DRUG SUPPLY CHAIN OPTIMIZATION FOR ADAPTIVE CLINICAL TRIALS

by

Wei-An Chen

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THE PURDUE UNIVERSITY GRADUATE SCHOOL
STATEMENT OF COMMITTEE APPROVAL

Dr. Nan Kong, Co-Chair
Weldon School of Biomedical Engineering
Dr. Gintaras V. Reklaitis, Co-Chair
Davidson School of Chemical Engineering
Dr. Joseph F. Pekny
Davidson School of Chemical Engineering
Dr. Carl D. Laird
Davidson School of Chemical Engineering

Approved by:
Dr. David S. Corti
Head of the Graduate Program

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LIST OF ABBREVIATIONS

ACT – Adaptive Clinical Trial

API – Active Pharmaceutical Ingredient

DMC – Data Monitoring Committee

DRC – Data Review Committee

TSC – Trial Steering Committee

TMG – Trial Management Group

NAC – Non-anticipativity Constraint

MPD – Minimum Packaged Dosage

LP – Linear Programming

IP – Integer Programming

MILP – Mixed-Integer Linear Programming

MINLP – Mixed-Integer Non-Linear Programming

GLOSSARY

Placebo	A harmless pill or medicine contains no active pharmaceutical ingredient, or a procedure prescribed more for the psychological benefit to the patient than for any physiological effect.
Endpoint	A clinical endpoint is an outcome that represents direct clinical benefit, such as survival, decreased pain, or the absence of disease.
Randomization	A procedure of allocating patients/subjects to trial arms/treatments according to probabilities.

ABSTRACT

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As adaptive clinical trials (ACTs) receive growing attention and exhibit promising performance in practical trials during last decade, they also present challenges to drug supply chain management. As indicated by Burnham et al. (2015), the challenges include the uncertainty of maximum drug supply needed, the shifting of supply requirement, and rapid availability of new supply at decision points [1]. To facilitate drug supply decision making and the development of mathematical analysis tools, we propose two trial supply chain optimization problems that represent different mindsets in response to trial adaptations. In the first problem, we treat the impacts of ACTs as exogenous uncertainties and study important aspects of trial supply, including drug wastage, resupply policy, trial length, and costs minimization, via a two-stage stochastic program. In the second problem, we incorporate the adaptation rules of ACTs with supply chain management and numerically study the impact of joint optimization on the trial and drug supply planning through a mixed-integer nonlinear program (MINLP). For solution approaches to the problems, we use progressive hedging algorithm (PHA) and particle swarm optimization (PSO) respectively, and take advantages of the problem structures to enhance the solution efficiency. With case studies, we see that the proposed models capture the features of ACT drug supply and the mechanisms of trial conduction well. The solutions not only reflect the impact of trial adaptations but also provide managerial suggestions, e.g. the prediction of needed production amount, storage capacity at clinical sites, and resupply schemes. The joint optimization also suggests a new angle and research extension in the field of ACT design and supply.

1. INTRODUCTION

1.1 Motivation

According to the annual report published by Pharmaceutical Research and Manufacturers of America (PhRMA), America's biopharmaceutical companies sponsored more than 4,500 clinical trials in 2017 alone, involving more than 920,000 participants, and the overall economic impact of company investments in U.S. clinical trial sites is more than $42 billion [2]. Chang and Balser (2016) pointed out the increase in investments, however, does not reflect an increased success rate of pharmaceutical development, and one obvious area for improvement is the design, conduct, and analysis of clinical trials [3]. Although adaptive designs have the potential to improve the efficiency of clinical trials in practice [4-9], Burnham et al. (2015) and the DIA Adaptive Design Scientific Working Group revealed the drug supply dilemma for ACTs [1].

According to Burnham et al. (2015),

- Nevertheless, the operational challenge of drug supply continues to be a barrier preventing greater uptake of adaptive designs.
- Adaptive designs are potentially more costly than traditional studies, and much of that cost is driven by increased drug supply costs.
- Modern tools for the planning and execution of drug supply for adaptive clinical trials are simulation approaches

These motivate us to develop optimization tools to facilitate the decision making and analysis of drug supply chain planning in response to challenges resulted from ACTs. Our goal is to enhance the understanding and connection between the fields of clinical trial design research and pharmaceutical supply chain management. We also hope that our findings suggest where it may be best to dedicate future research efforts in the joint area.

1.2 Adaptive Clinical Trial Basics

Adaptive clinical trials (ACTs), in contrast to traditional fixed trials, are trials that allow the visitation and analysis of the latest sample data and allow the alteration and adaptation of trial

design and protocol during the conduct of the trials. In other words, the trial design and protocol parameters can be modified in the halfway of the trial based on the newly collected patient responses to the treatments and investigational dugs. The visitation of the trial sample data, i.e. patient responses, is called “interim analysis” and usually will put the trial on a brief pause. An ACT can have more than one interim analysis time point, which is defined prior to the implementation of the trial. Note that adaptations can only be made at each interim analysis point.

The processes of conducting an ACT is illustrated in Fig 1.1. After a trial (with its protocol) is designed, the trial starts with advertisement via phone call, television, newspaper, or web banner. The advertisement is the beginning of the incessant recruitment process and is followed by several screening steps, where the interested patients are examined and picked based on age, gender, personal and family medical history, physical and blood tests, etc. The qualified patients will be enrolled into the trial and assigned to a specific treatment arm or group according to the randomization scheme. Then the patients receive the specific treatment and drug during a treatment span. Meanwhile, clinicians observe and record the patients’ responses to the treatment and drug in terms of certain medical measure quantitatively, i.e. an endpoint. After treating a cohort of patients or reaching a pre-specified time point, the trial goes through a brief pause, where the Data Monitoring/Review Committee (DMC or DRC) analyzes the latest data regarding patients’ responses and adapts the trial design and protocol. When the trial resumes, newly enrolled patients and Trial Management Groups (TMGs) must follow the new protocol until the next interim analysis point or the satisfaction of termination criteria. Apart from drug safety and trial integrity issues, a trial is considered as completion when a pre-determined number of patient responses, i.e. target sample size, are collected. Note that some patients may dropout from the treatment and trial, resulting in sample loss, and that the trial protocol describes randomization scheme, conditions of having an interim analysis, how treatments are performed, and all the information needed to conduct the trial. Further details about the implementation of ACT can be seen in these references [10].

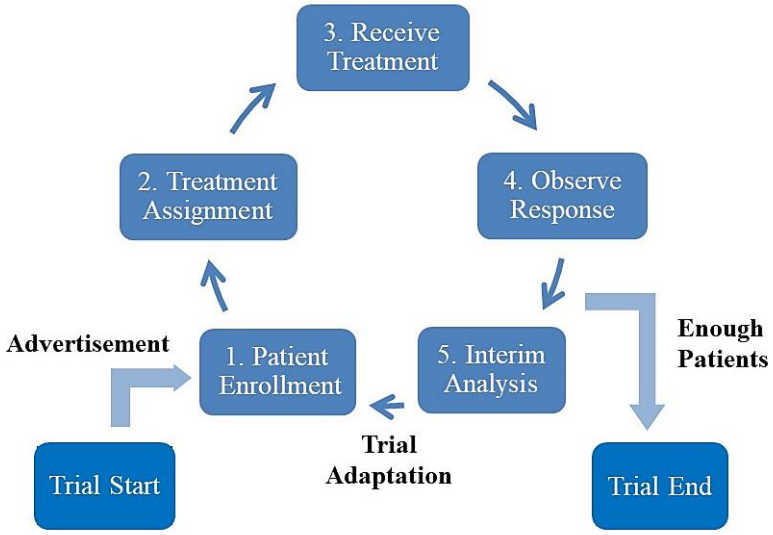

Fig 1.1 Processes of Adaptive Clinical Trial.

ACTs have been proven to be more beneficial than fixed trials in many aspects. Because of the usage of newly learned information and the flexibility of making adaptations accordingly, ACTs can retrieve better drug/dosage information per unit of resources invested, which generally contributes to higher chances of verifying the drug efficacy and shortening the trial length. In regard to patient well-being, early identification of effective dosage/treatment and appropriate adaptations will contribute to less portion of patients taking ineffective drugs. As for commercial benefits, higher probability of trial success and shorter trial length will lead to less time-to-market of medicines and higher future profits due to the competition between other biopharmaceutical companies. Note that these benefits come at a price, e.g. higher expenses of conducting the trial and supplying drugs.

1.3 Types of Adaptive Trials

A large number of adaptive designs are developed nowadays due to multitudinous situations and requirements in pharmaceutical research and development. I recommend understanding them from two aspects: (1) the purpose it serves (2) the design/protocol parameters it adapts. Regarding the purpose, traditional trials generally can be either exploratory or confirmatory, and the so-called phase 0, I, II, III, and IV trials are also classified based on specific purpose. For ACTs, we can see not only the purpose-oriented naming strategy, e.g. adaptive dose-finding design, but also a

purpose-combined design, e.g. adaptive seamless phase II/III design. As for ACTs named after adaptations, there are group sequential design (GSD), sample size re-estimation design (SSR), adaptive randomization design, etc. In this dissertation, we only introduce the designs that are commonly used and have direct impact on drug supply. A summary of different types of ACTs is shown in Fig 1.2 [8], and the usage percentage is reported by Fig 1.3 [3].

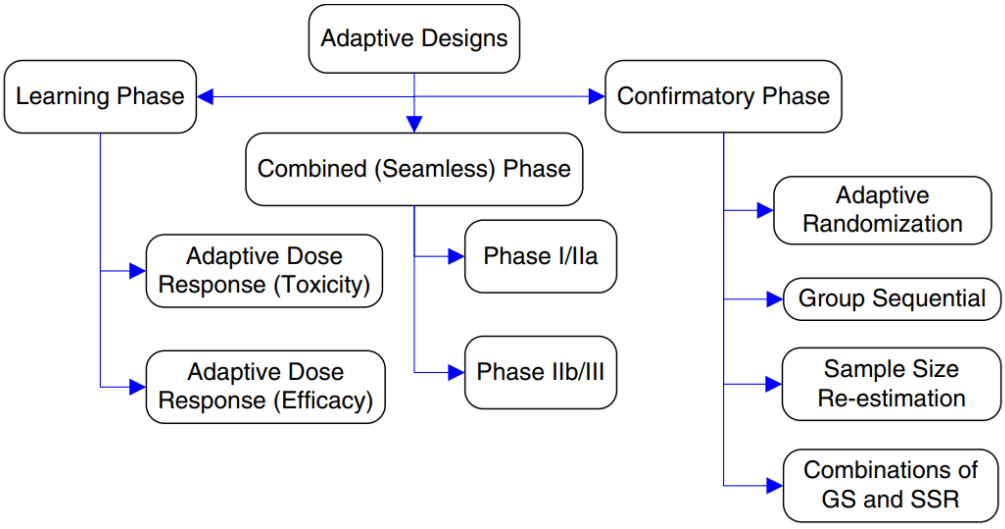

Fig 1.2 Summary of Different Types of Adaptive Designs for Clinical Trials [8].

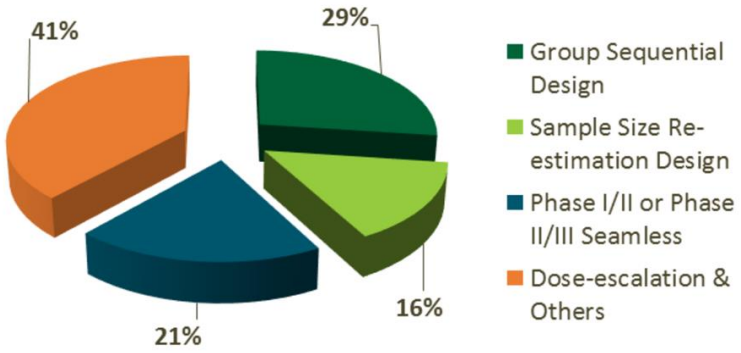

Fig 1.3 Current Use of Adaptive Design Types [3].

A sample size re-estimation (SSR) trial allows the adjustment in the target sample size based on the data reviewed in an interim analysis. The reason of having a sufficient number of subjects is to achieve a desired study power for correctly detecting a clinically meaningful difference. When

the collected data reveals quite higher or lower variability than the initial understanding, a re-estimation of sample size can prevent an underpowered or overpowered trial in the end. A response-adaptive randomization (RAR) trial allows the adjustment in the patient allocation ratio/proportion/number of treatments, i.e. changing the plan of assigning patients to treatments, based on the patient responses to the treatments/drugs reviewed in an interim analysis. A benefit of this type of adaptation is that more patients may receive a superior treatment/drug by the end of the trial. An adaptive seamless phase II/III trial that addresses the objectives that are normally achieved through separate trials in phases IIb and III, within a single trial to achieve benefits such as savings in time or sample size. The adaptation of sample size or randomization are possible in seamless designs. More details and other types of ACTs that are not addressed in this dissertation can be seen in these references [3, 5, 6, 8, 9, 11, 12].

1.4 Resupply Schemes

Two widely used inventory control policies in practice are quantity-reorder (Q-r) and floor-ceiling (S-s). Fig 1.4 shows the typical inventory profiles of the two policy. In Q-r policy, only when the current inventory level drops below the reorder point r, a replenishment of quantity Q will be triggered, where the Q and r are fixed values throughout the supply horizon. In S-s policy, there also exist a resupply threshold s. Only when the current inventory level drops below the threshold, a replenishment can occur. The quantity of the replenishment is designated to fill the inventory up to a “ceiling” level S. The S and s are fixed values throughout the supply horizon. Note that the replenishment of inventory in practice are usually not instantons like Fig 1.4. Instead, there exist a lead time and the current inventory level keeps dropping before the initialized shipment arrives.

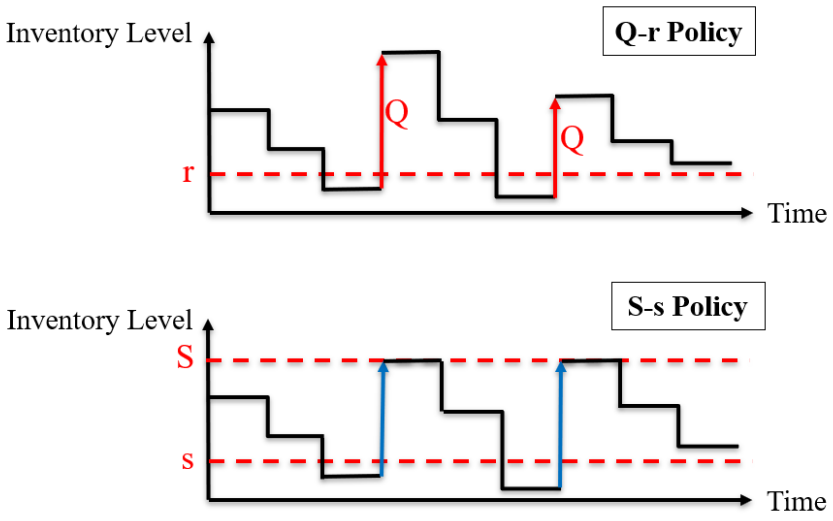

Fig 1.4 Illustration of Q-r and S-s Resupply Schemes

1.5 Contribution of the Dissertation

This is a work that bridges the gap between adaptive clinical trial (ACT) planning and drug supply chain management and involves the use of knowledge from diverse areas, including clinical trial design, clinical statistics, supply chain management, and mathematical optimization.

For the research project in Chapter 3, a contribution is that we introduce a new type of supply chain management problem to the literature. The unique characteristics are (uncertain) finite-customer supply horizon, demand-repeating and length-fixed window of customers' stay, uncertain customer arrival, uncertain customer drop-out rate, 100% customer service level, and (uncertain) multi-product demands per customer. That is, the supply of multiple products will be terminated when an uncertain finite number of customers are successfully supplied throughout their staying windows. Every randomly arrived customer must be supplied immediately, without backlog or delay, until the end of their staying windows or they randomly dropout from it.

For the research project in Chapter 4, a contribution is that we incorporate the trial-side operations into supply chain management and propose a joint optimization problem, where we identify the individual patient assignment as the key decision/linkage between trial adaptation and drug supply.

It is the first work in the relevant field that introduces the integration between trial design problem and drug supply problem, which may potentially pave a path to future research domain.

Both works also satisfy the need of better optimization tools for adaptive trial supply management, given that current practice is using simulation tools. Other contributions include building ACT-oriented uncertainty simulators, building mathematical programming models for the problem, adapting modern solution methods to the optimization programs, studying the performance of different drug resupply schemes, and addressing the drug overage and production amount estimation issues.

1.6 Organization of the Dissertation

This dissertation is composed of two major research projects, presented in Chapter 3 and Chapter 4 respectively. The literature related to the two projects is reviewed in Chapter 2, including the latest works within relevant fields and the important studies that help the development of our projects. The solution methods used in the two projects are reviewed in Chapter 3 and 4 rather than Chapter 2. Chapter 3 is a research study for drug supply chain optimization under exogenous uncertainties incurred by ACTs. Chapter 4 is a research study for integration between drug supply and trial design and its joint optimization. Both Chapter 3 and 4 have subsections of problem statement, model formulation, solution method, numerical case study, and conclusions.

2. LITERATURE REVIEW

2.1 Clinical Trial Supply Chain Management

Early researches focus on only single or few aspects of the trial supply chain, e.g. drug wastage, supply scheme, demand forecast, supply cost, and most of the approaches rely on simulations. Ho and Hamilton (2004) proposed a dynamic drug supply procedure for stratified clinical trials and demonstrated its ability of reducing drug waste by simulations. The key concept is to replenish the inventories based on the coverage of future randomized patients, rather than focusing on individual inventory levels [13]. Peterson et al. (2004) built a simulation model for a computer-controlled medication system that automatically maintains sufficient supplies at each study site. Through several simulation experiments, they showed that the automated medication management system has superior performance to the traditional method in terms of reducing wasted medication [14]. Abdelkafi et al. (2009) proposed a simulation model, a reevaluation scheme to select for optimal supply strategy that balances supply costs against the risk of medication shortage. The simulation model consists of treatment process and the supply process, which respectively simulate the drug demands and the performance of supply strategy, while the reevaluation scheme follows Bayesian principle to reevaluate supply strategies with large number of observations [15]. Anisimov (2009) proposed a statistical technique for modeling the patient recruitment of multi-center clinical trials, which serves as an approach to predicting number of recruited patients, total recruitment time, and minimal number of centers required. The author also utilizes it to develop a risk-based supply modelling tool that evaluates/predicts the needed supply amount and drug overage [16].

From recent articles, we can see more comprehensive aspects of drug supply chain for clinical trials as well as the use of optimization programming. Two threads of research are reviewed. One is developed by Chen and Reklaitis; the other is developed by Fleischhacker and Zhao. Chen et al. (2012) proposed a simulation-optimization framework for the management of entire supply chain, which includes patient demand simulation and demand scenario forecast, mathematical programming based planning, and discrete event simulation of the supply chain. Given simulated drug demand scenarios, the quality and robustness of the plans generated from the planning model are assessed by replicated simulation runs of the discrete event simulation model [17]. Building

upon this work, Chen et al. (2013) added an outer loop optimization in order to determine appropriate pooled safety stock levels. The outer optimization problem is solved via a direct search algorithm [18]. Fleischhacker and Zhao (2011) built a dynamic programming model for a production lot size problem that includes the risk of trial failure. For trials with finite time horizon, the author assumed the drug demand is known in all periods and drugs can be produced at every period with zero lead-time [19]. Fleischhacker et al. (2015) built a nonlinear integer programming (NIP) model for a multi-echelon inventory problem, where quantity-reorder policy is embedded and the network is composed of a central warehouse, several country depots, and multiple site-level inventories. The NIP is linearized and solved by standard integer programming solvers. This works studies the impact of various factors, e.g. shipment lead time, patient arrival rate, number of sites per country, on supply costs and inventory overage [20].

2.2 Adaptive Clinical Trial Supply Chain Management

The literature that addresses the supply chain management for ACTs is much rare. The content of this subsection is mainly reported by Burnham et al. (2015) [1], which is a pioneer article that records practical observations and effective strategies for drug manufacturing, labeling, packaging, and randomization.

Important observations or suggestions reported in Burnham et al. (2015) [1]:

- Total cycle time to ready the active pharmaceutical ingredient (API) and comparators for packaging is anywhere from 6 to 16 months.
- The nature of the adaptive design demanded prepackaging for all possible allocation scenarios before study start. Flexibility in dosing outweighed the cost of maximum overage.
- Just-in-time or on-demand packaging and labeling is a strategy to reduce overage and increase supply utilization. However, this approach requires the ability to quickly turnaround treatment-specific packaging and release and ship drug supply.
- If a trial is long enough, supplies can be manufactured and/or packaged in separate campaigns to preserve material.
- To maintain study blinding, it may be important to keep the number of tablets taken per day consistent across treatment arms.

- During the course of the trial, adjustments to threshold levels triggering resupply of study drug must reflect changes to the randomization schedule.
- In many adaptive studies, there is a delay between completion of a cohort and implementation of an adaptive change, which is most often driven by the availability of supplies at sites.
- If the delay (previous bullet point) is lengthy relative to enrollment rate, the clinical team will decide whether to supply sites in advance for all possible allocations or shut randomization down until new supplies arrive.
- Among many factors other than trial size, patient accrual rate influences drug supply estimates the most.
- For modeling site-level accrual, Poisson models have been shown to fit data from several trials across therapeutic areas in large pharmaceutical companies.
- As in other industries, the "floor/ceiling'' system of inventory control with joint replenishment is commonly used in clinical trials.
- Drug supply planning must take into account the uncertainty of maximum drug needed and the shifting of supply requirement. The need for immediate drug availability at sites must be balanced by the amount of overage.
- Adaptive designs are potentially more costly than traditional studies, and much of that cost is driven by increased drug supply costs.

One effective strategy for reducing drug overage is to produce minimal packaged dosage (MPD) units. Take a thrombosis prevention trial sponsored by GlaxoSmithKline as an example [21], shown in Table 2.1, the manufacturer only produces two MPDs, 125 mg API and the placebo. Every patient will receive 4 bottles that correspond to the treatment which this person is assigned to, and take one tablet from each bottle to reach the target investigational dosage. In comparison to producing 5 treatment dosages, this MPD strategy can better accommodate drug demand uncertainties and reduce drug wastage, especially when one or a few of the treatments may be excluded in the halfway of the ACT.

Table 2.1 An Example of Minimal Packaged Dosage Strategy [21]

Different Treatments / Dosages	Bottle 1	Bottle 2	Bottle 3	Bottle 4
Treatment A: 0 mg	Placebo	Placebo	Placebo	Placebo
Treatment B: 125 mg	Placebo	Placebo	Placebo	Active
Treatment C: 250 mg	Placebo	Placebo	Active	Active
Treatment D: 375 mg	Placebo	Active	Active	Active
Treatment E: 500 mg	Active	Active	Active	Active

The use of modeling and simulation approach is also emphasized by Burnham et al. (2015). Typically, there are two simulation programs, trial design simulation and drug supply simulation. The trial design simulation estimates subject recruitment, overall treatment allocation, and adaptations of randomization ratios, and outputs the generated scenarios to the drug supply simulation. The drug supply simulation then estimates the drug supply required based on an assumed supply environment, including the structure of inventories, addition/deletion of clinical sites, packaging campaigns, subject recruitment and dropout rates. This simulation framework can investigate the impact of a variety of alternative scenarios through adjusting the supply environment and allow the clinical team to evaluate operational decisions [1]. A comprehensive simulation study was performed and presented by the chairman of Cytel Inc., Nitin R Patel, at Clinical Supply Forecasting Summit, in which a placebo-controlled, double-blind, phase II dose-finding trial with continuous primary endpoint that are normally distributed is considered [22, 23]. There is another study that use two simulation tools, CytelSim and MedSim, for estimating clinical trial and supply decisions respectively, under different scenarios [24].

2.3 Adaptive Design of Patient Allocation

Patient and treatment allocation have been a very important part of clinical trial design and can strongly affect the management of resources used in a trial. Here we review some representative works that focus on optimal allocation design, listed in Table 2.2, where different designs and modifications are proposed and analyzed for trials with different characteristics. Note that our work is not aiming at improving the allocation design. Instead, we focus on identifying and incorporating adaptive design rules with drug supply problem. Since our work is the first attempt

to merge supply chain management considerations into the patient-treatment allocation design, we target on characteristics of two arms and binary patient response.

Table 2.2 Representative References Focusing on Optimal Allocation Design

Reference	**# Arms**	**Response**	**Sample Size**	**Description**
RSIHR (2001) [25]	2	binary	fixed	Proposed an allocation design that minimizes the number of negative responses
Biswas and Mandal (2004) [26]	2	normal and exponential	fixed	Extended the work of RSIHR (2001) and considered responses with covariates
Zhang and Rosenberger (2006) [27]	2	normal	fixed	Proposed an allocation design with objective of acquiring desirable expected response
Biswas et. Al (2007) [28]	2	normal	fixed	Indicated the conditions of failure in the design by Zhang and Rosenberger (2006) and developed a unified new framework
Tymofyeyev (2007) [29]	≥2	binary	sequential design	Proposed an allocation design that minimizes the weighted sum of sample sizes and maintains certain level of statistical power
Hu and Zhang (2004) [30]	≥2	general form	sequential design	Proposed a general doubly biased coin design and studied the asymptotic properties
Zhu and Hu (2010) [31]	2	binary and normal	sequential design	Proposed a sequential monitoring procedure to control the inflation of type I error for several common allocation designs

Among these papers, two representative allocation rules are frequently mentioned and used in comparison with various approaches: RSIHR and Neyman allocation. RSIHR allocation is firstly proposed by Rosenberger et al. (2001) [25] for minimizing the expected number of treatment failures or maximizing the expected number of successes in a trial with a fixed asymptotic variance of $\hat{p}_1 - \hat{p}_2$, where $\hat{p}_1$ and $\hat{p}_2$ are estimators of the success probabilities on each treatment p_1 and p_2 [30, 32]. The optimal target allocation proportions ρ_1^* and ρ_2^* can be expressed as (1).

$$\rho_1^* = \frac{\sqrt{p_1}}{\sqrt{p_1} + \sqrt{p_2}} \ , \qquad \rho_2^* = \frac{\sqrt{p_2}}{\sqrt{p_1} + \sqrt{p_2}} \tag{1}$$

Neyman allocation is firstly proposed by Melfi and Page (1998) [33] for minimizing the variance of $\hat{p}_1 - \hat{p}_2$ or maximizing the precision of estimators [29, 30]. The Neyman allocation follows (2), where $q_1 = 1 - p_1$ and $q_2 = 1 - p_2$.

$$\rho_1^* = \frac{\sqrt{p_1 q_1}}{\sqrt{p_1 q_1} + \sqrt{p_2 q_2}} \ , \qquad \rho_2^* = \frac{\sqrt{p_2 q_2}}{\sqrt{p_1 q_1} + \sqrt{p_2 q_2}} \tag{2}$$

To achieve the desired allocations and maintain/control trial power and variance, several approaches are proposed. Note adaptive designs, including RAR, are sequential procedures, and therefore these approaches contain sequential process and analysis. Urn models is one of the approaches to adaptively randomizing patients. Zhang et al. (2006) proposed a sequential estimated-adjusted urn (SEU) model as a patient assignment procedure targeting an allocation proportion [34]. Zhang et al. (2011) proposed a broad class of immigrated urn models, which can control the treatment allocation in a multi-arm trial to the desired allocation target [35]. Another approach is sequential maximum likelihood estimation (SMLE), which uses a suitable function to adjust randomization probabilities according to the current estimation on the model parameters. One famous method is the doubly adaptive biased coin design (DBCD), firstly proposed by Eisele (1994) [36]. Hu and Zhang (2004) proposed a new family of DBCD that is applicable to any given allocation proportion, in which the target/optimal allocation is a continuous, twice-differentiable vector function of trial parameters, i.e. treatment success probabilities in the case of binary response [30]. The general procedure for a *K*-treatment trial fellows (3), where $\phi_{j+1,k}$ is the

allocation probability of the $(j+1)^{\text{th}}$ patient to treatment k, $\hat{\rho}_k^*$ is the current estimation of target allocation to treatment k, N_{kj}/j is the proportion of j patients assigned to treatment k, and γ is a user-defined parameter governing the degree of randomness [37].

$$\phi_{j+1,k} = \frac{\hat{\rho}_k^* \left(\frac{\hat{\rho}_k^*}{N_{kj}/j}\right)^{\gamma}}{\sum_{i=1}^{K} \hat{\rho}_i^* \left(\frac{\hat{\rho}_i^*}{N_{ij}/j}\right)^{\gamma}} \quad , \quad k = 1, \dots, K \tag{3}$$

This DBCD procedure is adapted for our joint optimization problem, where we discretize the sequential process of assignment into time periods to align with the drug supply problem and adjust the allocation probability of the cohort of patients arrived at each (next) period, instead of each individual.

In addition, Zhu and Hu (2010) have numerically demonstrated that Neyman allocation proportion can be targeted well by DBCD, and the type-I error along with standard deviation can be controlled within a reasonably small range. In their work, $\gamma = 2$ is applied [31].

2.4 Sample Size Re-estimation

The field of sample size re-estimation is another broad area of clinical trial design research. Here we only mention the rules and equations that fit the case of our interest, two-arms trial with binary responses that follow Binomial distribution, because our intention is not improving the adaptive design but seeking the integration of design information into supply chain management.

To evaluate the statistical significance, normal-theory test, e.g. Z-test, can be applied if we assume normal the normal approximation to the binomial distribution is valid. Then the acceptance and rejection of the null hypothesis can be determined by the Z value, illustrated as Fig 2.1. The criteria $Z_{1-\alpha/2}$ and $Z_{\alpha/2}$ have strong relation with the power and significance of a trial [38].

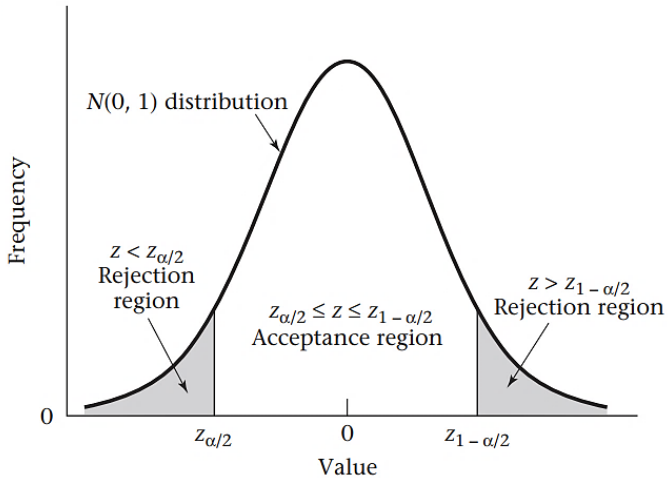

Fig 2.1 Illustration of Acceptance and Rejection Regions [38]

For the two-independent-sample study/test for incidence/success rates, the minimum number of subjects N needed to attain certain study power can be calculated as (4), where α and β are the probabilities of type I and II error, p_1 and p_2 are incidence rates of group 1 and 2, ρ_1 and ρ_2 are allocation ratios of group 1 and 2 to the entire population, $\rho_1 + \rho_2 = 1$ [38].

$$N = \left\{ Z_{1-\alpha/2} \sqrt{\frac{\bar{p}\,\bar{q}}{\rho_1 \rho_2}} + Z_{1-\beta} \sqrt{\frac{p_1 q_1}{\rho_1} + \frac{p_2 q_2}{\rho_2}} \right\}^2 \Big/ \Delta^2 \qquad (4)$$

where $q_1 = 1 - p_1$, $q_2 = 1 - p_2$, $\bar{p} = \rho_1 p_1 + \rho_2 p_2$, $\bar{q} = 1 - \bar{p}$, $\Delta = |p_1 - p_2|$

In our joint optimization problem, we consider this calculation as a termination criterion that specifies whether we have collected enough samples at the end of every period. The α and β are chosen to be the commonly seen values 0.05 and 0.2 respectively, which result in $Z_{1-\alpha/2} = 1.96$ and $Z_{1-\beta} = 0.84$.

3. DRUG SUPPLY CHAIN OPTIMIZATION FOR ADAPTIVE CLINICAL TRIALS

3.1 A Novel Production-Inventory-Transportation Problem

This problem aims at facilitating the drug supply chain management in response to the uncertainties resulted from ACTs and numerically studying the impact of ACTs on several important aspects of trial supply, including drug wastage, resupply policy, trial length, and overall costs. For trial design and adaptation, we focus on the adaptations commonly seen in SSR and adaptive seamless phase II/III trial, including target sample size changes, dosage dropping, and randomization adaptations. For drug supply, we have a multi-dosage, multi-site, multi-period, and multi-echelon supply chain framework. In this problem, the trial adaptations are reflected on stochastic parameters/random variables that govern the demands for drugs, and we optimize supply decisions under the uncertainties of patient arrival, patient dropout, and trial adaptations, for minimum production, inventory, transportation, drug wastage, and recruitment costs. The unique features of our problem are:

- Finite-customer supply horizon
- Demand-repeating and length-fixed window of customers' stay
- Uncertain customer drop-out from staying windows

In terms of the trial, we targeted on a randomized, double-blinded trial with multiple parallel treatments and one interim analysis timepoint. Random number of patients will be enrolled at different clinical sites and discrete time periods, and no one can be rejected or missed due to any reason. Enrolled patient will keep consuming drugs in the duration of their treatments. However, every time period, a random proportion of them will drop out from the trial. The is terminated when there is enough number of patients who enrolled and finished their treatments, i.e. the satisfaction of the target total sample size. Note that the target sample size could change after an interim analysis time point.

As for the supply, the immediate availability of drugs is always enforced, and no backlog or cross shipment between sites is allowed. All dosages are produced in one campaign prior to the

beginning of the trial and stored at a centralized distribution center (DC). Note the produced dosages are minimum packaged dosages (MPDs) mentioned in Chapter 2.2 instead of the investigational dosages used in the trial. Drug demands are generally expressed as the multiplication of two (stochastic) parameters: the number of patients and the averaged consumption of the MPD per patient. The calculation of the averaged consumption involves the randomization ratios between treatments and the composition of the treatment dosage respective to the MPDs. Three types of resupply policy are applied in this problem, freely resupply, quantity-reorder (Q-r), and floor-ceiling (S-s), the introduction and characteristics of which are written in Chapter 1.4 and Table 3.9. The distances between the DC and clinical sites vary, which are reflected on shipping costs instead of shipping time. The lead time of shipment is shorter than the treatment span/duration. All dosages are shipped together in boxes with same capacity via FedEx cold chain service. The cost of storing drugs is higher at clinical sites than at the DC. When the trial is terminated, no shipment or change in inventory levels is allowed.

3.2 A Two-Stage Stochastic Program

We have sets of dosages, sites, periods, and scenarios defined as Table 3.1. Note that the minimal packaged dosages (MPDs) is the unit dosages that are manufactured and consist of the investigational dosages used in treatments. The setting of MPDs has been proven to effectively reduce the drug waste in ACTs [21].

Table 3.1 Sets and Indices of the Production-Inventory-Transportation Problem

I	The set of (minimal packaged) dosages indices i
S	The set of clinical sites indices s
T	The set of time periods t
K	The set of scenarios indices k

All parameters used in the model are listed in Table 3.2. The values of stochastic parameters differ at each scenario and are sampled from certain distributions described in Chapter 3.4.1. Although D_t^k and γ_{it}^k are subscripted by t, their values in a scenario only change after the prespecified time periods where an interim analysis occurs.

Table 3.2 Parameters of the Production-Inventory-Transportation Problem

Parameters	
c_i^p	Production cost of (minimal packaged) dosage i; *$/dose*
c_s^r	Recruitment and enrollment cost of site s; *$/week*
c_s^s	Shipping cost of site s; *$/box*
c^h	Holding cost at distribution center; *$/dose/week*
c_s^h	Holding cost at site n; $c_s^h > c^h$; *$/dose/week*
c_{ni}^w	Disposal/recycle cost of dosage i left at site n at the end of horizon; *$/dose*
L	Shipment lead time of all dosages and sites; $L > 0$; *week*
τ	Addition periods required to finish the treatment; $\tau \geq L$; *week*
V	Volume of a dose; in^3
Q_{box}	Capacity of a cold shipping box; in^3
Q_s	Capacity limit of site s; in^3
M	Large number
Stochastic Parameters	
n_{st}^k	Number of enrolled patients at site s at period t
α_{st}^k	Period-based patient drop-out rate of site s at period t
D_t^k	Target sample size of the trial at period t
γ_{it}^k	Average consumption of dosage i at period t; *dose/patient*

The decision variables needed to form this problem are listed in Table 3.3, where the production decisions x_i are not superscripted by k because they are here-and-now decisions and determined without the realization of future scenarios, i.e. prior to the reveal of stochastic data. The rest of the variables are wait-and-see decisions and belong to the second stage.

Table 3.3 Decision Variables of the Production-Inventory-Transportation Problem

x_i	Produced amount of dosage i; *dose*
N_{st}^k	Cumulative number of samples collected from site s at the end of period t
y_{it}^k	Inventory of dosage i at distribution center at the end of period t; *dose*
y_{sit}^k	Inventory of dosage i at site s at the end of period t; *dose*
u_{si}^k	Amount of dosage i shipped to site s before the trial starts; *dose*
u_{sit}^k	Amount of dosage i shipped to site s at period t; *dose*
v_s^k	Number of boxes used for the shipment to site s before the trial starts
v_{st}^k	Number of boxes used for the shipment to site s at period t
δ_t^k	Binary status of open enrollment; 0 means terminated
θ_t^k	Binary status of drug supply; 0 means terminated

The deterministic equivalent of the two-stage stochastic program for this problem is formulated as below, where the number of second-stage problems corresponds to the size of set K. The two-stage structure is usually resolved by reformulating into extensive form (EF) [39-41], for which we substitute the corresponding (7) into (5) and minimize all the variables together subject to (6) and (8)-(28) with respect to each k. The resulting EF problem is a large mixed-integer nonlinear program (MINLP) and is referred to original problem in the following content.

First Stage:

$$\min_{x_i} \sum_{i\in I} c_i^p x_i + \sum_{k\in K} \frac{1}{|K|}\phi^k(x_i) \tag{5}$$

$$x_i \in \mathbb{R}_+ \qquad \forall i \tag{6}$$

Second Stage:

Minimize

$$\phi^k = \sum_{t\in T}\sum_{s\in S} c_s^r \delta_t^k + \sum_{s\in S} c_s^s v_s^k + \sum_{t\in T}\sum_{s\in S} c_s^s v_{st}^k + \sum_{t\in T}\sum_{i\in I} c^h \theta_t^k y_{it}^k + \sum_{t\in T}\sum_{s\in S}\sum_{i\in I} c_s^h \theta_t^k y_{sit}^k + \sum_{s\in S}\sum_{i\in I} c_{si}^w y_{siT}^k \tag{7}$$

Subject to

Sample Size

$$N_{st}^k = N_{s,t-1}^k + \delta_{t-\tau}^k n_{s,t-\tau}^k \prod_{m=0}^{\tau-1}\left(1-\alpha_{s,t-m}^k\right) \qquad \forall s, t > \tau \tag{8}$$

	$N_{st}^k = 0$	$\forall s, t \leq \tau$	(9)
Trial	$\theta_t^k = 1$	$t = 1$	(10)
Termination	$D_{t-1}^k \leq \sum_{s \in S} N_{s,t-1}^k + M\theta_t^k$	$\forall t > 1$	(11)
	$\sum_{s \in S} N_{s,t-1}^k < D_{t-1}^k + M(1 - \theta_t^k)$	$\forall t > 1$	(12)
	$\delta_t^k = \theta_{t+\tau}^k$	$\forall t \in [1, \lvert T \rvert - \tau\,]$	(13)
	$D_t^k \leq \sum_{s \in S} N_{st}^k$	$t = T$	(14)
Inventory of	$y_{it}^k = y_{i,t-1}^k - \theta_t^k \sum_{s \in S} u_{sit}^k$	$\forall i, t > 1$	(15)
DC	$y_{it}^k = x_i - \sum_{s \in S} u_{si}^k - \sum_{s \in S} u_{sit}^k$	$\forall i, t = 1$	(16)
Inventory of	$y_{sit}^k = y_{si,t-1}^k + \theta_{t-L}^k u_{si,t-L}^k - d_{ksit}^1$	$\forall s, i, t > \tau$	(17)
Sites	$y_{sit}^k = y_{si,t-1}^k + \theta_{t-L}^k u_{si,t-L}^k - d_{ksit}^2$	$\forall s, i, t \in (L, \tau]$	(18)
	$y_{sit}^k = y_{si,t-1}^k - d_{ksit}^3$	$\forall s, i, t \in (1, L]$	(19)
	$y_{sit}^k = u_{si}^k - \gamma_{it}^k \delta_t^k n_{st}^k$	$\forall s, i, t = 1$	(20)
Capacity	$\sum_{i \in I} V u_{si}^k \leq Q_s$	$\forall s$	(21)
restriction	$\sum_{i \in I} V y_{si,t-1}^k + \sum_{i \in S} V u_{si,t-L}^k \leq Q_s$	$\forall s, t > L$	(22)
	$\sum_{i \in I} V y_{sit}^k \leq Q_s$	$\forall s, t \leq L$	(23)
Shipment	$\sum_{i \in I} V u_{si}^k \leq Q_{box} v_s^k$	$\forall s$	(24)
	$\sum_{i \in I} V u_{sit}^k \leq Q_{box} v_{st}^k$	$\forall s, t$	(25)
Bounds	$\delta_t^k, \theta_t^k \in \{0,1\}$	$\forall i, s, t, j \in \mathrm{J}^{st}$	(26)
	$N_{st}^k, y_{it}^k, y_{sit}^k, u_{si}^k, u_{sit}^k \in \{0, \mathbb{R}_+\}$	$\forall s, i, t$	(27)
	$v_s^k, v_{st}^k \in \{0, \mathbb{Z}_+\}$	$\forall s, i, t$	(28)

Note that the d_{ksit}^1, d_{ksit}^2, and d_{ksit}^3 in (17)-(19) are functions of δ_t, expressed as (29)-(31), and consist of drug consumption terms contributed by currently enrolled patients and patients who arrived in early periods but have not finished their treatments. Note that a portion of patients will drop out at every period, so there exists cumulative multiplication of $1 - \alpha_{st}^k$.

$$d_{ksit}^1 = \gamma_{it}^k \delta_t^k n_{st}^k + \sum_{j=1}^{\tau} \gamma_{i,t-j}^k \delta_{t-j}^k n_{s,t-j}^k \prod_{m=0}^{j-1} \left(1 - \alpha_{s,t-m}^k\right) \quad (29)$$

$$d_{ksit}^2 = \gamma_{it}^k \delta_t^k n_{st}^k + \sum_{j=1}^{\mathrm{t-L}} \gamma_{i,t-j}^k \delta_{t-j}^k n_{s,t-j}^k \prod_{m=0}^{j-1} \left(1 - \alpha_{s,t-m}^k\right) \quad (30)$$

$$d^3_{ksit} = \gamma^k_{it}\delta^k_t n^k_{st} + \sum_{j=1}^{t-1} \gamma^k_{i,t-j}\delta^k_{t-j} n^k_{s,t-j} \prod_{m=0}^{j-1}\left(1-\alpha^k_{s,t-m}\right) \quad (31)$$

The objective function of the EF problem, (5) and (7), consists of production cost and the expectation of the recruitment costs, initial shipping costs, shipping costs incurred during the trial horizon, holding costs of the distribution center, holding cost of sites, and the recycling costs of drug wastage by the end of the horizon respectively.

Regarding the trial termination, constraint (8) ensures the incremental number of samples, i.e. patients who finished their treatments, at current period is the number of patients enrolled τ-periods ago multiplied by according drop-out rates, and constraint (9) is its initial condition. Constraint (10) specifies that the initial status of drug supply is on. Constraint (11) and (12) ensures that the supply is terminated only as the target sample sized is reached, otherwise the supply continues. Constraint (13) specifies that the open enrollment status is τ-periods ahead of the supply status. when the enrollment stops, the last cohort of patients still require the availability of drugs during the treatment span. Hence, the termination of the supply is τ-periods later. Constraint (14) specifies that there will be enough samples collected by the end of the horizon. Otherwise, the problem is infeasible because the trial is doomed to fail or be incomplete due to insufficient patient arrival.

As for the drug supply, constraint (15) and (16) ensure that the inventory difference between the end of current and the immediately previous periods equals to the amount of drugs shipped out of the DC. Similarly, constraints (17)-(20) ensure the inventory balance at clinical sites due to drug resupply and consumption. Constraint (21)-(23) ensure that the amount of resupply or the inventory at the beginning of any period will not exceed the space limit of clinical sites. Constraints (24) and (25) impose the capacity restriction on every shipments and specify the number of boxes needed in each shipment. Finally, Constraints (26)-(28) indicate bounds on the decision variables.

Note that this stochastic program is not fixed recourse, not relatively complete recourse, non-linear, and not fully continuous, which results in considerable difficulty in solving it efficiently. For the nonlinearity, we may resort to linearization-reformulation techniques. The non-linear constraints (15), (17), and (18) can be linearized via Big-M method. Take constraint (17) as an example, $y^k_{sit} - y^k_{si,t-1} + d^1_{ksit} = \theta^k_{t-L} u^k_{si,t-L}$ can be reformulated as (32)-(35).

$$y_{sit}^{k} - y_{si,t-1}^{k} + d_{ksit}^{1} \geq u_{si,t-L}^{k} + M(1 - \theta_{t-L}^{k}) \qquad \forall s, i, t > \tau \qquad (32)$$

$$y_{sit}^{k} - y_{si,t-1}^{k} + d_{ksit}^{1} \leq u_{si,t-L}^{k} + M(1 - \theta_{t-L}^{k}) \qquad \forall s, i, t > \tau \qquad (33)$$

$$y_{sit}^{k} - y_{si,t-1}^{k} + d_{ksit}^{1} \geq 0 + M\theta_{t-L}^{k} \qquad \forall s, i, t > \tau \qquad (34)$$

$$y_{sit}^{k} - y_{si,t-1}^{k} + d_{ksit}^{1} \leq 0 + M\theta_{t-L}^{k} \qquad \forall s, i, t > \tau \qquad (35)$$

In addition to the above formulation for the freely resupply problem, we introduce the additional variables and constraints below for the four resupply schemes in our study: Q-r, S-s, $(\text{Q-r})_{si}$, and $(\text{S-s})_{si}$. The $(\text{Q-r})_{si}$ and $(\text{S-s})_{si}$ are the cases in which the safety stock level and shipment trigger criteria are independent of sites and dosages. In contrast, all sites and dosages in Q-r and S-s cases respectively follow a universal policy. The z_{sit}^{k} indicates whether the current inventory level is below the replenishing threshold; the z'^{k}_{sit} indicates whether a shipment is triggered. Constraint $z_{sit}^{k} - z_{si,t-1}^{k} \geq 1$ prevents repeating replenishments due to shipping lead time.

$(\text{S-s})_{si}$ scheme	$S_{si}^{k}, s_{si}^{k} \in \mathbb{Z}_{+}$	$\forall s, i$	
	$z_{sit}^{k}, z'^{k}_{sit} \in \{0,1\}$	$\forall s, i, t$	
	$S_{si}^{k} \geq s_{si}^{k}$	$\forall s, i$	
	$\begin{bmatrix} z_{sit}^{k} = 1 \\ y_{sit}^{k} < s_{si}^{k} \end{bmatrix} \vee \begin{bmatrix} z_{sit}^{k} = 0 \\ y_{sit}^{k} \geq s_{si}^{k} \end{bmatrix}$	$\forall s, i, t$	(36)
	$\begin{bmatrix} z'^{k}_{sit} = 1 \\ z_{sit}^{k} - z_{si,t-1}^{k} \geq 1 \end{bmatrix} \vee \begin{bmatrix} z'^{k}_{sit} = 0 \\ z_{sit}^{k} - z_{si,t-1}^{k} < 1 \end{bmatrix}$	$\forall s, i, t > 1$	
	$u_{sit}^{k} = z'^{k}_{sit}\left(S_{si}^{k} - y_{sit}^{k}\right)$	$\forall s, i, t$	
$(\text{Q-r})_{si}$ scheme	$Q_{si}^{k}, r_{si}^{k} \in \mathbb{Z}_{+}$	$\forall s, i$	
	$z_{sit}^{k}, z'^{k}_{sit} \in \{0,1\}$	$\forall s, i, t$	
	$\begin{bmatrix} z_{sit}^{k} = 1 \\ y_{sit}^{k} < r_{si}^{k} \end{bmatrix} \vee \begin{bmatrix} z_{sit}^{k} = 0 \\ y_{sit}^{k} \geq r_{si}^{k} \end{bmatrix}$	$\forall s, i, t$	(37)
	$\begin{bmatrix} z'^{k}_{sit} = 1 \\ z_{sit}^{k} - z_{si,t-1}^{k} \geq 1 \end{bmatrix} \vee \begin{bmatrix} z'^{k}_{sit} = 0 \\ z_{sit}^{k} - z_{si,t-1}^{k} < 1 \end{bmatrix}$	$\forall s, i, t > 1$	
	$u_{sit}^{k} = z'^{k}_{sit} Q_{si}^{k}$	$\forall s, i, t$	

S-s scheme	$S^k, s^k \in \mathbb{Z}_+$		
	$z^k_{sit}, z'^k_{sit} \in \{0,1\}$	$\forall s, i, t$	
	$S^k \geq s^k$		
	$\begin{bmatrix} z^k_{sit} = 1 \\ y^k_{sit} < s^k \end{bmatrix} \vee \begin{bmatrix} z^k_{sit} = 0 \\ y^k_{sit} \geq s^k \end{bmatrix}$	$\forall s, i, t$	(38)
	$\begin{bmatrix} z'^k_{sit} = 1 \\ z^k_{sit} - z^k_{si,t-1} \geq 1 \end{bmatrix} \vee \begin{bmatrix} z'^k_{sit} = 0 \\ z^k_{sit} - z^k_{si,t-1} < 1 \end{bmatrix}$	$\forall s, i, t > 1$	
	$u^k_{sit} = z'^k_{sit}(S^k - y^k_{sit})$	$\forall s, i, t$	
Q-r scheme	$Q^k, r^k \in \mathbb{Z}_+$		
	$z^k_{sit}, z'^k_{sit} \in \{0,1\}$	$\forall s, i, t$	
	$\begin{bmatrix} z^k_{sit} = 1 \\ y^k_{sit} < r^k \end{bmatrix} \vee \begin{bmatrix} z^k_{sit} = 0 \\ y^k_{sit} \geq r^k \end{bmatrix}$	$\forall s, i, t$	(39)
	$\begin{bmatrix} z'^k_{sit} = 1 \\ z^k_{sit} - z^k_{si,t-1} \geq 1 \end{bmatrix} \vee \begin{bmatrix} z'^k_{sit} = 0 \\ z^k_{sit} - z^k_{si,t-1} < 1 \end{bmatrix}$	$\forall s, i, t > 1$	
	$u^k_{sit} = z'^k_{sit} Q^k$	$\forall s, i, t$	

3.3 A Progressive Hedging based Heuristic

Progressive hedging (PH) is a popular and flexible scenario-based decomposition approach to solving large-scale stochastic mixed-integer programs (SMIPs) [40, 42-44]. The computational difficulty associated with large problem instances is mitigated by decomposing the problem into smaller scenario problems that have similar or the same problem structure, which facilitates the use of parallel computing and preserves the flexibility of incorporating other existing approaches to the deterministic scenario subproblems [39, 45]. PH does not guarantee the convergence and is usually used as heuristic methods for proximate solutions [41].

To perform scenario decomposition, we introduce the copies of first-stage variables respective to scenarios and enforce the equalities between them, known as non-anticipativity constraints (NACs). This reformulation leads to the so-called extensive form of scenario formulation (EFS) of the stochastic program. With shorthand notations, let the EFS of our problem violating the NACs be expressed as (40)-(41), where x^k and y^k are the vectors of first-stage and second-stage

variables with respect to scenario k, C and G are first-stage and second-stage cost vectors, and $\mathbb{X}^k$ denotes the partitioned feasible region that violates the NACs. Note that (40)-(41) is scenario decomposable and the feasible solutions of (40)-(41) that happen to satisfy the NACs are also feasible to the original problem.

$$\min_{\text{all } x^k, y^k} \sum_{k \in K} \frac{1}{|K|} (Cx^k + Gy^k) \tag{40}$$

$$\text{s.t. } (x^k, y^k) \in \mathbb{X}^k \ \forall k \tag{41}$$

Progressive hedging algorithm (PHA) aims at iteratively driving the feasible solution of (40)-(41) to satisfy the NACs and meanwhile minimizing the objective function, i.e. (40) or (5). The driving force of satisfying NACs is resulted from minimizing (40) along with proximal terms that measure the deviation of the scenario solutions x^k. The general procedure of PHA can be illustrated as Fig 3.1, where ρ is a user-specific parameter vector, ω^k are called dual price vectors, i denotes iterations, and k still denotes scenarios.

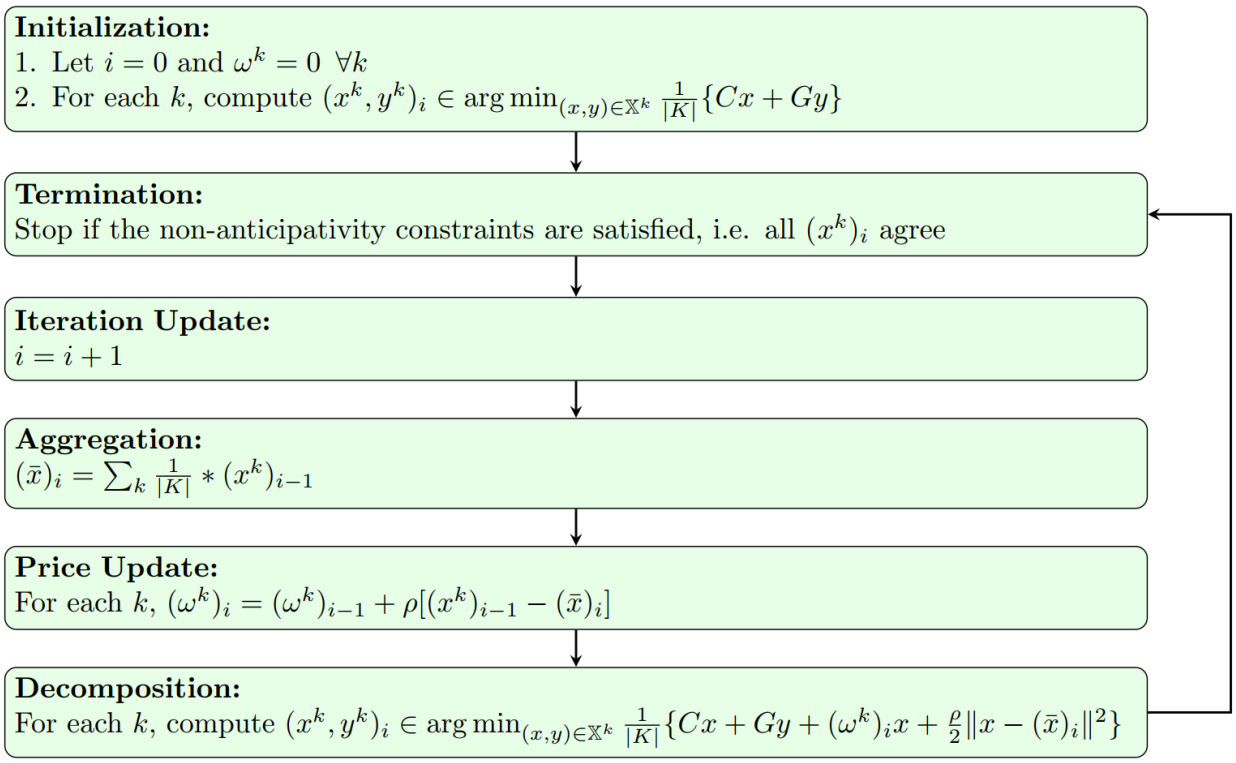

Fig 3.1 Flowchart of Progressive Hedging Algorithm for Two-Stage SMIPs

Since our first-stage variables are continuous, the algorithm is considered as terminated when the x^k converges to within a small tolerance, for which we use maximal difference, i.e. $\max\{x^k \mid k \in K\} - \min\{x^k \mid k \in K\} \leq \epsilon$, as the criterion and the tolerance ϵ is set to be 0.3 in our study. The selection of ρ follows the cost-proportional principle demonstrated by Watson et al. (2007) [40].

We then propose a pre-solving procedure to reduce the computational burden because we observed that a scenario-specific subproblem, e.g. $\min\{C\mathrm{x} + G\mathrm{y} | (\mathrm{x}, \mathrm{y}) \in \mathbb{X}^k\}$, cannot be solved through commercial MIP solvers within reasonable amount of time. This proposed procedure takes advantage of the problem structure to separate the trial termination problem from the drug supply problem. By solving the trial termination problem separately, we can obtain optimal termination decisions of the scenario-specific subproblem, i.e. δ_t^k and θ_t^k, in advance. The reduction in computational time of solving the scenario-specific subproblem results from the fixation of δ_t^k and

θ_t^k. The procedure is shown as Fig 3.2 below and incorporated into every step that requires solving scenario subproblem in the PHA.

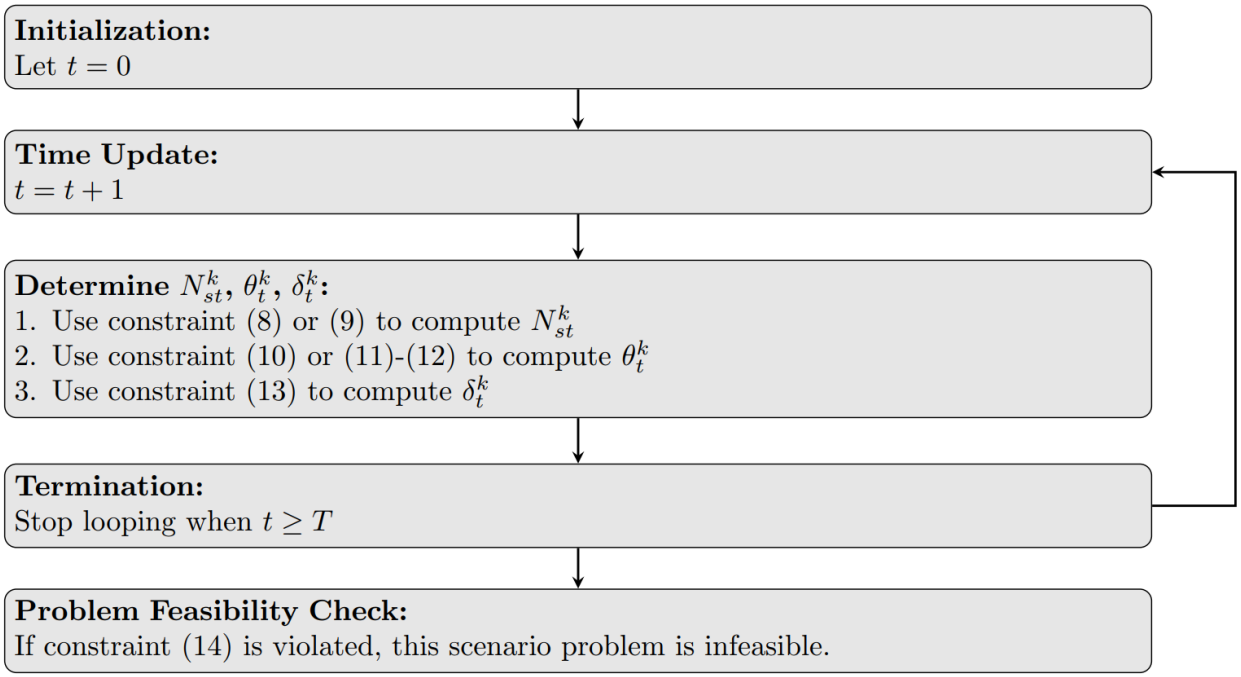

Fig 3.2 Flowchart of Proposed Presolving Procedure

In addition, we apply scenario bundling technique to the PHA, where the problem is decomposed according to bundles of scenarios instead of individual scenarios. By treating the bundles as decomposition units, the convergence at the master level of PHA can be enhanced. However, the bundles are computationally more difficult than single scenarios. Many studies focus on the efficiency of scenario bundling/clustering [39, 46-48]. For our problem, we choose the bundle size of 3 scenarios and considered two bundling schemes: random bundling and maximal similarity, where the similarity measure is the termination time obtained via the presolving procedure.

3.4 Numerical Case Study

3.4.1 Instance Generation

The information of the case for study is listed in Table 3.4. Regarding the stochastic parameters, we created distributions to simulate the uncertainties. First, the number of patients enrolled at each

clinical site and period, n_{st}, independently follows a Poisson distribution, where the mean is set to 7.14 for enough samples to be collected in the trial. Second, the patient drop-out rate at each site and period, α_{st}, follows a triangular distribution where the mean is set to be $1 - \sqrt[\tau]{0.7}$ because the average dropout rate across all clinical trials is around 30% [49]. Third, a new target sample size is governed by two distributions. One is a discrete uniform distribution over three outcomes that represent increase, no change, and decrease respectively. The other is a discrete uniform distribution over 10 outcomes, {5%, 10%, …, 50%}, representing the percentage change in the size. Fourth, new average consumption of each dosages is independently governed by a uniform distribution over [0, 4], which includes all possible dose-consumption outcomes resulted from adaptive randomization and arm-dropping. For each scenario k, a set of n_{st}^k, α_{st}^k, D_t^k, and γ_{it}^k are sampled from the distributions accordingly. Note that sampling new values for D_t^k, and γ_{it}^k are restricted by the interim analysis timepoints and that $\sum_{i \in I} \gamma_{it}^k = 4$ for all $t \in T$ is enforced.

Table 3.4 Basic Information of the Case

Trial Information		Drug Supply Information	
Maximum Trial Duration	16 weeks	Clinical Sites	5
Trial Arms	multiple	Produced Dosages	3 MPDs
Treatment Span	2 weeks	Drug Form	tablet (or shot)
Initial Target Size	200 patients	Drug Consumption	4 blind doses/patient/week
Interim Analysis Point	8th week	Shipment Leadtime	1 week
Treatment Allocation	adaptive		
Trial Sample Size	adaptive		

For production costs c_i^p, we use the information of average API price per kilogram reported by Hill, A. M., et al. (2018) [50] to generate the price per dose: \$0.5, \$25.5, and \$50.5 for the 3 MPDs. For recruitment and enrollment costs c_s^r, we use the information of screening rates reported by Forte Research [51] and screening prices reported by Pivotal Financial Consulting [52] to generate the period-based cost for each sites, which depends on the previously estimated mean patient arrival and approximately ranges within \$2,000-\$4,000 per week. Holding costs of the distribution center and sites c^h and c_s^h are \$0.5 and \$2.5/dose/week, respectively. As for shipments, we refer

to the cold shipping service provided by FedEx. A small standard duration box has the volume of 64 in^3 and the price of $46. One-third of the sites will need longer cooling duration and cost $57/box. The volume of a dose V is 0.426 in^3/tablet or 2.56 in^3/shot. As for the capacity limit of sites Q_s, we choose larger numbers in order to see the space needed for optimal inventory solution. Disposal and recycle costs c_{ni}^w are estimated based on factors used in generating production and shipping cost and have prices of $25.55/dose or $31.05/dose regardless of dosages.

3.4.2 Performance of Bundling Schemes

We applied two bundling schemes with size of 3 scenarios to our PHA and compare the CPU time required to solve the same problem instances with using no scenario bundle, shown as Table 3.5. Two instances with different number of scenarios are generated and solved under freely resupply scheme.

Table 3.5 CPU Time between Different Scenario Bundling Schemes

Bundling Scheme	5 scenarios	15 scenarios
Random bundling	2,790 s	33,607 s
Maximal Similarity	14,411 s	39,755 s
No bundling	25,692 s	>120,611 s

From Table 3.5, we can see that scenario bundling can facilitated the solution time and that the random bundling scheme has the best performance for our problem. The results also suggest that the convergence in first-stage variables is now computationally more difficult than solving decomposed subproblems. Note that, before we apply the presolving procedure, the CPU time it takes to solve a scenario subproblem is more than 5 days.

3.4.3 Impact of Adaptations Types

We have incorporated the adaptations of ACTs into the supply chain problem, and the uncertainty of the adaptations are reflected on two stochastic parameters, D_t^k and γ_{it}^k. Here we investigate the impact of trial size and dose consumption uncertainties by comparing four cases, None-adapted, Size-only, Dose-only, and All-adapted, shown as Table 3.6, where no changes means the trial size or dose consumption stays the same as the initial values throughout the entire horizon.

Table 3.6 Cases of Adaptation Types

Types	Changes in D_t^k	Changes in γ_{it}^k
None-adapted	No	No
Size-only	Yes	No
Dose-only	No	Yes
All-adapted	Yes	Yes

An instance with 5 scenarios is generated and solved under Q-r resupply scheme by the PHA with random bundling. The results are presented in Table 3.7 and Table 3.8, where drug overage is defined as the total manufactured doses divided by the actual doses consumed in the trial and the wastage cost is the cost of disposing/recycling the doses left at clinical sites in the end of supply. Note the results are expected values with respective to scenarios.

Table 3.7 Basic Comparison between Adaptation Types

	CPU Time (s)	Trial Length	Total Cost ($)	Drug Overage
None-adapted	19,169	9.8	200,418	1.0655
Size-only	50,785	9.4	214,029	1.4932
Dose-only	29,952	9.8	202,556	1.1320
All-adapted	30,558	9.4	222,026	1.5905

Table 3.8 Cost Distribution between Adaptation Types

	Production Cost ($)	Inventory Cost ($)	Shipping Cost ($)	Recruitment Cost ($)	Wastage Cost ($)
None-adapted	56,716	16,930	965	124,746	1,061
Size-only	72,603	20,583	956	119,076	811
Dose-only	57,940	17,898	1,120	124,746	852
All-adapted	80,452	21,053	967	119,076	478

In Table 3.7, None-adapted cases is the benchmark representing a drug supply case in absence of trial adaptation certainty, i.e. only patient arrival and dropout uncertainties. According to the trial length of Size-only case, we know that the adaptations of trial sample size in this specific instance has an overall effect of trial length reduction. However, overall shorter trial and less patients needed did not lead to less total cost or drug overage because the supply planning has to accommodate the uncertainty of having longer trial and more patients in some scenarios. In the comparison between Size-only and Dose-only, we see that the impact of size adaptation is much heavier than the adaptions related to dose consumption in terms of total cost and drug overage. Base on Table 3.8, we see that the increase of supply cost in Size-only case is majorly contributed by production and inventory because of the need of covering large-sample-size scenarios and storing the excess doses in small-sample-size scenarios. However, the increase of supply cost in Dose-only case are distributed quite evenly in each category. Finally, when both adaptations are presented, i.e. All-adapted case, we see even higher total cost and drug overage because of the higher extent of uncertainties.

3.4.4 Comparison between Resupply schemes

In this subsection, we study the advantages or disadvantages between different resupply schemes. Characteristics of the five schemes are summarized in Table 3.9, and the details of implementation is described as (36)-(39).

Table 3.9 Characteristics of Resupply Schemes

Resupply Schemes	Trigger of Resupply	Replenishment	Same policy for all sites and dosages?
freely	anytime	any quantity	N/A
$(Q\text{-}r)_{si}$	threshold-controlled	fixed quantity	No
$(S\text{-}s)_{si}$	threshold-controlled	threshold-controlled	No
Q-r	threshold-controlled	fixed quantity	Yes
S-s	threshold-controlled	threshold-controlled	Yes

An instance with 5 scenarios is generated and solved by the PHA with random bundling. The results of supplying tablet-form drugs are presented in Table 3.10, where drug overage is defined

as the total manufactured doses divided by the actual doses consumed in the trial and the wastage cost is the disposal/recycle cost. Note the results are expected values with respective to scenarios. All five resupply schemes have same expected trial length of 9.4 weeks and recruitment cost of $119,075 because patient arrival and dropout are the same in an instance.

Table 3.10 Costs and Drug Overage of Tablet-form Drugs Supply

Resupply Schemes	CPU Time (s)	Total Cost ($)	Production Cost ($)	Inventory Cost ($)	Shipping Cost ($)	Wastage Cost ($)	Drug Overage
freely	2,789	209,316	80,144	7,891	2,205	0	1.5767
$(Q\text{-}r)_{si}$	50,927	215,626	80,253	14,506	1,262	529	1.5795
$(S\text{-}s)_{si}$	9,468	216,914	80,299	16,174	1,105	260	1.5813
Q-r	133,408	221,529	80,512	20,237	979	725	1.5885
S-s	8,862	221,094	80,290	16,764	4,693	272	1.5804

Table 3.11 Storage Space Required at Sites for Tablet-form Drugs Supply

Resupply Schemes	Site #1 (in^3)	Site #2 (in^3)	Site #3 (in^3)	Site #4 (in^3)	Site #5 (in^3)
freely	36	33	31	42	36
$(Q\text{-}r)_{si}$	129	159	133	145	116
$(S\text{-}s)_{si}$	134	159	125	129	120
Q-r	142	159	169	159	206
S-s	193	168	188	233	162

From Table 3.10, we see that the freely resupply scheme has the best performance in terms of total cost, drug overage, and solution time. The other schemes in the order of high performance are $(Q\text{-}r)_{si}$, $(S\text{-}s)_{si}$, Q-r, and S-s. This shows that a resupply scheme with higher flexibility, i.e. less (universal) restrictions on resupply trigger and amount, will have better supply performance. In the comparison between quantity-reorder and floor-ceiling schemes, quantity-reorder schemes are generally favored in this ACT supply problem, which may result from the short finite-patient horizon. Floor-ceiling schemes are only favored in terms of less shipping cost, and $(S\text{-}s)_{si}$ is

preferred to $(\text{Q-r})_{si}$ in terms of less drug wastage cost. As for the storage capacities needed at each site, a better resupply scheme also requires less storage spaces in general. The difference in needed space is small between the schemes other than freely resupply.

To further examine the performance of the resupply schemes, we consider the supply of drugs with much larger volume. The shot form of medicine has volume of 2.56 in^3, while previously the tablet form is 0.426 in^3. Note the instance we used here is the same as the previous one, except the volume of a dose, parameter V, is raised. The results are presented in Table 3.11 and Table 3.12, and the trial length and recruitment cost remain the same.

Table 3.12 Costs and Drug Overage of Shot-form Drugs Supply

Resupply Schemes	CPU Time (s)	Total Cost ($)	Production Cost ($)	Inventory Cost ($)	Shipping Cost ($)	Wastage Cost ($)	Drug Overage
freely	2,664	211,767	80,144	8,036	4,512	0	1.5769
$(\text{Q-r})_{si}$	4,365	218,650	80,174	14,036	4,894	470	1.5774
$(\text{S-s})_{si}$	2,669	220,777	80,323	16,460	4,659	261	1.5809
Q-r	3,153	225,152	80,211	20,698	4,542	625	1.5830
S-s	14,059	224,284	80,306	19,557	4,517	829	1.5906

Table 3.13 Storage Space Required at Sites for Shot-form Drugs Supply

Resupply Schemes	Site #1 (in^3)	Site #2 (in^3)	Site #3 (in^3)	Site #4 (in^3)	Site #5 (in^3)
freely	221	215	186	230	193
$(\text{Q-r})_{si}$	601	537	690	559	505
$(\text{S-s})_{si}$	776	878	749	755	753
Q-r	1,594	1,374	1,446	1,019	869
S-s	830	972	1,046	1,004	1,295

It is not surprising that all five schemes here have the increased total supply cost, contribute by an increase in shipping cost. However, the performance of S-s becomes superior to Q-r in terms of total cost and required space at sites, even though S-s still has worse drug overage and wastage cost. The other resupply schemes remain the same order of performance. In addition, the higher shipping cost due to the change drug-form drives the supply to have more discreet prediction on production amount, resulting in the decrease in drug overage.

3.5 Conclusions

This work introduces a special type of drug supply chain management problem to the literature. The unique characteristics include uncertain finite-customer supply horizon, demand-repeating and length-fixed window of customers' stay, uncertain customer arrival and drop-out, and uncertain multi-product demands per customer. To facilitate drug supply chain management in the presence of different sources of uncertainties resulted from ACTs, we proposed a two-stage stochastic MINLP and study several important aspects of trial supply, including drug wastage, resupply policy, trial length, and overall costs.

The key finding of our numerical study is that the impact of trial sample size adaptation is much significant than the adaptions related to average dose consumption per patient, e.g. changes in randomization ratios, in terms of total cost and drug overage. In addition, even though the size re-estimation may lead to expected shorter trial, the expected supply cost and drug overage will still be higher than the case in absence of trial adaptations, which aligns with the observation that "adaptive designs are potentially more costly than traditional studies" by Burnham et al. (2015) [1]. As for the resupply policy, quantity-reorder schemes are generally favored, compared to floor-ceiling schemes, in this ACT supply problem. In addition, when the medicine is in the form of shots with much larger volume than tablets, the shipping cost becomes a driver to the more discreet prediction on production quantity, resulting in decreased drug overage.

We also noticed that a resupply scheme with less restrictions on the replenishment quantity and trigger will result in better management performance. In most of industries, the benefit of freely resupply is probably hard to achieve. However, in clinical trials, the consumption of treatment dosages is specified according to the randomization schedules and recorded in a centralized

management system, e.g. interactive web response system (IWRS), which enables the implementation of more complicated resupply solutions than traditional policies.

A limitation of this project is that we do not have real data to have deeper practical managerial insights. What we can suggest based on our findings is that, when adapting trial size and randomization are both feasible options to achieve the objective of ACTs, adapting the randomization will cause less burden on the supply chain side. The future extensions of this work include expanding the distribution network to international drug supply, adding clinical sites selection to study the characteristics of promising sites, and embedding advertisement problem to study the optimal investment plan in terms of trial completion and costs.

4. TRIAL ADAPTATION AND DRUG SUPPLY JOINT OPTIMIZATION FOR ADAPTATIVE CLINICAL TRIALS

4.1 A Patient Assignment and Drug Supply Problem

This problem aims at incorporating adaptive designs and adaptation procedures with the drug supply chain problem and studying the impact of the joint optimization on trial and supply management numerically. For trial design and adaptation, we consider two types of adaptive trials, SSR and RAR, and focus on their key adaptations, target total sample size and patient allocation/assignment. For drug supply, we still have a multi-dosage, multi-sites, multi-period, and multi-echelon supply chain framework. The connection between them lies in drug demand, which relates to patient arrival, patient response to dosage/treatment, and patient allocation/assignment to arms. In this problem, we optimize supply and patient assignment decisions subject to design rules of the ACTs, given the predicted information of patient arrival and responses, for minimum production, inventory, transportation, and recruitment costs.

With respect to the trial, we targeted on a randomized sequential trial with two parallel arms and binary response, where the size re-estimation and randomization adaptation occur in every time period (except for the first few periods of treatment lead time). Random number of patients will be enrolled at different clinical sites and at discrete time periods, and each one of them will be allocated to a specific arm/treatment that represents the use of a specific dosage of the investigational drug. Patient responses can only be observed after a prespecified treatment duration/span, which is independent of arms/treatments due to trial blindness. The trial termination is the satisfaction of the target total sample size re-estimated every period.

In terms of the supply, the immediate availability of drugs is always enforced, and no backlog or cross shipment between sites is allowed. All dosages are produced in one campaign prior to the beginning of the trial and stored at one distribution center (DC). The distances between the DC and sites vary and are reflected on shipping costs instead of shipping time. The lead time of shipment is shorter than the treatment span/duration. All dosages are shipped together in boxes with same capacity via FedEx cold chain service. The cost of storing drugs is higher at clinical

sites than at the DC. When the trial is terminated, no shipment or change in inventory levels is allowed.

4.2 A Mixed-Integer Nonlinear Program

We have sets of arms, sites, periods, and patients defined in Table 4.1, where the size of patient set J^{st} corresponds to the number of enrolled patients n_{st}. The number of sets J^{st} we have in the model depends on the size of $S \times T$. We also define the union set Ω_J^{St} for the convenience of reviewing the patient responses collected from the beginning to period t across all sites.

Table 4.1 Sets and Indices in the Model

I	The set of arms/treatments/dosages indices i
S	The set of clinical sites indices s
T	The set of time periods t
J^{st}	The set of patients indices j who enrolled at site s time t; $J^{st} = \{1, \dots, n_{st}\}$
Ω_J^{St}	The union of sets J^{st} for all sites and time periods earlier than and equal to t; $\Omega_J^{St} = \{J^{11}, \dots, J^{\lvert S\rvert 1}, J^{12}, \dots, J^{\lvert S\rvert 2}, \dots, J^{1t}, \dots, J^{\lvert S\rvert t}\}$

All the parameters used in the model are listed in Table 4.2. Note the n_{st} and X_{ij}^{st} are usually treated as uncertainty sources. However, to prevent from an overly complicated model beyond regular solution approaches, we consider them as deterministic parameters and sample the values of them via a simulator.

Table 4.2 Parameters in the Model

c_i^p	Production cost of dosage i; *$/dose*
c_s^r	Recruitment and enrollment cost of site s; *$/week*
c_s^s	Shipping cost of site s; *$/box*
c^h	Holding cost at distribution center; *$/dose/week*
c_s^h	Holding cost at site n; $c_s^h > c^h$; *$/dose/week*
L	Shipment lead time of all dosages and sites; $L > 0$; *week*
τ	Addition periods required to finish the treatment; $\tau \geq L$; *week*
V	Volume of a dose; in^3
Q_{box}	Capacity of a (cold) shipping box; in^3
Q_s	Capacity limit of site s; in^3
γ_i	Number of doses needed per period per patient in arm/treatment i; *dose/week/patient*
D_0	Initial target of total sample size designed for this trial
Δ	Critically important difference between two arms
M	Large number
n_{st}	Number of enrolled patients at site s at period t
X_{ij}^{st}	Binary response of patient j enrolled at site s and period t and receiving dosage i

The decision variables needed to form this problem are listed in Table 4.3.

Table 4.3 Decision Variables in the Model

x_i	Produced amount of dosage i; *dose*
π_{ij}^{st}	Binary decision of assigning patient j who enrolled at site s and period t to arm i
N_{it}	Cumulative number of patients who finished treatment i by the end of period t
$\widehat{D}_t$	Total sample size needed for this trial estimated at the end of period t
$\hat{p}_{it}$	Positive/success rate/possibility of dosage i estimated at period $t > \tau$
ρ_{1t}	Allocation proportion of arm $i = 1$ implemented in period t
y_{it}	Inventory of dosage i at distribution center at the end of period t; *dose*
y_{sit}	Inventory of dosage i at site s at the end of period t; *dose*
u_{si}	Amount of dosage i shipped to site s before the trial starts; *dose*
u_{sit}	Amount of dosage i shipped to site s at period t; *dose*
v_s	Number of boxes used for the shipment to site s before the trial starts
v_{st}	Number of boxes used for the shipment to site s at period t
δ_t	Binary status of open enrollment; 0 means terminated
θ_t	Binary status of drug supply; 0 means terminated

A mixed-integer nonlinear program (MINLP) can therefore be formulated as below. The objective function (42) consists of production cost, recruitment cost, initial shipping cost, shipping costs incurred during the trial horizon, holding cost at the distribution center, and holding cost at sites respectively.

Minimize

$$\sum_{i\in I} c_i^p x_i + \sum_{t\in T}\sum_{s\in S} c_s^r \delta_t + \sum_{s\in S} c_s^s v_s + \sum_{t\in T}\sum_{s\in S} c_s^s v_{st} + \sum_{t\in T}\sum_{i\in I} c^h \theta_t y_{it} + \sum_{t\in T}\sum_{s\in S}\sum_{i\in I} c_s^h \theta_t y_{sit} \quad (42)$$

Subject to

$$\hat{p}_{it} = \sum_{j\in\Omega_j^{s,t-\tau}} \delta_{t-\tau}\pi_{ij}^{s,t-\tau} X_{ij}^{s,t-\tau} / N_{i,t-\tau} \qquad \forall i, t > \tau \quad (43)$$

Sample Size

$$N_{it} = N_{i,t-1} + \sum_{s\in S, j\in J^{s,t-\tau}} \delta_{t-\tau}\pi_{ij}^{s,t-\tau} \qquad \forall i, t > \tau \quad (44)$$

	$N_{it} = 0$	$\forall i, t \leq \tau$	(45)
	$\widehat{D}_t = f(N_{it}, \hat{p}_{it})$	$\forall t > \tau$	(46)
	$\widehat{D}_t = D_0$	$\forall t \leq \tau$	(47)
Patient	$\sum_{i \in I} \pi_{ij}^{st} = 1$	$\forall s, t, j \in J^{st}$	(48)
Allocation	$\rho_{1t} n_{st} - 1 < \sum_{j \in J^{st}} \pi_{1j}^{st} < \rho_{1t} n_{st} + 1$	$\forall s, t$	(49)
	$\rho_{1t} = g(N_{it}, \hat{p}_{it})$	$\forall t > \tau + 1$	(50)
	$\rho_{1t} = 0.5$	$\forall t \leq \tau + 1$	(51)
Trial	$\theta_t = 1$	$t = 1$	(52)
Termination	$\widehat{D}_{t-1} \leq \sum_{i \in I} N_{i,t-1} + M_1 \theta_t$	$\forall t > 1$	(53)
	$\sum_{i \in I} N_{i,t-1} < \widehat{D}_{t-1} + M_1 (1 - \theta_t)$	$\forall t > 1$	(54)
	$\delta_t = \theta_{t+\tau}$	$\forall t \in [1, \lvert T \rvert - \tau\,]$	(55)
Inventory of	$y_{it} = y_{i,t-1} - \theta_t \sum_{s \in S} u_{sit}$	$\forall i, t > 1$	(56)
DC	$y_{it} = x_i - \sum_{s \in S} u_{si} - \sum_{s \in S} u_{sit}$	$\forall i, t = 1$	(57)
Inventory of	$y_{sit} = y_{si,t-1} + \theta_{t-L} u_{si,t-L} - d_{sit}^1$	$\forall s, i, t > \tau$	(58)
Sites	$y_{sit} = y_{si,t-1} + \theta_{t-L} u_{si,t-L} - d_{sit}^2$	$\forall s, i, t \in (L, \tau]$	(59)
	$y_{sit} = y_{si,t-1} - d_{sit}^3$	$\forall s, i, t \in (1, L]$	(60)
	$y_{sit} = u_{si} - \gamma_i \sum_{j \in J^{st}} \pi_{ij}^{st}$	$\forall s, i, t = 1$	(61)
Capacity	$\sum_{i \in I} V u_{si} \leq Q_s$	$\forall s$	(62)
restriction	$\sum_{i \in I} V y_{si,t-1} + \sum_{i \in S} V u_{si,t-L} \leq Q_s$	$\forall s, t > L$	(63)
	$\sum_{i \in I} V y_{sit} \leq Q_s$	$\forall s, t \leq L$	(64)
Shipment	$\sum_{i \in I} V u_{si} \leq Q_{box} v_s$	$\forall s$	(65)
	$\sum_{i \in I} V u_{sit} \leq Q_{box} v_{st}$	$\forall s, t$	(66)
Bounds	$\delta_t, \theta_t, \pi_{ij}^{st} \in \{0,1\}$	$\forall i, s, t, j \in \mathrm{J}^{st}$	(67)
	$x_i, \hat{p}_{it}, \rho_{1t}, y_{it}, y_{sit}, u_{si}, u_{sit} \in \{0, \mathbb{R}_+\}$	$\forall s, i, t$	(68)
	$N_{it}, \widehat{D}_t, v_s, v_{st} \in \{0, \mathbb{Z}_+\}$	$\forall s, i, t$	(69)

Note that the d_{sit}^1, d_{sit}^2, and d_{sit}^3 in (58)-(60) are functions of δ_t and π_{ij}^{st}, expressed as (70)-(72).

$$d_{sit}^{1} = \gamma_i \delta_t \sum_{j \in J^{st}} \pi_{ij}^{st} + \gamma_i \sum_{m=1}^{\tau} \delta_{t-m} \sum_{j \in J^{s,t-m}} \pi_{ij}^{s,t-m} \quad (70)$$

$$d_{sit}^{2} = \gamma_i \delta_t \sum_{j \in J^{st}} \pi_{ij}^{st} + \gamma_i \sum_{m=1}^{\mathrm{t-L}} \delta_{t-m} \sum_{j \in J^{s,t-m}} \pi_{ij}^{s,t-m} \quad (71)$$

$$d_{sit}^{3} = \gamma_i \delta_t \sum_{j \in J^{st}} \pi_{ij}^{st} + \gamma_i \sum_{m=1}^{\mathrm{t-1}} \delta_{t-m} \sum_{j \in J^{s,t-m}} \pi_{ij}^{s,t-m} \quad (72)$$

Note the size re-estimation function $f(N_{it}, \hat{p}_{it})$ in (46) is adapted from (4) and expressed as (73).

$$f(N_{it}, \hat{p}_{it}) = \left\{ 1.96 \sqrt{\frac{\bar{p}_t(1-\bar{p}_t)}{(N_{1t}/\sum_{i \in I} N_{it})(N_{2t}/\sum_{i \in I} N_{it})}} + 0.84 \sqrt{\frac{\hat{p}_{1t}(1-\hat{p}_{1t})}{N_{1t}/\sum_{i \in I} N_{it}} + \frac{\hat{p}_{2t}(1-\hat{p}_{2t})}{N_{2t}/\sum_{i \in I} N_{it}}} \right\}^2 / \Delta^2 \quad (73)$$

where $\bar{p}_t = \hat{p}_{1t}(N_{1t}/\sum_{i \in I} N_{it}) + \hat{p}_{2t}(1 - N_{1t}/\sum_{i \in I} N_{it})$

Note that the update function of allocation probability/proportion $g(N_{it}, \hat{p}_{it})$ in (50) is adapted from (3) and expressed as (74), where RSIHR and Neyman allocation rules are incorporated as (75) and (76) respectively.

$$g(N_{it}, \hat{p}_{it}) = \hat{\rho}_{1,t-1}^{*} \left(\frac{\hat{\rho}_{1,t-1}^{*}}{N_{1,t-1}/\sum_{i \in I} N_{i,t-1}} \right)^2 \Big/ \sum_{i \in I} \hat{\rho}_{i,t-1}^{*} \left(\frac{\hat{\rho}_{i,t-1}^{*}}{N_{i,t-1}/\sum_{i \in I} N_{i,t-1}} \right)^2 \quad (74)$$

$$\hat{\rho}_{i,t-1}^{*} = \sqrt{\hat{p}_{i,t-1}} \Big/ \left(\sqrt{\hat{p}_{1,t-1}} + \sqrt{\hat{p}_{2,t-1}} \right) \quad (75)$$

$$\hat{\rho}_{i,t-1}^{*} = \sqrt{\hat{p}_{i,t-1}(1-\hat{p}_{i,t-1})} \Big/ \left(\sqrt{\hat{p}_{1,t-1}(1-\hat{p}_{1,t-1})} + \sqrt{\hat{p}_{2,t-1}(1-\hat{p}_{2,t-1})} \right) \quad (76)$$

In regard to trial design, constraint (43) specifies the simple mean estimation on the success rates of certain treatment based on the patient responses observed so far. Constraint (44) ensures the incremental number of patients who finished certain treatment at current period is the number of patients assigned to the treatment τ-periods ago, and constraint (45) is its initial condition. Constraint (46) specifies the rule of re-estimating sample size under adequate statistic power, which is a function of $\hat{p}_{it}$ and N_{it}, and constraint (47) is its initial condition. Constraint (48) ensures that a patient can only be assigned to one arm. Constraint (49) ensures the number of assignments to certain treatment is restricted by the allocation proportion designated at this period. Constraints (50) specifies the rule of adapting allocation proportion based on previously estimated drug success rates and previously implemented allocation proportion. Constraint (51) specifies the equal allocation in the beginning of the trial.

With respect to the trial termination criteria, constraint (52) specifies that the initial status of drug supply is on. Constraint (53) and (54) ensures that the supply is terminated only as the target sample sized is reached, otherwise the supply continues. Constraint (55) specifies that the open enrollment status is τ-periods ahead of the supply status. when the enrollment stops, the last cohort of patients still require the availability of drugs during the treatment span. Hence, the termination of supply is τ-periods later.

As for drug supply, constraint (56) and (57) ensure that the inventory difference between the end of current and the immediately previous periods equals to the amount of drugs shipped out of the DC. Similarly, constraints (58)-(61) ensure the inventory balance at clinical sites due to drug resupply and consumption. Note that the drug consumption terms, d_{sit}^1, d_{sit}^2, and d_{sit}^3, include not only the consumption from newly enrolled patients at current period, but the consumption from previously enrolled patients who have not finished their treatments. Constraint (62)-(64) ensure that the amount of resupply or the inventory at the beginning of a period will not exceed the space limit of clinical sites. Constraints (65) and (66) impose the capacity restriction on every shipments and specify the number of boxes needed in each shipment. Finally, Constraints (67)- (69) indicate bounds on the decision variables.

4.3 A Particle Swarm Optimization Based Heuristic

Particle swarm optimization (PSO) algorithm is a population-based search algorithm inspired by biological social behavior. PSO is originally introduced by Eberhart and Kennedy [53] in 1995 and then developed to solve various optimization problems, including nonlinear programs. In PSO algorithm, multiple potential solutions to the problem (called particles) are iteratively moving within a hyperdimensional search space under the influence of particles' best-known positions, which are evaluated via a fitness function (usually the objective function). At each iteration, the movement (called velocity) of each particle is randomized and updated based on three components: personal inertial motion, personal best-known position, and the best-known position of the swarm or its neighbors. Further details and variants of PSOs are reviewed in the literature [54-56].

For a problem involving binary variables, binary particle swarm optimization (BPSO) algorithms are developed because the discretized space prohibits the usage of continuous velocities in basic

PSO. Kennedy and Eberhart (1997) proposed a new interpretation of the velocity and particle trajectories, where velocities are transferred to the range of [0, 1] via Sigmoid function and used as the possibility of moving to one of the binary values [57]. Noticing this moving scheme losses the memory of current positions, Khanesar et al. (2007) proposed a novel BPSO, where they introduced two velocities to separately represent the probability of having binary values and the use of them is dependent of the current position [58].

Our proposed algorithm uses the framework of BPSO and takes advantage of the problem structure. Firstly, we examined the relation between all variables and separated the trial design constraints, (43)-(55), from the drug supply subproblem, (42) and (56)-(66). Note that the linkage between them lies in π_{ij}^{st}, δ_t, and θ_t. For every combination of the three linkage variables that is feasible, we can acquire a solution to the original problem and its objective value by solving the linear supply subproblem, i.e. (42) and (56)-(66) with the fixation of π_{ij}^{st}, δ_t, and θ_t. Secondly, after analyzing the trial design constraints, we see that all the involved variables, N_{it}, $\hat{p}_{it}$, ρ_{1t}, $\widehat{D}_t$, δ_t, and θ_t, are strictly constrained by π_{ij}^{st}, and their values have one-on-one correspondence to a feasible π_{ij}^{st} due to the equalities in (43)-(47), (50)-(52), and (55) and the binary disjunctive concept in (53)-(54). That is, given π_{ij}^{st}, we can compute the values of all other variables in the trial design constraints, and we can define the searching space of PSO as the feasible region of π_{ij}^{st}, which is a much more efficient way than letting particles moving within the hyper-dimensional space formed by all variables and then checking the feasibility through (43)-(55). The above properties allow us to adapt the designs in Khanesar et al. (2007) [58] and Hu and Eberhart (2002) [59] into the framework below.

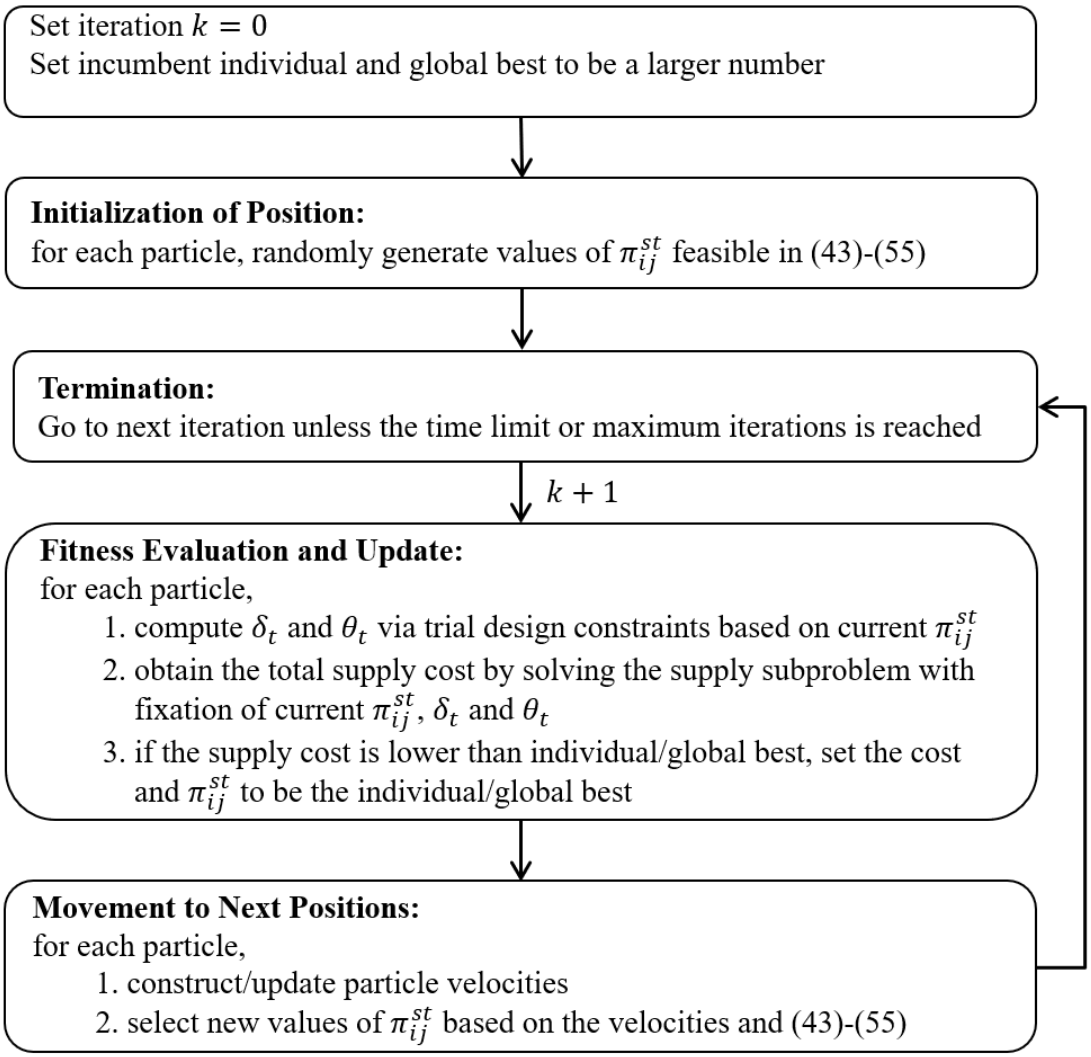

Fig 4.1 The Flowchart of Proposed PSO Algorithm.

As for the construction and update of particle velocities, in the work of Khanesar et al. (2007), each dimension of a particle, referring to each π_{ij}^{st} in our problem context, has two velocities updated as (77)-(78). The velocities of moving to binary values in the next iteration, V_{next}^{1} and V_{next}^{0}, are contributed by three components: current velocities V_{now}^{1} and V_{now}^{0}, individual's best information d_{ibest}^{1} and d_{ibest}^{0}, and global best information d_{gbest}^{1} and d_{gbest}^{0}. The latter two contributions are dependent of incumbent best-know position values P_{ibest} and P_{gbest}, shown as (79)-(80). The w, c_1 and c_2 are fixed user-specified parameters, and r_1 and r_2 are two random variables within the range of (0, 1), which are rerolled at each iteration.

$$V_{next}^{1} = wV_{now}^{1} + d_{ibest}^{1} + d_{gbest}^{1} \tag{77}$$

$$V_{next}^{0} = wV_{now}^{0} + d_{ibest}^{0} + d_{gbest}^{0} \tag{78}$$

$$\begin{cases} d_{ibest}^{1} = c_1 r_1 \text{ and } d_{ibest}^{0} = -c_1 r_1 \text{ , if } P_{ibest} = 1 \\ d_{ibest}^{1} = -c_1 r_1 \text{ and } d_{ibest}^{0} = c_1 r_1 \text{ , if } P_{ibest} = 0 \end{cases} \tag{79}$$

$$\begin{cases} d_{gbest}^{1} = c_2 r_2 \text{ and } d_{gbest}^{0} = -c_2 r_2 \text{ , if } P_{gbest} = 1 \\ d_{gbest}^{1} = -c_2 r_2 \text{ and } d_{gbest}^{0} = c_2 r_2 \text{ , if } P_{gbest} = 0 \end{cases} \tag{80}$$

Because our problem has constraint (49) that restricts the number of value 1 among certain π_{ij}^{st}, we set the value of 1 to those with higher $V_{next}^{1} - V_{next}^{0}$ during the step of movement to next positions. In addition, because of the existence of constraint (48), we only determine the patient assignment of one treatment, which leads to the reduction in the search space of PSO to a half. The supply subproblem is solved by Gurobi MIP solver, and parameters w, c_1 and c_2 are set to be 1/3, 7, and 13 respectively.

4.4 Numerical Case Study

4.4.1 Instance generation

The case for study has information listed in Table 4.4. The number of patients arrived at each clinical site and period, n_{st}, is independent of others and follows Poisson distribution. The mean of the Poisson distribution is set to 1.75 and differs slightly with respective to sites. In this case, we simulate responses of every patient, X_{ij}^{st}, via Bernoulli distribution. The probability of success/positive response is set to be 0.5 and 0.7 for treatment 1 and 2 respectively. In addition, the critically important difference between two treatments, Δ, is set to 0.2 so that we will not end up with a trial instance that is impossible to complete.

Table 4.4 Basic Information of the Case

Trial Information		Drug Supply Information	
Maximum Trial Duration	16 weeks	Clinical Sites	10
Trial Arms	2 dosages	Produced Dosages	2
Treatment Span	4 weeks	Drug Form	tablet (0.426 in^3)
Treatment Allocation	adaptive	Drug Consumption	7 tablets/patient/week
Trial Sample Size	adaptive	Shipment Leadtime	1 week
Adaptation Frequency	weekly		
Patient Response	binary		

The rest of supply-related parameters are generated in the same way of Chapter 3.4.1, and we only address the final values here. Production costs are \$0.5/tablet and \$25.5/tablet. Recruitment costs of sites depends on the mean arrival rates and approximately range within \$500-\$900 per week. Holding costs of the distribution center and sites are \$0.5/tablet/week and \$2.5/tablet/week respectively. Shipping costs of one-third of the sites are \$57/box; the others are \$46/box. The volume of shipping boxes is 64 in^3/box.

4.4.2 Performance of PSO-based heuristic

To evaluate the performance of the proposed PSO-based heuristic, we implemented a random search algorithm (RSA) to solve the same instance. The RSA also takes advantage of problem structure by only searching the feasible region of patient assignments, π_{ij}^{st}. Once feasible assignments are sampled, the trial-related variables, N_{it}, $\hat{p}_{it}$, ρ_{1t}, $\widehat{D}_t$, δ_t, and θ_t, are determined accordingly through constraints (43)-(55). Then the rest of the problem is optimized by using the Gurobi MIP solver. Fig 4.2 and Fig 4.3 show the relationship between incumbent objective values and solving time for PSO and RSA respectively. Note that RSA searched more than 1,000 feasible solutions within 500 seconds.

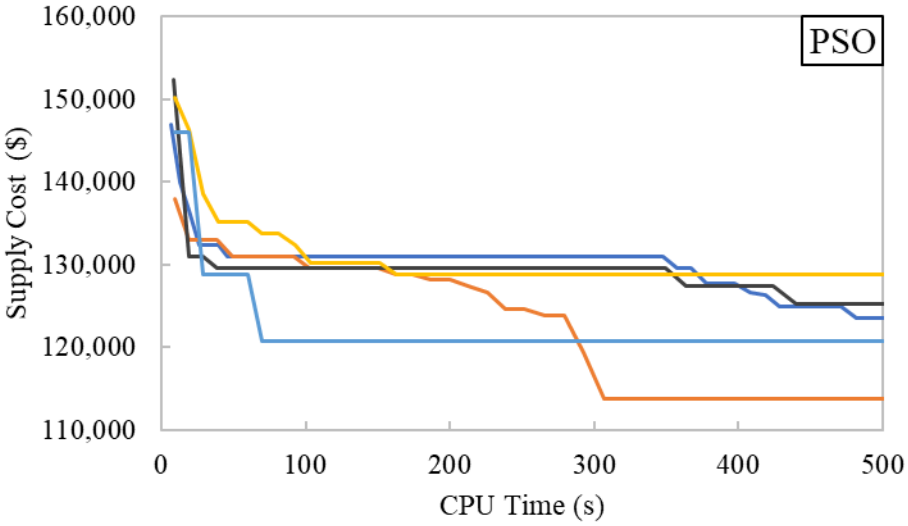

Fig 4.2 Performance of PSO Algorithm with Five Repetitions

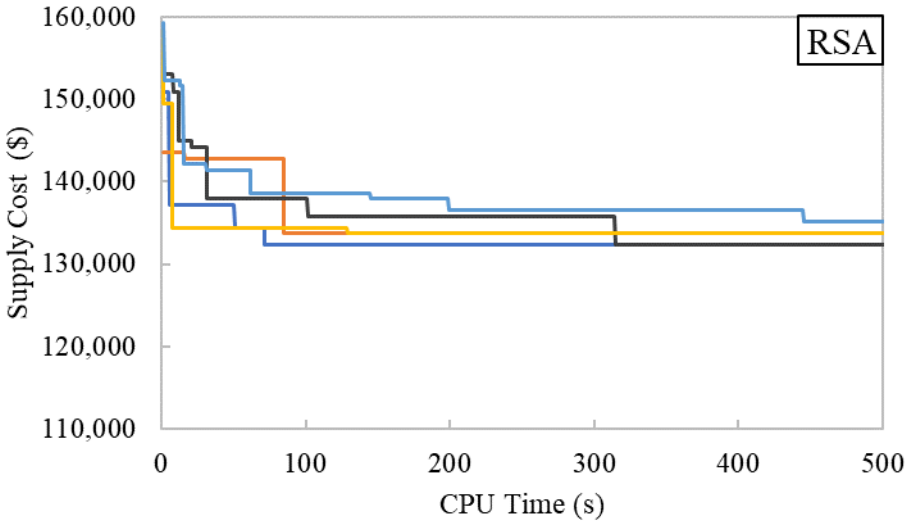

Fig 4.3 Performance of RSA with Five Repetitions

According to the figures, RSA rarely improved solution quality after 150 seconds, and by 500 seconds the best solutions found contribute to objective values higher than 130,00 dollars. In contrast, all five repetitions in PSO reached better objective values, which shows the superiority of using PSO algorithm in this problem.

4.4.3 Impact of joint optimization

To evaluate the impact of the joint optimization proposed in Chapter 4.2, we compare its best solutions found by the PSO algorithm with the solutions obtained by randomly assigning patients, i.e. randomly generating values of π_{ij}^{st} that are feasible to the entire problem (42)-(69), and then optimizing for minimum supply cost. For each instance, we conducted this random assignment optimization 1,000 times and the average results are presented in Table 4.5 and Table 4.6, where N_1, N_2, $\hat{p}_1$, and $\hat{p}_2$ are the total number of patients assigned to treatment 1 and 2 and the observed success rate of treatment 1 and 2 by the end of the trial.

Table 4.5 Results of Joint Optimization under RSIHR Allocation Rule

Instance Index	Optimization Choice	Total Cost ($)	Trial Length	N_1	N_2	$\hat{p}_1$	$\hat{p}_2$
1	Random Assignment	169,065	13.9	104.7	123.9	0.51	0.69
	Joint Optimization	135,127	12	109	77	0.58	0.71
2	Random Assignment	169,828	14.3	88.7	119.5	0.49	0.69
	Joint Optimization	138,271	13	86	107	0.52	0.72
3	Random Assignment	160,941	13.2	92.9	119.6	0.51	0.72
	Joint Optimization	123,798	11	96	74	0.59	0.80
4	Random Assignment	157,582	13.2	84.5	118.6	0.47	0.75
	Joint Optimization	124,445	11	92	78	0.57	0.79
5	Random Assignment	165,548	14.0	100.2	120.0	0.48	0.67
	Joint Optimization	147,939	13	115	83	0.51	0.64

Table 4.6 Results of Joint Optimization under Neyman Allocation Rule

Instance Index	Optimization Choice	Total Cost ($)	Trial Length	N_1	N_2	$\hat{p}_1$	$\hat{p}_2$
1	Random Assignment	158,127	13.9	119.4	109.5	0.50	0.69
	Joint Optimization	120,046	12	112	74	0.52	0.77
2	Random Assignment	150,874	14.2	112.6	94.3	0.48	0.69
	Joint Optimization	123,571	13	119	74	0.50	0.76
3	Random Assignment	143,917	13.3	117.5	95.9	0.52	0.73
	Joint Optimization	122,498	12	132	58	0.55	0.88
4	Random Assignment	141,491	13.4	117.6	89.6	0.48	0.73
	Joint Optimization	116,745	11	103	67	0.50	0.88
5	Random Assignment	155,219	14.0	116.3	103.7	0.48	0.68
	Joint Optimization	140,939	13	125	73	0.49	0.74

In comparison to random assignment, joint optimization obviously reduces the supply cost, trial length, and the total number of samples/patients collected/needed in the trial $N_1 + N_2$ in all instances and both allocation rules. As for the patient allocation, we see that joint optimization inclines toward higher allocation to treatment 1, i.e. $N_1 > N_2$, under both allocation rules because of the lower unit price of producing dosage 1. As for the final observation of treatment success rate, we see that random assignment observed values that are very close to the mean values 0.5 and 0.7 we used in the instance generator, while joint optimization tends to observe better success rates, i.e. larger $\hat{p}_1$ and $\hat{p}_2$. As for the cost analysis, we see from Table 4.7 that the major reduction in supply cost is contributed by production, followed by inventory, recruitment, and transportation.

Table 4.7 Cost Reduction of Joint Optimization against Random Assignment

Instance Index	Allocation Rule	Costs Reduction Percentage in Categories				
		Total	Production	Recruitment	Inventory	Transportation
1	RSIHR	-20.1%	-30.6%	-9.1%	-17.0%	-5.9%
	Neyman	-24.1%	-28.0%	-19.3%	-30.4%	-14.9%
2	RSIHR	-18.6%	-23.7%	-12.6%	-20.9%	-10.3%
	Neyman	-18.1%	-25.2%	-11.6%	-19.8%	-10.0%
3	RSIHR	-23.1%	-31.9%	-13.2%	-21.5%	-9.8%
	Neyman	-14.9%	-30.4%	-2.9%	-4.4%	-2.8%
4	RSIHR	-21.0%	-28.6%	-12.6%	-18.9%	-7.7%
	Neyman	-17.5%	-19.4%	-15.3%	-22.5%	-9.6%
5	RSIHR	-10.6%	-22.3%	-0.1%	-0.2%	-0.1%
	Neyman	-9.2%	-20.9%	0.0%	0.0%	0.0%

In comparison to Neyman allocation rules, RSIHR tends to assign more patients to treatment 2, i.e. larger N_2 in Table 4.5 than Table 4.6, which is aligned with the objective of RSIHR rule: minimizing the expected number of treatment failures. That is, RSIHR rule tends to allocate patients to the treatment with higher success rate, which is treatment 2 in our case, and therefore leads to higher supply cost in Table 4.5 than Table 4.6.

According to the above results, we noticed the joint optimization solution is strongly affected by the unit price difference between manufacturing doses for the two treatments. To further understand the impact of joint optimization, we raised the unit price of producing dosage 1 to be the same as dosage 2 and rerun the five instances. The average results of the five instances are summarized in Table 4.8 as well as the cost reduction percentage in Table 4.9.

Table 4.8 Summary of Joint Optimization Results

Allocation Rule	Drug Unit Cost	Optimization Choice	Total Cost ($)	Trial Length	N_1	N_2	$\hat{p}_1$	$\hat{p}_2$
RSIHR	Different	Random Assignment	164,593	13.7	94.2	120.3	0.49	0.70
		Joint Optimization	133,916	12.0	99.6	83.8	0.55	0.73
	Same	Random Assignment	224,475	13.7	94.2	120.3	0.49	0.70
		Joint Optimization	203,776	11.8	83.4	96.0	0.52	0.74
Neyman	Different	Random Assignment	149,926	13.8	116.7	98.6	0.49	0.70
		Joint Optimization	124,760	12.2	118.2	69.2	0.51	0.81
	Same	Random Assignment	225,661	13.8	116.8	98.7	0.49	0.70
		Joint Optimization	208,561	12.0	96.2	87.2	0.53	0.73

Table 4.9 Summary of Cost Reduction

Allocation Rule	Drug Unit Cost	Costs Reduction Percentage in Categories				
		Total	Production	Recruitment	Inventory	Transportation
RSIHR	Different	-18.6%	-27.4%	-9.4%	-15.4%	-6.7%
	Same	-9.2%	-8.6%	-9.4%	-15.3%	-7.1%
Neyman	Different	-16.8%	-24.8%	-9.8%	-15.2%	-7.6%
	Same	-7.6%	-7.0%	-7.9%	-12.3%	-5.6%

First, for the random assignment cases under an allocation rule in Table 4.8, we see the adjustment of drug unit cost only affects the total cost because the assignment of patients is not altered due to supply chain factors. Second, for the comparison between joint optimization and random assignment, we see obvious reductions in supply cost, trial length, and the total number of patients even though the drug unit prices are even. As for the number of patients assigned to the two treatments, we see the distribution between N_1 and N_2 becomes proportional to the distribution in the random assignment case when the drug unit prices are even, which implies that the tendency of patient allocations in RSIHR and Neyman rules will be preserved if there is no huge difference in drug unit price between treatments. In addition, when the drug unit costs are adjusted to be even, the sampled treatment success rates in the end of the trial is closer to the real means, 0.5 and 0.7,

especially for Neyman allocation. Fourth, for the cost reduction comparisons in Table 4.9, we see that the percentage reduction in production cost is no longer the highest after the adjustment in drug unit cost. The percentage reduction in inventory cost becomes the highest and other categories are at approximately same level of reduction. Fifth, no matter the unit cost of drugs, the joint optimization under RSIHR allocation rule overall results in higher reduction in total cost, trial length, and total number of patients than under Neyman allocation.

4.5 Conclusions

Patient-Treatment Allocation plays essential role of bridging the gap between adaptive clinical trial (ACT) planning and drug supply chain management. Patient assignment affects not only the trial performance, including trial size, trial length, and statistic power, but also the resources management, including drug distribution, drug wastage, and supply costs. With the proposed joint optimization model, we study the impact of incorporating supply consideration into ACT design and incorporating trial design rules into drug supply chain in terms of trial performance and supply costs numerically.

The key finding of our research is that, when there is no significant difference in unit production price between the treatment drugs, the proposed integration between trial design and supply management is beneficial to lower supply costs, trial length, and total number of patients needed in a trial without jeopardizing the study power and the sampled treatment success rates. In addition, the cost reduction does not center on certain category in the supply chain. Instead, the production, inventory transportation, and recruitment costs have more than 7% reduction. We also noticed that the joint optimization has better effect on RSIHR allocation rule than Neyman allocation.

A limitation of this project lies in the deterministic programming model. It is not the nature of a randomization trial to assign individual patients to treatments according to deterministic prediction of patient arrival and response to treatments/dosages. Therefore, we will consider the stochastic extension in future research. We hope the proposed concept of joint optimization and the numerical results may suggest a new angle or domain extension regarding the conduction and design research of ACTs and facilitate the development of optimization tools for adapting trials in coordination with drug supply planning.

5. FUTURE RESEARCH AND REFLECTIONS

5.1 Future Research

In addition to stochastic extension of Chapter 4, it is interesting to use the proposed models to study other important issues or problems in clinical trial and supply management. First one is multi-trial management. Many non-adaptive and adaptive clinical trials are implemented with time overlap and using many common resources, e.g. clinical sites and personnel, patients with similar symptoms, and drug supply facilities. According to the industry people we have contact with, multi-trial management is one of major concerns in practice. Second one is the advertisement and recruitment. Insufficient number of subjects has been an obstacle to trial completion and success, and many research works treat patient arrival as an independent uncertainty. If we can model the relation between different advertisement media and clinical site recruitment, then the integration with supply chain model may suggest more insightful results. Third one is clinical site selection. Current practice is close to choosing sites based on the feasibility of conducting trials, e.g. whether an airport is nearby the hospitals or whether trained clinical trial investigators and treatment facilities are available. However, the economic considerations of the entire drug supply chain are not taken into account at the trial planning stage. The mathematical model/tools that integrates the trial design and supply can more insightfully suggest the good characteristics of a clinical site for any specific case, which may lead to reduction in operational cost and resource wastage along the clinical trial process.

5.2 Reflections

Upon the completion of this dissertation, I am glad I became an independent learner, thinker, and explorer. I recall the moments of trying to connect adaptive trial design with drug supply and develop a dissertation topic/problem. Many questions, assumptions, doubts, and guesses surround me all the time no matter how hard I try to find answers from published papers. After countless attempts, I learned to resort to website posts, news reports, or even the introductions of company's services to gather the bigger picture of backgrounds that my potential research problems may lie in. By immerging myself in this environment, I started to be able to "see" many connections or answers. This is one of the experiences during my Ph.D. journey that cultivates my skill of

exploring and learning as well as the valuable fruit of my Ph.D. study. The knowledge in this dissertation might become outdated one day; however, there are more unknown domains ahead of me. This Ph.D. journey feeds back to me with confidence in facing unknowns in my life thereafter.

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