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A Comprehensive Study on Exploring Operational Research Techniques to Enhance Efficiency in CRO Delivery Models for Patient-Centric Trials

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ABSTRACT

This study presents a comprehensive exploration of Operational Research (OR) techniques aimed at enhancing the efficiency of Contract Research Organization (CRO) delivery models in the context of patient-centric clinical trials. As the pharmaceutical and biotechnology industries increasingly prioritize patient engagement and outcomes, the need for optimized trial designs and execution strategies becomes paramount. This research investigates various OR methodologies, including simulation modeling, linear programming, and decision analysis, to identify bottlenecks and streamline processes within CRO operations. By analyzing case studies and real-world applications, we demonstrate how these techniques can improve resource allocation, reduce trial timelines, and enhance patient recruitment and retention. The findings highlight the potential for OR to transform CRO delivery models, fostering a more agile and responsive framework that aligns with the evolving demands of patient-centric trials. Ultimately, this study contributes to the growing body of knowledge on integrating operational research into clinical trial management, offering actionable insights for CROs seeking to improve their service delivery and patient outcomes.

Keywords: *Operational research , Patient-centric, Graph theory, Game theory, Network optimization, Linear programming, CRO delivery model*

1. INTRODUCTION

Clinical Research Organizations (CROs) globally support pharmaceutical and biotechnological firms in the domain of medical devices and biophysics for developing syndicate registration studies and managing them till approval. Because of emerging competition within the pharmaceutical industry and constrained resources, the bio-pharmaceutical industries are stressed to minimize costs and implementation of the studies in limited time frames. Several strategies for enhancing trial efficiency have been proposed. Maximizing the efficiency of study execution can be conducted effectively using a well-established organized approach, called Operational Research (OR) (Stamenovic & Dobraca, 2017). This paper outlines how OR can be effectively utilized in CROs for enhancing the overall effectiveness of the studies. First, the necessity of patient-centric trials and efficient delivery models fitting for them are briefly described. Later, particular OR approaches that can greatly tighten some trial processes are discussed. Some abstracts that seem profitable for controlling the studies of clinical targets, research sites, and patient selection are elaborated. It is reliable to achieve these discussions by creating an evident sense of the processes and bottlenecks in necessary ways. An operational research (OR) is the discipline of translating committed knowledge into an enhanced strategy whereby policy or decision can be taken through rigorous analysis and investigation. CROs are outsourcing staffs that provide a wide range of services in the pharmaceutical industry. They build up a lot of functions that appear to be enigmatic and difficult from an operational research point of view. CROs have their own delivery conversion services caused in capabilities which prevent but also augment the market for OR as these services are become more patient-centric. The approaches of algorithmization and estimation

remain above the sophistication and confidence threshold for the vast majority of functionally rich OR.

An agenda for (quasi-) academics is therefore evinced to invent functionally rich OR to overcome such research industry split. Here several UK examples of OR deployment in CRO settings are presented such that an aspirational weak boundary is offered (Monks, 2016).

1.1. Background and Significance

Clinical trials are an essential phase for the advancement of innovative pharmaceutical products from the laboratory to the shelf. This is where the effectiveness and safety of a particular therapeutic agent or medical device aimed at treating or detecting specific diseases are studied and verified. Such studies have evolved over the past two decades, changing from the traditional, investigator-centric approach to patient-centric clinical trials (I Nebie et al., 2024). This is where patients are actively involved in the planning and conduct of the trial. Historically, trials have been highly controlled, ensuring participants comply with protocol-defined criteria. However, the complexity and duration of such trials have increased significantly. This is further amplified by limited resources both by the sites and the Contract Research Organizations (CROs). Moreover, there are increasing calls for urgency and transparency in complex management and reporting of clinical research. In the post-era, the design and delivery of clinical trials have significantly evolved towards OPTIMAL Research techniques.

The first universally acknowledged challenge in transforming the traditional clinical trial delivery model to a more patient-centric mode is the capability issue. Critical operational barriers are foreseen, concerning patient identification, recruitment, and retention. Late-stage patient encounters in the typical drug development process raise significant challenges for CROs . Patients, as the object of the study, must have a detailed understanding of the research program and their informed consent obligations, but CROs typically have limited resources and personnel to communicate in this manner with patients. Therefore, the rise of a patient-centric clinical trial model may further exacerbate the potential capability gap.

Parallelly, a sharp increase in the complexity of patient recruitment and retention is anticipated, since CROs are traditionally less patient-facing and conversant than site staff and PIs. In addition, the massive inflow of patient data generated by such novel patient trials could lead to significant challenges for CROs, with gaps in data management capabilities at all sites. Specifically, the implementation of subject schedules as part of the patient's clinical trial experience is a new workload for the sites and may be particularly resource intensive in the absence of automation. Furthermore, since the timely delivery of documented actions would be subject to a wide range of care, compliance, and operational constraints, the decentralized result would likely exhibit a different character. Early strict action delivery could cause more FFDs at sites, which usually wait until the last day of grace to allow as much time as needed to irregular patients. As a result, the traditional model could lose in efficiency, suffering from a rise in sites' FFD, and a decrease of regular patient performance.

2. STUDY OBJECTIVES

The main objective of this research is to explore operational research techniques to enhance the efficiency of Clinical Research Organizations delivery models. It is interesting to note how clinical and operational efforts have evolved; therefore, emphasis has moved from procedure-focused trials to patients and patient needs. Moreover, operational efforts are very much provider-centric and intend to improve processes and communication, which involves patient participation. This also impacts the usability of trial sites, reduces their demand, and therefore increases the costs of bringing new treatments into the process. Additional reasons include the lack of scientifically sound methods that optimize patient flow and logistics, and the isolated view of various stakeholders, with limited joint optimization. Although great progress has been made, there is still a compelling need to research and develop methods, technology, and organizational structures that substantially reduce supply-side inefficiencies in multi-center trials. On one side, this may be achieved by providing methodological and analytical researchers with a comprehensive understanding of the problem to stimulate innovation. On the other side, it may be achieved by implementing and evaluating these innovations in a real-case setting. The overall intention is to use such a new understanding as a basis for CROs, pharmaceutical companies, and trial sites to establish and jointly enhance patient-centric operational structures.

- To conduct an analysis of available literature and to examine existing models and frameworks within the CRO industry (specifically focusing on patient-centric trials), with emphasis on any reported utilization of mathematical modeling techniques.
- Identify mechanisms of mapping linear programming within existing frameworks and patient trials models.
- Develop a comparative Life Cycle Analysis of current and next generation models, detailing where operational enhancements are potentially achievable.

3. LITERATURE REVIEW

This paper presents a systematic analysis of Contract Research Organizations (CROs) within healthcare, exploring methodologies, key findings from past literature, the contributions of prior research to a broader sociotechnical perspective, and proposes future research paths within the framework of Industry 4.0 (Stamenovic & Dobraca, 2017). Operational

research techniques can be used to increase the efficiency of the conduct of clinical trials, without compromising the ethical principles. Many authors have investigated some operational aspects of clinical trials which differ statistically (including issues like recruitment, dropout rates, etc.). However, far less attention has been paid to the conduct of trials from an operational viewpoint, focusing more on the practical functioning of the organization and the relative effectiveness and efficiency of them. The focus of the review is on the time-performance of procedures which patients have to comply with in the context of clinical trials. The conduct of a comprehensive study to address the gap is described. The term patient-centric is used here to refer to clinical trials where patient-oriented outcomes are more relevant, stopping rules consider how much treatment has been received or how patients are responding to treatment. Some other forecast, characterization or criticism about the future of clinical trials is distinguished from the comprehensive study.

The purpose of this paper is to offer an in-depth perspective on the understanding of CRO function beyond the established frameworks of the field, assessing CROs as emblematic of a broader category of symbiotic organizations within the context of developing novel socio-technical and operational

solutions. Given the inherent risks and costs involved, there is a broad interest in optimizing the operational efficiency of the conduct of patient-centric clinical trials. Operational research techniques provide a variety of methodologies and approaches which may be implemented to fulfil such objective. A comprehensive literature review on the topic has been carried out so as to identify the state of the art, trends, methodologies and the most successful techniques penned. There is a clear consensus among trialists, organisations and regulators on the desirability to increase trial efficiency before the comprehensive study address. Factors contributing to operational effectiveness and efficiency in the procedures followed by a patient to participate in a clinical trial are examined, by making effective studied comparisons and evaluating relevance of patient engagement in the light of a comprehensive set of patient-centric and non-patient-centric clinical trials (I Nebie et al., 2024).

4. LITERATURE GAP

Hundreds of patient-centric approaches have been developed to improve the efficiency of clinical trials, but little is known about measurements for a comprehensive understanding (I Nebie et al., 2024). Patient-specific considerations in patient-centric trial design are not captured by the measures most frequently used in the literature despite being crucial to understanding the change in operational difficulties for each patient-group involved. Therefore, it is important to quantify the effort spared in medical pre-screening to estimate the demand. Besides, empirical findings are lacking despite the growing amount of publications on patient-centric methods in an academic or a professional context.

Thus, the operational gains of patient-centric approaches cannot be put into relation with the effort to design and run such a trial. Further study about the efficiency of patient-centric approaches is crucial to guide stakeholders in the choice of applicable methods.

The operational gains of patient-centric approaches save resources at sponsor as well as investigator's sites. However, so far empirical results were missing about how much an individual patient-group can advance the design and conduct of a clinical trial. Furthermore, clinical trials are mainly regulated, but so far the operational difficulties from the patient's perspective were bemused. Yet, patients are essential, as clinical trials rely on the willingness of patients to participate. Despite this, the conducted trials are neglecting the perspective of the patient as a key resource in every step of the trial. The focus is often on patient satisfaction, recruitment problems, and GCP issues, and it seams as if improvement in "soft" things can only be considered in the conduct of a trial. Thus, broadening the view to the full variety of the patient-specific issues could significantly advance the design and conduct of patient- centric trials. The operational planning of patient-centric clinical trials has received little academic discourse; none, as far as the author is aware, tilling the soil of operational research and efficiency enhancing techniques. Yet, without consideration of such factors, it will be viewed as unlikely that patient-centric clinical trial designs will be widely utilized as a method to both increase the ethical treatment of trial participants and the likelihood of trial's producing statistically and clinically valuable results. The results of the study reflect how particular patient engagement may change the suggested distribution of volunteer recruitment materials and motivations.

Despite an increasing emphasis on patient-centricity in clinical trials, a holistic view revealing the interrelations between different aspects of clinical trials, as well as the nature of the interventions being tested, is lacking in the current literature; A total of 10 methodological and operational tools, solutions, and examples for improving patient-centricity in different parts of clinical trials are introduced, which are useful for clinical trial practitioners of all types of organizations; Several ideas for future research and key considerations for critical thinking when planning or conducting patient- centric clinical trials are proposed. A systematic review of recent articles is conducted.

The role that operational research could play for highlighting a predominant patient-centric approach in the design, readiness, and improvement of clinical trials is focused on. By using the lens of patient- centricity, the interrelations with different aspects of trials are discussed.

A better understanding is provided regarding all the operational and methodological decisions that can contribute to improve the patient experience in clinical trials and how different types of interventions shape these choices. Combined, Pharma-sponsored trials, Institutional Review Board approval, multivariate adjustments, monitoring practices, management

oversight, and participation of phase II conducted selectors are 81% or 10.4 times more likely compared to Investigator Initiated Clinical Trials with respect to time in target. Additionally, accompanied project management, activation, and unexpected events values indicate slight to fair inter-decision recognition. Referencing a possibility to confuse study design speed of target enrollment and time in target, this study used time in target as primary measure. With few perceived stakes, rarely reported, managerial descriptor approaches are also explored.

5. OPERATIONAL RESEARCH TECHNIQUES IN CROS

The shifting paradigm in clinical research towards patient-centric approaches necessitates new delivery models to match the changes. Clinical Research Organization (CRO) services are evolving to deliver patient-centric trials (PCTs). The efficiency of CRO delivery models in this changing paradigm is important as it underpins patient engagement and trial outcomes. CROs face challenges in accommodating these patient-centric demands in delivered services (Doga et al., 2024). A brief review of CRO engagement in current PCTs shows these models vary but do not meet the changing needs of clinical trials. Aligning with patient-centric CRO trends and with an innovative angle on analytical methods, a linear programming (LP) framework is developed to provide CROs' guidance to utilize their operational resources such as PE and SOPs effectively. This study aims to review different OR applications and model designed for PCTs to fill this gap (Anisimov & Austin, 2022).

5.1 Linear Programming

Linear programming (LP) is a type of mathematical optimization technique that is widely used to find the best solution to a problem involving many constraints that have a linear relationship. In layman's terms, LP finds the best way to do something at the lowest possible cost given the existing resources. It was developed by George B. Dantzig and his collaborators in the 1940s. Although LP was originally conceptualized as a technique for allocation of resources, it has been extensively used in various domains including industry, way-faring, fabrication, channel covering, and transportation (Success Ikechi et al., 2014). Healthcare operations have also heavily borrowed this technique for the

betterment of health facilities and patient care services. Long-term strategic planning, decision-making, and resource allocation can be made markedly efficient and practicable using LP, given the invidious competition and costs fluctuations in the healthcare market. Moreover, LP yields cost-effectiveness

and quality enhancement to the decision-making and resource allocation processes.

The primary aim of this review is twofold: To map linear programming applications within existing CRO frameworks, including an understanding of challenging facets for CROs in implementing linear programming within their existing models and to deliver practical research-based enablers and recommendations. To achieve these aims, an understanding of existing models/frameworks and how to influence these to adopt next generation algorithms, How new enhancements can affect operational processes moving forward must be gained, What utilization of LP algorithms could mean in terms of both tangible operational throughput/cost metrics, but also wider patient/partner relations, The overall industry landscape and likely timescales around which emerging/new tech can be adopted by different parties within CRO/Sponsor partnership.

Integration of Linear Programming in CRO Delivery Models

In this paper, linear programming was studied in the context of CROs in an attempt to offer a generic methodology that will be useful in executing an optimized model for CRO delivery systems. A mathematical procedure in which an objective function is maximized under certain constraints can be interpreted as linear programming. Several operational components of CRO delivery systems, such as resource assignment, the preparation of the project schedule and patient recruitment strategy, were addressed and a comprehensive review of the methodology was carried out for each of them. This analysis suggests that a national policy aimed at the learning and teaching of operational research and various supporting programs would be needed for an appropriate vision and realization of LP strategies and that such strategies must be closely adjusted with the concepts of patient-centred care to reach their desired level of potential success. Equally, the optimal deployment of linear programming can yield improved, cost-effective and consistent support for clinical trial delivery models across CROs.

Awareness of how the benefits and advantages of linear programming techniques when integrated into CRO delivery models can significantly enhance the efficiency of patient-centric clinical trials is only now beginning to affect how decisions are made – decisions that may significantly impact organizations for years into the future. CROs have, in the past, tended to rely on their modus operandi (sometimes, even if tacitly, trusting "gut-feel") with respect to the ways in which they operate; a very "hands-on" approach. The utilization of linear programming can inform a more "hands-off" clinical trials management strategy, providing optimal, "scientifically justified" resource allocation strategies that can revolutionize the way in which CROs approach operational procedures (Narola, 2018).

Patient-centric clinical trials that are rooted in the results of resource allocation optimizations can lead to significantly reduced operational expenditure, improved patient recruitment and retention rates, as well as offering vast overall efficiency gains. A prototypical patient-centric clinical trial model that centered around the efficient utilization of resources via the application of resource allocation optimization is presented.

This subsection sheds light on the strategies that can be implemented to integrate Linear Programming techniques within the CRO delivery model. It is worthy to start by assessing the employee's skill and competency level in dealing with LP techniques. Efforts should be made to identify problems or situations where LP could be used, and it would be beneficial to the organization to engage employees in the process. Training sessions may be planned, as well as, follow-up visits to facilitate making the first LP model. The first or pilot LP models are investments in time and resources by CRO, which are later on expected to pay for themselves in terms of improved decision-making process; a desired change in the delivery model; or the healthier bottom-line.

The client begins by discussing this request. Initial meetings are intended to establish client expectations, as well as the scope or problem and the period over which the LP analysis must be conducted. It is at this stage that the internal freelance specialists and the project manager meet the client representatives. Most CRO client representatives do not understand or know LP, and it is important to unemotionally educate them. The availability and quality of data is reviewed. It is recommended that CRO procurement and IT are involved in the initial meeting to prepare client expectations. CRO client representatives are more acquainted with MS Excel and MS Access applications and it is suggested that LP models are developed in one of these two packages. It is additionally recommended that the client prepares a list of potential questions to be addressed during the first meeting, as this often accomplishes some of the basic groundwork. Following the initial meeting, freelance LP specialists start to develop their models. Additional data or clarifications are requested regularly to the client (Crown et al., 2018)

During the literature review, a case scenario was observed that an Australian arm of a global CRO was awarded a contract to deliver services for a medium-sized patient-centric clinical trial that aimed at testing the efficacy of a new pharmaceutical in preventing premature aging caused by exposure to industrial toxins. The trial ran over a 2-year period across 5 sites throughout Melbourne (South-East, South-West, North-West, Eastern Suburbs, CBD), with four dominantly male cohorts aged between 50-65 years and 20-25 individuals per cohort. There were several constraints to minimize cost and time input while optimizing the overall expected value for the bio-pharmaceutical company.

Regression analysis on historical data uncovered that specific weather conditions could significantly impact patient recruitment rates at clinical trial sites (Crown et al., 2018). This analysis was used to produce a recruitment rate forecasting tool that provided forecasts two weeks in advance. Forecast outputs influenced several key operational decisions throughout the trial. Linear Programming (LP) was successfully employed to find the optimal allocation of a finite number of mentor-patients across a set of visiting sites for each cohort. The output of the LP model was used to inform dedicated transition events at visiting sites. The additional support and knowledge transfer given effectively established a mentor network that streamlined the embedding process. Overall, this model allowed an incremental 15% cost saving across the project life cycle. The bio-pharmaceutical company's monetary investment in the contracted gathering of real-world patient-centric clinical trial data to inform future trials was hailed as a strategic move.

Further review is required to investigate how linear programming could be used to ensure that trial objectives are met with the minimum excess costs over the trial duration, and how to closely examine if, how, and why different patients are chosen across resource-scarce treatments in commercially- sponsored trials.

Summary table:

CRO Delivery Model Area	Application of Linear Programming	Objective	Key LP Variables
Resource Allocation	Optimizing allocation of staff (e.g., CRAs, data managers) across multiple projects	Maximize resource utilization & minimize project delays	Staff hours, project requirements, costs
Project Scheduling	Sequencing multiple clinical trials phases and tasks	Minimize total project time or cost	Task durations, dependencies, start/end times
Site Selection & Management	Selecting optimal clinical trial sites based on cost, patient availability, and compliance	Maximize patient enrollment and minimize operational cost	Site capacity, distance, cost, enrollment rate
Budget Optimization	Allocating budget across departments or study phases	Minimize costs while meeting regulatory and quality goals	Cost per activity, quality constraints, budget limits

Patient Recruitment	Determining optimal number of patients to recruit at each site	Maximize recruitment efficiency and trial speed	Site capacity, recruitment rate, regulatory quotas
Logistics & Supply Chain Management	Optimizing the distribution of clinical trial materials	Minimize transportation and storage costs	Inventory levels, shipment schedules, transport cost
Vendor Management	Choosing the best vendors for outsourced services	Minimize outsourcing cost while meeting timelines	Vendor capacity, service quality, turnaround time
Risk Management	Modeling risk mitigation strategies across various trial scenarios	Minimize risk impact on timelines and budgets	Probability of risks, cost of mitigation, project impact

5.2 Network Optimization Model

The network model at its core is a data-linked graph with nodes that depict potential sites and links that can represent direct or indirect measures of interest, which are established between these sites. Three types of networks exist, namely: transportation, assignment, and transshipment problems.

Transportation models involve the delivery of a homogeneous product from sources to destinations, while assignment problems generally consider assigning different products to distinct destinations. The majority of the delivery concepts suit the transportation model basis. The need to optimize these delivery models warrants the relaxation of some assumptions on the associated cost evaluations, delivery capacity constraints, fatigue, and the fact that recovery opportunities should not be explicitly zero.

The generalized assignment problem model would help in determining the candidate site and preferred country. The model is tasked with the problem of one-to-one mapping from a set of servers or facilities into the set of clients. Where the unavailability of one facility per statistical site could hinder an efficient service process, the operator selects more than one statistical site in more than one geographic location, allowing staff to recover from their work or injury-related travel while providing virtual clinical research support.

In recent years, there has been a rapid emergence of data analytics and machine learning models that can be broadly classified under the framework of network analysis. The focus is on mathematical network optimization models that can facilitate the decision-making process for clinical research. The discussion is limited to the statistical/econometric models that leverage empirical data to understand and predict network behavior. Other interesting graph theory or agent-based models that do not rely on data are outside the discussion.

A network of clinical sites generally attended by Clinical Research Organizations is considered. A brief overview is provided of ongoing discussions and suggests future research directions. The views expressed are of interest not only to the academic audience but also the industry professionals. A main goal in patient-centric clinical trials is two-fold: patients should be retained in the trials and the patients should frequently visit the clinical sites. Leverage this knowledge to suggest an optimal site selection strategy for the sponsor. It is shown that the sponsor should not only select sites that have a

high likelihood of recouping fast but also sites that are estimated to retain patients in the trials for a long time. Considering both types of sites simultaneously, it is observed that the optimal selection is a good mix of sites that have different characteristics. On the supply and demand of investigational staff members, a two-sided platform model is proposed. For the small and large market cases, the unique symmetric equilibrium in pure stationary strategies is established. Prospect theory, consisting of loss aversion and probability weighting, is integrated into the classic choice model while the trial is ongoing. Based on the history of the trial, conduct the out-of-sample prediction on the available data of the sponsor. Such a strategy should be considered more often to adjust the recruitment strategy during the trial to better cope with the insider knowledge of the observed patient recruitment.

Data analytics and machine learning are becoming increasingly important in developing network strategy and tactics for optimizing how sites are selected and activated in patient-centric studies. The former uses various methods to harness the vast amount of real-world data now available to decipher actionable insights for the planning and execution of trials. These include everything from creating predictive models to understand site performance and patient accrual, to innovative exploration of how real-world evidence (RWE) can benefit the design and operation of trials (Nanzayi Ngayua et al., 2021). Building the tools and expertise to interpret these insights is developing rapidly, which will allow this analysis to evolve over time. The recent focus on machine learning and the large investments in those algorithms is probably what has prevented this type of analysis, but there are now a burgeoning number of applications demonstrating the ability to use those algorithms

to improve network strategy.

Predictive modeling based on extensive analysis of previous trial data is one of efforts to change almost everything connected with the decision-making on how patient recruitment and site activation will proceed. The refinement and testing of those models take time, as does the development of the principles and philosophy underpinning them, but there is no doubt that a new generation of models could have a profound impact. A brute force approach is currently being pursued by some of the world's largest CROs, with borderline overwhelming array of data inputs being fed into predictive models, which are used to stream the most satisfactory options. Other organizations have recognized the difficulties and the potential unintended consequences of such an approach, instead focusing on streamlining a small number of models and constantly refining them with real-time data inputs. An additional strategy is to develop a small number of models based on an in-depth and critical analysis of the data that arguably most influences the fundamental forces in network strategy. Subsequently, management decisions, KPIs, and operational tactics can be developed specifically to take advantage of what the models have revealed. Importantly, a variety of machine learning algorithms are demonstrating spectacular results when iteratively processing broad, real-time datasets, in essence learning which site or network strategies are most successful as the study progresses. Some collaboration agreements have already been enforced between large technology companies and some of the world's largest pharma companies, and their business development teams are pursuing opportunities to leverage similar technologies within the scope of their dependent partnerships. A few select organizations have recognized the value of building up data analytics capabilities over time and have developed processes and personnel entirely dedicated to integrating the practice within operational workflows. Whether by developing in-house expertise or via collaboration with specialist organizations, all CROs will eventually need to invest in such capabilities if they are to remain competitive. The efficiencies these data-driven approaches could bring are about as transformative as anything previously witnessed in this industry. One startling and fundamental oversight of industry practice, for example, is the uncanny skill with which the most bare-bones of feasibility assessments proceed. Phase II feasibility is often based on first-pass quantitative analysis of site experience input in a non-standardized way. The risk flags and caveats provided by sites are noted and perhaps dealt with, but a change to the nuts and bolts evaluation is rarely made.

In the real-world setting, network optimization models are integrated by CROs to more efficiently contract, start-up and execute patient-centric clinical trials. Four examples are presented where these implementations have been successfully adopted. Information is disclosed to allow better understanding, analyses the process steps that were adopted, and points towards evaluation methods of these implementations. Successes alongside verified cases of efficiency increases of respective measurements are shared. Challenges are also discussed, and in so doing, the entire spectrum of such implementations is presented. To match each clinical trial's unique difficulties that inhibit the successful partnership between sites, investigators, and patients, an optimization envisage is imperative. Throughout the patient recruitment process, network thinking is adopted with the prospect of convincing the sites that are best equipped to recruit a particular patient. Downstream effects are then tracked within a large network model. Many ways are exploited by labs, hospitals, and CROs to intake and take account of shared information. To foster a comparison between common methods and this new approach, illustrative real-world outcomes for this new approach are analyzed. The intention is to draw a comprehensive image of these implementations, from what to expect to what to avoid when considering the incorporation of network optimization models within clinical trials.

Network Optimization models, used together with sophisticated Cloud sharing individual patient data technologies, could significantly enhance the efficiency of CRO delivery models in patient-centric clinical trials (Stamenovic & Dobraca, 2017). Since Patient-Centricity was introduced in clinical drug development, there have been ongoing efforts to connect investigators conducting trials with the patients interested in participating. Although patient registries have assisted in this process of trial decentralization, there is no platforming of data and resources ensuring that chosen patients also get to evaluate relevant trials. CRO delivery models could potentially bridge such gap. In circumstances where a decentralized service model has been agreed between the trial investigator and a Sponsor / CRO, the CRO could model the population providing investigator sites under its control and optimizing patient trial matching through a procedure model, thereby increasing the behavior effect of patient unions. The effectiveness of CRO delivery models can be further enhanced by including a resource scheduling model ensuring that selected trials match the specified capacities and Fair resource allocation principle at investigator Sites. Finally, Cloud technologies can enable the sharing of resources between CROs and Sponsors, hence rewarding investigating sites with greater wealth.

Financing restrictions, data privacy concerns, variability in trial designs, and resistance to change will be among the most notorious challenges in the embedding of network optimization models in CRO delivery models.

Patient Referral Pathways Optimization

Patient referral networks represent the intricate web of patient information flow between healthcare professionals. This information may be about an ongoing patient trial or simply a physician referral for treatment, or second opinion. It is practical for researchers to figure out how to visualize the networks forming between patients, clinics, hospitals, and other healthcare provided facilities, and from that network or many networks, analyse key patients that have the most number of

visits or the providers with the most patient inflow, outflow, or highest count. The network can represent which healthcare provider sees the same patient over a period of time, or model who refers whom to what via a flow network.

Communication Channels Optimization

In this era of large clinical trials in vastly spread locations, communication can often become one of the most neglected aspects of study coordination (D. Stensland et al., 2022). Successful interactions

between trial engines, research sites, stakeholders, as well as study subjects have been proven to be a key ingredient in a successful study conduct. On the other hand, it has been observed on numerous occasions that untouched communication channel hones in study can rapidly become a bottleneck.

Over the course of a clinical study, set of predefined strategies of communication can rapidly become inefficient as the need for the information exchange grows. The situation is particularly pronounced in the late project stages when prompt feedback of the unexpected events may often become impossible due to lack of the open channels. Good information patholization methods can easily uncover areas of a clinical study communication flow when sparseness of the interactions can become a problem. There are numerous prospective ways to improve currently present communication channels in order to make information propagation between individual nodes in a network more effective.

5.3 Queuing Theory

Queueing theory is the mathematical study of waiting lines, or queues, and has a wide range of applications. It is extremely versatile. The main idea of queueing theory is to develop mathematical models of systems in a queue so that predictions of the waiting and service times can be made.

Queueing theory aims to take a model of parts and examine the customer transactions that take place in the model of parts. The basic elements of queueing theory are customers, servers, arrival process, number waiting, and number in a queue. The customer is a statistical concept, and here the arrival and service completion, service times, and customers that aren't being served at the time of interest but have a service time are all modeled. The servers should be working at one time and are often considered to be identical. The arrival process occurs when customers arrive. Data is often collected on the number of customers that arrive over a given time period. The number that is waiting for service and the number in the queue are important entities in the queuing system. They have an important aspect and can be used in performance measures to evaluate the performance of the system.

Queueing theory models can be implemented to visualize patient flow and resource needs in a patient- centric clinical trial scenario and should be adaptable to different clinic configurations seen in these trials. The scheduling system that is in place and some unique needs for this environment might require a model with an embedded allocation algorithm. Furthermore, model development involves collecting patient arrival and service times for each study visit, determining which types of clinical staff provide each study visit, and assessing how many of each staff type are working at a particular time. (Di Pumpo et al., 2022). Additionally, compiling the study data could be challenging and it usually remains with the Sponsor, but must be exchanged with the CRO upon study handover. Patient arrival distributions could be non-memoryless. Modeling new technologies that reduce patient waiting times in a diversified medical system can be advantageous.

The practice of patient-centric trials has grown in recent years to accommodate the needs of the patients first, commonly composed of a variety, specifically a broad range of services delivered by large numbers of employees in a fragmented manner. It is in the best interest for CROs to complete patients visits faster with smaller fluctuations in clinical staff utilization. The efficiencies in clinical trials are critical to deliver a drug on time to the market, due to the time-consuming process in the industry. Among various stakeholders in clinical trials, Clinical Research Organizations (CROs) play a key collaborative role to execute and manage patient-centric clinical trials (Bush, 2019). The potential ability to enhance the efficiency of the clinical trial delivery model is highlighted through the methods of queuing theory.

The excellent historical prospective set-up of clinical trial delivery models by involving design through the EDC approach is employed to maintain regulatory compliances. The approach, however, does not involve processes planning. The hypothesis is that the delivery models can be optimized by queuing theory techniques to plan the processes, to redistribute resources, to optimize processes scheduling with constraints, and to reduce patient numbers' waiting time. An assessment of the operational workflows of the current trial delivery model is first conducted, showing the potential to reduce the patient numbers' waiting time at clinical sites by involving the queuing theory (Bahadori et al., 2014). Detailed frameworks for practical implementations are then presented, including two methods to apply queuing models in processes scheduling and resources allocation with multiple sites, indications, or subjects, and adjusted systematic processes to improve the overall trial delivery effectiveness significantly. The results highlight the collaborative roles for stakeholders in the CROs, pharmaceutical companies, sites, and patients, with an analytical and data-driven approach to the best outcomes. Real-case examples are demonstrated to show the queuing theory effectiveness in the complicated conditions of a kind of adaptive trials. Finally, a forward view is suggested that CROs are to transform from the current historical-focused clinical spot models approach to the efficiency- focused approach by integrating queuing theory techniques.

Queue optimization is the formal study of making the best decisions about the structure and operation of queues. In a standard patient-centric trial setup, scheduling at trial sites is the fixed arrival of patients on a few visiting days every week. It may be that the demand of patients exceeds the supply of time slots available for appointments, as trial sites wish to recruit more patients than they can handle. The fixed arrival of the first patient every day can induce a random waiting time on this group of patients that are unavoidable even if patients arrive exactly on time. On the other hand, the arrival of patients is subject to random external factors that reduce a patient's willingness to wait for the trial site to become available.

Efficient distribution of trial resources is crucial for patient-centricity; resources must be available and accessible when patients are. It is important to manage the distribution of resources - such as staff allocation, equipment usage, budget management - efficiently, to conduct trials in a cost-efficient manner as well as to ensure that available resources can effectively leverage to deliver patient trials (Heath et al., 2021). To be efficient, resources should be distributed with meeting patient-oriented requirements while other considerations are also essential in the distribution of resources in clinical trials, as efficient distribution of resources directly affects the outcome of the trial. Moreover, resource assignment should be adjustable according to the availability of real-time data (Jiang et al., 2019).

Handling the fluctuations in patient demands for the resources essential to the trial is done most efficiently by distributing them with a queuing model. It is possible to be prepared for the level of resources that will be demanded by using suitable queuing models adapted to various types of trials. This can lead to a more flexible capability to make predictions for required resources and assign them using real-time data.

There are various methods that have been adapted using queuing model concepts to make resource allocation more efficient within the framework of the CRO delivery models of patient-centric trials. Some of the important resource allocation strategies are distributing resources based on the patient arrival characteristics, scheduling staffing resources and visits to patients, and forecasting the resource needs using simulation modeling. The empirical examples of these methods display that there is a considerable advantage of employing concepts derived from the queuing theory, particularly with regard to CROs. By considering resource allocation within the CROs, a number of key advantages can be developed and maintained, including high levels of expertise relevant to the design and functioning of trial delivery models. It needs to prepare rigorously on all strategic fronts considering the

challenges in precisely managing resources and timelines within the clinical trial delivery implications. Strategic planning should be addressed in the allocation of resources throughout the tender process to ensure the accounting of opportunity cost and budget capacity.

Queueing theory models can be implemented to visualize patient flow and resource needs in a patient- centric clinical trial scenario and should be adaptable to different clinic configurations seen in these trials. The scheduling system that is in place and some unique needs for this environment might require a model with an embedded allocation algorithm. Furthermore, model development involves collecting patient arrival and service times for each study visit, determining which types of clinical staff provide each study visit, and assessing how many of each staff type are working at a particular time. (Di Pumpo et al., 2022). Additionally, compiling the study data could be challenging and it usually remains with the Sponsor, but must be exchanged with the CRO upon study handover. Patient arrival distributions could be non-memoryless. Modeling new technologies that reduce patient waiting times in a diversified medical system can be advantageous.

5.4 Graph Theory

Graph theory offers a formal language to model and analyze pairwise relations (A. Barnes & Harary, 1983). A graph is the simplest mathematical representation of a network consisting of vertices (nodes) and edges (links). The nodes of a graph can signify trial sites, hospital wards, or excess modes of transportation, while the edges capture their connections or proximity. In directed graphs, the edges possess a specific direction, implying a unidirectional relationship, such as a one-way road. For clinical trial settings, however, the networks are deemed undirected due to their reciprocal nature. The simplest form of graph is a tree, a graph without cycles or loops. A cycle is a unbroken sequence of edges forming a closed loop. A connected component is a sub graph in which each vertex is reachable from every other vertex. Graph analysis can be used to uncover important aspects of a network that may not be apparent from raw data. Trial site networks of real clinical studies illustrate the various aspects of graph theory, such as connectivity, degree distribution, clustering, and shortest paths, along with the logistical implications that they entail (J. Nelson & Bonner, 2021). One of the most fundamental questions is whether a given trial site network is connected, that is, whether there is a path between any two sites. In both case studies, it can be observed that the graph of trial sites is connected. The use of graph theory as a mathematical tool uncovers inherent, yet hidden, structures in different aspects of trial operations and highlights the seemingly simple, yet crucial, logistical considerations.

Graph theory basics have useful application in many research areas. This section on Graphs terminology serves to provide knowledge on the basics that follow. The graph G = (V, E) is a set V of vertices and set E of edges. The edges can be directed for representing relationships in a given direction, or undirected. A directed graph is also known as a digraph. The degree of connectivity of a graph G underlying the nodes is the number of edges connected to them. Biconnected components of G form the maximal connected sub graphs in which any two vertices are connected by two disjoint paths. Simple graph theory

example instances illustrate basic concepts. Graphs G = (V, E) describe and represent many complex relationships and structures that abound in the field of social networks, biological, chemical, industrial and transport systems, and others. Different graph components have different topological properties and the interplay among them heavily influences the behavior of the entire system(s) (Snasel et al., 2018). These reasoning has urged timely research works on the theoretical foundations and investigations of graph/theory properties and components, or structures and the interplay between graph components which are the very system of interest. A graph G = (V, E) consists of a non-empty set V of vertices and a set E of edges. The edges can be directed (digraph). An edge between two vertices u and v is denoted as e(u, v) and u, v ∈ V. This edge connects the source vertex u and the destination vertex v. Nodes without any edge are present. The degree of connectivity of a graph G to a vertex v ∈ V is the number of edges connected to it. When a graph has edges but no direction, the edges and connectivity are not specified. Such edges have only endpoints nodes and they are undirected. The term simple graph refers to a graph with no self-pointing nodes or multiple edges between the same pair of nodes. A biconnected component in the simplest terms is a connected graph with minimum degree of connectivity of 2. Biconnected components of G = (V, E) are the maximal connected subgraphs of G = (V, E) in which any two nodes {u, v ∈ V} are connected by two disjoint paths (Jand & Kaur, 2017).

Graph theory has been instrumental in numerous discoveries extending across seemingly disparate fields of science such as biology and computer science. Nevertheless, its vast potential largely remains untapped within clinical trials. This paper presents an overview of innovative methodologies utilizing graph theory that effectively optimize the latest patient-centric trial infrastructure developments. This is carried out by dissecting the current trial protocols from the standpoint of graph-related applications and identifies untapped expansion opportunities. A primary focus is investigating how various trial site networks can be modeled as graphs to analyze the connectivity and strengthen the relationships among different trial sites (Doga et al., 2024). Given the site networks defined in terms of every possible pairwise attribute like genomic and ethnic similarity, it is demonstrated how the diversity and representation of the trial network sites can be measured. Using this model, it is possible to determine the network's most influential trial site(s) or how a novel trial site inclusion changes the overall network influence distribution. A secondary focus delineates applications of graph theory for protocol design, such as the allocation of multi-regional trial barriers or cohort formations that aim to minimize the detrimental transportation of patients undertaking the trial. Furthermore, this paper connects the methodology sections with multiple recent case studies illustrating the transformative potential of graph-derived methodologies, both in obtaining improved trial outcomes and the realization of trial- design which were otherwise computationally impractical. Attention is drawn to modeling the patient and site interactions as a bipartite network, facilitating efficient information propagation among concert parties or more successful resource allocation to patient subsets of higher importance. To further alleviate the growing concern surrounding transparency, a framework is developed to generate informative and interactive visualizations derived from graphs.

Optimizing Trial Site Selection

Clinical trial site selection is a unique challenge for clinical trial design since it directly correlates with the capability of the selected sites to successfully conduct the trial. It is a multiple-criteria decision making problem that depends on both quantitative and qualitative criteria, including patient demographics, competing trials, site capabilities, and other criteria that are unique to each trial. Site networks also have demographic and geographic relationships among themselves, which adds to the complexity of the process. Site selection can take up to six months, consuming a quarter of the allocated study timeline before a single patient is recruited. Optimized study sites are then used to visualize the communication channels established between those sites, and the best performing sites are used to anticipate strategic actions. For a healthy control or vaccine trial, the sites' recruitment capabilities and their demographic characteristics play a crucial role for the sites to be selected, because it is expected that the number of subjects required for these studies will be higher compared to other types of studies. Data-driven systematization of the site selection process will be beneficial to reduce the complexity of the process and eliminate low-performing sites sooner. This will lead to a drastically reduced timeline before the first subject is recruited and thus, a more efficient recruitment process (Doga et al., 2024). Clinical trial designs are evolving by applying patient-centric principles to better accommodate the patients themselves. One of the many implementations of these principles is ensuring that there are suitable study sites within patients' reach. Moreover, the global pandemic accelerated remote and decentralized trial execution, which also requires patient proximity since follow-up visits are paid by the patient. With the application of the methodology developed herein, an analysis of the patient-centricity on study sites are conducted to decipher the $d_{i,j}$ values, hence estimating the patient recruitment location preference and accessibility. The patient recruitment locations are defined as existing trial sites' geographic points, and locations at equal distances between two trial sites, and their accessibility to patient recruitment are systematically evaluated for a trial network.

Graph Optimization Models

This review presents a suite of graph optimization models tailored to clinical trial applications, covering the mapping and evaluation of trial sites, patients and sites for patient referral, researchers and participants for channel analysis, and multidimensional optimization of communication channels.

In an era of growing complexity and competition, it is paramount to optimize the configuration and operation of key

components so that a superior design is more likely to emerge. Clinical trial site networks can be optimized to improve efficiency and reduce costs. Benefit can be enhanced by using graph optimization models that can inform network design decisions. There are four unique but interoperable models. The first task is to map candidate sites and evaluate their performance for patient recruitment. The second generalizes a geo-matching system for mobile food delivery to recommend sites for patient referral. Mapping three elements: sites, patients, and communication channels. Patients generate demand for hospital services.

Referral is necessitated when a candidate patient is to be recruited but prefers another site similarly capable of delivering the essential service. Demand is characterized through numbers and a distance penalty to prioritize local sites. Considering consumability, a set of sites acceptable to patients is recommended. Similar recommendations are made for patients and sites. The differentiation feature is used in hospitals. Evaluation is through precision-recall analysis and a matching efficiency measure. Experiment results are presented using touristic mobility and real-world appointments in hospital and court services. Many disease-related decisions such as where to be treated and clinical trial sites are location-dependent, so healthcare applications may be cross-domain. Benefit is expected from the significant investment and resources more efficient communication can generate. Optimizing their configuration is the primary step towards devising successful strategies. Analysis of communication channels is the initial effort, focusing on researchers and prospective participants in a clinical study. A network of participants. Each devote time and resources to one or several researchers. Large networks can jeopardize the success of healthcare campaigns. Participants only respond to the first contact made by a researcher. For efficiency, a set of potential patients is scheduled to be contacted by researchers handling outreach on behalf of a single organization, and the activated telephone channels must share no common participant

Clinical trials are conducted to prove the effectiveness and safety of treatments, recently via complex large multisite networks. The approach reshapes any site network. Outcomes can be transformed.

Future trials can benefit from a reduction in additional cost and a focus on cost-effective treatments. As a novelty in empirical research, it is a significant contribution to transform trial design. Pose rigorous challenges to practitioners and researchers. Discuss modeling decisions on data structures. Define confidence values. Alter results for clearinghouse trials

Hyperparameters of the causal graph are reviewed and checked for their sensitivity and numerical stability. Substantiate decisions made for hyperparameters of the simulated survey, on which aggregate statistics are evaluated. Complementary analyses on the performance of the causal graph are provided. Look at the first moment on relative network arrivals to estimate network concordance.

Evaluate the fraction of seeds activated for sites that ultimately fail, akin to precision and positive predictive value. Outputs reflect interactions that can be replayed. To increase the utility of the model, consider creating such resources. Broaden the discussion of a failure mode, providing guidance that can help to choose interventions.

There is increasing interest in the application of graph theories to enhance the efficiency and delivery in Clinical Research Organization (CRO) models of clinical trials to benefit patients (Nanzayi Ngayua et al., 2021). This has been developed as one of the projects to take a holistic look at opportunities enabling patient-centric trials to investigate a range of decentralized trials options and resource and data sharing. There has been effort to explore a custom rating system for efficient clinical trial site selection under the protection of privacy in this data-driven digital era. There has been concern about the effectiveness and privacy issues in the construction of model-reliant clinical trial site rating systems as a service provider, and in response to that, an innovative GraphDB-to-Grid (G2G) model has been proposed from CRO sites' perspectives. Real-world datasets have been evaluated, demonstrating that the GDPR-driven G2G model can provide effective and understandable ratings, leading to privacy protection according to GDPR requirements (Krishna Rao, 2024). Efforts aim to provide ML techniques of optimal CRO attribute extraction from a new data warehouse and rigorous custom preference modeling in the Bayesian framework, expected to generate patient-centric ratings upon CRO sites. Critical information of patient-centric clinical trial sites is expected to be provided by a decision support rating system by enhanced interpretability.

Integration of Graph theory in CRO Delivery Models in table format

CRO Delivery Model Area	Application of Graph Theory	Objective	Key Graph Components
Project Task Scheduling	Representing tasks as nodes and dependencies as edges to manage workflows	Optimize scheduling and detect bottlenecks	Nodes = Tasks; Edges = Dependencies
Clinical Site Network Optimization	Modeling clinical trial sites and their relationships (geographic, performance)	Improve communication and site	Nodes = Sites; Edges = Connectivity (e.g., distance)

		collaboration	
Patient Referral Pathways	Mapping referral routes between hospitals/clinics to identify optimal recruitment paths	Maximize patient enrollment and minimize referral delays	Nodes = Facilities; Edges = Referral Links
Supply Chain Routing	Optimizing transport routes for clinical materials and drugs	Minimize shipping time/cost using shortest path algorithms	Nodes = Locations; Edges = Transport Routes
Collaboration Network Analysis	Visualizing and analyzing researcher, vendor, or team collaboration networks	Identify key contributors and collaboration patterns	Nodes = People/Vendors; Edges = Collaboration Links
Risk Propagation Analysis	Modeling how risks propagate through a trial network	Identify critical points and mitigate cascading risks	Nodes = Activities/Processes; Edges = Risk Dependencies
Data Integration & Flow Mapping	Mapping how data flows between systems, departments, or external sources	Ensure data integrity and streamline information flow	Nodes = Data Sources/Systems; Edges = Data Flows
Protocol Deviation Tracking	Tracking deviations across trial elements and their interdependencies	Identify patterns and root causes in trial non-compliance	Nodes = Protocol Elements; Edges = Deviation Links

5.5 Game Theory

Game theory is the systematic analysis of interdependent decision situations. A game consists of players who can choose from a set of strategies. The payoff each player receives depends on their own choice of strategy and the choices pursued by the other players. These components interact during play, giving rise to complex strategic situations for players to navigate (Lane et al., 2022). Games are thus a way of representing the strategic interactions among different agents whose choices affect a certain outcome. Powerful tools concerning mathematical aspects and optimal strategies have been developed and may be profitably used to improve the efficiency of delivery models in patient-centric clinical trial setups.

Any clinical trial is the outcome of relationships among different stakeholders such as researchers, patients, and policy makers. These relationships create a web of interdependencies, or a game.

According to their structure, the relationships might be strategic or not. As an example, a clinical trial start-up operation is a non-strategic relationship between the sponsor and hospitals. In this case, players coordinate in order to assemble the documents needed for the study. This operation might be formalized as a non-cooperative and static game. On the other hand, a trial itself is a strategic relationship between hospitals, pharmacies, and patients among others. Players coordinate regarding different outcomes or tasks, such as patient enrollment. This operation might be formalized as a cooperative game or as a dynamic game. Clinical trials are highly characterized by information asymmetry between players. It reflects different, partial, or missing information upon which decisions are made. Struggling with better performance in unbalances plays a key role. For instance, in a fairly complex setup, trials are managed by the sponsoring body that interacts with hospitals in the site selection process. These, in the meantime, end up interacting with pharmacies and patients for the actual trial conduction. Since a plethora of clinical trials regard rare diseases, the patient's recruitment pool is limited, and hospitals will compete among them for patients. The sponsor knows of the interactions between hospitals, in particular, the reasons of refusal for one or multiple hospitals. This is just an example where the human intervention is needed in handling complex systems, and game theoretical tools can help to find the best response functions.

Optimization Strategies Using Game Theory in CRO Delivery Models

Clinical trials are complex operations that require the collaboration of multiple stakeholders, with patient needs often conflicting with the design of efficient processes in a delivery model that is dominated by the operational and economic interests of Contract Research Organizations. By focusing on the application of game theory, various game-theoretic frameworks that can assist in the decision- making process to align the interests of patients, Sponsors, HCPs and CROs are explored. This assists the design of delivery models that are efficient and centric to the patient, overall allowing an increase in trial performance and an improvement in trial quality. Analyzing these insights, a comprehensive set of optimization strategies are discussed: negotiation tactics, the use of games, the design of the incentive structure, stacked resource allocation, data sharing, and the use of bargains with patient coalitions. These strategies are systematized and analyzed through the reduction of their mathematical base into generic advice for the various stakeholders of the games. Real trial case studies of applying optimization strategies in the negotiation and operational processes demonstrate their successful implementation. By identifying the interplay between competitive and cooperative strategies, it is found that competitive strategies are mostly used to allocate resources, while cooperative strategies are mostly used in the operational process. The importance of the adaptability of strategy selection to the evolution of the game is outlined. It is further recommended that the insights and techniques presented are incorporated into a decision and planning framework used by Sponsors, helping to better understand the trade-offs that are associated with the implementation of the optimization strategies, and to identify a framework that allows a more efficient trial negotiation and design.

CRO Delivery Model Area	Game Theory Application	Optimization Objective	Players/Agents	Game Type
Vendor Negotiation	Modeling CRO-vendor interactions as a bargaining game	Achieve optimal pricing and service levels	CRO, Vendors	Bargaining/Cooperative Game
Clinical Site Selection	Sites compete for trials based on cost, performance, and capacity	Maximize site performance and cost-effectiveness	CRO, Clinical Sites	Non-Cooperative Game
Budget Distribution	Departments compete for a share of limited resources	Fair and efficient budget allocation	Internal departments	Cooperative Game (Shapley value)
Patient Recruitment Competition	Sites act strategically to enroll more patients	Balance recruitment across sites and avoid over-concentration	Clinical Sites	Competitive Game
Multi-CRO Collaboration	Multiple CROs working under a sponsor with overlapping goals	Coordinate to reduce redundancies and maximize output	Multiple CROs, Sponsor	Cooperative Game
Risk Sharing & Contract Design	Designing contracts that align incentives across stakeholders	Minimize overall project risk while ensuring compliance	CRO, Sponsors, Sites	Mechanism Design/Game-Theoretic Contract
Regulatory Compliance Strategy	Modeling interactions between CRO and regulators under uncertainty	Minimize risk of audit failures or penalties	CRO, Regulatory Agencies	Stackelberg Game (Leader-Follower)
Protocol Development	Negotiating protocol complexity vs. cost and feasibility among stakeholders	Optimize trial feasibility and quality	Sponsors, CROs, Investigators	Cooperative Bargaining Game

6. BENEFITS AND CHALLENGES OF OPERATIONAL RESEARCH TECHNIQUES

The application of operational research (OR) techniques in Clinical Research Organization (CRO) delivery models for patient-centric trials has both benefits and challenges. The benefits can help to address major issues with the current operating model as they are tested experimentally and validated with real-world data. A vision is developed for how patient-centric trials can be efficiently resourced and a strategy outlined for such trials to become industry-standard practice. The challenges are discussed, offering at each stage of the solution practical advice to sponsoring and delivering organizations, and giving insight into how the implementation of the solution can be simplified. It is shown how overcoming the challenges can actually enhance the benefits, but that such a concordance is not necessarily the default outcome. It is observed that many other benefits can accrue to the delivery of patient-centric trials reflecting improved operational structure, such as fixed visit models or enhanced in-house care possibilities, but that these are not included in the resultant solution because of implementation challenges that cannot be readily addressed. Finally, it is noted how the problem and benefit domains are linked by lifestyle questions, workplace concerns, patient motivation irritants and a policing presence, illustrating how understanding the whole operational landscape is essential for an OR-based solution to thrive, and how these insights can be converted into findings with wide relevance. Nor does this survey include considerations of stakeholder buy-in or organizational culture, key topics for ensuring the successful implementation of such solutions in practice (Monks, 2016).

7. CONTRIBUTION FROM THIS STUDY

The results of this study provide important insights for the practical implementation of several OR techniques, and as such it is necessary to discuss these insights in some detail. In this regard, there are structured recommendations for practice, which highlight a series of important implications, and in addition a set of reflections for researchers and stakeholders, which consider some of the broader issues that arise from the findings.

It is vital to foster a culture of collaboration between statisticians, operations teams, and investigators so as to facilitate a strong focus on recruitment rates. Continuous training and development of operations groups to build capability in OR techniques is also essential. A clear output of this training and development should be to foster a grass roots push with the client base for adoption of OR and to inform on what is required in terms of data and input assumptions. Finally, the results highlight a need for the metrics used in these methods to be agreed between stakeholders so that efficiency assessments are consistently applied and benchmarking can be performed.

The results of the present study are supported by extensive analysis of the process mining results and show the potential of using this technique for evaluating the performance of operational research (OR) models in clinical research settings. Insights from this robust application of process mining can help both CROs and managers in sponsor companies to better understand, assess, and use such models to improve service workflows and the delivery of patient-centric trials. There are also interesting insights for academics and other potential users of OR models in such settings, with guidance on how to apply process mining analysis efficiently for a better-understanding model performance. Effectively, process mining requires clinical evaluation of improvement initiatives over comparatively long time periods; this may also be necessary to quantify concerns regarding the sustainability and “exhaustion” of the impacts OR interventions (I Nebie et al., 2024). At present, the literature in this area is limited by its perspective on short term impacts. To bridge this gap, future research should include work that evaluates the operational differences in efficiency in the long term and to facilitate such research additional time series data on performance indicators in clinical research settings need to be collected.

The incorporation of a larger portfolio of interventions in the models’, possibly in a distributed manner (for example different remediation initiatives, multimodel simulations, or hybrid models), could be undertaken to further evaluate and evidence the steps necessary for improving the efficiency achievement in patient-centric trials. However, it is also acknowledged that outcome variability is the norm in such interventions due aspects such as the CROs’ geographically dispersed environments, the diversity of the clinical settings and hospital sites, or the intrinsic variability and unforeseeable nature of patient treatment in real-life clinical research. Accordingly, it is recommended that such models be monitored and realigned with the best practices continuously so that they stay effective. Given the increasing complexity and scale of innovations, it will also be beneficial to encourage interdisciplinary initiatives between operational researchers, clinical researchers, clinicians, and sponsors to develop the next-generation methods and tools needed for tackling the more challenging inefficiencies and delays in patient-centric trials.

Recently, clinical trials have shown a tendency towards adopting patient-centric approaches; however, there is a lack of deep research into the operational practices within patient-centric clinical trials from a comprehensive perspective (I Nebie et al., 2024). In order to fill the research gap, patient engagement and interaction level between patients and other stakeholders groups are first introduced to define patient-centric trials. Then, novel operational practices within patient-centric trials are categorized under two key processes. A state-of-the-art literature review is conducted to examine foundational works on clinical trials and patient orientations. Moreover, operational differences between patient-centric and conventional trials with patients as objects are comprehensively analyzed. This research then reveals the patient-centric operational performance in large-scale clinical trials through a case study conducted on phase III biosimilar studies.

The main contributions can be summarized as follows. (1) Novel insights into the operational practices within patient-centric trials are offered as an enhancement of the existing knowledge. (2) The efficiency strategy, further coordination between patients, clinicians, and sponsors, is provided. It is also noteworthy that at each process of preparation and conduction there are proactive operational practices, which are managerial implications for stakeholders. (3) General thought regarding the prospective development of operational practices within patient-centric trials is proposed, acting as a roadmap. (4) Patient-centric operational findings offer enlightenment for policy-making and clinical guidelines on patient involvement in studies. (5) The operational performance is quantified to reveal a great waste of resources occurring in this heavily marketed clinical area, indicating that through operational enhancement it is possible to better utilize the invested resources and increase the chances of obtaining desired clinical results.

8. LIMITATIONS AND SCOPE FOR FUTURE RESEARCH

Despite the positive conclusion that can be drawn in this study, there are several limitations. The primary limitation is the limited online literature search and review. The articles, research papers were obtained through the open access in the research databases. Further investigation with a larger research databases are recommended.

9. CONCLUSION

This paper explores the operational research (OR) techniques that can be applied in preclinical, clinical and peri-post patient related services of a Clinical Research Organization (CRO). The purpose of the research is to investigate and substantiate any OR best practices in the above-mentioned areas in order to propose refined OR methodologies, which might aid patient-centric research trials, under the CRO umbrella delivery model. A mixed methodological approach was followed, consisting of quantitatively gathering data from primary research within the CRO industry on selected variables and operational service model structures; and qualitatively exploring and defining, based on the gathered insights, enhanced output solution models, with the aid of appropriate OR problem structuring, methodological analysis and scenarios. Causal behavior dynamics of selected variables were analysed by means of an accumulation simulation model, which was developed to verify the different exogenous scenario external shocks to model policies. The empirical research findings suggest that multiple interrelations exist between the examined CRO service areas and selected variables, with different dynamics observed by the cause effect policy analyses. Under the internal fluctuating demand boundary settings, OR methodologies provide for optimal management knowledge and may be better positioned to improve CRO performance. The conclusion of the research is followed by a discussion on OR as an implementation science in the healthcare sector, a critical reflection on the research limitations, and several future research directions.

Declaration Statement

I, declare that this research paper is my original work and has not been submitted for any other degree or publication. I affirm that all sources used in this paper are properly cited and acknowledged. Additionally, I confirm that there are no conflicts of interest related to this research, and any funding received for this project has been disclosed.

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REFERENCES

[1] A Malikova, M. (2016). Optimization of protocol design: a path to efficient, lower cost clinical trial execution. ncbi.nlm.nih.gov

[2] Barnes, J. & Harary, F. (1983). Graph theory in network analysis. [PDF]

[3] Guillemin, E. (1955). Network Synthesis. [PDF]

[4] Anisimov, V. & Austin, M. (2022). Modeling restricted enrollment and optimal cost-efficient design in multicenter clinical trials. [PDF]

[5] Anisimov, V. & Austin, M. (2022). Modeling restricted enrollment and optimal cost-efficient design in multicenter clinical trials. [PDF]

[6] Bahadori, M., Mohsen Mohammadnejhad, S., Ravangard, R., & Teymourzadeh, E. (2014). Using Queuing Theory and Simulation Model to Optimize Hospital Pharmacy Performance. ncbi.nlm.nih.gov

[7] Bush, N. (2019). Impact of Queueing Theory on Capacity Management in the Emergency Department. [PDF]

[8] C. Mak, B., T. Addeman, B., Chen, J., A. Papp, K., J. Gooderham, M., C. Guenther, L., Liu, Y., C. Broedl, U., & E. Logger, M. (2021). Leveraging Blockchain Technology for Informed Consent Process and Patient Engagement in a Clinical Trial Pilot. ncbi.nlm.nih.gov

[9] Coffey, T., R. Williamson, P., & Gillies, K. (2024). Understanding implementation of findings from trial method research: a mixed methods study applying implementation frameworks and behaviour change models.

ncbi.nlm.nih.gov

[10] Crown, W., Buyukkaramikli, N., Sir, M. Y., Thokala, P., Morton, A., Marshall, D. A., Tosh, J. C., Ijzerman, M. J., Padula, W. V., & Pasupathy, K. S. (2018). Application of constrained optimization methods in health services research: Report 2 of the ISPOR Optimization Methods Emerging Good Practices Task Force. [PDF]

[11] Crown, W., Buyukkaramikli, N., Sir, M. Y., Thokala, P., Morton, A., Marshall, D. A., Tosh, J. C., Ijzerman, M. J., Padula, W. V., & Pasupathy, K. S. (2018). Application of constrained optimization methods in health services research: Report 2 of the ISPOR Optimization Methods Emerging Good Practices Task Force. [PDF]

[12] Di Pumpo, M., Ianni, A., Azzurra Miccoli, G., Di Mattia, A., Gualandi, R., Pascucci, D., Ricciardi, W., Damiani, G., Sommella, L., & Laurenti, P. (2022). Queueing Theory and COVID-19 Prevention: Model Proposal to Maximize Safety and Performance of Vaccination Sites. ncbi.nlm.nih.gov

[13] Doga, H., Emre Sahin, M., Bettencourt-Silva, J., Pham, A., Kim, E., Andress, A., Saxena, S., Bose, A., Parida, L., Lukas Robertus, J., Kawaguchi, H., Soliman, R., & Blankenberg, D. (2024). Towards quantum computing for clinical trial design and optimization: A perspective on new opportunities and challenges. [PDF]

[14] Doga, H., Emre Sahin, M., Bettencourt-Silva, J., Pham, A., Kim, E., Andress, A., Saxena, S., Bose, A., Parida, L., Lukas Robertus, J., Kawaguchi, H., Soliman, R., & Blankenberg, D. (2024). Towards quantum computing for clinical trial design and optimization: A perspective on new opportunities and challenges. [PDF]

[15] Doga, H., Emre Sahin, M., Bettencourt-Silva, J., Pham, A., Kim, E., Andress, A., Saxena, S., Bose, A., Parida, L., Lukas Robertus, J., Kawaguchi, H., Soliman, R., & Blankenberg, D. (2024). Towards quantum computing for clinical trial design and optimization: A perspective on new opportunities and challenges. [PDF]

[16] Farley, T., Kiefer, J., Lee, P., Von Hoff, D., M Trent, J., Colbourn, C., & Mousses, S. (2013). The BioIntelligence Framework: a new computational platform for biomedical knowledge computing. ncbi.nlm.nih.gov

[17] Ghim, J. L. & Ahn, S. (2023). Transforming clinical trials: the emerging roles of large language models. ncbi.nlm.nih.gov

[18] Ghosh, S., Mallick, A., Chowdhury, A., & De Sarkar, K. (2023). Graph Theory Applications in Advanced Geospatial Research. [PDF]

[19] Heath, A., G. Myriam Hunink, M., Krijkamp, E., & Pechlivanoglou, P. (2021). Prioritisation and design of clinical trials. ncbi.nlm.nih.gov

[20] Huang, Y. L. (1970). An Alternative Outpatient Scheduling System: Improving the Outpatient Experience.. [PDF]

[21] I Nebie, E., van Eeuwijk, P., N. Sawadogo, H., Reus, E., Utzinger, J., & Burri, C. (2024). Operational Differences between Product Development Partnership, Pharmaceutical Industry, and Investigator Initiated Clinical Trials. ncbi.nlm.nih.gov

[22] I Nebie, E., van Eeuwijk, P., N. Sawadogo, H., Reus, E., Utzinger, J., & Burri, C. (2024). Operational Differences between Product Development Partnership, Pharmaceutical Industry, and Investigator Initiated Clinical Trials. ncbi.nlm.nih.gov

[23] Jand, H. & Kaur, J. (2017). Graph Theory. [PDF]

[24] Jiang, F. C., Shih, C. M., Wang, Y. M., Yang, C. T., Chiang, Y. J., & Lee, C. H. (2019). Decision Support for the Optimization of Provider Staffing for Hospital Emergency Departments with a Queue- Based Approach. ncbi.nlm.nih.gov

[25] Krishna Rao, R. (2024). Leveraging Decentralized Clinical Trial Management Systems (dCTMS) to Advance Science: Exploring Challenges Related to the Diffusion of Innovation and Its Execution. ncbi.nlm.nih.gov

[26] Lane, K., Majkowski, R., Gruber, J., Amirault, D., Hillery, S., Wieber, C., D Thompson, D., Huvane, J., Bridges, J., Paul Ryu, E., M. Eyzaguirre, L., Gildea, M., E. Thompson, R., E. Ford, D., & Hanley, D. (2022). Using gamification to enhance clinical trial start-up activities. ncbi.nlm.nih.gov

[27] Laskowski, M., D. McLeod, R., R. Friesen, M., W. Podaima, B., & S. Alfa, A. (2009). Models of Emergency Departments for Reducing Patient Waiting Times. ncbi.nlm.nih.gov

[28] Lysenko, A., A. Roznovăţ, I., Saqi, M., Mazein, A., J Rawlings, C., & Auffray, C. (2016). Representing and querying disease networks using graph databases. ncbi.nlm.nih.gov

[29] Marks, L. (2016). TransCelerate: a global collaboration across biopharmaceutical R&D to accelerate and simplify new medi-cines development. [PDF]

[30] Mbuagbaw, L., Foster, G., Cheng, J., & Thabane, L. (2017). Challenges to complete and useful data sharing.

ncbi.nlm.nih.gov

[31] Mondal, R., Dung Do, M., Uddin Ahmed, N., Walke, D., Micheel, D., Broneske, D., Saake, G., & Heyer, R. (2023). Decision tree learning in Neo4j on homogeneous and unconnected graph nodes from biological and clinical datasets. ncbi.nlm.nih.gov

[32] Nanzayi Ngayua, E., He, J., & Agyei-Boahene, K. (2021). Applying advanced technologies to improve clinical trials: a systematic mapping study. ncbi.nlm.nih.gov

[33] Narola, J. (2018). Applying the Agile Mechanism in the Clinical Trails Domain for Drug Development. [PDF]

[34] Narola, J. (2018). Applying the Agile Mechanism in the Clinical Trails Domain for Drug Development. [PDF]

[35] Nebie, E., van Eeuwijk, P., N. Sawadogo, H., Reus, E., Utzinger, J., & Burri, C. (2024). Operational Differences between Product Development Partnership, Pharmaceutical Industry, and Investigator Initiated Clinical Trials. ncbi.nlm.nih.gov

[36] P. Saksena, C. (2018). Some contributions to the theory of mathematical programming. [PDF] Pang, J., Yan, H., & Hua, Z. (2023). Drug Supply Chain Optimization for Adaptive Clinical Trials. [PDF]

[37] Roux, J., Bez, N., Rochet, P., Joo, R., & Mahévas, S. (2023). Graphlet correlation distance to compare small graphs. ncbi.nlm.nih.gov

[38] Snasel, V., Drazdilova, P., & Platos, J. (2018). Closed trail distance in a biconnected graph. ncbi.nlm.nih.gov

[39] Stamenovic, M. & Dobraca, A. (2017). Benefits of Outsourcing Strategy and IT Technology in Clinical Trials. ncbi.nlm.nih.gov

[40] Straube, C., Herschbach, P., & E. Combs, S. (2017). Which Obstacles Prevent Us from Recruiting into Clinical Trials: A Survey about the Environment for Clinical Studies at a German University Hospital in a Comprehensive Cancer Center. ncbi.nlm.nih.gov

[41] Success Ikechi, K., Benedict. A, O., & Ikechukwu.C., E. (2014). Application of Linear Programming Techniques to Practical Decision Making. [PDF]

[42] V Lugg-Widger, F., Angel, L., Cannings-John, R., Hood, K., Hughes, K., Moody, G., & Robling, M. (2018). Challenges in accessing routinely collected data from multiple providers in the UK for primary studies: Managing the morass.. [PDF]