency (WMDA, 2018) which has 75 accredited registries in 53 countries across the world. Advanced blood-gene tests are then needed to find good matches between potential donors and patients. These tests can only be done in highly specialized histocompatibility and immunogenetics (H&I) laboratories. Within a country, these laboratories are linked with a network of stem-cell donation centres, which is normally managed by the national health authority as in Turkey, China, Spain, and France or some transplantation foundation as in Canada and UK. The stem-cell donation centres support patients in need of stem-cell transplants with donor search procedures and advanced blood-gene tests. Although recent advances in data management may speed up initial steps of the donor search process, the advanced blood testing remains the bottleneck of the whole process given the limited resources for H&I tests at those stem-cell donation centres. It is therefore important to efficiently allocate resources in terms of capacity planning for these stem-cell donation centres within the national network.

The main objective of the stem-cell donation centres is to find in time as many good matches as possible for patients who need stem-cell transplants. In general, life expectancy of patients waiting for a stem-cell transplant is short (Odejide, 2014); in other words, the probability of patient death or being not suitable for the transplantation due to the deterioration in their medical condition during the search is high. Therefore, the processing time to search for the best match is the most crucial factor for the survival of these patients (Heemskerk et al., 2005; Dini et al., 2000). For a donation centre with over-utilized testing capacity, the search process generally takes longer and the number of patient deaths is likely to increase (Oudshoorn et al., 2006). For example, in Turkey, around 70 out of 1000 patients die over a year due to the lack of suitable stem-cell donations (Beksac, 2014). Diler et al. (2008) suggest that the national network of Turkish stem-cell donation centres needs to be restructured and the resources for advanced testing should be increased to decrease the number of patient deaths. It shows that the network structure of stem-cell donation centres also plays an important role in supporting their main performance objective of increasing the number of successful transplants. Another study

by Heemskerk et al. (2005) shows that in Netherlands, although the matching probabilities for patients has increased with a larger donor database, the total number of (successful) transplantations is still significantly affected by long search durations. This indicates that to achieve the main performance objective of increasing the number of successful transplants, it is important for stem-cell donation centres to improve search durations with effective capacity planning. In this paper, we are concerned with a capacity planning problem for networks of stem-cell donation centres, which aim to achieve the best overall performance in terms of the number of successful transplants while taking into account their search operations.

The search operations conducted by stem-cell donation centres depend on several uncertain factors including patient arrivals and waiting times for advanced blood tests. The final outcomes of these search operations rely on test results as well as health conditions of patients. These uncertain factors need to be fully considered since their variabilities may result in excessive waiting times and poor utilization of facility resources (Salzarulo et al., 2011). In this paper, we propose a novel approach which combines both stochastic programming and robust optimization techniques to handle the capacity planning problem for networks of stem-cell donation centres under uncertainty. More specifically, our contributions and the structure of the paper are as follows:

(1) In Section 2, we model complex search operations of stem-cell donation centres and their outcomes using a scenario-based stochastic programming approach in which patient arrivals and test results are represented with appropriate scenarios.

(2) In Section 3, we approximate waiting times for advanced blood tests using a robust optimization model for queuing systems. We reformulate the (non-linear) capacity planning problem as a mixed-integer linear optimization problem.

(3) Finally, in Section 4, we introduce design of experiments and data generation. In Section 5 we provide numerical results to demonstrate the performance of our approach as compared to that of existing policies. We also analyze effects of different parameters such as patient arrival rates on the performance of stem-cell donation centres.

Related Literature

Capacity planning concerns the utilization of available resources to meet demands for products or services and it is an important and challenging problem in healthcare management given the limited resources of staff, hospital beds, and specialized medical equipment among others. In addition, uncertain factors such as patient

demands, staff availability, and medical results make the capacity planning problem in healthcare more challenging. Different modelling and solution approaches have been widely used to solve capacity planning problems under uncertainty for healthcare operations management. In this section, we will briefly review these approaches and how uncertainty is handled in healthcare capacity planning applications and also explicitly state how our approach is different from the existing ones.

Queuing theory, a modelling approach to obtain performance measures in queuing systems, has been widely applied for the capacity planning of healthcare services; a related review can be found in Fomundam and Hermann (2007). Creemers and Lambrecht (2009) use built-in queuing formulas to find the number of servers, i.e., capacity level, required to achieve a certain degree of performance. Hulshof et al. (2013) use the queuing theory to model the elective patient admission process and study the resource allocation problem for hospitals with uncertain treatment pathways. They consider different queues for different types of services with time-dependent capacity levels of resources. Similarly, Cochran and Roche (2009) apply the queuing theory to test various capacity design alternatives to be used in real time when the capacity cannot meet the demand. Bretthauer et al. (2011) consider the capacity planning problem for healthcare operations with blocking between different units. Castillo et al. (2009) determine capacity and location of healthcare facilities using queuing models with exponential service times and poisson arrivals. By considering time-varying demands in hospitals, Green et al. (2007) analyze the staffing requirement in hospitals based on queuing analysis. The main drawback of queuing models comes from their intractability due to nonlinear formulations of performance metrics under certain distribution assumptions for arrival and service processes.

Simulation is an alternative approach to model the service systems when the queuing formulations are not useful due to their complexities. Harper et al. (2010) introduce a discrete-event simulation model to analyze the operations management of an intensive care unit and use the data generated by the simulation approach to solve the stochastic optimization model which computes the optimum number of nurses required to achieve the service targets. De Angelis et al. (2003) consider simulation optimization to determine the capacity of a transfusion centre under multiple objectives: cost minimization to achieve a fixed waiting time and minimization of waiting time under a limited budget. The queuing system is modelled with a discrete-event simulation and the objective functions are approximated by function fitting with data generated by the simulation model. Similarly, Alfonso et al. (2013) model processes in a blood collection unit with a simulation-based approach. They evaluate possible blood-collection server configurations from a cost-effectiveness perspective. Although simulation is very useful to model complex systems, it can only provide approximate solutions that are affected by the bias of data generation.

Optimization models in healthcare capacity planning focus not only on single hospital or department but also the interconnection between departments and hospitals, which usually has significant effects on the overall performance. Several studies focus on this interconnection in different capacity planning problems modelled for networks of hospitals or departments. Flessa (2000) develops a model to allocate resources in the preventive and curative services in hospitals. The deterministic optimization model distributes a fixed budget among different institutions based on the expected patient arrivals. Stummer et al. (2004), Govind et al. (2008), Santibanez et al. (2009) and Gunes et al. (2010) focus on the location and number of beds in hospitals within a network to minimize operation cost and maximize patient utility. Also, they consider the patient flows either at the unit level or regional level to find the optimum bed/staff capacities. The parameters in these problems such as patient arrivals are assumed to be deterministic. Mahar et al. (2011) study a different capacity planning problem for specialized services such as imaging or neonatal intensive care services and identify which hospitals in a network should offer these specialized care services.

The hospital network capacity planning models developed in the literature are not directly applicable to modelling of search operations within stem-cell donation centres. The stem-cell donation centres have distinctive and complex operations, making the problem novel in this sense. Besides, the capacity planning model introduced in this paper incorporates the queuing theory that has not been widely studied in the network capacity planning under uncertainty, apart from Pehlivan et al. (2012) and Asaduzzaman et al. (2010) which incorporate queuing formulas into the optimization model. Pehlivan et al. (2012) develop a mixed-integer optimization model to determine the capacity of maternity facilities in a network in view of uncertain patient arrivals and service times. The objective is to minimize the number of refused admissions which is formulated by using available queuing formulations. They assume the interarrival and service times are exponentially distributed. They also minimize the cost of reorganizing the available capacity. They do not consider a scenario-based programming to model other uncertainties in the model. On the other hand, Asaduzzaman et al. (2010) develop a queuing model to find the optimum capacities of neonatal centres to minimize refusal and overflow probabilities. They also assume exponential interarrival and service times. Besides, they do not develop an optimization model but rather a simulation model which is used to compute expected performance measures for different capacity combinations. In this paper, we employ a novel robust approach to derive the maximum waiting time in a queuing system. The resulting nonlinear integer formulation is then approximated as a linear integer model that can be solved by exact methods.

2. Stochastic Capacity Planning Model

In this section we first present problem description and underlying model assumptions, and then introduce mathematical formulation of the stochastic capacity planning problem.

2.1. Problem Descriptions and Assumptions

We consider a network of stem-cell donation centres managed and financially supported by a central authority. There are usually several stem-cell donation centres located strategically within a country which aim to support regional patients effectively without causing long-distance travel for these patients. As mentioned previously, capacities for advanced blood testing at these donation centres significantly affect the transplantation outcomes and the central authority needs to allocate resources efficiently with respect to these capacities to maximize the overall performance.

Given the network of stem-cell donation centres, patients who need a stem-cell transplant have to register with a donation centre, usually their regional one. The search operations start with an online database search for potential donors who possess the same blood characteristics as those of the patient. A number of suitable donors is contacted to provide blood samples for advanced blood tests. These tests can take place when the blood samples are delivered to the donation centre. Patients need to wait for results of these blood tests and waiting times depend significantly on testing capacities of donation centres. If the advanced blood tests result in a good matching between the patient and a potential donor, a transplantation can take place, assuming that the patient is still well enough after waiting for results of those advanced blood tests. Otherwise, an international search might be initiated as the final stage of the search process. In this case, the search operations are completed with or without a transplantation depending on the outcome of the international search and health conditions of the patient.

The search process emphasizes that capacities for advanced blood tests at donation centres play an important role in determining overall performance of the network. It is crucial to determine appropriate service capacities for all stem-cell donation centres within the network, especially when several uncertain factors need to be taken into account. Before introducing the mathematical formulation of the capacity planning problem for the network of these stem-cell donation centres, we shall discuss all assumptions needed for the model development.

Assumption 1 (Donor Database). *The online search process for potential donors uses the same national donor database for all patients. Over the planning horizon, although there might be an increase in the donor database level, we assume that the probability of a successful match remains unchanged. According to Muller et al. (2003), for a significant increase in the probability of a successful match (such as 0.01), there should be a very significant increase in the donor database level (such as 100,000). In reality, the increase in the donor database level is usually significantly less, e.g., the Turkish national donor database only reaches the level of 30,000 donors after 30 years, Savran-Oguz (2013).*

Assumption 2 (Advanced Blood Tests' Completion Time). *A donor search at the national level is terminated only when the advanced blood tests for all suitable donors are completed regardless of their outcomes. Recall that a transplantation can be conducted only when a good match from suitable donors is found (Antony Nolan, 2017). Having said that, there might be a better match resulting from subsequent tests of blood samples of other donors. In addition, the first matched donor may not be available (for medical and non-medical reasons such as no-shows) and there should be back-up donors (Walraven et al., 2005). Technically, this assumption with the consideration of the longest possible completion time also fits into the worst-case approach that we are going to consider later in the proposed model.*

Assumption 3 (International Search). *In general, an international search starts only after the results of all advanced blood tests are revealed. However, for cases where the medical situation of a patient is very critical, an international search may start as soon as the patient is admitted. Although these special cases are not taken into account in the proposed model, the problem formulation can be easily modified to incorporate the medical condition of a patient. In addition, we assume that the international search is an independent process. The advanced blood tests of blood samples to be collected from suitable international donors, are assumed to be conducted at their own centres. It is worthwhile to mention that these tests of international donors might be done at the stem-cell donation centre where the patient is registered. For the sake of simplicity, these cases are omitted in the problem formulation.*

Assumption 4 (Unmatched Patients). *Unmatched patients, i.e., those patients with unsuccessful national and international search operations, might return to the system for new searches. We shall consider these patients as new arrivals in the proposed model given that in practice, they should wait for a certain period of time for donor databases to be updated with new donors. During that waiting period, we assume that these patients would consider other available therapies before being considered again (Weisdorf et al., 2002).*

Assumption 5 (Patient's Remaining Lifetime). *Health conditions of patients affect the outcome of donor searches since they need to be well enough for transplantation when a good match is found. Most of the patients seeking transplants have critical health conditions. In the proposed model, we shall use patient's remaining lifetime as the main factor to determine whether a transplant could take place after a good match is found. Given a particular patient, his/her random remaining lifetime can only be estimated by doctors and for registered patients who are still alive after the searches, their actual remaining lifetimes are still unknown. In other words, one can only obtain probabilistic information of a patient's remaining lifetime given his/her conditions. We, therefore, assume that this random remaining lifetime factor is represented by a known probability distribution for each patient as a part of patient data in the proposed model.*

2.2. Problem Formulation

We consider the capacity planning problem over a planning horizon for a network consisting of J stem-cell donation centres. The planning horizon is discretized into T time periods. For example, each time period might correspond to one week in practice while the planning horizon lasts for one year with $T = 52$. Throughout the paper, uncertain parameters are indicated by a tilde $\tilde{}$.

Let $\tilde{I}_j$ denote the number of patients who arrive to centre j, $j = 1, \cdots, J$, during the planning horizon. There can be a single or a batch arrival of patients in any time period. For each patient i, $i = 1, \cdots, \tilde{I}_j$, suppose that there are $\tilde{p}_{ij}$ suitable donors found from the online search. These candidate donors are then invited to supply blood samples for further advanced blood tests. Let $\tilde{t}_{ijk}$ denote the time between the arrival of patient

i to centre j and the arrival of blood samples of his/her candidate donor k, $k = 1, \cdots, \tilde{p}_{ij}$, for advanced blood tests.

Let x_j be the decision variable representing the capacity for advanced blood tests at centre j, $j = 1, \cdots, J$. One unit of capacity consists of one specialized equipment for advanced blood tests and all personnel needed to operate the equipment. Given this capacity x_j, let $\widetilde{W}_{ijk}(x_j)$ represent the waiting time before blood samples of donor k of patient i can be tested. It is clear that these waiting times directly depend on the capacity of the centre and the number of blood samples which have already arrived. $\widetilde{W}_{ijk}(x_j) = 0$ if there are available capacities when the blood samples of donor k arrives; otherwise, $\widetilde{W}_{ijk}(x_j) > 0$.

We introduce $\tilde{o}_{ijk}$ to represent the duration of advanced blood tests for blood samples of donor k of patient i at centre j. Note that, even though the variation in durations of these tests is usually small in practice and it might be ignored completely without any significant impact, we still consider these durations to be uncertain so that the proposed model can be as general as possible. We can compute the completion time $\tilde{u}_{ijk}(x_j)$ of advanced blood tests for blood samples of donor k of patient i since his/her arrival as follows:

$$\tilde{u}_{ijk}(x_j) = \tilde{t}_{ijk} + \tilde{o}_{ijk} + \widetilde{W}_{ijk}(x_j). \tag{1}$$

Now, let's define $\tilde{r}_{ij}$ and $\tilde{z}_{ij}$ to represent the search results obtained by the national and international sources, respectively, for patient i admitted to centre j. If at least one blood test result is positive, then $\tilde{r}_{ij}$ takes 1. If the results of all blood tests are negative, then $\tilde{r}_{ij}$ is assigned to 0. Similarly, if the search using international sources for patient i is successful, then $\tilde{z}_{ij}$ takes 1; otherwise, it takes 0. If a search at the international level is never initiated, then it is fixed at zero ($\tilde{z}_{ij} = 0$). Let $\tilde{v}_{ij}$ denote the duration of the international search for patient i admitted to centre j if the search is needed. Note that under Assumption 3, the international search is an independent process, which does not depend on capacities of (national) donation centres.

Given all these information, we are interested in computing how long it takes to obtain a good match for patients. Let $\tilde{d}_{ij}(x_j)$ be the time duration from the admission of patient i to centre j until a suitable match is found. If at least one positive outcome from the national search is achieved, i.e., $\tilde{r}_{ij} = 1$, then we have: $\tilde{d}_{ij}(x_j) = \max\limits_{k=1,\cdots,\tilde{p}_{ij}} \{\tilde{u}_{ijk}(x_j)\}$. Note that under Assumption 2, the final national search result is obtained when advanced blood tests of all candidate donors of the patient are completed. On the other hand, if no suitable match is found from the national search ($\tilde{r}_{ij} = 0$) but the international search is successful ($\tilde{z}_{ij} = 1$), then clearly, $\tilde{d}_{ij}(x_j) = \max\limits_{k=1,\cdots,\tilde{p}_{ij}} \{\tilde{u}_{ijk}(x_j)\} + \tilde{v}_{ij}$. If both national and international searches are unsuccessful ($\tilde{r}_{ij} = \tilde{z}_{ij} = 0$), there is no suitable match found for the patient, which means $\tilde{d}_{ij}(x_j) = +\infty$. Under Assumption 4, the unmatched patients will be considered as new arrivals when new searches are initiated again later for them.

Finally, the case $\tilde{z}_{ij} = \tilde{r}_{ij} = 1$ never occurs since a search at the international level for patient i is only initiated after no suitable donor is identified from the national search as stated in Assumption 3. The computation of $\tilde{d}_{ij}(x_j)$ can be summarized as follows:

$$\tilde{d}_{ij}(x_j) = \begin{cases} \max\limits_{k=1,\cdots,\tilde{p}_{ij}} \{\tilde{u}_{ijk}(x_j)\}, & \text{if } \tilde{r}_{ij} = 1, \\ \max\limits_{k=1,\cdots,\tilde{p}_{ij}} \{\tilde{u}_{ijk}(x_j)\} + \tilde{v}_{ij}, & \text{if } \tilde{r}_{ij} = 0 \ \& \ \tilde{z}_{ij} = 1, \\ +\infty, & \text{if } \tilde{r}_{ij} = \tilde{z}_{ij} = 0. \end{cases} \tag{2}$$

A successful search process (at either national or international level) leads to a transplant if the patient is still alive when the search process is completed. Suppose that $\tilde{l}_{ij}$ is the random remaining lifetime of patient i, which is estimated with a complete probability distribution φ_{ij} as indicated in Assumption 5, when s/he is admitted to centre j. Let $\tilde{y}_{ij}(x_j)$ be the indicator of whether the search for patient i admitted to centre j is unsuccessful with no transplant taken place. We have:

$$\tilde{y}_{ij}(x_j) = \begin{cases} 1, & \text{if} \quad \tilde{d}_{ij}(x_j) > \tilde{l}_{ij}, \\ 0, & \text{otherwise.} \end{cases}$$

Given these indicators, the number of searches conducted at centre j resulting in no transplant can then be computed as $\sum\limits_{i=1}^{\tilde{I}_j} \tilde{y}_{ij}(x_j)$. We are now ready to formulate the capacity planning problem.

The integer decisions which the central authority needs to make are the capacities $x_j \in \mathbb{Z}^+$ for advanced blood tests at donation centres $j = 1, \cdots, J$. The overall performance of the network of stem-cell donation centres can be measured by the total expected number of successful transplants (the higher the better) or equivalently, the expected number of unsuccessful searches without transplants (the lower the better). Given that the network of stem-cell donation centres is managed by a central authority, there are several constraints (imposed by the central authority) that need to be addressed in the model. One of the important constraints is the budget constraint. For the budget B and the unit cost C_j of managing specialized equipment and personnel at each centre j, $j = 1, \cdots, J$, the budget constraint can be simply stated as $\sum\limits_{j=1}^{J} C_j x_j \leq B$. We will discuss some of these constraints in detail in Section 5 but for now, we assume that the vector of decision variables $\boldsymbol{x} = (x_1, \cdots, x_J)$ belongs to a general feasible set $\mathcal{X}$, $\boldsymbol{x} \in \mathcal{X}$. For example, if only the budget constraint is considered, the feasible set $\mathcal{X}$ is written as $\mathcal{X} = \left\{ \boldsymbol{x} \,\middle|\, \sum\limits_{j=1}^{J} C_j x_j \leq B;\ x_j \in \mathbb{Z}^+,\ j = 1, \cdots, J \right\}$. The general stochastic capacity planning model SCP for a network of stem-cell donation centres can then be formulated as

follows:

$$\text{SCP:} \quad \min \quad \sum_{j=1}^{J} \mathbb{E}\left[\sum_{i=1}^{\tilde{I}_j} \tilde{y}_{ij}(x_j)\right],$$
$$\text{s.t.} \quad \boldsymbol{x} \in \mathcal{X}.$$

The expectation in the objective function depends on several uncertain factors mentioned above. In order to capture these uncertain factors which arise in the real-life operations of a stem-cell donation network, we introduce a finite number of discrete scenarios (or so-called cases), each of which represents a possible future realization of random patient arrivals and search results. In general, these scenarios can be generated by using past data and statistics. Let S denote the total number of scenarios. Each scenario s, $s = 1, \cdots, S$, displays a sequence of patient arrivals with the corresponding probability ω_s where $\sum_{s=1}^{S} \omega_s = 1$. The notation used for a specific scenario s along with the operational diagram is illustrated in Figure 1.

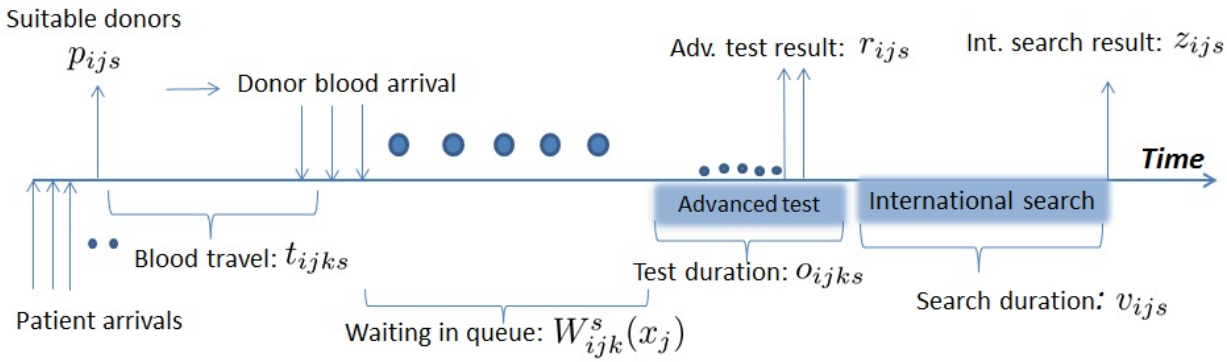


Figure 1: A description of search operations along with notation used for scenario s.

There are I_{js} patients arriving to centre j, $j = 1, \cdots, J$, during the planning horizon in scenario s for $s = 1, \cdots, S$. For each patient i, $i = 1, \cdots, I_{js}$, number of candidate donors identified from the initial online search is p_{ijs}. Blood samples of candidate donor k, $k = 1, \cdots, p_{ijs}$, of patient i arrive to centre j after t_{ijks} time periods. The waiting time is $W^s_{ijk}(x_j)$ for these blood samples of candidate donor k before they are tested. The duration of advanced blood tests for these blood samples is o_{ijks} whereas v_{ijs} is the duration of internal search for patient i at centre j under scenario s. In addition, the search results obtained by the national and international sources are denoted by r_{ijs} and z_{ijs}, respectively, for patient i in centre j under scenario s. Finally, the probability distribution of the random remaining lifetime $\tilde{l}_{ijs}$ of patient i at centre j under scenario s is set to be φ_{ijs}. Given these data inputs for each scenario s, $s = 1, \cdots, S$, we can compute $\tilde{y}_{ijs}(x_j)$, the indicator whether the donor search conducted at centre j for patient i is unsuccessful with no transplant, as follows:

$$\tilde{y}_{ijs}(x_j) = \begin{cases} 0, & \text{if } \max\limits_{k=1,\cdots,p_{ijs}} \{t_{ijks} + o_{ijks} + W^s_{ijk}(x_j)\} - \tilde{l}_{ijs} < 0 \ \& \ r_{ijs} = 1, \\ 0, & \text{if } \max\limits_{k=1,\cdots,p_{ijs}} \{t_{ijks} + o_{ijks} + W^s_{ijk}(x_j)\} + v_{ijs} - \tilde{l}_{ijs} < 0 \ \ \& \ \ r_{ijs} = 0 \ \& \ z_{ijs} = 1, \\ 1, & \text{otherwise.} \end{cases} \tag{3}$$

We can then state the scenario-based stochastic capacity planning model SCP_{scen} as follows:

$$\begin{aligned} \text{SCP}_{\text{scen}}: \quad & \min \quad \sum_{s=1}^{S} \omega_s \sum_{j=1}^{J} \sum_{i=1}^{I_{js}} \mathbb{E}_{\varphi_{ijs}}[\tilde{y}_{ijs}(x_j)], \\ & \text{s.t.} \quad \boldsymbol{x} \in \mathcal{X}. \end{aligned}$$

In order to solve the SCP_{scen} model, we need to compute $\mathbb{E}_{\varphi_{ijs}}[\tilde{y}_{ijs}(x_j)]$, which involves computation of waiting times $W^s_{ijk}(x_j)$. The exact computation of waiting times in each scenario given capacity $\boldsymbol{x}$ is difficult due to complexity of the queuing system resulting from the search operations. The computational intractability due to combinatorial number of calculations has already been proven for a queuing system of multiple servers with exponential arrivals and general service time distribution (Tijms et al. 1981). In the next section, we shall approximate waiting times with a robust optimization model for queuing systems and develop a tractable approximate model for the scenario-based stochastic capacity planning problem SCP_{scen}.

3. Approximate Capacity Planning Model with Robust Queuing Theory

Given the difficulty of computing individual waiting times exactly, one can consider the average waiting time instead. However, capacity planning decisions based on average waiting times can cause severe delays when there are more patient arrivals than average. In this proposed model, we will approximate individual waiting times by their maximum waiting time. In this application of stem-cell transplantation, this worst-case approach is reasonable given that it is important to be able to find as many suitable matches as possible in time for patients even in the situations when waiting times are longer than usual. In addition, the approximation approach that we are going to adopt is a parametric approach whose conservativeness level can be handled easily by changing appropriate parameters. We are going to analyze the effect of these parameters in detail in Section 5.

There exist different methods to approximate the maximum waiting time in a queuing system; for instance, see Gupta and Osogami (2011). However, according to Bandi and Bertsimas (2012), these approximations usually do not lead to realistic results when the arrival process follows a distribution different from Poisson. In order to overcome this problem, Bandi and Bertsimas (2012) proposed an alternative method based on robust optimization to approximate the maximum waiting time when the arrival and service times are independent and

identically distributed (i.i.d.) random parameters following an unknown distribution for a first-come first-serve (FCFS) queue with a fixed number of servers x. We now provide a brief overview of this approach and then explain how to apply it in our model.

Let T_k and Y_k represent random interarrival and service times for blood samples $k = 1, \cdots, K$, respectively. Following the robust optimization approach, T_k and Y_k are assumed to belong to uncertainty sets U^{arrv} and U^{serv}, respectively. The structure of these uncertainty sets is inspired from the central limit theorem that asserts asymptotic results for a large set of i.i.d. random variables. Readers are referred to Bandi and Bertsimas (2012) and references therein for more details regarding the motivation of the uncertainty set structures as well as the general robust optimization approach. Moreover, the sizes of these uncertainty sets are determined by parameters Γ^{arrv} and Γ^{serv} that basically measure the variability of interarrival and service times, respectively. The uncertainty set U^{arrv} for interarrival times T_k of samples $k = 1, \cdots, K$ is defined as follows:

$$U^{arrv} = \left\{ (T_1, T_2, \cdots, T_K) \;\middle|\; \frac{\left| \sum_{k=m+1}^{K} T_k - \frac{K-m}{\lambda} \right|}{\sqrt{K-m}} \leq \Gamma^{arrv}, \quad \forall\, m \leq m_0 \right\}, \tag{4}$$

where $1/\lambda$ is the expected interarrival time. According to Bandi and Bertsimas (2012), the parameter m_0 should be selected such that the central limit theorem is valid for the random variables $T_1, \cdots, T_{m_0}$ and a typical value is $m_0 = K - 30$. Similarly, the uncertainty set U^{serv} for service times Y_k of samples $k = 1, \cdots, K$ is

$$U^{serv} = \left\{ (Y_1, Y_2, \cdots, Y_K) \;\middle|\; \frac{\left| \sum_{i=m+1}^{\kappa} Y_{i\cdot x+n} - \frac{\kappa-m}{\mu} \right|}{\sqrt{\kappa-m}} \leq \Gamma^{serv}, \quad \forall\, m \leq \kappa - 1,\ 0 \leq n < x \right\}, \tag{5}$$

where $1/\mu$ is the expected service time and $\kappa = \lfloor K/x \rfloor$. The idea here is that for multi-server queuing systems, the uncertainty set is built with constraints which are constructed based on the central limit theorem separately for each server n, $n = 0, \cdots, x-1$ using κ arrivals assigned to each server from a round-robin allocation of arrivals, hence the indices $(i \cdot x + n)$ for $i = 0, \cdots, \kappa - 1$ in (5) (see Bandi and Bertsimas (2012) and references therein for more details). The following proposition provides an upper-bound $\overline{W}(x)$ for the waiting time $W(x)$ in view of these uncertainty sets for stable queue systems with traffic density $\rho = \dfrac{\lambda}{\mu x} < 1$.

Proposition 1. *(Bandi and Bertsimas, 2012) Assume that the interarrival and service times for a FCFS queue with x servers belong to the uncertainty sets U^{arrv} and U^{serv}, respectively. The upper bound $\overline{W}(x)$ on the waiting time of the queue can be calculated as,*

$$\overline{W}(x) = \frac{\lambda(\Gamma^{arrv} + \Gamma^{serv}/\sqrt{x})^2}{4\big[1 - \lambda/(\mu x)\big]}. \tag{6}$$

Proof. The reader is referred to Bandi and Bertsimas (2012) for its proof and details of parameter estimation. ■

We are ready to use Proposition 1 to approximate the waiting time $W^s_{ijk}(x_j)$ with the upper bound $\overline{W}_j(x_j)$. In order to compute $\overline{W}_j(x_j)$, parameters λ_j, μ_j, Γ^{arrv}_j, and Γ^{serv}_j are derived from scenario data. The arrival sequence of blood samples to each centre in each scenario s, $s = 1, \cdots, S$, can be used to derive their interarrival times while service times, i.e., durations of the advanced blood tests, are already available. λ_j and μ_j are the inverse of expected interarrival time and service time, respectively. Following the suggestion in Bandi and Bertsimas (2012), we set $\Gamma^{arrv}_j = k \cdot \sigma^{arrv}_j$ and $\Gamma^{serv}_j = k \cdot \sigma^{serv}_j$ with $k > 0$, where σ^{arrv}_j and σ^{serv}_j are the standard deviation of interarrival time and service time, respectively. The parameter k acts as an indicator of the conservativeness level of the robust optimization approach we adopt here. The effect of conservativeness level will be further analyzed in numerical experiments in Section 5.

Now, let us define $\tilde{y}'_{ijs}(x_j)$ by replacing $W^s_{ijk}(x_j)$ with $\overline{W}_j(x_j)$ in (3) as follows;

$$\tilde{y}'_{ijs}(x_j) = \begin{cases} 0, & \text{if } \overline{W}_j(x_j) - \tilde{l}_{ijs} + \max\limits_{k=1,\cdots,p_{ijs}} \{t_{ijks} + o_{ijks}\} < 0 \ \& \ r_{ijs} = 1, \\ 0, & \text{if } \overline{W}_j(x_j) - \tilde{l}_{ijs} + \max\limits_{k=1,\cdots,p_{ijs}} \{t_{ijks} + o_{ijks}\} + v_{ijs} < 0 \ \& \ r_{ijs} = 0 \ \& \ z_{ijs} = 1, \\ 1, & \text{otherwise.} \end{cases} \tag{7}$$

Since $\overline{W}_j(x_j) \geq W^s_{ijk}(x_j)$, we have: $\tilde{y}'_{ijs}(x_j) \geq \tilde{y}_{ijs}(x_j)$. Replacing $\tilde{y}_{ijs}(x_j)$ with $\tilde{y}'_{ijs}(x_j)$ in the scenario-based stochastic capacity planning model SCP_{scen}, we obtain the following approximate optimization model

$$\begin{aligned} \text{SCP}_{\text{appx}}: \quad & \min \quad \sum_{s=1}^{S} \omega_s \sum_{j=1}^{J} \sum_{i=1}^{I_{js}} \mathbb{E}_{\varphi_{ijs}}[\tilde{y}'_{ijs}(x_j)] \\ & \text{s.t.} \quad \boldsymbol{x} \in \mathcal{X}. \end{aligned}$$

The model SCP_{appx} is a robust (or safe) approximation of SCP_{scen}, which follows the worst-case principle of robust optimization (Ben-Tal et al. (2009)). The replacement of $W^s_{ijk}(x_j)$ by its upper bound $\overline{W}_j(x_j)$ (and $\tilde{y}_{ijs}(x_j)$ with $\tilde{y}'_{ijs}(x_j)$) covers the worst-case scenario when the waiting times are much longer than average. The conservativeness level of this robust approximation is controlled by the setting of Γ^{arrv}_j, and Γ^{serv}_j and its effects will be analyzed in Section 5. In the rest of this section, we shall focus on

developing further the approximate model SCP_{appx}, especially on how to represent the expectation $\mathbb{E}_{\varphi_{ijs}}[\tilde{y}'_{ijs}(x_j)]$ with detailed information of the probability distribution φ_{ijs}, as follows.

Let $\Theta_{ijs} = \{\underline{l}_{ijs}, \cdots, \bar{l}_{ijs}\}$ be the support set of the (discrete) probability distribution φ_{ijs} and define $q_{ijs}(w) = \Pr(\tilde{l}_{ijs} = w)$ for $w \in \Theta_{ijs}$. Note that the planning horizon is discretized; therefore, discrete distributions are appropriate to be considered for patients' random remaining lifetimes. For the sake of convenience,

we introduce random parameters

$$\tilde{l}'_{ijs} = \tilde{l}_{ijs} - \max_{k=1,\cdots,p_{ijs}} \{t_{ijks} + o_{ijks}\} \text{ and } \tilde{l}''_{ijs} = \tilde{l}_{ijs} - \max_{k=1,\cdots,p_{ijs}} \{t_{ijks} + o_{ijks}\} - v_{ijs},$$

with the corresponding support sets $\underline{\Theta}_{ijs} = \{\underline{l}'_{ijs}, \cdots, \overline{l}'_{ijs}\}$ and $\overline{\Theta}_{ijs} = \{\underline{l}''_{ijs}, \cdots, \overline{l}''_{ijs}\}$, which can be easily derived from Θ_{ijs}. Similarly, we can define the probability distribution functions for these parameters as $q'_{ijs}(w) = \Pr(\tilde{l}'_{ijs} = w)$ for $w \in \underline{\Theta}_{ijs}$ and $q''_{ijs}(w) = \Pr(\tilde{l}''_{ijs} = w)$ for $w \in \overline{\Theta}_{ijs}$, respectively. Moreover, let's introduce an indicator function as $\psi_j(w) = \mathbb{1}(w > \beta_j)$ for $w \in \underline{\Theta}_{ijs} \cup \overline{\Theta}_{ijs}$, $j = 1, \cdots, J$ and $s = 1, \cdots, S$. Note that a characteristic (indicator) function $\mathbb{1}(\bullet)$ takes 1 if $\bullet$ holds and 0, otherwise.

Proposition 2. *The model SCP_{appx} with discrete distributions of patients' random remaining lifetimes is equivalent to the following integer linear optimization problem $SCP_{ip\text{-}appx}$ with additional binary decision variables τ_{wj} for $j = 1, \ldots, J$, and $w \in \underline{\Theta}_{ijs} \cup \overline{\Theta}_{ijs}$, where $s = 1, \ldots, S$, and $i = 1, \ldots, I_{js}$:*

$$\begin{aligned} SCP_{ip\text{-}appx}: \quad \min_{x_j, \tau_{wj}} \quad & \sum_{s=1}^{S} \omega_s \sum_{j=1}^{J} \sum_{i=1}^{I_{js}} \left(r_{ijs} \sum_{w \in \underline{\Theta}_{ijs}} q'_{ijs}(w)(1 - \psi_j(w)\tau_{wj}) \right) + \\ & \sum_{s=1}^{S} \omega_s \sum_{j=1}^{J} \sum_{i=1}^{I_{js}} \left(z_{ijs} \sum_{w \in \overline{\Theta}_{ijs}} q''_{ijs}(w)(1 - \psi_j(w)\tau_{wj}) + (1 - r_{ijs})(1 - z_{ijs}) \right) \\ s.t. \quad & \boldsymbol{x} \in \mathcal{X}, \\ & \phi_j(w) - x_j \le M(1 - \tau_{wj}), \quad w \in \underline{\Theta}_{ijs} \cup \overline{\Theta}_{ijs}, \quad \forall j,\ s,\ i = 1, \cdots, I_{js}, \\ & \tau_{wj} \in \{0, 1\}, \quad w \in \underline{\Theta}_{ijs} \cup \overline{\Theta}_{ijs}, \quad \forall j,\ s,\ i = 1, \cdots, I_{js}, \end{aligned}$$

where M represents a sufficiently big number and

$$\phi_j(w) = \frac{\left[\Gamma_j^{arrv}\Gamma_j^{serv} + \sqrt{(1-\lambda_j^2)(\Gamma_j^{arrv}\Gamma_j^{serv})^2 + \dfrac{4\lambda_j w}{\mu_j}(4w - \lambda_j(\Gamma_j^{arrv})^2) + 4\lambda_j w(\Gamma_j^{serv})^2} \right]^2}{\left[\lambda_j(\Gamma_j^{arrv})^2 - 4w \right]^2}.$$

Proof.

For clarity of exposition, we rewrite the upper bound $\overline{W}_j(x_j) = \dfrac{\lambda_j(\Gamma_j^{arrv} + \Gamma_j^{serv}/\sqrt{x_j})^2}{4\left[1 - \lambda_j/(\mu_j x_j)\right]}$ on the waiting times at centre j as $\overline{W}_j(x_j) = \dfrac{\beta_j x_j + \gamma_j\sqrt{x_j} + \eta_j}{x_j - \pi_j}$ by setting parameters $\beta_j = \dfrac{(\Gamma_j^{arrv})^2\lambda_j}{4}$, $\gamma_j = \dfrac{\Gamma_j^{arrv}\Gamma_j^{serv}}{2}$, $\eta_j = \dfrac{(\Gamma_j^{serv})^2\lambda_j}{4}$, and $\pi_j = \dfrac{\lambda_j}{\mu_j}$. Then, the expected number of unsuccessful searches becomes

$$\mathbb{E}_{\varphi_{ijs}}[\tilde{y}'_{ijs}(x_j)] = \begin{cases} \Pr\left(\overline{W}_j(x_j) - \tilde{l}_{ijs} + \max\limits_{k=1,\cdots,p_{ijs}} \{t_{ijks} + o_{ijks}\} > 0\right), & \text{if } r_{ijs} = 1, \\ \Pr\left(\overline{W}_j(x_j) - \tilde{l}_{ijs} + \max\limits_{k=1,\cdots,p_{ijs}} \{t_{ijks} + o_{ijks}\} + v_{ijs} > 0\right), & \text{if } z_{ijs} = 1, \\ 1, & \text{otherwise.} \end{cases} \tag{8}$$

From the first two conditions $\overline{W}_j(x_j) - \tilde{l}'_{ijs} > 0$ and $\overline{W}_j(x_j) - \tilde{l}''_{ijs} > 0$ in (8), we obtain the following inequalities: $\frac{(\beta_j - \tilde{l}'_{ijs})x_j + \gamma_j\sqrt{x_j} + \eta_j + \tilde{l}'_{ijs}\pi_j}{x_j - \pi_j} > 0$ and $\frac{(\beta_j - \tilde{l}''_{ijs})x_j + \gamma_j\sqrt{x_j} + \eta_j + \tilde{l}''_{ijs}\pi_j}{x_j - \pi_j} > 0$, respectively. Since $(x_j - \pi_j)$ is always positive due to the traffic intensity condition, we can rewrite (8) as follows;

$$\mathbb{E}_{\varphi_{ijs}}[\tilde{y}'_{ijs}(x_j)] = \begin{cases} \Pr\big((\beta_j - \tilde{l}'_{ijs})x_j + \gamma_j\sqrt{x_j} + \eta_j + \tilde{l}'_{ijs}\pi_j > 0\big), & \text{if } r_{ijs} = 1, \\ \Pr\big((\beta_j - \tilde{l}''_{ijs})x_j + \gamma_j\sqrt{x_j} + \eta_j + \tilde{l}''_{ijs}\pi_j > 0\big), & \text{if } z_{ijs} = 1, \\ 1, & \text{otherwise.} \end{cases} \tag{9}$$

Let us define $\xi_j = \sqrt{x_j}$ in order to analyze the first condition in (9). In this case, we have a quadratic function $h(\xi_j) = (\beta_j - \tilde{l}'_{ijs})\xi_j^2 + \gamma_j\xi_j + \eta_j + \tilde{l}'_{ijs}\pi_j$.

- If $\beta_j - \tilde{l}'_{ijs} \geq 0$, then $h(\xi_j) > 0$ since $\gamma_j,\ \xi_j,\ \eta_j,\ \tilde{l}'_{ijs},\ \pi_j$ are all positive.
- On the other hand, if $\beta_j - \tilde{l}'_{ijs} < 0$, then $h(\xi_j) = (\beta_j - \tilde{l}'_{ijs})(\xi_j - \xi_j^+)(\xi_j - \xi_j^-)$, where ξ_j^+ and ξ_j^- are positive and negative roots of $h(\xi_j)$, which can be computed as $\xi_j^+ = \frac{-\gamma_j - \sqrt{\gamma_j^2 - 4(\beta_j - \tilde{l}'_{ijs})(\eta_j + \tilde{l}'_{ijs}\pi_j)}}{2(\beta_j - \tilde{l}'_{ijs})}$ and $\xi_j^- = \frac{-\gamma_j + \sqrt{\gamma_j^2 - 4(\beta_j - \tilde{l}'_{ijs})(\eta_j + \tilde{l}'_{ijs}\pi_j)}}{2(\beta_j - \tilde{l}'_{ijs})}$, respectively. Thus $h(\xi_j) > 0$ is satisfied if and only if $\xi_j = \sqrt{x_j} < \xi_j^+$, which implies that $x_j < (\xi_j^+)^2$. Let's introduce $\phi_j(\tilde{l}'_{ijs}) = (\xi_j^+)^2$, which can be explicitly written as $\phi_j(\tilde{l}'_{ijs}) = \frac{\left(\gamma_j + \sqrt{\gamma_j^2 - 4(\beta_j - \tilde{l}'_{ijs})(\eta_j + \tilde{l}'_{ijs}\pi_j)}\right)^2}{4(\beta_j - \tilde{l}'_{ijs})^2}$. Then we have $x_j < \phi_j(\tilde{l}'_{ijs})$.

As a result, $h(\xi_j) > 0$ in the first probability of (9) is valid only when $\beta_j - \tilde{l}'_{ijs} \geq 0$ or $\beta_j - \tilde{l}'_{ijs} < 0$ and $x_j < \phi_j(\tilde{l}'_{ijs})$. Then we can easily show that

$$\Pr\big((\beta_j - \tilde{l}'_{ijs})x_j + \gamma_j\sqrt{x_j} + \eta_j + \tilde{l}'_{ijs}\pi_j > 0\big) = 1 - \Pr\big(\beta_j - \tilde{l}'_{ijs} < 0,\ x_j \geq \phi_j(\tilde{l}'_{ijs})\big)$$

by using the following relationship between probability functions

$$\Pr\big(\beta_j - \tilde{l}'_{ijs} < 0\big) = \Pr\big(\beta_j - \tilde{l}'_{ijs} < 0,\ x_j < \phi_j(\tilde{l}'_{ijs})\big) + \Pr\big(\beta_j - \tilde{l}'_{ijs} < 0,\ x_j \geq \phi_j(\tilde{l}'_{ijs})\big).$$

By applying the same procedure, equivalent conditions for $(\beta_j - \tilde{l}''_{ijs})x_j + \gamma_j\sqrt{x_j} + \eta_j + \tilde{l}''_{ijs}\pi_j > 0$ in the second probability of (9) are obtained. Moreover, we have

$$\Pr\big((\beta_j - \tilde{l}''_{ijs})x_j + \gamma_j\sqrt{x_j} + \eta_j + \tilde{l}''_{ijs}\pi_j > 0\big) = 1 - \Pr\big(\beta_j - \tilde{l}''_{ijs} < 0,\ x_j \geq \phi_j(\tilde{l}''_{ijs})\big).$$

Then, the expected number of unsuccessful searches in view of $\overline{W}_j(x_j)$ for patient i at centre j under scenario s can be computed as follows;

$$\mathbb{E}_{\varphi_{ijs}}[\tilde{y}'_{ijs}(x_j)] = \begin{cases} 1 - \Pr\left(\beta_j - \tilde{l}'_{ijs} < 0, x_j \geq \phi_j(\tilde{l}'_{ijs})\right), & \text{if } r_{ijs} = 1, \\ 1 - \Pr\left(\beta_j - \tilde{l}''_{ijs} < 0, x_j \geq \phi_j(\tilde{l}''_{ijs})\right), & \text{if } z_{ijs} = 1, \\ 1, & \text{otherwise.} \end{cases} \tag{10}$$

that can also be equivalently rewritten as

$$\begin{aligned} \mathbb{E}_{\varphi_{ijs}}[\tilde{y}'_{ijs}(x_j)] \quad = \quad & \left[1 - \Pr(\beta_j - \tilde{l}'_{ijs} < 0,\, x_j \geq \phi_j(\tilde{l}'_{ijs})\right] r_{ijs} + \\ & \left[1 - \Pr(\beta_j - \tilde{l}''_{ijs} < 0,\, x_j \geq \phi_j(\tilde{l}''_{ijs})\right] z_{ijs} + (1 - r_{ijs})(1 - z_{ijs}). \end{aligned}$$

Under the general lifetime distribution assumption, probabilities in (10) are calculated as

$$\begin{aligned} \Pr\left(\tilde{l}'_{ijs} > \beta_j,\, x_j \geq \phi_j(\tilde{l}'_{ijs})\right) &= \sum_{w \in \underline{\Theta}_{ijs}} {q'}_{ijs}(w) \mathbb{1}(w > \beta_j,\, x_j \geq \phi_j(w)) \\ &= \sum_{w \in \underline{\Theta}_{ijs}} {q'}_{ijs}(w) \mathbb{1}(w > \beta_j) \mathbb{1}(x_j \geq \phi_j(w)) \\ &= \sum_{w \in \underline{\Theta}_{ijs}} {q'}_{ijs}(w) \psi_j(w)\ \mathbb{1}(x_j \geq \phi_j(w)), \end{aligned} \tag{11}$$

and

$$\begin{aligned} \Pr\left(\tilde{l}''_{ijs} > \beta_j,\, x_j \geq \phi_j(\tilde{l}''_{ijs})\right) &= \sum_{w \in \overline{\Theta}_{ijs}} {q''}_{ijs}(w) \mathbb{1}(w > \beta_j,\, x_j \geq \phi_j(w)) \\ &= \sum_{w \in \overline{\Theta}_{ijs}} {q''}_{ijs}(w) \mathbb{1}(w > \beta_j) \mathbb{1}(x_j \geq \phi_j(w)) \\ &= \sum_{w \in \overline{\Theta}_{ijs}} {q''}_{ijs}(w) \psi_j(w)\ \mathbb{1}(x_j \geq \phi_j(w)). \end{aligned} \tag{12}$$

In order to express $\mathbb{1}(x_j \geq \phi_j(w))$, we introduce binary variable τ_{wj} for $w \in \underline{\Theta}_{ijs} \cup \overline{\Theta}_{ijs}$ and patient $i = 1, \cdots, I_{js}$ under scenario $s = 1, \cdots, S$ such that

$$\tau_{wj} = \begin{cases} 1, & \text{if } x_j \geq \phi_j(w), \\ 0, & \text{otherwise.} \end{cases}$$

This relationship can be formulated as a set of constraints using the big M approach;

$$\phi_j(w) - x_j \leq M(1-\tau_{wj}),\ \ w \in \underline{\Theta}_{ijs} \cup \overline{\Theta}_{ijs},\ \ j=1,\cdots,J,\ \ i=1,\cdots,I_{js},\ \ s=1,\cdots,S.$$

The expected number of unsuccessful searches $\mathbb{E}_{\varphi_{ijs}}[\tilde{y}'_{ijs}(x_j)]$ in view of generally distributed life expectancy of patients can be computed as

$$\begin{aligned}\mathbb{E}_{\varphi_{ijs}}[\tilde{y}'_{ijs}(x_j)] = &\sum_{s=1}^{S}\omega_s\sum_{j=1}^{J}\sum_{i=1}^{I_{js}}\left(r_{ijs}\sum_{w\in\underline{\Theta}_{ijs}} q'_{ijs}(w)(1-\psi_j(w)\tau_{wj})\right)+\\ &\sum_{s=1}^{S}\omega_s\sum_{j=1}^{J}\sum_{i=1}^{I_{js}}\left(z_{ijs}\sum_{w\in\overline{\Theta}_{ijs}} q''_{ijs}(w)(1-\psi_j(w)\tau_{wj})+(1-r_{ijs})(1-z_{ijs})\right).\end{aligned} \tag{13}$$

The stochastic capacity planning problem SCP_{appx} can then be reformulated as the stated integer (linear) programming model $\text{SCP}_{\text{ip-appx}}$ with $\phi_j(w)$ represented using the original parameters of Γ_j^{arrv}, Γ_j^{serv}, λ_j, and μ_j instead of β_j, γ_j, η_j, and π_j for all $j=1,\ldots,J$.

■

The reformulation presented in this proposition is an integer linear optimization model if $\mathcal{X}$ is specified by linear constraints in $\boldsymbol{x}$: i.e., $\mathcal{X}$ is polyhedral. In addition to integer decision variables $\boldsymbol{x}$, there are additional binary decision variables τ_{wj}, whose total number depends on the number of patients arriving at the donation centres in each scenario as well as the size of supports of distributions of patients' random remaining lifetimes. Computationally, the resulting optimization models with polyhedral $\mathcal{X}$ can be solved with standard optimization solvers such as CPLEX solver. In the next section, we will focus on those integer linear optimization models resulting from polyhedral $\mathcal{X}$ in our computational experiments.

4. Design of Computational Experiments and Input Data

We design a series of computational experiments in order to illustrate performance of the capacity planning model for a network of stem-cell donation centres. The integer (linear) optimization model $\text{SCP}_{\text{ip-appx}}$ with polyhedral $\mathcal{X}$ is implemented in IBM ILOG CPLEX and solved by the CPLEX solver. All computational experiments are carried out on a laptop with Windows XP operating system, CPU 2.26GHz Intel Core i5 and 8GB of RAM. We can report that the CPU time taken to solve the underlying optimization model with any size of network and parameter specifications specified in our computational experiments is at most 5 minutes. A discrete event simulation model is developed in Matlab to validate the results obtained from the stochastic capacity planning optimization model $\text{SCP}_{\text{ip-appx}}$.

For numerical experiments, we start with a two-centre network, which is based on the current existing network in Turkey with two stem-cell donation centres located in Istanbul and Ankara. A planning horizon is set for one year with $T = 350$ one-day time periods. Data for this two-centre network are gathered from different sources such as published research papers in the literature as well as interviews with staff from Istanbul Faculty of Medicine, Istanbul University. Table 1 shows a description of input data used for numerical experiments and the corresponding sources from where the data are obtained.

Table 1: Input data for model parameters used in the numerical experiments

Description of Parameters	**Value/Range**	**Source of Data**	**Distribution**
Patient arrival rates for two centres, respectively	2 and 1.5 patient/day	Kibank (2016)	Exponential
Probability of finding a perfect match via national and international sources, respectively	0.12 and 0.4	Querol et al. (2009a)	Binomial
International search duration	[25, 165] days	Querol et al. (2009a)	Uniform
Travel time of donors (samples)	[5, 15] days	Interviews	Uniform
Average service (blood-testing) time	5 days	DYBMS (2015)	Uniform
Number of donors found by initial search	[0, 6] donors	Interviews	Uniform
Patients' remaining lifetime distributions	Uniform	Salomon et al., (2001)	Uniform
Lower bound of remaining lifetime distribution	[40, 45] days	Costa et al. (2007)	Uniform
Range of remaining lifetime distribution	[30, 70] days	Costa et al. (2007)	Uniform
Variabilities (σ) of interarrival and service times	0.5 and 0.015	Interviews	–

Based on information provided in Table 1, we generate $S = 200$ scenarios with equal probabilities (i.e., $\omega_s = 1/S$, $s = 1, \cdots, S$) as input to the optimization model. In addition, we randomly generate 2000 scenarios to use for out-of-sample tests. Note that in these computational experiments, we assume that *remaining patient lifetimes* follow uniform (discrete) distributions as suggested by Salomon et al. (2001). Each patient has a different uniform distribution for his/her random remaining lifetime whose lower bound and range are generated randomly. As shown in Table 1, these two parameters also follow uniform distributions.

As suggested by Bertsimas and Bandi (2012), the interarrival time variability (Γ^{arrv}) is set to three times of the standard deviation in the generated interarrival times, i.e., $k = 3$. Similarly, the service time variability (Γ^{serv}) is set to the three times of the standard deviation in the generated service times.

For the feasible set $\mathcal{X}$, we impose the simple budget constraint in most of the computational experiments, i.e., $\mathcal{X} = \left\{ \boldsymbol{x} \,\middle|\, \sum_{j=1}^{J} C_j x_j \leq B;\ x_j \in \mathbb{Z}^+,\ j = 1, \cdots, J \right\}$, as discussed before. We normalize the unit cost to 1\$/day, i.e., $C_j = 1$ for all $j = 1, \ldots, J$. According to [29], the estimated total capacity of the two-centre network in Turkey is 100. We shall initially set the budget to 100\$, which can cover for that estimated total capacity of the considered network. The effect of budget on the performance of the network will be analyzed in the next section.

5. Numerical Results

In this section, we present the numerical results to illustrate performance of the proposed capacity planning model and effects of various model parameters on capacity decisions and total number of successful searches.

5.1. Performance of Capacity Planning Strategies

We solve the model $\text{SCP}_{\text{ip-appx}}$ with data generated as discussed. The results show that there should be $x_1^* = 55$ capacity units for advanced blood tests in the first centre and $x_2^* = 45$ units in the second centre given the budget. The expected number of successful searches is 230 out of 700 expected patient arrivals (32.8%) at the first centre throughout the planning horizon and 200 out of 525 (38.10%) at the second centre. The bound on the longest waiting time in both centres is 28 days. Using these capacity settings, we simulate the operations of the given two-centre network with out-of-sample data. Figure 2 displays relative frequency histograms of the longest waiting time for test results (left plot) and the number of successful searches (right plot) using out-of-sample data for the first donation centre. Similar results are obtained for the second centre.

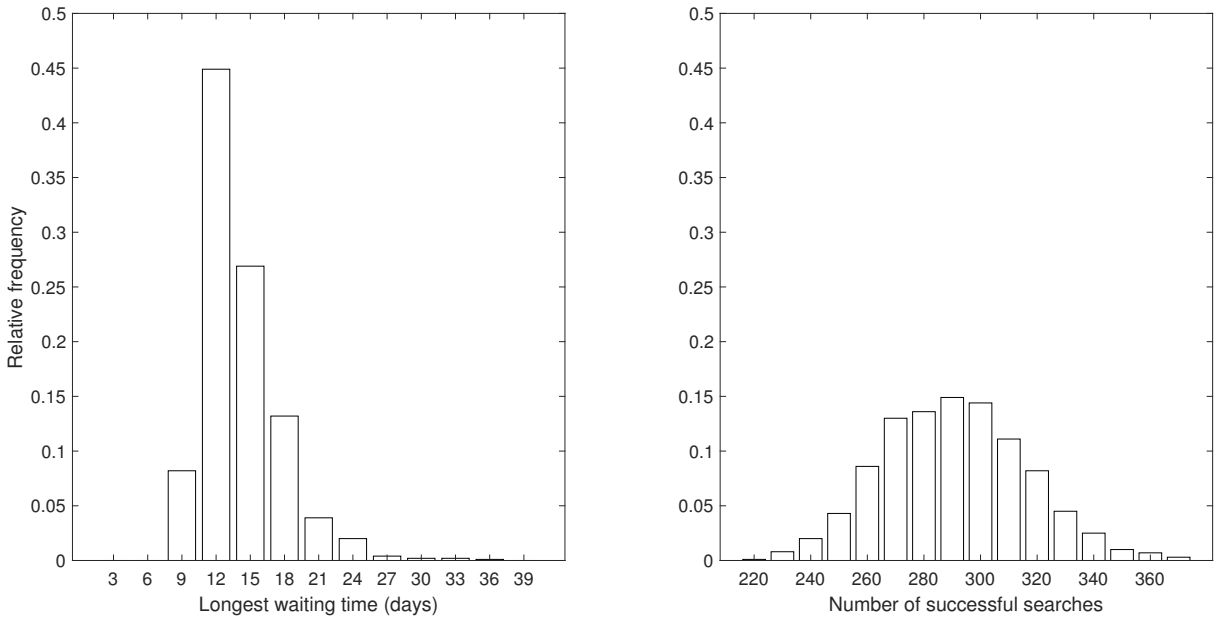


Figure 2: Histograms of the longest waiting time (left) and the number of successful searches (right) obtained at a stem-cell donation centre using the out-of-sample data

The results show that the actual longest waiting time is 36 days as compared to the upper bound of 28 days (based on Bandi and Bertsimas (2012)) in the optimization model. This implies that there are out-of-sample scenarios that do not belong to uncertainty sets used in the optimization model. As shown in Figure 2, the number of such scenarios with longer waiting times is very small. We will show later that the effect of these

scenarios with longer waiting times (i.e., outliers) on the performance is not very significant when uncertainty sets are appropriately selected. As compared to the expected number of successful searches of 249 obtained from the optimization model, the actual number of successful searches ranges from 211 to 368 with the mean of 284. It shows that the proposed optimization model with robust approximation of waiting times is a good robust (or safe) approximation model for the capacity planning problem in the out-of-sample test.

The proposed model $\text{SCP}_{\text{ip-appx}}$ can accommodate a more general feasible set $\mathcal{X}$. To demonstrate this aspect of the model, we construct a larger instance of the network with five stem-cell centres. Note that in reality, larger networks exist in other countries such as UK and Italy that have four and seventeen centres, respectively, and the Turkish policy makers also plan to increase the number of stem-cell donation centres in Turkey to better serve patients in remote areas of the country (Diler et al., 2008). For this instance, the centres are assumed to be located in five geographically different areas in Turkey. The interarrival rates to donation centres are determined based on the population of regions as 1, 1, 0.75, 0.5, and 0.25 patient/days, respectively. All other model parameters remain the same as specified in Table 1.

We now introduce additional constraints to be included in the model. For the given network instance with five donation centres, there might be concerns about staff availability in some (remote) regions. Generally, we can impose the following additional constraints

$$\sum_{r \in R_n} x_r \leq H_n, \; n = 1, \cdots, K, \tag{14}$$

to indicate that there is a certain capacity limit H_n in each region n which covers all stem-cell centres in the set R_n, $n = 1, \cdots, K$. For the given instance, we consider a single region of $R_1 = \{1, 2\}$ with capacity limit $H_1 = 50$. The optimal capacities of stem-cell centres without staff constraints are obtained as {26, 28, 21, 15, 10} with the total expected number of successful search of 460. On the other hand, with the staff capacity constraint for R_1, the capacities of stem-cell centres are found as {25, 25, 21, 17, 12} with the total expected number of successful search of 413. Figure 3 shows the histograms of the total number of successful searches achieved from the network with/without the additional staff capacity constraint. This case clearly illustrates that the additional constraint can affect the performance of the network in terms of successful searches.

The results above demonstrate how the proposed model $\text{SCP}_{\text{ip-appx}}$ can handle additional constraints, which results in different optimal capacity planning solutions. Even with only the simple budget constraint, the optimal solutions obtained from the proposed model are not easy to determine or approximate due to the non-linearity of waiting time functions. An intuitive heuristic for the capacity planning problem is to allocate the budget

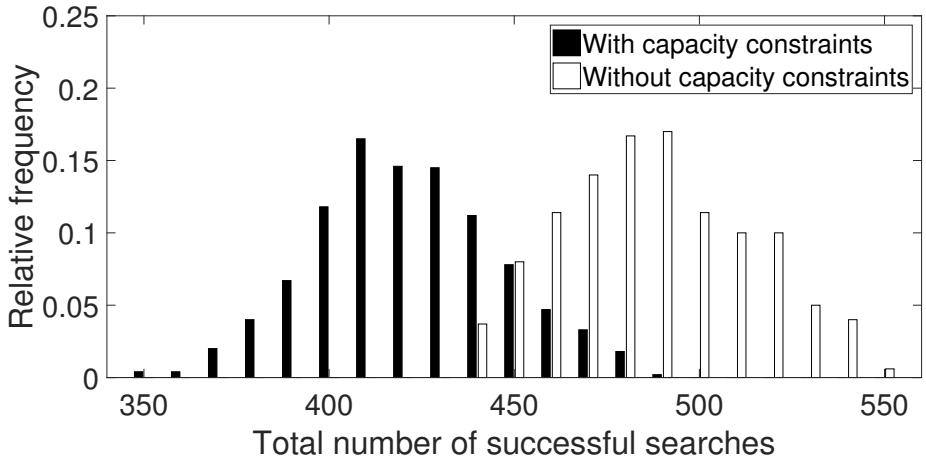


Figure 3: Histograms of total number of successful searches obtained by the optimization model with/without additional capacity constraint using out-of-sample data

among the centres according to patient arrival rates. More precisely, given the budget constraint $\sum_{j=1}^{J} x_j \leq B$ with normalized unit costs, the heuristic solutions are obtained as $x_j^H \approx \lambda_j B \cdot \left(\sum_{j=1}^{J} \lambda_j\right)^{-1}$ for $j = 1, \cdots, J$. Applying this heuristic to the given instance of the network with five centres, we obtain the capacity planning solutions as $\{29, 29, 21, 14, 7\}$ for five centres.

The performance of network in terms of total number of successful searches is presented in Figure 4. From performance comparison of the heuristic and optimization based approaches, we observe that the solutions obtained from the proposed model is indeed better than the heuristic solutions. In other words, the optimal capacities found by the proposed optimization model provide higher number of successful searches than those obtained by the heuristic approach. The relationship between capacity and patient arrival rate is in general more complicated than the simple linear relationship assumed by the heuristic approach. This relationship is better captured in the proposed optimization model using the non-linear relationship between (approximate) waiting time and patient arrival rate as shown in (6). It provides a possible explanation why the proposed model performs better than the heuristic approach.

Overall, the numerical experiments so far show that the proposed model $\text{SCP}_{\text{ip-appx}}$ is appropriate for the capacity planning problem and also capable of handling additional constraints and better than the ad-hoc heuristic which allocates the budget based on arrival rates of patients to stem-cell donation centres.

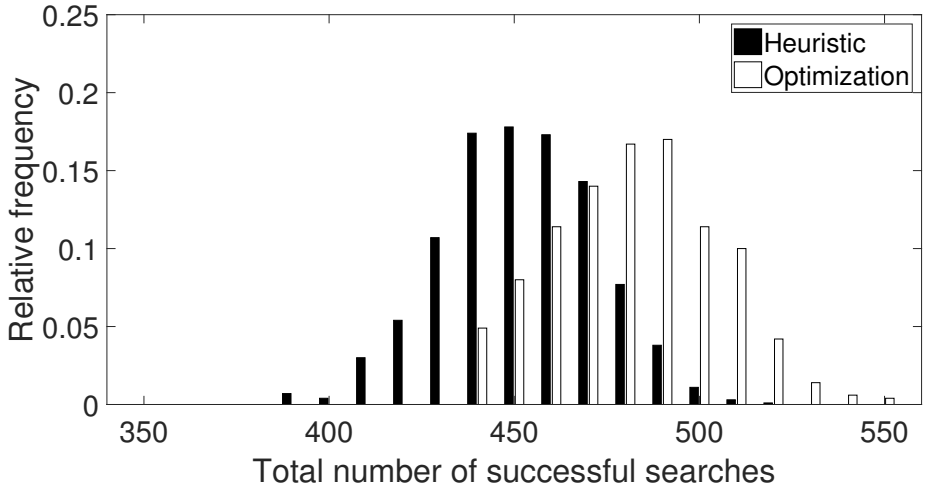


Figure 4: Histograms of total number of successful searches obtained by the optimization and heuristic approaches using out-of-sample data

5.2. Impact of Model Parameters

We now focus on impacts of various model parameters on the performance of capacity planning solutions obtained from the proposed model. The numerical results are reported for instances of the network with two centres and the simple budget constraint. We start with the daily budget by varying it from \$70 to \$120. We present the optimal capacities of individual (two) centres as well as the total capacity of the whole network of centres given at different budgets in Figure 5 (left). The results indicate that for small budgets, the first centre (with higher patient arrival rate) seems to be more important as it keeps being allocated with additional budgets. When the budget is large enough, the focus is then shifted to the second centre. One possible explanation is that the performance of centres with higher patient arrival rates in terms of waiting time is much worse than that of centres with lower patient arrival rates when the capacity is low given the non-linear relationship between capacity and patient arrival rates. It is therefore preferable in these situations to first improve the performance of centres with higher patients arrival rates if additional budgets are available.

Figure 5 (right) also shows the box plots of total number of successful searches obtained by the optimization model at different budgets using out-of-sample data. The performance of the network measured in terms of the number of successful searches improves significantly with the increase of the budget (as total budget is increased from \$70 to \$90) when the budget is small. The improvement becomes less significant when the budget is sufficiently large. It indicates that large budget is not necessarily preferable and the decision makers need to select an appropriate level of budget by taking into account how it affects the overall performance.

As discussed in Section 3, the variability parameters (denoted by Γ^{arrv} and Γ^{serv}) define the conservativeness of the underlying uncertainty sets for random interarrival and service times used to find upper bounds of waiting

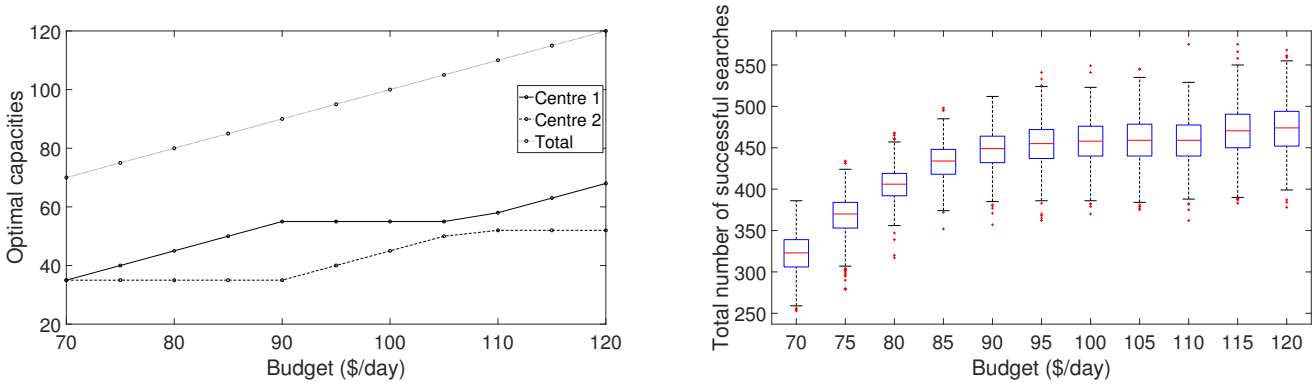


Figure 5: Impact of total budget on optimal capacities of the two-centre network (left) and number of successful searches (right)

times in the proposed optimization model. In other words, a larger variability corresponds to more conservative uncertainty set since they cover a larger number of corresponding realizations. In this experiment, we vary the ratio k from 0.5 to 5 and set accordingly $\Gamma^{arrv} = k \cdot \sigma^{arrv}$ and $\Gamma^{serv} = k \cdot \sigma^{serv}$. Note that when $k = 5$, the uncertainty sets cover almost all possible realizations of interarrival times and service times. We present the optimal capacities of two centres obtained from the proposed model for varying values of k in Figure 6 (left). When $0.5 \leq k \leq 2.5$, more capacities are allocated to the first centre (with higher patient arrival rate), which might be due to the fact that two uncertainty sets concentrate more on two nominal scenarios, which are different in terms of patient arrival rates. The capacity solutions remain the same when $k \geq 2.5$. Figure 6 (right) also shows the box plots of total number of successful searches for different variabilities of uncertainty sets determined by k. There is a significant improvement in terms of number of successful searches when k increases from 1.0 to 1.5. For large k values, given that the capacity solutions remain the same (or very similar), the optimization model displays similar performance in terms of number of successful searches. These results indicate that there is no need to consider very large uncertainty sets in general to achieve good performance given that (a small percentage of) scenarios with long waiting times (i.e., outliers) would not significantly affect the overall expected number of successful searches.

Next, we test our proposed model with different settings for uniform distributions of remaining lifetime. In this case, the minimum lifetime and lifetime range are varied. New scenarios are generated to build uncertainty sets (200 scenarios) and to carry out-of-sample tests (1000 scenarios) in each settings. Even though the capacity solutions remain the same in all settings, the overall performance of the network changes. Figure 7 shows the box plots of the total number of successful searches for different settings of minimum lifetime and lifetime range of patients. The results indicate that the higher the lower bound is, the better the performance is achieved given that the whole range of remaining lifetime is shifted. Similarly, the larger the range is, the better the

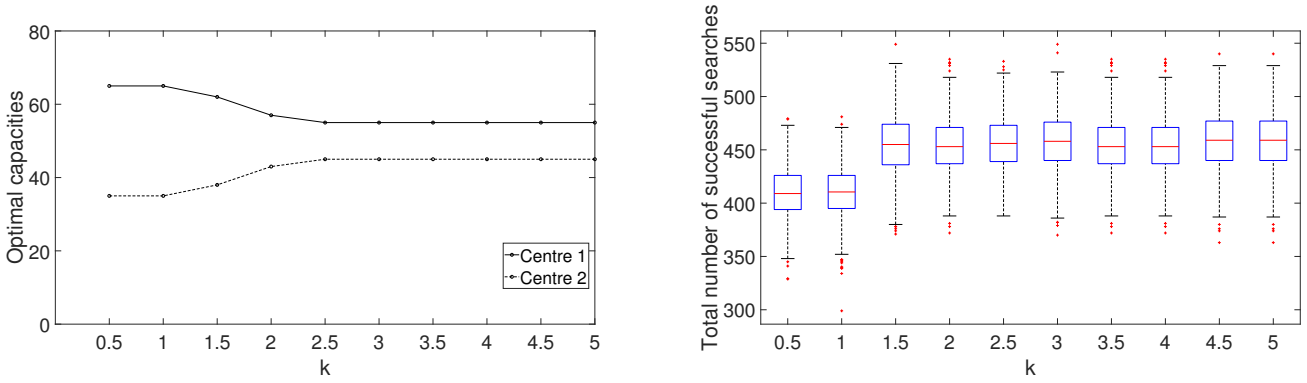


Figure 6: Impact of conservativeness of uncertainty sets for random interarrival and service times on optimal capacities of the two-centre network (left) and number of successful searches (right)

performance is obtained, but the effect is less significant since the minimum lifetime remains the same.

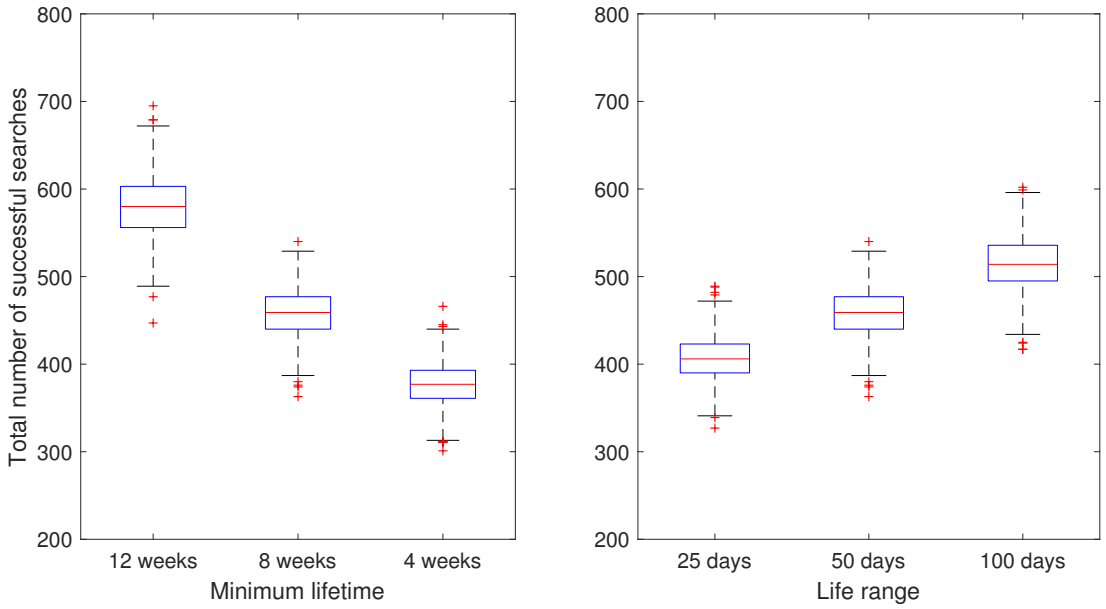
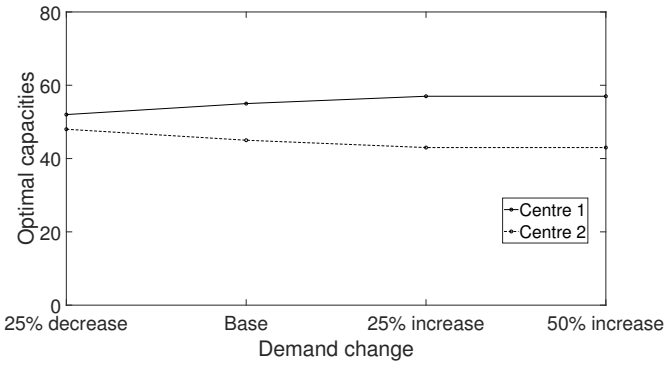


Figure 7: Box plots of the total number of successful searches for different settings of patient's remaining lifetime distribution using out-of-sample data

Finally, we would like to illustrate performance of the proposed capacity planning model at increasing patient arrival rates. We change the patient arrival rates for both centres and use them to generate 200 scenarios, which in turns, are used to build the uncertainty sets. Similarly, 1000 scenarios are generated again for out-of-sample tests. Figure 8 (left) shows the optimal capacities of two centres in response to the changes in the patient arrival rates. The results indicate that when the arrival rates of both centres increase, more capacities are allocated to the first centre to achieve good performance. We also present the box plots of the rate of successful searches for different patient arrival rates using out-of-sample data in Figure 8 (right).



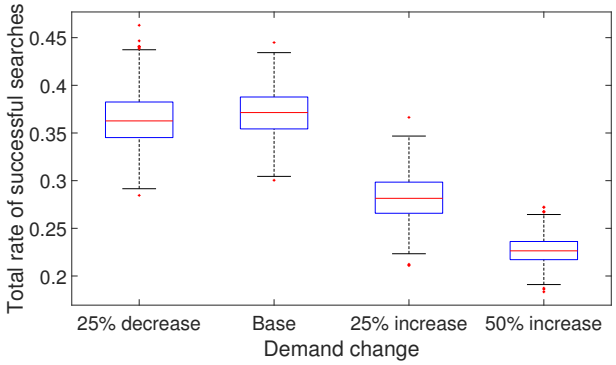


Figure 8: Impact of varying patient arrival rates on optimal capacities of the two-centre network (left) and number of successful searches (right)

Rates instead of total number of successful searches are used given that when the patient arrival rates change, the total number of patient arrivals is also changed accordingly. The results show that when the patient arrival rates increase, the rate of successful searches decreases significantly. This implies that the total budget should be increased to improve the performance of the network if patient arrival rates are increased.

6. Conclusions

Stem-cell donation centres serve patients with an urgent need of stem-cell transplantation. The search process for a suitable stem-cell donor consists of several steps and requires time-consuming and expensive advanced blood tests. In this paper, we propose an optimization model with robust queuing approximation for the capacity planning problem faced by these stem-cell donation centres which takes into account several uncertain factors such as unknown distributions of patient arrivals and service times.

The computational experiments show that the proposed optimization model is appropriate for the capacity planning problem and flexible enough to incorporate additional practical constraints. The model performs better than the simple heuristic that allocates the budget based on arrival rates. The sensitivity analysis demonstrates that the conservativeness of the model can be controlled by the variabilities of patient arrivals and service times set by decision makers. The numerical results illustrate that patient remaining lifetime mainly affects the performance of the network. Although the increase in patient arrival rates affects both capacity solutions and performance of the network of stem-cell centres, an increase in the total budget might be needed to improve the overall performance the network in such cases. On future work, robust queuing approximation could be considered in other relevant applications and the proposed optimization model could be further developed to address other practical constraints in real case studies.

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