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CLINICAL TRIAL SIMULATION: MODELING AND PRACTICAL CONSIDERATIONS

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ABSTRACT

As clinical trials are increasingly globalized with complex footprints over hundreds of sites worldwide, sponsors and contract research organizations constantly seek to make better and faster decisions on their investigational products, and drug supply planning must evolve to ensure efficient, effective supply chain for every study. This endeavor is challenging due to unique characteristics of multi-center trials including randomization schemes for multiple treatment arms, finite recruitment target (that is, across all sites, only a finite number of subjects need be satisfied) and uncertainty in recruitment rates, etc. Simulation has great potential for being the ideal tool which companies can utilize to make better decisions with considerations to both supply chain risks and costs. To achieve this goal, it is important to understand the specifics of clinical trial supply chains. Built upon this knowledge, our paper provides an advanced tutorial on modeling and practical considerations in clinical supply simulation.

1 INTRODUCTION

Preventing drug overages while ensuring that patients receive the right medication at the right time is challenging, especially as clinical trials become more and more global and complex. Indeed, unique characteristics such as random patient enrollment, study designs (stratification and randomization) and dropouts can induce many uncertainties in clinical supply planning. These uncertainties lead to two inherent risks in the supply chains. First, the upstream supply chain can have stock-out if the patient enrollment is faster than predicted, which may take weeks to months to replenish from the central warehouse. Second, the downstream supply chain can be out of stock, and must wait for replenishment from upstream, which takes a couple of days to replenish.

Certainly, these risks of stock-out could be alleviated by maintaining an excessive amount of drug throughout the supply chain. However, while keeping inventory is necessary to cover demand variability, having too much inventory can result in costly overage, particularly with increasingly expensive investigational and comparative drugs. Another possibility is to increase the frequency of shipments; in this case,

shipping costs may become a major drain on resources. Thus, to better mitigate the aforementioned risks, it must be a joint effort between transportation logistics and inventory allocation.

For decades, common approaches to drug supply planning employed by pharmaceutical companies have involved largely deterministic calculations using averages and different ad hoc techniques (Anisimov 2009), while uncertainty is not modelled explicitly. In recent years, some companies have advocated the use of simulation for patient recruitment and drug supply planing. But, this undertaking is only outlined in white papers with no technical details (Bonate 2000; Holford et al. 2010).

In the academic literature, there exist a few simulation models (Peterson et al. 2004; Abdelkafi et al. 2009; Chen et al. 2012) that address the challenges in clinical supply planning. The first paper is due to Peterson et al. (2004). The authors searched for acceptable trigger and order-up-to levels at sites while controlling the risk of stock-out. They assume that throughout recruitment, patient arrivals follow stationary Poisson processes with known rates. This assumption is restrictive and has certain drawback since estimation of site enrollment rates before trial commencement tends to be inaccurate (see, e.g., Patel et al., 2014). Further, brute-force Monte Carlo simulation can be computationally expensive and known to be unscalable in high dimensions. To tackle this issue, Anisimov (2009, 2010) incorporated advanced statistical modeling of patient recruitment and prediction into the process of supply planning. In particular, using the Poisson-Gamma recruitment model, he generated predictions on the number of randomized patients and then computed the respective amount of supply to cover demand at some given risk level. However, these papers mainly focus on the tactical planning phase, while operational details have not been explored.

The combination of Poisson-Gamma demand and multi-echelon inventory model has been applied in other contexts. Specifically, our problem setting is somewhat related to previous work done for service parts where inventory is reviewed continuously in time. For a thorough review, we refer the readers to Zipkin (2000) and Muckstadt (2005). One seminal work in this stream of research is by Sherbrooke (1968) on managing inventory for recoverable items for the United States Air Force. Due to the unknown compound Poisson demand rates, the author used a Gamma prior on the mean demand rate and proposed an approximation procedure for the distribution of backorders at the base-depot in a two-echelon distribution system when one-for-one ordering policies are used. Notable improvement upon this approximation is the two-moment approximation by Slay (1984) who proposed a recursive formula for computing the mean and variance of the number of expected backorders. All aforementioned work focusing on one-for-one ordering policies and batch ordering policies, which account for economies of scale, have drawn limited attention.

Poisson-Gamma demand, in connection with periodic review policy and multi-echelon model, was investigated by Zacks, Fennell (1972, 1974) and Zacks (1974). The authors presented the asymptotically optimal inventory allocation for a two-echelon multi-station system to minimize the total expected discounted cost of ordering for any finite planning horizon, while assuming the lead-time is the same across locations. Regardless of the type of inventory control systems (continuous or periodic review), there exists no extension for general multi-echelon systems with demand updates. Moreover, service level constraints on the basis of Poisson-Gamma demand have never been studied in the literature. Most importantly, the existing models all consider an infinite time horizon with unlimited resupply opportunities where demand must be satisfied as much as possible.

The drug supply planning in clinical trials calls for a new variation of the Bayesian multi-echelon inventory models where we only need to satisfy a target number of demand from all downstream locations. In particular, this feature gives rise to a transient supply chain which terminates when the recruitment target is reached (see Section 2) and, consequently, brings significant changes to classical inventory models (1) the inventory policy needs to be time-dependent (2) service levels cannot be evaluated in steady-state. Another level of complexity is due to block randomization when each patient is assigned to different treatment arms given by a pre-generated list. Because of these unique characteristics, we are not aware of any existing model in multi-echelon inventory research that can be applicable to this class of problems. In this paper, we focus on development of a decision-making tool using multi-echelon inventory models to incorporate the unique features of multi-center clinical studies.

The remainder of this tutorial is organized as follows. In Section 2, we present an overview of clinical trials, explaining key challenges for supply planning process, and outline a simulation framework with demand updates and respective inventory control. In Section 3, we provide a brief description of the Poisson-Gamma model and emphasize its suitability to modeling of patient recruitment in clinical trials. In Section 4, we discuss the multi-echelon structure of the supply network and point out suitable inventory policies for different randomization schemes. In Section 5, we highlight unresolved research questions and possible extensions of clinical trial supply planning.

2 CLINICAL TRIAL OVERVIEW

The drug development process involves an extended sequence of steps, including discovery and development, animal trials, clinical trials, the Food and Drug Administration (FDA) review, as well as post-market safety monitoring. Coupled with many risks and uncertainty, it can take many years and a significant expense to bring a new drug to market. This figure could be up to $ 2.6 billions according to an estimate released by the Tufts Center for the Study of Drug Development (see, e.g., Avorn 2015). Clinical trials alone constitute nearly one half of costs for the development process.

Clinical trials, as mandated by FDA, are designed to evaluate the effectiveness and safety of drugs or medical devices. They are done in four primary phases. Phase I tests the drug on healthy volunteers or people with the disease/condition for dose-ranging. Phase II further tests the drug on patients for efficacy and side effects. Phase III aims to provide the definitive assessment on the efficacy results from a large group of patients, and to monitor adverse effects of the treatment. Assuming success in Phase III, a drug is approved for commercialization and then Phase IV is put in place for safety surveillance to help detect any rare or long-term adverse effects.

As clinical trials are increasingly globalized with complex footprints over hundreds of sites worldwide, sponsors constantly seek to make better and faster decisions on their treatments, and drug supply planning must evolve to ensure efficient, effective supply chain for each and every study (Rowland and McMahon 2004; Thiers et al. 2008). Despite the increasing effort to reduce wastage in the industry, a recent statistic from 200 clinical trials shows that clinical supply overage remains high at 62% (Durr 2017). This is especially undesirable since spending by pharmaceutical companies is already under public scrutiny due to rising drug prices. In contrast, clinical supply shortages could delay the time-to-market of the candidate, jeopardizing patent exclusivity and associated revenue.

The global clinical trial supply chains are complex and span many regions and countries. In particular, clinical supplies need to be stocked, shipped, replenished through a multi-echelon network of central, regional depots, and local sites. Under enrollment uncertainty, it is critical to ensure that inventory be produced in sufficient quantity to meet demand, and be properly positioned in the supply chain to satisfy incoming patients. In what follows, we highlight key challenges in drug supply planning process faced by sponsors and clinical research organizations (CROs).

2.1 Unique Characteristics of Clinical Trial

Drug supply planning for multi-center trials is posed with many challenges due to unique features in clinical studies including unknown demands in patient recruitment, block randomization designs, and enrollment stopping rules. A brief explanation on these concepts follows.

(C1) *Unknown recruitment rates:* Consider a trial where the recruitment starts in a clinical center when this center is initiated and there are no patients waiting for the trial before the study begins. In real trials, the recruitment rates vary across the centers and cannot be predicted with certainty.

(C2) *Block randomization designs:* Randomization is one of the key elements in a clinical trial design. It is carried out with the purpose of allocating patients to treatments randomly, preserving study blindness and achieving balance in the number of patients on treatment arms. The choice of randomization affects the power of statistical tests and the amount of drug supply required to satisfy

patient demand. The properties of imbalance caused by using permuted block randomization were studied in Anisimov (2011), Anisimov et al. (2017).

(C3) *Enrollment stopping rules:* In clinical trials, a common stopping rule is based on predefined recruitment target, S, which is the necessary sample size for the study. The calculation of the sample size requires the combined knowledge of experienced biostatisticians and physician-researchers. It is an essential part of protocol design and must be specified prior to trial commencement. Once the target is reached, recruitment is closed, and no more patients will be enrolled in the trial.

To mitigate the aforementioned challenges, a recent survey of pharmaceutical executives conducted by Pharma IQ (see, Jacob and Jaucot 2018) emphasizes the importance of patient enrollment prediction to supply planning. Indeed, to alleviate risk of running out of stock due to poor demand forecasting, study sponsors tend to overproduce and oversupply depots and centers. Despite a variety of modeling choices for patient recruitment modeling (see, e.g., Heitjan et al. 2015; Anisimov 2016), there seems to be a disconnect between demand forecast and supply planning for multi-center trials. Thus, this tutorial aims to provide an operational planning framework for drug supply in multi-center trials, driven by advanced stochastic modeling of patient recruitment, to balance key important metrics (KPI), that is, to reduce the amount of unused drug while maintaining an acceptable level of stock-out risk for any patient.

2.2 Supply Chain Considerations

In the literature, clinical supply decisions are often calculated based on the assumption that the patients' arrival rates are known (see, e.g., Fleischhacker et al. 2015; Zhao et al. 2018). A potential drawback to this approach is that inaccurate estimates on arrival rates will almost surely lead to poor supply planning. With the newly developed Bayesian approach for patient recruitment modeling by Anisimov and Fedorov (2007) and Anisimov (2009, 2011), we can have a much better plan for clinical supply since estimates on arrival rates are progressively improved over time. Further, the Bayesian approach can enable seamless translation to drug supply prediction via closed-form formulas and, hence, giving rise to an analytic-based simulation.

- *Poisson-Gamma model:* The Poisson model is used in conjunction with a gamma distribution of the recruitment rates and can be viewed as a mixed Poisson model in the empirical Bayesian setting. This approach allows modeling of complex demand in clinical trials and has been validated on large-scale studies (see, e.g., Anisimov and Fedorov 2007). In particular, it can capture the variation in recruitment over time and in recruitment rates between centers.
- *Dynamic inventory policy:* The finite patient horizon brings about the "end-of-horizon" effect, that is, as soon as the target number of patients is met, all future demand vanishes. This effect calls for a dynamic inventory policy based on the stage of recruitment, in that the stock levels should decrease towards the end of recruitment. Poisson-Gamma model facilitates planning at the initial stage based on prior estimate of recruitment rates and allows efficient learning of demand over time and Bayesian re-estimation of recruitment rates as real recruitment data becomes available.

Besides the previously mentioned considerations, there might be other aspects pertaining to a study that could be included in the simulation. For example, patients' visit schedule, expiry dates, etc. can also affect supply planning. These details are provided in the study protocol, i.e., a document that "describe the objectives, design, methodology, statistical considerations and aspects related to the organization of clinical trials" (Guideline for Good Clinical Practice 2001). For more information on clinical trials, we refer the reader to ClinicalTrial.gov, which is one of the largest clinical trials database, holding registrations from over 230,000 privately and publicly funded trials worldwide.

3 PATIENT RECRUITMENT MODELING

To properly plan for drug supply in a multi-center trial, it is crucial to understand the stochastic model of recruitment modeling. Poisson–gamma model offers a very convenient, flexible and realistic approach. It has been validated (Anisimov and Fedorov 2007; Anisimov 2009; Minois et al. 2015, 2017; Minois et al. 2017) for many real trials with large enough numbers of centres for reliable validation results (> 10). In addition, this model allows accurate prediction of drug supply demand at both the design and later stage of a clinical trial utilizing data collected at some interim time. Note that there exists other models for global enrollment for large trials such as the Brownian motion models (Lai et al. 2001; Zhang and Lai 2011; Heitjan et al. 2015); however, these models are not suitable to model enrollment in individual centers (Anisimov 2016), which is much needed in supply planning so that inventory levels can be calculated for a given risk level. Thus, in what follows, we focus on the Poisson-Gamma model.

3.1 Poisson-Gamma Model

Consider a multi-center trial in which S patients (the sample size) must be recruited by M clinical trial sites with location index set $\mathscr{M} = \{1,2,\ldots,M\}$. It is well-known (see,e.g, Senn 1997,1998; Anisimov and Fedorov 2007) that the patient recruitment process in center $m \in \mathscr{M}$ can be described by a Poisson process with some generally unknown rate $\lambda_m > 0$. Note that these centers may have different recruitment rates depending on the type of center, the size of patient population in the regions and other factors. Further, because λ_m's are unknown, one may need to use historical data from previous studies to provide estimates of the recruitment rates in the centres yet to be initiated and then update them as more information becomes available.

Using a Poisson-gamma model (see, e.g., Anisimov, Fedorov, 2007, Anisimov et al., 2007, Anisimov, 2009), we can model the variation in the recruitment rates by first assuming that the rates $\lambda_m, (m \in M)$ are drawn from a random mixing distribution with only a small number of parameters. Gamma distribution is a perfect choice since it is conjugate to the Poisson distribution. The probability density function (pdf) of the Gamma distribution is given by

$$p(x,\alpha,\beta) = \frac{e^{-\beta x}\beta^{\alpha}x^{\alpha-1}}{\Gamma(\alpha)}, \tag{1}$$

where α,β are some known parameters (shape and rate parameters). This means that the mean rate is equal to α/β, and the variance is equal to α/β^2; hence, $1/\sqrt{\alpha}$ is the coefficient of variation.

Using a Poisson-Gamma model allows one to predict the behavior of the recruitment in the regions at different stages of the study. Consider prediction of the recruitment for the duration of the recruitment period at the study start. Assume that all centers are initiated simultaneously when the study commences. In region I_s with M_s centers, let N_m be the total number of patients arrive at centre m and designate $N_{I_s} = \sum_{m\in I_s} N_m$ as the total number of patients which have arrived to region I_s when the study reaches the sample size. Consider the respective total recruitment rates in region I_s and of the global process, denoted by $\lambda(I_s)$ and Λ, defined as

$$\lambda_(I_s) = \sum_{m\in I_s} \lambda_m,\ \Lambda = \sum_{m=1}^{M} \lambda_m. \tag{2}$$

Note that for fixed rates λ_m the number of patients which have arrived in region I_s, N_{I_s}, has a binomial distribution with parameters $(S, p(I_s))$, where $p(I_s) = \lambda(I_s)/\lambda$. However, as in the framework of a Poisson-Gamma model, λ_m are gamma distributed with parameters (α,β), thus the rates $\lambda(I_s)$ and Λ are also gamma distributed with parameters $(\alpha M_s,\beta)$ and $(\alpha M;\beta)$, respectively. This implies that $p(I_s)$ has a beta distribution with parameters $(\alpha M_s, \alpha(M-M_s))$ and, consequently, N_{I_s} has a beta-binomial distribution with

probability mass function given by

$$P\{N_{I_s} = n_{I_s}\} = \binom{S}{n_{I_s}} \frac{B(\alpha M_s + n_{I_s}, \alpha(M - M_s) + S - n_{I_s})}{B(\alpha M_s, \alpha(M - M_s))}, \tag{3}$$

where $B(a,b) = \int_0^1 x^{\alpha-1}(1-x)^{b-1}dx$ is a beta function. To this end, designate

$$P\{N_{I_s} = n_{I_s}\} = p(S, M, M_s, \alpha, n_{I_s}). \tag{4}$$

3.2 Prediction of Ongoing Recruitment

Assume that the clinical trial has reached some intermediate time point τ and denote by $\kappa_m(\tau)$ the number of patients arrived at center m up to now. Let τ_m be the length of the operating period of center m. Our aim is to construct the prediction of the remaining recruitment time using the interim data $\{\kappa_m(\tau_m), \tau_m, m \in \mathscr{M}\}$.

Given the number of patient arrivals $\kappa_m(\tau_m)$ and duration τ_m, the total rate Λ has the same posterior distribution as

$$\tilde{\Lambda}_1 = \sum_{m=1}^{M} \gamma(\alpha + \kappa_m(\tau_m), \beta + \tau_m). \tag{5}$$

If all centers are initiated at the same time, then $\tau_m = \tau$, and $\tilde{\Lambda}_1 = \gamma(\alpha M + \kappa, \beta + \tau)$ where κ is the total number of arrivals up to time τ. This relation implies that the remaining time $\tilde{T}$ can be simplified to the form below (see Anisimov and Fedorov 2007)

$$\tilde{T} = \frac{\gamma(S - \kappa, 1)}{\gamma(\alpha M + \kappa, \beta + \tau)} \tag{6}$$

This means that $\tilde{T}$ has a Pearson type VI distribution.

To this end, note that random patient dropout may affect both the calculation of the sample size and the supply strategy. However, Anisimov (2009) and Anisimov et al. (2014) proved that dropout leads to an insignificant sample size increase compared to the averaged design, regardless of the randomization schemes.

4 DRUG SUPPLY MODELING

Section 4.1 gives further details of randomized controlled trials necessary to proper supply planning. Next, Section 4.2 reviews some basic inventory control models and discusses their relevance to clinical trial supply chains. Note that supply planning considers the trade-offs between overage cost, shipping costs and service levels. Finally, Section 4.3 studies the impact of randomization schemes to supply planning.

4.1 Randomized Controlled Trials

Randomized controlled trials are often considered the "gold standard" for testing the safety and efficacy of drugs and treatments (see, e.g., Akobeng 2015). Randomization aims to ensure that patient populations are similar in test and control groups so that sound statistical inference can be made. A clinical trial is often blinded. It is called a double blind study if both patients and investigators are unaware of each patient's assigned treatment.

In a randomized controlled trial, when a patient arrives at a particular site, he/she is registered after a screening period and randomized to a treatment arm. A treatment arm can either be the target drug, an active comparator (e.g., a competitive therapy to treat the same condition as the investigative product), a placebo comparator (an inactive therapy), a sham comparator (an inactive therapy with identical look and feel to the active therapy to avoid unblinding the study), or no intervention. Specifically, there are two

randomization schemes that are most often used in practice: unstratified and center-stratified permuted block randomization. Unstratified randomization allocates patients to treatment arms based on independent randomly permuted blocks of a fixed size, regardless of the clinical center at which patients arrive. Center-stratified randomization allocates patients based on randomly permuted blocks for each clinical center. If drug inventories are available, the patient will be administered. Otherwise, that patient can either wait for a couple of days, or simply leave the system.

For example, suppose that the study has two treatment arms, denoted by a_1 and a_2. If the size of each block is 4 and the proportion within each block is $2:2$, then there are 6 permuted blocks

$$\{a_1,a_1,a_2,a_2\},\{a_1,a_2,a_1,a_2\},\{a_1,a_2,a_2,a_1\},\{a_2,a_1,a_1,a_2\},\{a_2,a_1,a_2,a_1\},\{a_2,a_2,a_1,a_1\}.$$

In general, a clinical study may have A different treatment arms and the allocation within each block is specified by a tuple $(k_1,\ldots,k_A)$. We refer to $K=\sum_{a=1}^{A}k_a$ as the block size. Intuitively, drug supply modeling should be carefully considered for each of the aforementioned randomization schemes due to different levels of randomness regarding the number of patients assigned to treatment arms. In particular, unstratified randomization reduces the imbalance in the number of patients on all treatment arms, but increases the imbalance in regions and individual centers as compared to center-stratified randomization.

Note that besides randomization controlled trials, there are other types of trial design, for example, the innovative adaptive trial designs which allow modifications based on data accumulating within a study (FDA 2018). Adaptations can be done to sample size, treatment arm selection, etc. and can significantly impact supply planning. For example, if the sample size is increased, there is a potential need for additional drug supply (Gallo et al. 2006). Since adaptive trials are very distinct compared to randomized control trials, the tutorial in this paper focuses on the latter.

4.2 Inventory Control

A typical scenario of drug supply planning for a single study means that there is a central warehouse along with multiple country depots indexed by I_s. Each depot is associated with several local centers. Delivery time from a depot to a local center can be a few days. Delivery time from a central warehouse to a regional depot can vary up to a couple of months, depending on the country customs. The multi-echelon structure of the clinical trial supply chain network is illustrated schematically in Figure 1.

As previously mentioned, the random arrival of patients can be sufficiently modelled by the Poisson–gamma approach in Section 3. For simplicity, we can assume unlimited supply capacities so that the central warehouse has no stock-out. Thus, supply planning involves the positioning of drugs at each echelon and selection of the respective replenishment strategy for each location. At this point, we shall digress slightly to review basic inventory control models and discuss their relevance to clinical supply management. The impact of randomization schemes on drug supply will be explored in Section 4.3.

Periodic review models. The inventory position (on-hand inventory plus quantity on order minus back-orders, if any) is reviewed at fixed intervals of time and an ordering decision is made after each review. In particular, at each review instant, enough can be ordered to raise the inventory position to a desired replenishment level S. This system is commonly used by companies not utilizing computer control (Silver et al. 1998) since it can be easily implemented. To avoid stock-out until the next order arrives, potentially caused by demand uncertainty during a review interval plus a shipping lead time, periodic review models often carry higher safety-stock compared to the one from continuous review models. The safety-stock level is computed based on the length of lead time, the stochasticity of lead time (constant or random) and specific service level requirement.

Continuous review models. In continuous review models, inventory level is assumed to be visible at any moment. An example policy that is widely used is the (r,Q) policy. In this policy, whenever the inventory level reaches the reorder point r, an order of size Q is placed to bring the inventory position to $r+Q$. Thus, there are two main decisions: the reorder point (when to order) and the order quantity (how much to

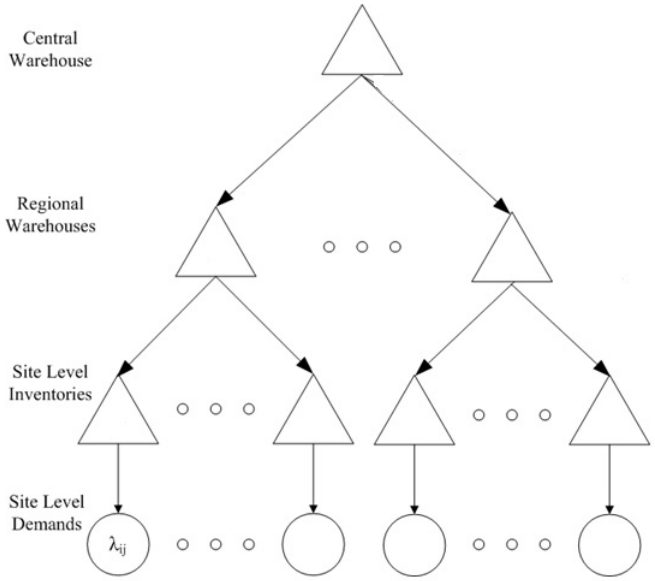

Figure 1: A general clinical trial supply chain.

order). These decisions should be made based on particular applications. For example, Q can be chosen using the economic ordering quantity (EOQ) quantity to balance shipping and holding costs. Intuitively, the larger the reorder quantity, the lower the shipping costs, but the higher the holding costs.

Periodic review models within the context of the multi-echelon research can be found in Clark and Scarf (1960), Federgruen and Zipkin (1984). For multi-echelon models where inventory is reviewed continuously in time, see reviews by Zipkin (2000), Muckstadt (2005), Simchi-Levi and Zhao (2012). One seminal work in this stream of literature is Sherbrooke (1968). The reader can also refer to the papers by Sherbrooke (1986), Graves (1985, 1986), Svoronos and Zipkin (1991), Axsäter (1990, 1993), Ravichandran (1995), Simchi-Levi and Zhao (2005), Simchi-Levi and Zhao (2012) and the references therein. For service constrained multi-echelon distribution systems, see Hopp et al. (1999), Caglar et al. (2004), Caggiano et al. (2007, 2009), Özer and Xiong (2008), Topan and Bayindir (2012). All are multi-echelon distribution (divergent) systems with stochastic demand, service level constraints, full backordering, deterministic lead times (may vary by location), no lateral shipments, and continuous review installation stock policies.

Given the realities of clinical trial supply chains and available technology, companies should select an appropriate inventory control model. In general, we can assume that

Assumption 1 (a) Inventory at each site is controlled by a continuous-review base-stock policy. A shipment is triggered every time a unit of inventory is dispensed at site (b) Inventory at each country depot is controlled by a continuous-review batch ordering inventory policy (r,Q). When the inventory position falls below r, the depot will trigger a replenishment order of size Q

Due to Interactive Response Technology (IRT) Services in modern clinical trials, the choice of a continuous-review inventory policy (1a and 1b) at sites and depots is appropriate. Note that IRT systems have the ability to facilitate drug randomization and supply in a blinded trial (Waters et al. 2010; Ruikar 2016). With it, both real-time inventory information can be maintained and automated shipments to replenish inventory can be triggered. While sometimes it will take multiple demands at a site to trigger an order, we make a simplifying assumption (1a), appropriate in high-value biologic trials, where an order is triggered each time a demand occurs.

4.3 Impacts of Randomization

In this section, we outline our main ideas on the drug supply strategies for both the initial stage and an on-going study. Recall that the arrival rates at site $\lambda_m, m \in \mathscr{M}$ are assumed to be randomly distributed according to a prior gamma distribution. Initially, recruitment data is unavailable and thus the parameters (α, β) must be estimated based on planned (or historical data from the same therapeutic area and similar countries) data provided by study managers. Based on these estimates, we can devise a tentative plan for the amount of supply needed and a more refined plan is attained over time given further observed recruitment data. In summary, at the initial stage, some initial amount of supply is sent to each regional depot to cover the patient demand for some period until the next shipment will be delivered. Note that this total supply quantity depends on the type of randomization.

At some interim time t_0, we are ready to update the parameters of the (r,Q) inventory policy specified in **Assumption 1**. In particular, the reorder point r will be adjusted according to available information up to t_0, so that there are smaller and smaller replenishment quantities shipped toward the end of the clinical trial. First, recall that the inventory level is defined as on-hand inventory minus back-orders, and inventory position as the sum of inventory level and outstanding orders. The inventory position at depots is continuously monitored and as soon as it drops to the reorder point, an order of certain size is placed to the central warehouse. In other words, the reorder point r dictates the level of inventory which triggers replenishment of clinical supplies for a particular treatment.

In particular, we can compute the reorder point for a given service-level ζ from $P(D(L) \leq r) \geq \zeta$, where $D(L)$ is the lead time demand, and ζ is a sufficiently high probability. Note that the lead time $L = \min(L_s, \tilde{T})$ is a random variable reflecting the minimum between the shipping time from the central warehouse to the depot in region I_s and the remaining time to complete the trial $\tilde{T}$. To facilitate the computation of r, in what follows we characterize the distribution of lead time demand for a given treatment a across all sites in region I_s.

Recall that the study needs to recruit S patients at M clinical centers. The predictions for the remaining recruitment process can be constructed using the collected information including the number of arrivals κ_m to site m and the actual duration of recruitment $\tau_m = t_0$ in center m. In particular, in each center, a new posterior recruitment rate has a gamma distribution with parameters $(\alpha + \kappa_m, \beta + \tau_m)$. Note that the number of patients $N_m(t_0,t)$ arriving at site m in the interval $[t_0,t]$ according to Anisimov (2011) is a negative-binomial random variable with probability mass function

$$P\{N_m(t_0,t) = n_m\} = \frac{\Gamma(\alpha+\kappa_m+n_m)}{n_m!\Gamma(\alpha+\kappa_m)} \frac{(t-t_0)^{n_m}(\beta+\nu)^{\alpha+\kappa_m}}{(\beta+\tau_m+(t-t_0))^{\alpha+\kappa_m+n_m}}, n_m = 0,1,\ldots \tag{7}$$

where $\hat{\lambda}_m = \gamma(\alpha+\kappa_m, \beta+\tau_m)$ is the predictive posterior rate for the site. Designate by $N(t_0,t) = \sum_{m\in\mathscr{M}} N_m(t_0,t)$ the total number of patients arriving to the trial in the same interval $[t_0,t]$. Its distribution can be computed by discrete convolution.

Suppose that there are A treatment arms with the allocation specified by $(k_1,\ldots,k_A)$, and the block size is given by $K = \sum_{a\in\mathscr{A}} k_a$. The number of complete blocks can be computed by $c = \lfloor S/K \rfloor$, where $\lfloor\rfloor$ is the floor function.

4.3.1 Unstratified Randomization

Consider the initial stage when we have to come up with a tentative supply plan based on the parameter estimates of the Gamma prior. The shipping quantities are chosen to cover demands until the next shipment will arrive. Since the unstratified randomization scheme stipulates that patients registered to the study are randomized to treatment arms according to a common list without regard to clinical sites, we can assume that the total number of patients planned to be recruited S is a multiple of K, without much loss of accuracy. Hence, given S arrivals to the system, we can count the total number of patients assigned to treatment arm a by $S^{(a)} = \lfloor Sk_a/K \rfloor$ in the whole study, where $a \in \mathscr{A}$. Given $S^{(a)}$, the number of patients on treatment a

in region I_s follows a beta distribution (see (3)), that is,

$$P\{N_{I_s}^{(a)} = n_{I_s}^{(a)}\} = p(S^{(a)}, M, M_s, \alpha, n_{I_s}^{(a)}). \tag{8}$$

Consequently, the initial shipping quantities can be easily computed to ensure a prescribed risk-level $P\{N_{I_s}^{(a)} \leq r_{I_s}\} \geq 1-\varepsilon$. Note that we have

$$P\{N_{I_s}^{(a)} \leq r_{I_s}\} = \sum_{i=0}^{r_{I_s}} p(S^{(a)}, M, M_s, \alpha, i). \tag{9}$$

In contrast to the planning stage, the reorder point r_{I_s} for an on-going study is supposed to cover the lead time demand only, denoted by $N_{I_s}^{(a)}(L)$. In the initial stage, the number of patients assigned to treatment arm a can be computed based on S, however, the number of arrivals during lead time is random and we need to characterize its distribution. First, note that we have

$$P\{N_{I_s}^{(a)}(L) = n_{I_s}^{(a)}\} = \int_{t=0}^{\infty} P\{N_{I_s}^{(a)}(t) = n_{I_s}^{(a)}\} f_L(t)dt, \tag{10}$$

where $f_L(t)$ is the pdf of the lead time. Thus, we need the distribution of patients assigned to a treatment arm in a specific region by conditioning on the number of patients arriving in the interval $[t_0, t]$. The number of patients assigned to arm a in region I_s is given by

$$P\{N_{I_s}^{(a)}(t_0,t) = n_{I_s}^{(a)}\} = \sum_n P\{N_{I_s}^{(a)}(t_0,t) = n_{I_s}^{(a)} | N(t_0,t) = n\} P\{N(t_0,t) = n\}, \tag{11}$$

where the conditional probability is a beta-binomial probability. Note that as the distribution of the remaining time to complete the trial $\tilde{T}$ can be calculated (Anisimov and Fedorov 2007; Anisimov 2011), so to the pdf of the lead time can be easily calculated.

By the definition of unstratified randomization, within each group the patients are distributed among centers according to beta-binomial distribution independently from other groups. Thus, for any region I_s, we have

$$P\{N_{I_s}^{(a)}(t_0,t) = n_{I_s}^{(a)} | N(t_0,t) = n)\} = p(\lfloor \frac{n}{K} k_a \rfloor, M, M_s, \alpha + \kappa_m, n_{I_s}^{(a)}), \tag{12}$$

where for any $n_{I_s}^{(a)} = 0, \ldots, S^{(a)}$,

$$p(S^{(a)}, M, M_s, \alpha, n_{I_s}^{(a)}) = \binom{S^{(a)}}{n_{I_s}^{(a)}} \frac{\mathscr{B}(\alpha M_s + n_{I_s}^{(a)}, \alpha(M-M_s) + S^{(a)} - n_{I_s}^{(a)})}{\mathscr{B}(\alpha M_s, \alpha(M-M_s))}. \tag{13}$$

4.3.2 Stratified Randomization

Similarly to unstratified randomization, in the initial stage, we provide a plan for the entire recruitment period using estimates of relevant model parameters. Denote by N_m the number of patients arrived to clinical site m. If it is not a multiple of K, then the number of complete blocks can be computed by $c_m = \lfloor N_m/K \rfloor$. There is also one incomplete block that may have an unbalanced number of patients on each treatment arm. Assume that center m has an incomplete block of size $i, i = 1, \ldots, K-1$. Let $\tilde{N}_m^{(a)}$ be the number of instances of treatment arm a in this block, which has a hypergeometric distribution

$$P\{\tilde{N}_m^{(a)} = n_m^{(a)}\} = \frac{\binom{k_a}{n_m^{(a)}} \binom{K-k_a}{i-n_m^{(a)}}}{\binom{K}{i}}, \tag{14}$$

for $n_m^{(a)} = 0, 1, \ldots, \min(k_a, i)$. The number of patients assigned to treatment a at site m is given by

$$N_m^{(a)} = \lfloor \frac{N_m}{K} \rfloor k_a + \tilde{N}_m^{(a)}. \tag{15}$$

Since the distribution of N_m is beta distributed, all characteristics of $N_m^{(a)}$ can be calculated numerically. Finally, the distribution of $N_{I_s}^{(a)} = \sum_{m \in I_s} N_m^{(a)}$ is computed via discrete convolution.

For an ongoing study, the reorder point is set to cover lead time demand only. Note that

$$P\{N_{I_s}^{(a)}(L) = n_{I_s}^{(a)}\} = \int_{t=0}^{\infty} P\{N_{I_s}^{(a)}(t) = n_{I_s}^{(a)}\} f_L(t) dt, \tag{16}$$

where $f_L(t)$ is the pdf of the lead time. Thus, we need to derive $P\{N_{I_s}^{(a)}(t) = n_{I_s}^{(a)}\}$. This can be achieved by convolving the distribution of $N_m^{(a)}(t)$. The distribution of $N_m^{(a)}(t)$ can be found in a similar way as in (15), however, in place of N_m should be $N_m(t)$ and the distribution of $N_m(t)$ is given in (7).

5 CONCLUSION

This tutorial offers an overview of clinical trial supply chains, highlighting modeling challenges and providing realistic assumptions for simulation of an end-to-end drug supply management system for multi-center trials. More importantly, it outlines an analytical simulation approach based on closed-form formulas, which has numerous advantages compared to pure simulation techniques, especially in computational efficiency. In particular, our approach is built upon a well-established stochastic model for patient recruitment, the Poisson-gamma model, to predict the lead time demand given a risk level. With the obtained closed-form formulas, the attendant simulation can help facilitate a systematic study of different effects (risk level, number of arms, number of depots, etc.) on the total supply chain costs.

Note that besides simulation, there exists several papers in the literature employing optimization methods to tackle supply planning and network design problems in clinical trials (see, e.g., Leachman et al. 2014; Fleischhacker et al. 2015, Zhao et al. 2018; Zhao et al. 2019). However, to gain computational tractability, these papers generally assume restricted conditions on randomization schemes or the number of arms in a study. Clearly, a benefit of analytical modeling is that the true optimal solution can be found quickly. In contrast, a pure simulation model requires the inventory policy as an input and then simulates the service level performance. Thus, prior to deciding an inventory policy, simulation models require multiple combinations of inventory policies to be tested with each one requiring multiple Monte Carlo simulations to ensure that the risk level is met (Anisimov 2011b).

It is worthwhile to explore simulation-optimization techniques for clinical trial supply simulation. Note that simulation-optimization has been used for other supply chain planning problems, see, e.g., Ingallis (1998), Hicks (1999), Banks et al. (2002), Chwif et al. (2002), Joines et al. (2002), Truong and Azadivar (2003), Deleris and Erhun (2005), Van Der Zee and Van Der Vorst (2005). For references on general simulation-optimization techniques, we refer the reader to Carson and Maria (1997), Andradóttir (1998a,b), April et al. (2003), Swisher et al. (2010), Fu (2002, 2013), Fu et al. (2014).

Lastly, we point out that there are other important problems in clinical trial supply chains that can greatly benefit from simulation. Site selection is a case in point. Site selection includes site identification, site assessment and selection of the best sites aligned with study goals and limited resources. It is one of the most important and challenging problems in clinical trials planning, and poor site selection may cause delays, wastage, and potentially compromise trial results. Utilizing historical data to estimate predicted arrival rates at sites under consideration, planners may perform simulations to assess the predicted production, shipping, and inventory costs under various site selection choices.

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