Pharmaceutical Cold Supply Chain Management Considering Medication Synchronization and Different Delivery Modes

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Abstract

Last-mile logistics in the healthcare supply chain is becoming increasingly important, especially in pharmacies where medication delivery to patients' homes is becoming prevalent. Therefore, this paper proposes a mathematical model for the last-mile logistics of the pharmaceutical supply chain and optimizes a pharmacy's logistical financial results while considering medication synchronization, different delivery modes, and temperature requirements. In this research, we create a Mixed Integer Linear Programming (MILP) model to find optimal solutions regarding the number of order batches, the composition of these batches, and the number of staff related to the preparation of the order batches. We create a case study by gathering, preparing, processing, and analyzing the data associated with an outpatient pharmacy of a Dutch hospital. Our results show that our optimal solution increases the pharmacy's logistical results by 34 percent. Besides, we propose other model variations and perform extensive scenario analysis to provide managerial insights useful for various pharmacies and distributors in the last step of cold supply chains. In particular, our scenario analysis of these results suggests that improving medication synchronization can significantly enhance the pharmacy's financial results. Furthermore, the model proves to be a tool for assessing multiple sets of scenarios relevant to the pharmacy.

Keywords: Cold Supply Chain, Data Analytics, Mixed Integer Linear Programming, Healthcare Delivery, Medication Synchronization

1. Introduction and background

The global supply chain management (SCM) market in healthcare was valued at $2.33 billion in 2021 and is expected to expand at a compound annual growth rate of 9.2% from 2022 to 2030 (Grand view research, 2020). Within the healthcare supply chain, the importance of last-mile logistics in the pharmaceutical sector is growing rapidly (Sun et al.,

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2022; Dcruz et al., 2022) as pharmacies tend to provide medication delivery to the homes of patients. While home delivery of medications can enhance patients' accessibility to pharmacy care by reducing their visits to the pharmacy, it also presents unique complexities that require special consideration in the supply chain (Srivastava et al., 2022). Examples of such considerations include implementing additional safety measures during transportation and delivery. This involves adhering to specific temperature and storage requirements for certain pharmaceuticals (Srivastava et al., 2022). Another crucial aspect of optimizing medication supply chains is medication synchronization or consolidation. This has the potential to reduce workload and costs (Melendez et al., 2020), as well as increase medication adherence (Ross et al., 2013). As a result, a growing number of researchers, including ourselves, are focusing on managing the distribution operations of these cold supply chains. We aim to explore the effects and potential implementation of medication synchronization, various delivery modes, and temperature requirements.

Supply chain management (SCM) is the strategic coordination of all activities involved in the sourcing, procurement, manufacturing, and delivery of products and services (Chopra and Meindl, 2013). In the healthcare setting, SCM plays a critical role in ensuring that patients receive high-quality care through timely access to safe and effective medications (Abdulsalam et al., 2015). Pharmaceutical SCM involves the management of the entire process of drug development, production, distribution, and dispensing. In recent years, there has been a growing interest in exploring different modes of pharmaceutical delivery from the pharmacy to the patient. This includes options such as bike couriers, electric vehicles, and even drones (Lamiscarre et al., 2022; Asadi et al., 2022), which have been shown to reduce carbon emissions and transportation costs and increase demand satisfaction. Additionally, telepharmacy has emerged as another delivery approach that leverages telecommunication and technology to provide pharmacy services and medication management to patients in remote or underserved areas (Baldoni et al., 2019).

In addition to delivery modes, medication synchronization is a crucial aspect of optimizing the delivery of pharmaceuticals. This process involves aligning the refill dates of a patient's medications to decrease the frequency of pharmacy visits (Melendez et al., 2020) and enhance medication adherence (Ross et al., 2013). Synchronization strategies like these have the potential to decrease environmental impacts and costs while improving the patient experience. However, their feasibility and effectiveness require further investigation.

An important challenge to the feasibility and effectiveness of delivery and synchronization strategies is the need for cold supply chains to store and distribute biopharmaceuticals, such as vaccines, antibiotics, and anti-rheumatoid injections, at low temperatures to ensure their efficacy. The recent example of mRNA vaccines for COVID-19 highlights the challenge of maintaining a cold supply chain at ultra-low temperatures (Bishara, 2006). Failure to maintain the recommended temperature range at one or multiple stages of the supply chain can lead to decreased effectiveness or even harm for various pharmaceuticals, which is not limited to the COVID-19 vaccine case (Nyirimanzi et al., 2023). This can result in waste of supplies, increased medical costs, and increased disease prevalence, as evidenced by previous research (Malik et al., 2022). Therefore, this research aims to contribute to solving these issues by improving cold SCM and avoiding the negative consequences of faulty management.

Optimizing the cold supply chain to accommodate factors such as temperature requirements, different delivery modes, and medication synchronization can add an extra layer of complexity and cost. However, pharmacies and other healthcare institutions can benefit from implementing these strategies if a proper framework is in place to optimize logistical results. In the pharmaceutical industry, where margins are typically thin (Garattini et al., 2008), positive net results are essential for the survival of these organizations. Therefore, the focus of this research is to optimize the logistical financial results of the supply chain as a critical factor in the success and sustainability of pharmaceutical businesses.

In this research, we propose an optimization model using Mixed-Integer Linear Programming (MILP) to maximize the logistical financial results of an outpatient pharmacy in the final stage of the cold supply chain - delivering medications to patients. Recent examples of MI(L)P models are the research of Chowdhury et al. (2022), which develops and optimizes a vaccine supply chain, considering three objectives: minimizing cost, ensuring environmental and social sustainability, and maximizing job opportunities. Furthermore, we recognize the work of Ala et al. (2023), which uses queuing theory and MILP optimization to optimize waiting time and patient arrivals at a minimum supply chain cost. A study by Aghazadeh et al. (2018) proposes a multi-objective MIP model for an organ transplant, aiming to reduce working center costs and optimize allocations of units and organs. We note there are other optimization models, including non-linear programming (Starita and Paola Scaparra, 2022; Juned et al., 2022), simulation models (Dui et al., 2023; Borges et al., 2020), and Markov decision processes (Abbaspour et al., 2021; Shakya et al., 2022), that are widely used in healthcare SCM. Due to the characteristics of our problem, including a deterministic setting and the ability to model the objective function and constraints using a linear function, we choose an MILP modeling approach.

We propose the Pharmaceutical Cold Supply Chain Management Considering Medication Synchronization and Different Delivery Modes (PCSCM-MSDM) problem by exploring the impact of delivery methods, medication synchronization, and cooling requirements on distribution costs and revenues. The model optimizes the number of order batches and the composition of these batches, as well as the staffing related to the preparation of the order batches. The model is validated and tested with a real-life case study prepared from data acquired from the outpatient pharmacy of the Sint Maartenskliniek (SMK) in Nijmegen, The Netherlands, called the Maartensapotheek (MA). We also provide scenario analysis on the results, as well as two model variations to explore the influence of tactical-level decisions on the pharmacy's profitability.

To the best of our knowledge, we are the first to (i) provide a mathematical formulation to manage the pharmaceutical cold supply chain while explicitly considering medication synchronization and different delivery modes, (ii) prepare, process, and provide a real case study of an outpatient pharmacy to be used for PCSCM-MSDM, (iii) provide the exact optimal solutions for the understudied problem, (iv) perform extensive sensitivity analysis and data analytics methods, including variations on the base model, to derive insights for managers including but not limited to the outpatient pharmacy managers.

The remainder of this paper is structured as follows. Section 2 discusses relevant literature related to the model, application and analytic methods presented in this paper. Section

3 presents the MILP model for the PCSCM-MSDM problem. Section 4 contains information about the MA case study, the data used, results and experiments, and alternative modeling choices. Finally, Section 5 concludes the paper, examines opportunities for further research, and discusses the limitations of this research.

2. Literature Review

This section explains the theoretical framework of this research. We elaborate on the cold supply chain and its applications in the pharmacy industry. In addition, we discuss research considering the applications of last-mile logistics with a focus on pharmaceutical supply chains and different delivery modes. We explain the concept of medication synchronization and provide some insights related to our work. Furthermore, we review related research on MILP models and highlight the novel contributions of our study in addressing existing scientific gaps. Additionally, we discuss other relevant papers that share our objectives but employ different modeling techniques.

2.1. The cold supply chain in the pharmacy industry

The pharmaceutical supply chain is a complex network that involves the manufacturing and distributing of medications to patients and organizations at the right time, quantity, and cost (Abdulghani et al., 2019). However, this process comes with many logistics, inventory management, and warehouse management challenges (Sinnei et al., 2023). In recent years, cost optimization has become a cross-sectional theme in all areas of the supply chain, especially with the rising pressure due to the COVID-19 outbreak and other geopolitical conflicts like Ukraine War (Fitch Solutions, 2022). For example, the high demand all across the globe and the temperature requirements of different vaccines, including the COVID-19 vaccine (depending on the brand and type, a temperature of approximately -70 ℃, -25 ℃ or between 2 ℃ and 8 ℃ are recommended (Balfour, 2021)), make a well-organized cold supply chain network a necessity. Cold supply chain management is increasingly vital in pharmacy logistics (Bishara, 2006), as biopharmaceuticals must be stored and distributed at low temperatures to maintain their efficacy (Turan and Ozturkoglu, 2022). Many researchers are studying SCM from different perspectives, including cold SCM, to address these challenges (Laganà and Colapinto, 2022; Dixit et al., 2019).

For instance, the work of Kartoglu and Milstien (2014) presents several tools and approaches to ensure the quality of vaccines throughout the cold chain wherein vaccines require adequate temperature storage, as they are either sensitive to heat or cold. Similar to our work, this research focuses on cold SCM with consideration of cost factors and different delivery systems. The study provides insights into possible qualitative solutions for pharmacies' cold chain challenges. Our work is quite different from Kartoglu and Milstien (2014)'s as we propose a quantitative approach, instead of a qualitative approach. We also focus more specifically on the impact of cold chain management on pharmaceuticals, the characteristics of vaccines within the cold supply chain, and proposed solutions to optimize the logistical operations of the pharmacy than the study of (Kartoglu and Milstien, 2014). Still, the tools and approaches for vaccine distribution presented in (Kartoglu and Milstien, 2014) are relevant and useful for our study, as these are needed to realize an improved cold supply chain for medications.

2.2. Last-mile delivery modes

Last-mile logistics refers to the final stage of the supply chain where a shipment is delivered to its ultimate destination (Giuffrida et al., 2022). In the case of pharmacy supply chains, adequate last-mile logistics ensures delivering medications to patients in a safe and timely manner. (Bhatnagar et al., 2018). Within the pharmacy supply chain, adequate last-mile logistics are very important as the patient needs to receive the medication safely (Abdulghani et al., 2019). To provide a foundation for our research, we review the literature on last-mile delivery strategies in pharmacy SCM, with a particular focus on different delivery modes proposed as given in our research. One example is the work of Handoko et al. (2014), which proposes a profit-maximizing model for determining which demands to serve using an Urban Consolidation Centre (UCC). The UCC reduces the number of large vehicles on city roads, thereby saving time and reducing congestion and emissions. Our study is different in that we focus not only on the modes of transportation and delivery, but on the whole picture of last-mile logistics for a pharmacy. We draw upon the research of (Handoko et al., 2014) as a source of last-mile logistics and delivery mode ideas for our study.

In addition to the urban consolidation center (UCC) model, there are other last-mile delivery modes that can be applied to pharmacy supply chain management. Crowd shipping is one such mode, which is discussed in Bajec and Tuljak-Suban (2022). The study highlights the benefits of crowd shipping, including low prices, reduced delivery times, and environmental impact. However, it also points out the risks associated with quality, reliability, and inefficiency. To mitigate these risks, the study recommends proper management of coalition members and optimal collaboration. Another relevant study is Azizi and Salhi (2022), which proposes and optimizes a hub-and-spoke system for transportation between multiple locations. This system involves using a hub as a link between several locations, possibly other hubs, in a distribution network. The study focuses on determining the optimal location of the hubs and demand allocation to all hubs. Moreover, Lamiscarre et al. (2022) evaluate the potential of drone-based last-mile logistics as a modern delivery mode that could supplement or replace traditional delivery options. The study explores a hybrid approach that combines both ground vehicles and Unmanned Aerial Vehicles (UAVs) and assesses the benefits of this approach in terms of time, pollution, and cost. The authors anticipate that the use of UAVs will become more prevalent in the near future. This research is relevant to our investigation of multiple delivery modes, and it provides valuable insights into the potential use of UAVs as one of these modes. Our study does not include UAVs as this is not a feasible solution in the case study at the MA. However, we consider bicycle delivery as a modern, low-cost and sustainable delivery mode.

2.3. Medication and order synchronization

Medication synchronization refers to the action of filling patients' medication prescriptions simultaneously (Nguyen and Sobieraj, 2017), which has been shown to improve medication adherence and reduce costs (Renfro et al., 2022). Ross et al. (2013) investigates medication refill consolidation, which is the synchronization of refill dates for patients that use multiple medications. Ross et al. (2013) conducts a survey of 50 patients using two or more medications with a supply limit of at least 30 days. The survey results suggest that poor refill consolidation is linked to reduced medication adherence, which could be harmful to patients. These findings emphasize the significance of incorporating medication synchronization in our research since there are several unfavorable outcomes when medication is not appropriately synchronized. Hughes et al. (2022) explores the barriers and facilitators associated with Med Sync (a medication synchronization service) in community pharmacies and generates practical solutions. While our research mainly focuses on the (financial) outcome of implementing medication synchronization in a pharmacy, Hughes et al. (2022) offers valuable practical solutions for implementing synchronization practices, including engaging staff, organizing programs effectively, and collaborating with providers. We recommend that those who adopt the model from our research utilize the practical solutions outlined in Hughes et al. (2022) to manage their synchronization process effectively.

2.4. MILP modelling techniques

The modeling choices made in the PCSCM-MDSM problem, particularly the use of MILP for result optimization, are widely used in many studies conducted on cost and revenue optimization across various industries, such as logistics, transportation, and manufacturing. For instance, MILP models have been used in logistics to optimize inventory management and distribution networks, while in transportation, they have been used for routing and scheduling problems. One example of using MILP for cost optimization outside the healthcare SCM field is the work of Risbeck et al. (2017), which develops an MILP model for real-time cost optimization of building heating, ventilation, and air conditioning equipment. Although this study is not directly related to the pharmaceutical industry, it shares similarities with our research in terms of the objective function, demand satisfaction, and the consideration of multiple factors. In related healthcare SCM work, Chowdhury et al. (2022) developed a vaccine supply chain using a multi-objective MILP model that aimed to minimize distribution costs, among other objectives. One of the objectives in Chowdhury et al. (2022) is to minimize the distribution cost, which is part of our objective function in the model. However, their work has additional objectives, including minimizing emissions and maximizing job opportunities, which are not included in our research. Although we consider limiting emissions through alternative distribution methods and staffing, our primary focus is on the optimization of one pharmacy, while the supply network is the main focus of Chowdhury et al. (2022). There are other related works in using MILP models for cost optimization in healthcare settings with a different focus. For instance, Ala et al. (2023) resolves the patient scheduling problem by designing an efficient healthcare chain, using both queuing theory and MILP modeling. This study is quite different from our research in that it is more focused on reducing waiting times and costs in a stochastic setting. In other research, Aghazadeh et al. (2018) proposes a multi-objective MIP model for organ transplant to reduce working center cost via optimized allocations for units and organs. Similar to our research, they build an optimization model to reduce costs while the transportation of units is considered similar to the last-mile deliveries of medications in our research. However, we note that Aghazadeh et al. (2018) has a multi-objective model, which is different from our single-objective model.

2.5. Alternative modeling techniques

The proposed MILP model for the PCSCM-MSDM problem is effective in capturing the most relevant complexities of the system in a deterministic manner. For example, studies such as Starita and Paola Scaparra (2022) and Juned et al. (2022) have used non-linear models to improve supply chain reliability and minimize delivery time, respectively. These studies are more suitable for a non-linear model due to the high degree of stochasticity in the input values. Additionally, studies such as Dui et al. (2023) and Borges et al. (2020) have used simulation modeling to analyze the resilience of hospital infrastructure systems and assess the impact of lean practices on the supply chain, respectively. Our research, however, has negligible variability in input values, making a simulation approach redundant. Finally, studies such as Abbaspour et al. (2021) and Shakya et al. (2022) have used Markov decision processes to address inventory management under uncertainty. While these studies have different modeling approaches and objectives than our study, they demonstrate the usefulness of alternative techniques in addressing similar problems.

2.6. Conclusion

In conclusion, the optimization of cold pharmaceutical supply chain management is a critical and challenging issue, with identified gaps in the existing literature. To address these gaps, we conducted research focused on optimizing operations within pharmacy organizations, with a particular emphasis on outpatient pharmacies. We especially consider different delivery modes, medication synchronization, and cold chain management. We proceed with the mathematical formulation of the problem in Section 3.

3. Problem Statement

This section explains our modeling approach for the Pharmaceutical Cold Supply Chain Management Considering Medication Synchronization and Different Delivery Modes (PCSCM-MSDM) problem. We propose a Mixed Integer Linear Programming (MILP) approach with the purpose of maximizing the financial result of an outpatient pharmacy considering various patient types, medication needs, the possibility of synchronizing medication, and different delivery modes. We also consider the staffing requirements for handling and distribution of orders in the optimization problem.

Section 3.1 explains the model and some background of the choices made. Section 3.2 states the assumptions made in the MILP model. Finally, Section 3.3 contains the mathematical formulation of the model: the sets, input parameters, decision variables, the objective function, and constraints.

3.1. Model description

The PCSCM-MDSM problem is inspired by the real application of an outpatient pharmacy, which serves a number of patients over a specified time horizon. The time horizon consists of multiple time intervals (we call them time periods) in which an order may be placed. The objective of the model is to optimize the logistical financial results of an outpatient pharmacy. The logistical financial results consist of the transportation cost, the handling cost, and the logistical turnover. The optimal solution yields the optimal number of order batches, the composition of these batches, and the number of employees needed to assemble and prepare the batches. The model contains patients who have a set of medications that they need to receive over the time horizon. Therefore, a patient orders all medications out of their set at least once over the time horizon. An order batch consists of all or a set of medications a patient needs repeatedly. From these sets of medications, an order batch can be composed, and the pharmacy receives a *prescription line fee* for each medication type in a batch.

The PCSCM-MDSM problem is formulated based on the regulations and requirements of the Dutch healthcare system, specifically in relation to the logistical turnover of medications in pharmacies. This legislation allows pharmacies to ask for a prescription line fee from their patients to cover the logistical costs of providing medication (Rijksoverheid, 2023; Zorginstituut Nederland, 2023). The prescription line fee is issued per medication type for each ordered batch. The dosage of medication within an order is irrelevant to the prescription line fee. Hence, in our model, the prescription line fee only depends on the number of different medication types per order.

Moreover, medications have cooling requirements independent of the prescription line fee type. Therefore, we classify medications based on their cooling types (e.g., cooled or not-cooled). In addition, there is another classification required for medicine deliveries (e.g., cooled, not-cooled, combined). Medications need to be transported with a transportation cooling method fitting to their medication cooling type. The transportation cooling type is combined when a batch contains medications with different cooling requirements. The transportation costs depend on the delivery type (e.g., bike, car) and delivery cooling type of an ordered batch. Lastly, our model considers the number of hours needed for handling each ordered batch, which may differ depending on the transportation cooling type of the batch. As mentioned, we define the *time period* as the shortest length of time that a patient may put one order. The time period should be in line with the practical requirements (e.g., a week, a month, etc.). The *time horizon* is the total running time of the model and consists of at least one time period.

We proceed by the assumptions considered to model PCSCM-MSDM, and the mathematical model in Section 3.3, which includes notation, parameters, decision variables, and the explanation of the model.

3.2. Assumptions

In this section, we provide the assumptions considered in the model. We note that the assumptions are in line with the case study requirements that will be presented in Section 4.

1. The demand can always be satisfied from the pharmacy's stock.
2. Our model is focused on satisfying demand while optimizing logistical revenues and costs, including handling, staffing, distribution, and delivery operations. Hence, the direct costs and earnings for medications (e.g., purchasing costs and health insurance reimbursements intended for the **direct** costs of medication) lie outside of the scope of this model.
3. In practice, the size of a batch hardly affects the handling time of the batch, and the size also does not affect the delivery costs or the prescription line fee. Hence, we do not consider the size of a batch in the model (i.e., the number of doses, boxes, packages, and so on). Only the unique types of medications are considered in our model. We note that we consider the maximum number of batches that can be delivered through various delivery options in our model.
4. Employees are assumed to be permanent staff. The number of employees of each type, therefore, needs to be the same in each time period.

3.3. Mathematical Formulation

This section presents the mathematical formulation of the PCSCM-MDSM problem by providing the sets, indices, decision variables, the objective function, and constraints.

First, we introduce the sets and indices used in the model that can be found in Table 1.

Table 1 Sets and indices of the MILP model

Set	Description
A	set of transportation cooling types, $a \in A$
C	set of cooling types related to medications, $c \in C$
D	set of delivery types, $d \in D$
E	set of employee types, $e \in E$
W	set of time periods, $w \in W$
K	set of medication types, $k \in K$
P	set of patient types, $p \in P$

3.3.1. Input parameters

We first explain the definition and notations of the input parameters.The time horizon for which we solve the model consists of W time periods. Parameter q_{ckp} states the number of unique medications of cooling type c and medication type k that a patient type p uses consistently over the time horizon. Hence, $\sum_{c\in C}\sum_{k\in K} q_{ckp}$ is the total number of unique medications that a patient p needs over the time horizon.

Our model has three revenue/cost components with associated parameters. The prescription line fee is revenue of the pharmacy that is collected from the insurer, patient, or hospital. We denote this fee with f_k, which depends on the number of unique medication types per batch. Hence, when the number of unique medication types increases in a batch, this fee also increases. The quantity of each unique medication is irrelevant, as the prescription line fee is meant to cover administrative costs regarding the processing of a certain type of medication. The transportation cost, t_{ad}, is incurred in each transportation of a batch from the pharmacy to the home of the patient. Therefore, t_{ad} depends on the combination of transportation cooling type a and transportation method d. The transportation cooling type a relates to the type of cooling assigned to the transportation of the batch, and the transportation method d relates to the type of transportation, such as truck, bicycle, or drone delivery. Finally, s_e is the staffing cost of employee type e time horizon.

Here, we define the required upper bounds and lower bounds for the parameters in the model. First, our preliminary data analysis shows that some patients need similar types of medications per time period; therefore, we classified similar patients into one group. This approach helps to reduce the number of decision variables and, in turn, the problem instance size. Hence, we define parameter ρ_p as the number of patients within patient type p. Depending on the patient type, we consider a lower bound on the number of orders per time period. The parameter values are extracted based on the behavior of different types of patients. For instance, some types of patients may forget part of their medications in one order, or some may receive specific test medications; therefore, $\sigma_p \geq 1$ allows more than one order over the time horizon. Second, there is a maximum level δ_{dw} for the number of batches that can be delivered with transportation method d, in time period w. Third, the maximum number of hours an employee e can work per period w is θ_{ew}. We note that it takes u_{ae} hours for employee type e to process one batch of type a considering the communication with the patient, back office work, packaging, and auxiliary activities. We summarize the description of input parameters in Table 2.

Table 2 Input parameters of the MILP model

Parameter	Description
q_{ckp}	Number of unique medicines with cooling type c, medication type k and for patient type p
f_k	Prescription line fee for medication type k
ρ_p	Number of patients of type p
σ_p	Minimum number of orders per time horizon of patient type p
t_{ad}	Transportation cost with transportation cooling a and delivery type d
δ_{dw}	Maximum number of orders to be delivered with method d in time period w
u_{ae}	Time (in hours) needed of employee type e to process one order of type a
θ_{ew}	Maximum number of hours an employee of type e can work per time period w
s_e	Salary of employee type e for the time horizon

3.3.2. Decision variables

The proposed model has four sets of decision variables. The first set of decisions pertains to whether an order is placed for patient p in period w, considering the transportation cooling type a and transportation method d. This decision is represented by the variable x_{adpw}. If the order is placed, the value of x_{adpw} is set to one; otherwise, it equals zero. The decision regarding the composition of the orders is denoted by variables o_{ckpw}. We define o_{ckpw} as the number of unique medications of type c and type k that are ordered by patient p in period w. The third decision encompasses the number of employees needed for the handling and distribution of the batches per time period. This decision is modeled by the variables m_{ew}, which is the number of employees of type e needed in time period w. The final decision variable set is the number of employees needed in a cycle. This decision is modeled by variables M_e, which is the number of employees e needed in a cycle. The decision variables for this model can be found in Table 3.

Table 3 Decision variables of the MILP model

Binary Variable	Description
x_{adpw}	1 if an order is placed in period w for patient type p with delivery type d and transportation cooling a, 0 otherwise
Integer Variables	**Description**
o_{ckpw}	Number of unique medicines in an order, with climatisation c, type k, ordered at time w and for patient type p.
m_{ew}	Number of employees of type e needed in period w.
M_e	Number of employees of type e needed in the time horizon.

3.3.3. Objective function

The objective of the model is to maximize the logistical financial result of an outpatient pharmacy which includes one revenue and two cost parts. The revenue part is the prescription line fee per unique medication per order (the first part of the objective function). The cost part includes the transportation costs per order (second part of the objective function) and the employee costs related to the distribution of medication (third part of the objective function. Equation 1 shows the objective function.

$$\max \sum_{c\in C}\sum_{k\in K}\sum_{p\in P}\sum_{w\in W} o_{ckpw} f_k \rho_p - \sum_{a\in A}\sum_{d\in D}\sum_{p\in P}\sum_{w\in W} x_{adpw} t_{ad} \rho_p - \sum_{e\in E} M_e s_e \tag{1}$$

3.3.4. Constraints

We have defined nine constraint sets to ensure that the model behaves as desired. Constraint set 2 limits the number of batches to one per time period for each patient, and only one combination of transportation cooling a and delivery type d can be selected for each batch. Constraint sets 3 and 4 ensure that the number of unique medications in a batch, o_{ckpw}, relates to x_{adpw}. That means, if no order is placed in period w for patient p, x_{adpw} equals 0, then o_{ckpw} must be zero since there cannot be any medications in an order that does not exist. Also, Constraints 3 and 4 make sure that the right type of transportation cooling a is related to the right type of medication cooling c in a batch. To clarify, a batch with only cooled medicine should be transported with cooled packaging, an order with only non-cooled medicine should be transported with non-cooled packaging, and an order with both cooled and non-cooled medication should be transported with combined packaging. Furthermore, constraint set 5 ensures that the medication requests for each patient type p for every medication type k with cooling type c, q_{ckp}, are met over the entire time horizon, ensuring that each patient receives the medications they need. We define the level of medication synchronization, σ_p, as the number of times that patient type p needs to receive batches of orders; therefore, Constraint 6 ensures that the total number of order batches for each patient type p equals or is greater than σ_p. The constraint ensures that the patients receive batches multiple times over the time horizon. Due to the limited capacity of the pharmacy to deliver medicines using different delivery modes, we use Constraint 7 to ensure that there are no more than δ_{dw} batches delivered with type d in each period w. Constraint 8 makes sure that for every period w, there are enough employees available to perform the labor related to packaging and distributing the orders. Constraint 9 makes sure that the number of employees of type e in the time horizon is greater than or equal to the number of employees of type e needed in each period w. Constraints 10 contain the type and sign restrictions of this model.

$$
\begin{aligned}
\text{s.t.} \quad & \sum_{a\in A}\sum_{d\in D} x_{adpw} \leq 1 && \forall p \in P, w \in W && (2)\\
& \sum_{c\in(c1)}\sum_{k\in K} o_{ckpw} \leq M_1 \sum_{a\in(a1,a3)}\sum_{d\in D} x_{adpw} && \forall p \in P, w \in W && (3)\\
& \sum_{c\in(c2)}\sum_{k\in K} o_{ckpw} \leq M_2 \sum_{a\in(a2,a3)}\sum_{d\in D} x_{adpw} && \forall p \in P, w \in W && (4)\\
& \sum_{w\in W} o_{ckpw} = q_{ckp}, && \forall c \in C, k \in K, p \in P && (5)\\
& \sum_{a\in A}\sum_{d\in D}\sum_{w\in W} x_{adpw} \geq \sigma_p, && \forall p \in P && (6)\\
& \sum_{a\in A}\sum_{p\in P} x_{adpw}\rho_p \leq \delta_{dw} && \forall d \in D, w \in W && (7)\\
& \sum_{a\in A}\sum_{d\in D}\sum_{p\in P} x_{adpw} u_{ae}\rho_p \leq m_{ew}\theta_{ew} && \forall w \in W && (8)\\
& M_e \geq m_{ew} && \forall e \in E, w \in W && (9)\\
& x_{adpw} \in \{0,1\}, o_{ckpw} \in \mathbb{Z}^+, m_{ew} \in \mathbb{Z}^+, M_e \in \mathbb{Z}^+ && && (10)
\end{aligned}
$$

4. Case study and results

In this section, we present the case study of the Maartensapotheek (MA) outpatient pharmacy and optimize their logistical results using the MILP model explained in Section 3. The MA pharmacy of the Sint Maartenskliniek (SMK) is located in Nijmegen, the Netherlands. The SMK is a hospital specializing in mobility and posture and has three main departments: orthopedics, rheumatology, and rehabilitation. The MA provides medication for patients of the SMK. This mostly concerns rheumatology patients, as the rheumatology department is the largest outpatient department of the SMK. Besides, medication for patients of the orthopedic and revalidation departments is often provided via the inpatient pharmacy of the SMK. This section explains the problem requirements of the MA, the data used for the case study, and the model scenarios.

The ultimate goal of MA is to provide a high-quality service to its patients by giving them the option of at-home delivery of medications for free. However, as this service is deemed to be expensive; therefore, the pharmacy wishes to get insight into its logistical costs and revenues to optimize the financial result. Hence, we propose the PCSCM-MDSM problem formulation to solve the MA case.

Section 4.1 outlines the input parameters used for the MA case and explains the data preparation procedure. In Section 4.3, we describe the scenarios used in the case study and explain the need for scenario analysis. Section 4.2 presents the results of all scenarios and relevant metrics. To explore the potential for future development of this case or its application to similar cases, Section 4.4 introduces two variations that slightly modify the model settings and relax certain assumptions. We compare the results of these model variations to the original results and provide managerial insights. Finally, in Section 4.5, we report on the applied solution methods and provide insights using reported statistics. We proceed with explaining the data used in our model.

4.1. Data

This section explains how and what data is collected and processed for the MA case. First, in the data collection phase, we explain our method and sources to gather relevant data. The data is mostly used for determining the values of input parameters that come from the medication orders of MA in 2021 and 2022. The data list of orders contains order batches from patients, which include at least one medication product per batch. The data contains three types of unique identifiers as follows.

- Order number: It is used to derive the order date, the delivery type, and the number of orders.
- Patient number: It is used to derive the location of the patient (which can be relevant for certain delivery types), the number of unique patients, the medications that the patients need, and the order composition per patient (in combination with the medication product numbers in the orders of each patient).
- Medication product: It is used to find the medication type and the medication cooling restriction.

The set elements used in the model are derived from patient and order data, as well as observations of the order preparation and delivery process and discussions with employees and management of the MA. Sets A and C are derived from the cooling restrictions and transportation cooling types that are used in the MA. Set D consists of the delivery types the management of the MA considers. Set E contains the two types of employees present in the MA. Set K is based on the height of the prescription line fee of a medication. The MA has two types: medication with and without a prescription line fee. Set W consists of four months, as this is the current maximum order period in the MA. The sets and their elements for the MA case are shown in Table 4. We explain set P further in the explanation of the parameter q_{ckp}, ρ_p, and σ_p.

Table 4 Set elements for the MA case

Set	Elements
A	{Cooled transportation, Non-cooled transportation, Combination transportation}
C	{Cooled medication, Non-cooled medication}
D	{Truck transportation, delivery hubs, bicycle transportation, pick-up}
E	{Pharmaceutical employee, pharmacy assistant}
K	{Medication w/o prescription line fee, Medication with prescription line fee}
P	$\{0, 1, \ldots, 224\}$
W	{January, February, March, April}

Every patient p has a value of q_{ckp} for each c and each k, which is shown in Table 5. We derive these values by first categorizing patients into four groups based on the medications they need. As there are two elements in sets C and K, the total number of combinations is four. Second, we consider how frequently patients have placed orders in the past, which relates to σ_p. In this regard, we use aggregation to create patient types such that irregular or infrequent orders are grouped with the closest patient types to ensure that set P is not too large. For example, a patient type could be a patient who needs two medications of c_0 and k_0 and three medications of c_1 and k_0 that typically orders twice every four months. From the data, we see that there are five patients with the same specifications and one patient who has the same medication types but orders three times every four months. We place that last patient into the same category $p \in P$, as we see this patient as an outlier. This means that ρ_p is $5 + 1 = 6$. Using this approach, we identify 225 patient types p. We determine σ_p by determining the number of times each patient p typically orders over four months period, and ρ_p by the number of patients in the same index p. Table 5 presents a summary of q_{ckp}, σ_p, and ρ_p. To enhance readability, we only show parts of the rows, so the minimum number of orders (shown in the rightmost column) in each row of the table happened to be one. Although not explicitly displayed in the table, it should be noted that $\sigma_p = 1$ for 157 patient types, $\sigma_p = 2$ for 57 patient types, and $\sigma_p = 3$ for 11 patient types. The comprehensive sets of values can be found in Tables A.18, A.19, and A.20 in Appendix A.

Table 5 Summary of q_{ckp}, ρ_p and σ_p: the number of unique medicines with cooling type c, medication type k and for patient type p; the number of patients of type p and the minimum number of orders for patient p.

	Nr. unique meds q_{ckp}				**Nr. patients ρ_p**	**Min. nr. orders σ_p**
Patient type p	$c_0; k_0$	$c_0; k_1$	$c_1; k_0$	$c_1; k_1$		
p_0	1	0	0	0	935	1
p_1	1	0	0	0	553	1
p_2	0	0	0	1	539	1
p_3	0	0	0	1	318	1
p_4	0	0	0	2	261	1
...	...	...	...	...	...	...
p_{224}	0	1	0	6	1	1

The prescription line fee is determined by grouping the medications into two sets: medications without a prescription line fee (k_0) and medications with a prescription line fee (k_1). Obviously, f_{k_0} equals zero. Within the medications with a prescription line fee k_1, there are differences that are often based on the type of order or other factors that are difficult to trace. Based on the available data, we estimate the differences in prescription line fees are quite low (coefficient of variation of 0.45). Therefore, we use a weighted average of historical values of the prescription line fee and find $f_{k_1} = €7.94$.

We obtain the transportation costs, t_{ad}, by using the agreements made with the delivery services employed by the MA. The pick-up costs are estimated by multiplying the hourly salary of a pharmaceutical employee with the time it takes for a pick-up, which is on average 3 minutes. It is important to note that a pick-up at the pharmacy is not the same as an at-home delivery or hub pick-up, which takes only a few seconds. This is because the pharmacy chooses to provide the additional service of verifying the order and patient details with individuals at the time of medication pick-up from the MA. The maximum number of transportation (travel between pharmacy and drop-off points) with each transportation method d, δ_{dw}, is determined based on agreements with the delivery services, which is typically fixed across all periods, w. In determining the monthly maximum number of transportation, we consider the locations of the patients and assess whether bicycle delivery and pick-up from the hubs are feasible options for those patients. Pick-up is not feasible for distances greater than 10 kilometers from the pick-up point (i.e., the MA location) or pick-up hub. Furthermore, bike delivery is not possible for distances exceeding 15 kilometers from the bicycle starting point (i.e., the MA location). The limit for truck transportation is much higher, and it is practically infinite, but we set it to a sufficiently large value to ensure that all transportation can always be conducted with this method. The values for t_{ad} and δ_{dw} are provided in Tables 6 and 7.

Table 6 Values of t_{ad}: the transportation cost with transportation cooling a and delivery type d

	Transportation cooling type *a*		
Delivery type *d*	Cooled (a_0)	Non-cooled (a_1)	Combination (a_2)
Truck transportation (d_0)	€ 16.62	€ 11.64	€ 17.32
Delivery hubs (d_1)	€ 3.00	€ 3.00	€ 3.01
Bicycle transportation (d_2)	€ 13.62	€ 8.64	€ 14.32
Pick-up (d_3)	€ 1.65	€ 1.65	€ 1.66

Table 7 Values of δ_{dw}: the maximum number of orders to be delivered with method d in time period w

Delivery type *d*	**Maximum number of orders δ_{dw} ($\forall w \in W$)**
Truck transportation (d_0)	6950
Delivery hubs (d_1)	271
Bicycle transportation (d_2)	120
Pick-up (d_3)	253

We determine the time required for employee type e to process a batch with cooling type a, denoted as u_{ae}, by measuring the order preparation time of all activities. Moreover, we determine θ_{ew} from the actual working hours of each employee type per period, w. Finally, we determine s_e based on each employee type's total hourly salary costs. The values for u_{ae}, θ_{ew}, and s_e are presented in Tables 8, 9, and 10, respectively.

Table 8 Values of u_{ae}: the time (in hours) needed of employee e to process one order of type a

	Transportation cooling type *a*		
Employee type *e*	Cooled (a_0)	Non-cooled (a_1)	Combination (a_2)
Pharmaceutical employee (e_0)	0.1293	0.1477	0.1779
Pharmacy assistant (e_1)	0.0233	0.0233	0.0233

Table 9 Values of θ_{ew}: the maximum number of hours an employee of type e can work per time period w

Employee type *e*	**Maximum number of hours θ_{ew} ($\forall w \in W$)**
Pharmaceutical employee (e_0)	126.667
Pharmacy assistant (e_1)	126.667

Table 10 Values of s_e: the salary of employee type e

Employee type *e*	**Salary s_e**
Pharmaceutical employee (e_0)	€ 33.00
Pharmacy assistant (e_1)	€ 40.00

Finally, the values for M_1 and M_2 are both set to 15. This is because $\sum_{c\in C}\sum_{k\in K} q_{ckp}$ out of the data has a maximum value of 15 $\forall p \in P$. Therefore, the values for M_1 and M_2 cannot exceed 15.

4.2. Computational results

In this section, we present the results of the model using the input data described in Section 4.1, referred to as the 'base case'. Additional scenarios are discussed in Section 4.3. We begin by introducing the key performance indicators (KPIs) used to evaluate the results. These KPIs are divided into two categories: output KPIs and decision KPIs. The output KPIs provide insights into the outcomes of implementing specific decisions, while the decision KPIs highlight the decisions required to achieve desired outcomes.

- Output KPIs
  - **KPI 1: Total annual result.** The total annual result is the financial result from the model multiplied by 3, as the model for the MA runs for four months. The annual result consists of the annual transportation costs, the annual handling costs, and the annual prescription line fee. This KPI shows the pharmacy the total picture of its result.
  - **KPI 2: Result per order.** The result per order is the result divided by the number of orders. This KPI shows the result relative to the orders, which can give a different perspective than the total result.
- Decision KPIs
  - **KPI 3: Annual number of order batches.** This KPI represents the total number of order batches that need to be processed by the pharmacy on an annual basis. It provides valuable information to the MA for enhancing synchronization strategies through effective communication with patients.
  - **KPI 4: Annual number of order batches per cooling type.** This KPI shows the division of transportation cooling types, which provides insights into the composition of order batches.
  - **KPI 5: Annual number of transportation per transportation types.** This KPI shows how much of each transportation mode the pharmacy should use for the transportation of their orders.
  - **KPI 6: Number of employees per time period.** This KPI demonstrates the number of pharmaceutical employees and assistants the pharmacy should hire.

Table 11 presents the results for KPIs 1 and 2, which include the breakdown of result into transportation cost, handling cost, and prescription line fee (revenue). The results indicate a negative total result and negative result per order, indicating that the pharmacy is operating at a loss in this aspect. However, it's important to note that the pharmacy is part of a larger hospital where the logistics expenses are compensated for by other areas, mitigating the impact of the logistical loss on the pharmacy or hospital as a whole. Additionally, this paper solely focuses on logistical result and does not consider results generated from procurement and sales. Furthermore, the total logistical result in 2022 was € -197,208.23, indicating that the utilization of the model increases the MA's result by 34%.

Table 11 Base case results for output KPIs: KPI 1 and 2

	KPI 1: Total annual result	**KPI 2: Result per order**
Total result	€ -130,874.47	€ -5.76
Transportation cost	€ -231,387.72	€ -10.18
Handling cost	€ -204,835.33	€ -9.01
Prescription line fee	€ 305,348.58	€ 13.43

Tables 12 and 13 show the results for the decision KPIs. To achieve the results in Table 11, the pharmacy needs to have 22,740 orders on a yearly basis. The number of orders in 2022 was 21,347, which is close to the model output. This shows that the order frequency resulting from the model is attainable for the MA. Furthermore, we see that most of the batches are delivered with non-cooled transportation (a_1, which was also the case in 2022. The number of batches delivered with this cooling method decreased from 49.5% to 46.4%, while the number of batches transported with combination transportation (a_2) increased slightly, from 19.7% to 23.8%. This shows that the model combines more orders thus synchronizing order batches more efficiently. The number of cooled transportations (a_0) was hardly affected. As for the transportation methods, we see that the most used transportation method is truck transportation (d_0). This is the most expensive transportation mode, but it is the only unrestricted mode of transport. We see that the other transportation modes are maximized to their full capability, showing the potential of alternative, cheaper transportation modes. Finally, we note that there are 3 pharmaceutical employees needed and 1 pharmacy assistant, for the logistical operations of the MA. This is the current occupation at the MA so the staffing does not need to change for this solution.

Table 12 Base case results for decision KPIs 3, 4 and 5

	Number of order batches	**Percentage of orders**
KPI 3: Annual number of order batches		
Total nr. of orders	22,740	100.0%
KPI 4: Annual number of order batches per cooling type		
Cooled transport (a_0)	6,783	29.8%
Non-cooled transport (a_1)	10,551	46.4%
Combination transport (a_2)	5,406	23.8%
KPI 5: Annual number of transportations per transportation types		
Truck transportation (d_0)	15,012	66.0%
Delivery hubs (d_1)	3,252	14.3%
Bicycle transportation (d_2)	1,440	6.3%
Pick-up (d_3)	3,036	13.4%

Table 13 Base case results for decision KPI 6

Employee *e*	**KPI 6: Number of employees per time period**
Pharmaceutical employee (e_0)	3
Pharmacy assistant (e_1)	1

The running time of this solution is 5.29 seconds, with an optimality gap of $1.83 * 10^{-15}$, showing that the solution is (virtually) optimal. We further analyze solution statistics, such as optimality gap, running time, and instance size, in Section 4.5.

Based on our analysis, we conclude that the MA can achieve a results increase of 34% by implementing small adjustments, particularly by exploring alternative transportation methods. These changes primarily involve optimizing the number of order batches. In Section 4.3, we evaluate more substantial modifications that the MA or other pharmacies can consider to enhance profitability and efficiency further.

4.3. Scenario analysis

This section presents the scenario analysis, which involves 23 modifications to the data discussed in Section 4.1. The purpose of the scenario analysis is to assess input changes that require more significant investments compared to the minor adjustments made to the pharmacy logistics in the model results presented in Section 4.2. Additionally, the scenario analysis allows us to evaluate the robustness of the model. We categorize the adaptations into four groups: the inclusion of annual unique patients, synchronization level, patient types, and order period. We begin by explaining these four types of adaptations and their impact on specific input parameters. Subsequently, we analyze and discuss the effects of the scenarios on the model results.

The first modification involves changing the number of patients in the model. Currently, the annual number of unique patients is 7,000. However, there are plans for the hospital to take over a department from a nearby hospital, which is expected to increase the number of patients. The projected annual number of patients is 10,000. This change in the annual number of patients impacts the parameter ρ_p in the model. Specifically, the current value of ρ_p is extrapolated to accommodate the new patient count. The sum of all ρ_p values, denoted as $\sum_{p \in P} \rho_p$, is adjusted from 7,000 to 10,000 to reflect the increased patient population.

The second modification involves changing the synchronization level, which is divided into three cases: 77%, 87%, and 100% synchronization. The synchronization level is determined by the completeness of an order, which is calculated based on the number of medications ordered compared to the total number of medications on the prescription. For example, if a patient has four medications prescribed but only orders three, the completeness of that order is 75%, which corresponds to the synchronization level. The overall synchronization percentage of 77% is a weighted average of these completeness percentages. The synchronization parameter, denoted as σ_p, is derived from this percentage, and patients are grouped into patient types, denoted as p, based on the synchronization level and the parameter q_{ckp}. To evaluate the potential for synchronization improvement, we adjust the σ_p parameter for each patient type p according to two scenarios: realistic improvement and ideal improvement. In the realistic improvement scenario, we collaborate with pharmacy management to assess feasible synchronization enhancements. For instance, a patient who currently orders three times in the time horizon may reduce their orders to two times. The average synchronization level for this realistic scenario is 87%. In the ideal improvement scenario, all patients order only once throughout the time horizon, resulting in 100% synchronization. To assess these adaptations, we adjust the parameter σ_p based on the specified synchronization level.

Thirdly, we consider an adaptation in the patient types served by the pharmacy. Currently, the MA serves all patients from the SMK or related hospitals who wish to order medication at the MA. However, the hospital is exploring a scenario where they only cater to patients with medication type k_0, which refers to medication without a prescription line fee. These are medications that cannot be obtained from other pharmacies, meaning patients are required to order them exclusively from the MA. Patients with other medication types (k_1), which include medications with a prescription line fee, have the freedom to visit their local pharmacy if they prefer. This scenario has an impact on parameter ρ_p as patients who do not have any medications of type k_0 in their prescription are excluded, resulting in their ρ_p value being set to 0. Consequently, this adaptation decreases the total number of patients, leading to a reduction in the sum of ρ_p values, denoted as $\sum_{p \in P} \rho_p$.

The final adaptation involves adjusting the length of the time horizon. Presently, the MA allows patients to order their medication for a maximum period of 4 months. However, there is an expectation that costs will decrease if the time horizon is extended to 6 months. This adaptation does not have any impact on the input parameters but rather expands the number of elements in set W from 4 to 6.

A total of 24 scenarios are formed by combining these four adaptations: two options for the number of patients, three options for the synchronization level, two options for the patient types, and two options for the order period. Table 14 provides a summary of the scenarios, including the total annual result for each scenario. Scenario 0 represents the base case analyzed in Section 4.2.

Table 14 Scenarios for the MA case

Scenario	# patients	Sync.	Patient types	Period	Profit
0	7000	77%	All patients	4 months	€ -130,874.47
1	7000	77%	All patients	6 months	€ -106,929.38
2	7000	77%	Only patients with type k_0	4 months	€ -190,511.50
3	7000	77%	Only patients with type k_0	6 months	€ -179,020.58
4	7000	87%	All patients	4 months	€ -124,559.17
5	7000	87%	All patients	6 months	€ -103,014.38
6	7000	87%	Only patients with type k_0	4 months	€ -185,448.10
7	7000	87%	Only patients with type k_0	6 months	€ -131,990.02
8	7000	100%	All patients	4 months	€ -117,366.55
9	7000	100%	All patients	6 months	€ - 97,687.64
10	7000	100%	Only patients with type k_0	4 months	€ -180,120.28
11	7000	100%	Only patients with type k_0	6 months	€ -127,906.42
12	10 000	77%	All patients	4 months	€ -175,874.75
13	10 000	77%	All patients	6 months	€ -135,188.37
14	10 000	77%	Only patients with type k_0	4 months	€ -206,118.67
15	10 000	77%	Only patients with type k_0	6 months	€ -189,240.38
16	10 000	87%	All patients	4 months	€ -139,635.38
17	10 000	87%	All patients	6 months	€ -129,336.71
18	10 000	87%	Only patients with type k_0	4 months	€ -198,920.32
19	10 000	87%	Only patients with type k_0	6 months	€ -184,463.56
20	10 000	100%	All patients	4 months	€ -80,187.73
21	10 000	100%	All patients	6 months	€ -73,574.30
22	10 000	100%	Only patients with type k_0	4 months	€ -191,244.67
23	10 000	100%	Only patients with type k_0	6 months	€ -179,309.32

Let's analyze the results of the scenarios based on the KPIs defined in Section 4.2. Figures 1 and 2 illustrates that the pharmacy experiences a net logistical loss in all scenarios. However, this outcome is not alarming, as the overall net total result of the pharmacy, considering all operations (beyond the scope of our model), is positive. The specific details of these operations and numbers are not presented due to privacy considerations. Among the scenarios, Scenario 21 stands out with the highest total result, while Scenario 20 exhibits the highest result per order batch. An interesting pattern emerges when examining the differences among patient types. Figure 2 demonstrates a consistently lower result per order batch when only patients with medication type k_0 are served at the MA. Additionally, Figure 1 shows that scenarios with only patients of type k_0 yield a lower total result compared to their counterparts with mixed patient types. The scenarios featuring only patients with medication type k_0 display a reduction in total costs, primarily due to a decrease in the number of patients. As most of these orders have no prescription line fee, the associated costs are significantly lower. However, it is clear that exclusively serving patients with medication type k_0 is financially inefficient. Therefore, the conclusion drawn from the analysis is that limiting the MA's service to patients with medication type k_0 proves to be financially ineffective.

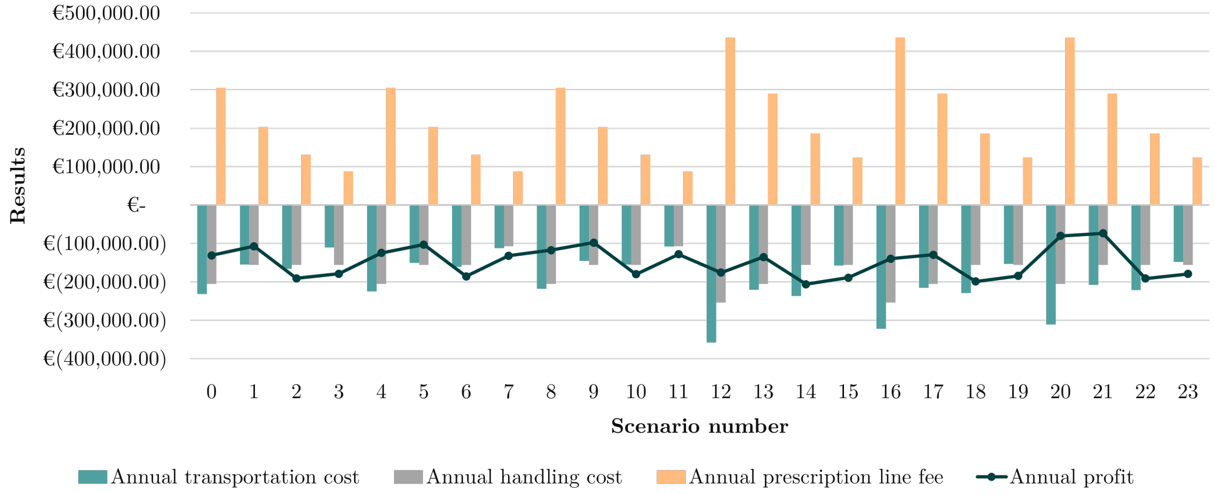

Figure 1 KPI 1: Comparison of the annual results for each scenario, including the result elements (transportation and handling costs and prescription line fee)

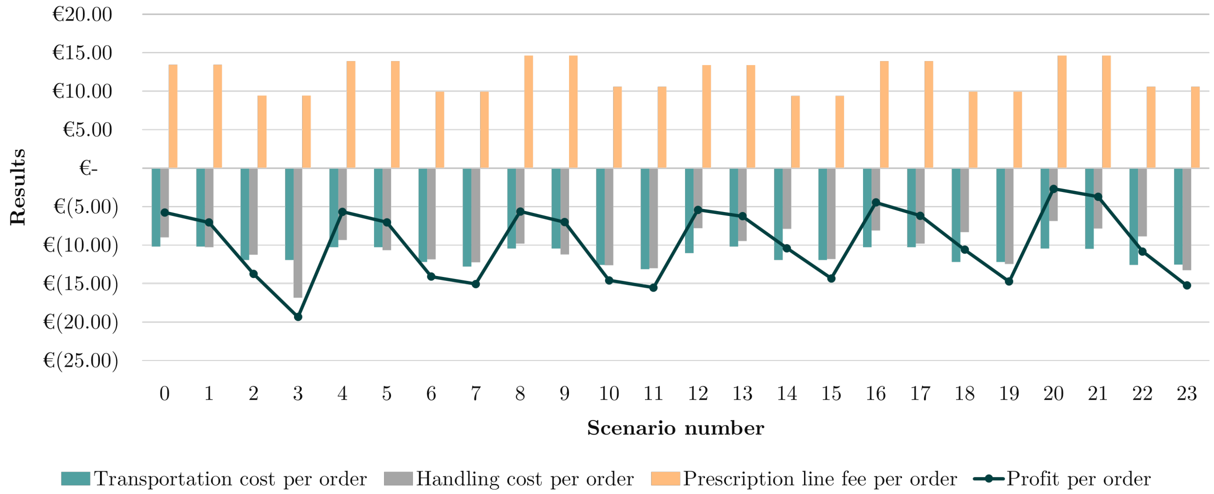

Figure 2 KPI 2: Comparison of the results per order batch, for each scenario, including the result elements (transportation and handling costs and prescription line fee)

Figure 3 provides an overview of the financial result differences compared to the base case, specifically focusing on the total annual logistical financial result and the logistical result per order batch (KPIs 1 and 2). Consistent with the findings from Figures 1 and 2, the patient type emerges as the most influential factor. Scenarios involving "Only patients with type k_0" exhibit the largest decrease in both total result and result per order batch. The number of patients has a variable impact on result. The alternative number of patients

(10,000 patients) demonstrates the most significant influence when combined with a different patient type scenario (scenario 14, yielding the lowest total annual result) or when combined with all alternative options (scenario 23, resulting in the lowest result per order batch for scenarios with 10,000 patients). Altering the number of patients leads to a general decline in total result compared to the base case, although the result per order batch shows slight improvement. This outcome can be attributed to the fact that costs increase at a higher rate than total earnings, but the total result is divided among a larger number of orders. Regarding the synchronization level, an increase in synchronization leads to higher total annual result and result per order batch. This correlation is logical since the prescription line fee remains constant across different synchronization levels (as indicated in Figure 1), while costs rise with lower synchronization levels due to a greater number of orders. Lastly, extending the order period from 4 to 6 months has a minor positive impact on the total annual result but adversely affects the result per order. This outcome can be attributed to the expectation of fewer orders when the order period is extended. Although total costs decrease, they are also spread across fewer orders.

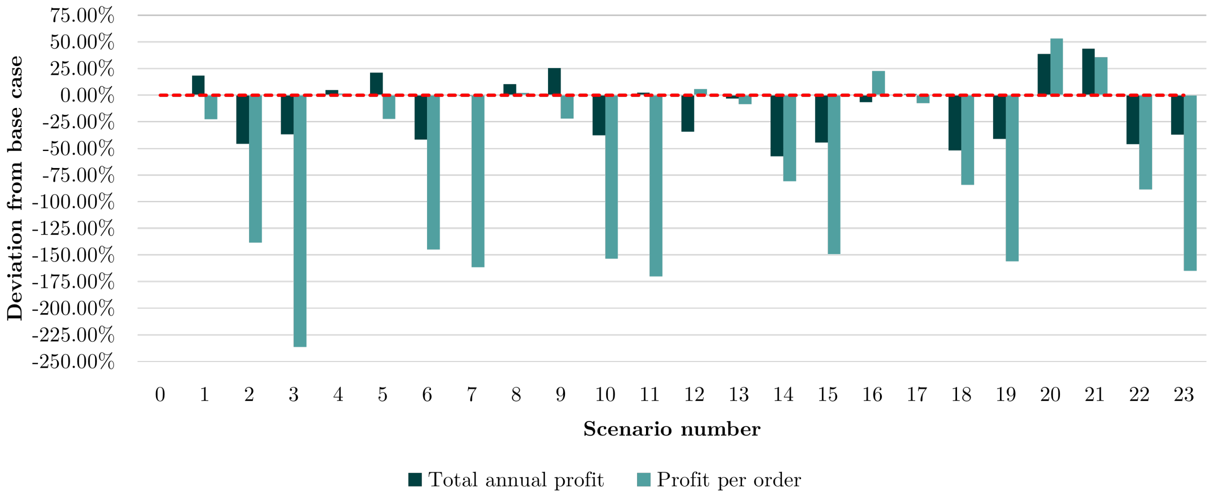

Figure 3 The influence on the base case result for each scenario: difference with KPIs 1 and 2 with respect to the base case (in percentage)

Let's analyze the decision KPIs associated with these result numbers. Figures 4 and 5 provide insights into the annual number of orders, which decreases under the following circumstances: (1) higher synchronization percentages, (2) exclusively serving patients with type k_0 medications, and (3) increasing the order period from 4 to 6 months. Conversely, the number of orders increases when the number of patients is increased. Figure 4 illustrates that the ratio between cooling types differs primarily when patient types differ. This observation can be easily explained by the dominance of cooled medication types when exclusively serving patients with medication type k_0, as these medications require cooling during transportation. Figure 5 indicates that the ratio between different delivery types remains relatively stable across scenarios. This suggests that the scenarios have limited influence on the investments in transportation modes (particularly cooling), mainly affecting the scale rather than the specific distribution of these investments. Lastly, Figure 6 presents the number of employees required for the pharmacy's logistics. We observe a consistent pattern between the number of pharmaceutical employees and the number of order batches. However, the number of pharmacy assistants remains constant at one employee. This can be attributed to the fact that pharmacy assistants have limited involvement in the logistical processes of the MA, thereby not necessitating the addition of a second assistant in any scenario due to a low workload threshold.

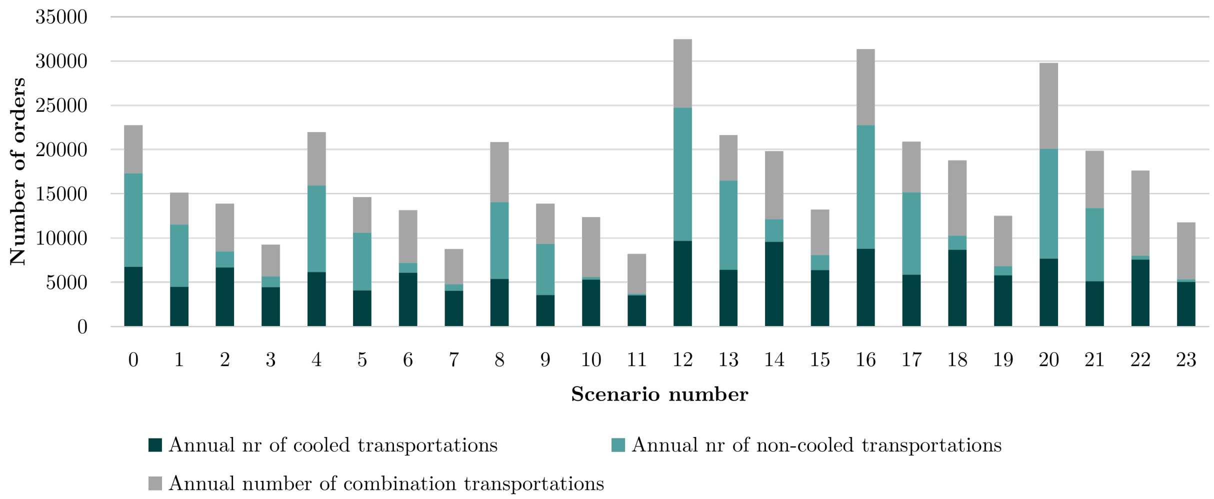

Figure 4 KPIs 3 and 4: Comparison of the number of order batches, divided into transportation cooling types

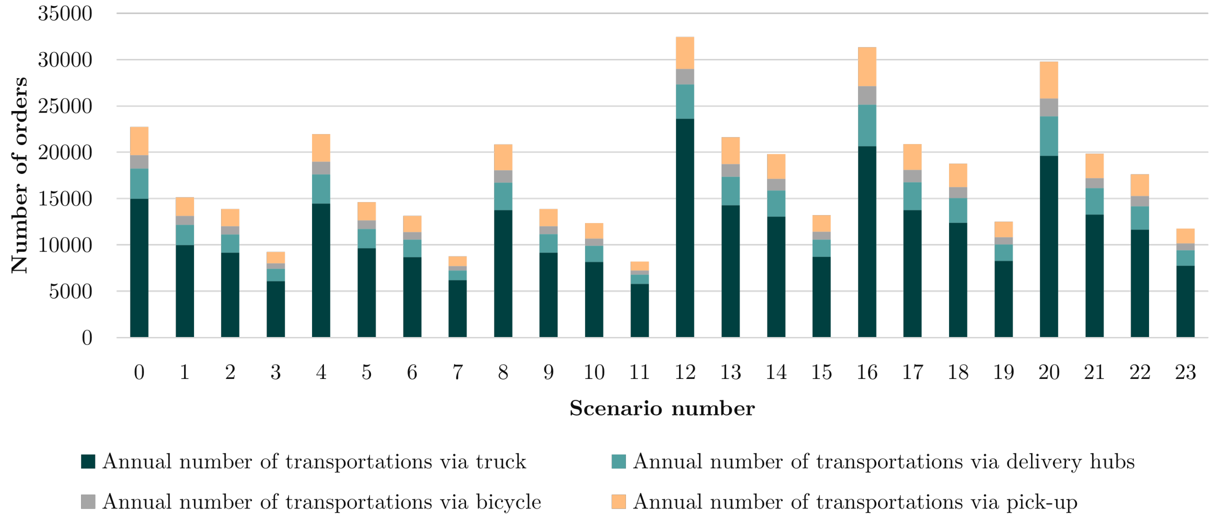

Figure 5 KPIs 3 and 5: Comparison of the number of order batches, divided into transportation types

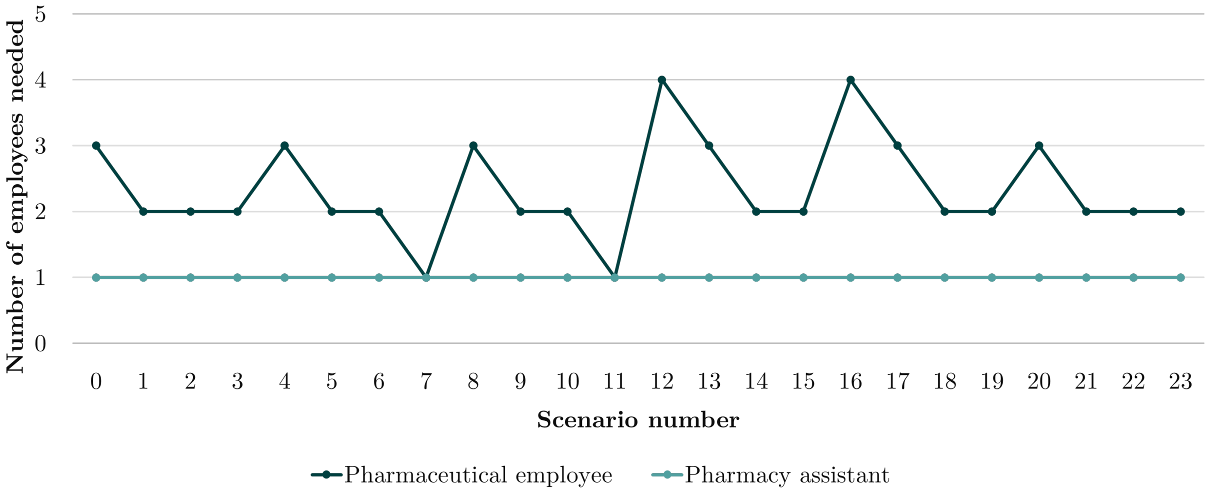

Figure 6 KPI 6: Comparison of the number of employees necessary in each scenario

These figures provide valuable insights for the strategic decision-making process faced by the MA. From a results perspective, scenarios 20 and 21 emerge as the most favorable choices. However, it is important to consider practical limitations when aiming for 100% synchronization, as it may be challenging or even impossible to achieve in reality. Additionally, the MA's priorities may extend beyond maximizing results, encompassing factors such as total transportation cost or transportation costs per order. In light of these considerations, it becomes crucial for management to carefully weigh these various factors and prioritize them according to the organization's specific goals and circumstances. The insights derived from this study can serve as a valuable resource to inform and support the decision-making process, helping management make well-informed strategic choices.

4.4. Model variations

This section introduces two model variations aimed at enhancing the adaptability of the model to specific situations. These variations enable us to explore the influence of tactical-level decisions on the pharmacy's profitability. Furthermore, based on the MA case study, it becomes evident that the standard model may not always accurately reflect the reality of the logistics in the most realistic manner.

4.4.1. Model variation 1: relaxing the order numbers and order composition

In this model variation, we introduce changes to Equation 5, resulting in Equations 11a and 11b. These modifications allow patients to either order their entire prescription every period w or a portion of it. Equation 11a ensures that the total demand over the entire time horizon is always met, ensuring that all medications are ordered at least once. On the other hand, Equation 11b ensures that each order does not exceed the quantity prescribed. The objective of this model variation is to maximize the capacity utilization of order batches while adhering to the limitations imposed by the prescribed medications.

$$\sum_{w \in W} o_{ckpw} \geq q_{ckp}, \qquad \forall c \in C, k \in K, p \in P \tag{11a}$$

$$o_{ckpw} \leq q_{ckp}, \qquad \forall c \in C, k \in K, p \in P, w \in W \tag{11b}$$

This model variation yields intriguing outcomes. One notable observation is the substantial increase in the number of orders. This phenomenon can be attributed to the fact that, in the case of the MA, the prescription line fees tend to outweigh the associated order costs. However, it remains a pertinent question whether such frequent ordering is practical or viable for the pharmacy. Nevertheless, this insight provides valuable information for other types of pharmacies seeking to evaluate the trade-off between prescription line fees (or other revenue streams) and distribution costs.

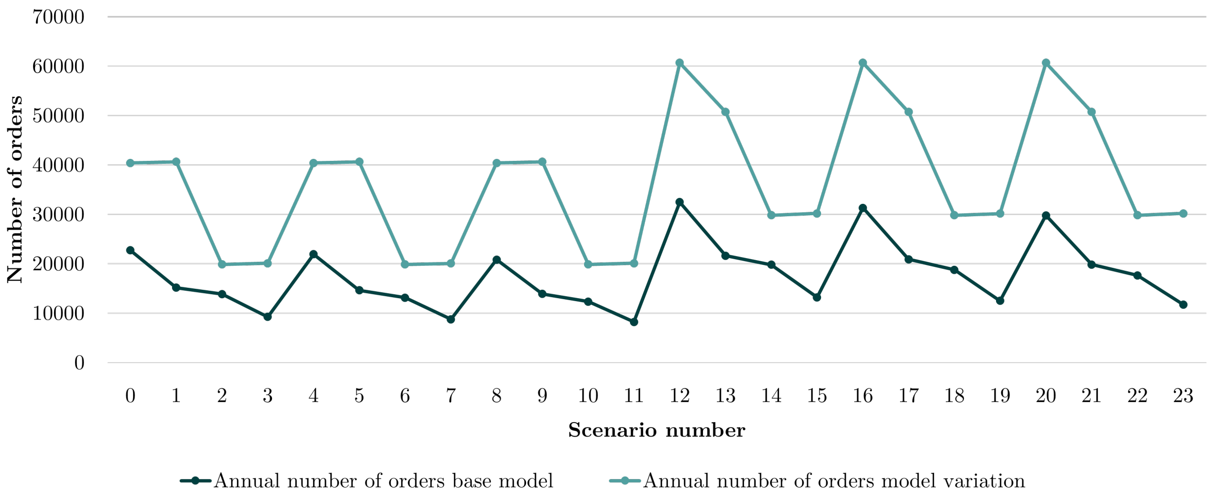

Figure 7 Comparison between the base model and the variation of the annual number of orders

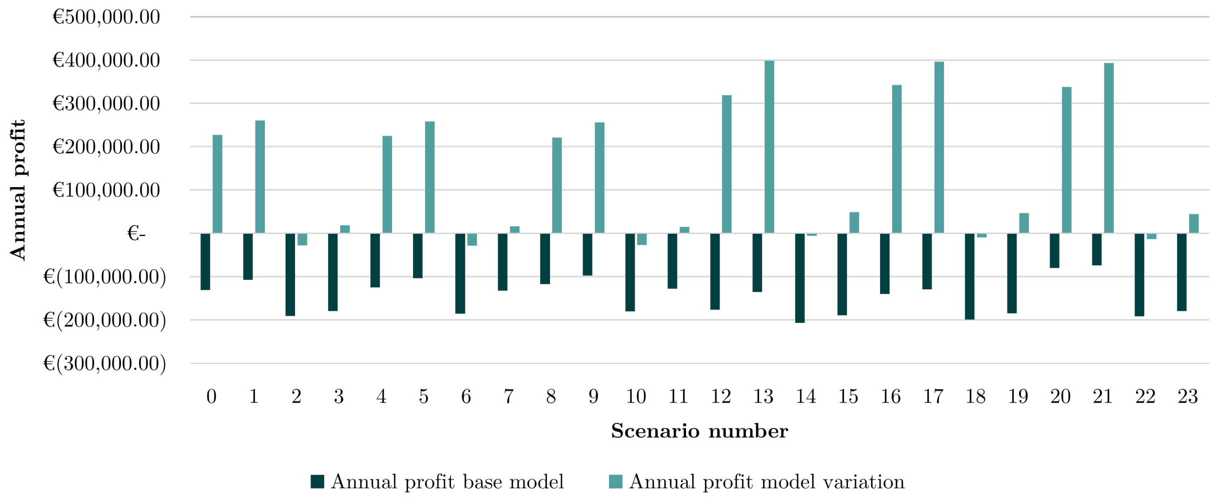

Figure 8 Comparison between the base model and the variation of the annual result

Figure 7 illustrates that, in most cases, the annual number of orders approximately doubles, accompanied by a more than threefold increase in results compared to the base model. This substantial growth can be attributed to the benefits of ordering more frequently in this model variation. The model intelligently evaluates whether the prescription line fee of a patient can offset the associated order costs, resulting in a positive net result per order. This effect is particularly evident in the SMK scenario within this model variation. To capitalize on these results, the pharmacy can adopt a strategy that encourages patients with multiple medications of type $k = k_1$ (which incur a non-zero prescription line fee) to order as frequently as possible, while simultaneously discouraging other patient types with a net loss from placing frequent orders.

4.4.2. Variation 2: employee hours instead of number of employees

This variation focuses on the number of employees required for logistical operations. According to KPI 6 and Figure 6, we observe instances where up to four logistical employees are needed in the MA. The current model is designed to add an additional employee to the solution when the maximum number of hours for a specific employee type per period, denoted as θ_{ew}, is exceeded. This approach is reasonable to prevent employees from consistently working overtime and to account for fluctuations in workload.

However, it is important to investigate the extent to which the θ_{ew} threshold is exceeded in each scenario. Figure 9 displays the number of hours required for each employee type compared to the thresholds set for one to four employees (assuming the same value of θ_{ew} applies to all e and w in the MA case). We argue that the current strategy might not be the most optimal for the MA, as it results in a significant amount of idle time for employees overall. Moreover, in the MA case, employees are involved in tasks beyond logistics. They dedicate a portion of their hours to other aspects of pharmacy operations, such as attending to patients or working in the inpatient pharmacy. To address these concerns, we propose an alternative approach that eliminates the need for parameter θ_{ew} and instead focuses on calculating the necessary hours directly. This approach allows the pharmacy to have more flexibility in allocating these hours among their employees.

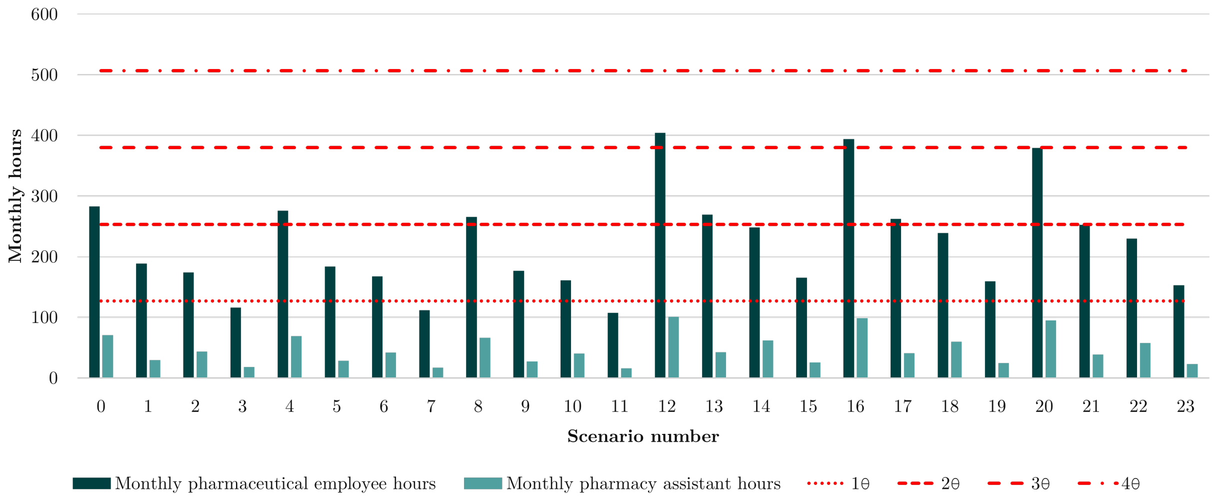

Figure 9 Number of hours needed of every employee type for each scenario

To implement this approach, we modify the definition of variable m_{ew} to represent a non-integer variable, denoting "the number of hours of employee e needed in period w." Consequently, we remove variable M_e and parameter θ_{ew} from the model. Additionally, we adjust the definition of parameter s_e to represent "the hourly salary of employee e."

By adopting this alternative formulation, the model provides the necessary hours required for each employee in each period, enabling the pharmacy to make informed decisions regarding the allocation of work hours among its employees. This approach offers greater flexibility and acknowledges that employees have responsibilities beyond logistics, accommodating their involvement in other pharmacy tasks such as patient care and inpatient pharmacy duties. The objective function is changed to Equation 12 to include the number of hours multiplied by the hourly wage of each employee e.

$$\max \sum_{c\in C}\sum_{k\in K}\sum_{p\in P}\sum_{w\in W} o_{ckpw} f_k \rho_p - \sum_{a\in A}\sum_{d\in D}\sum_{p\in P}\sum_{w\in W} x_{adpw} t_{ad} \rho_p - \sum_{e\in E}\sum_{w\in W} m_{ew} s_e \tag{12}$$

Constraint 8 is changed to Equation 13 and Constraint 9 is removed from the model.

$$\sum_{a\in A}\sum_{d\in D}\sum_{p\in P} x_{adpw} u_{ae} \rho_p \leq m_{ew} \qquad \forall w \in W \tag{13}$$

This model variation provides valuable insights in scenarios where pharmacy employees are involved in tasks beyond logistics. By excluding hours dedicated to non-logistical responsibilities such as direct patient care or administrative work, the model accurately captures the workload specifically related to medication distribution. This approach enhances the accuracy of handling cost estimations and ensures the model's effectiveness in optimizing the logistical aspect of pharmacy operations.

It is important to note that this variation does not directly address the question of how many employees to hire, as it focuses on workload allocation rather than immediate staffing solutions. However, for pharmacies willing to make informed decisions about workload distribution among their employees, the output of this variation model can offer valuable insights into the necessary hours required for efficient logistical operations. By understanding the optimal allocation of labor hours, pharmacies can enhance operational efficiency and make informed decisions regarding resource utilization.

4.5. Discussion on the solution methods and the problem Size

We model the MILP for the PCSCM-MSDM problem in Python 3.8 using the Python MIP package, and the Gurobi 10.0 solver. To evaluate the performance of the model, we conducted 200 runs of the base case (scenario 0) using the same data. This allowed us to perform a statistical analysis on the running times and optimality gap.

In all 200 runs, the Gurobi solver reported an optimality gap of no more than $1.8*10^{-13}\%$. The average running time for the base case was 3.99 seconds, with a 99% confidence interval of [3.79, 4.19] seconds. These results demonstrate that the model runs efficiently and achieves near-optimality.

The base model consists of 14,410 variables. To assess the feasibility of the exact solution method using Gurobi for larger problem instances, we tested different set sizes. Tables 15 and 16 present the number of indices and variables for three tested scenarios. The scenario numbers in the first column correspond to the first scenario (scenario 0) in Table 14, and the letters a, b, and c represent alternative variations in the number of variables.

Table 16 provides information on the number of variables for the three scenarios. The variations in set P are based on different classifications of the same patients, as described in Section 4.1. In scenario 0(a), the base case, there are 225 patient types. Scenario 0(b) includes 476 patient types without aggregating outlier patients, while scenario 0(c) involves separate classifications for each patient, resulting in 6783 patient types.

The largest set, scenario 0(c), is 2912.64% larger than the base scenario, with 434,122 variables compared to 14,410 variables in the base case, as shown in Table 16. These variations in set sizes allow us to examine the scalability and performance of the model for larger problem instances.

Table 15 Sizes of sets in different P size scenarios

	Sets						
Scenario nr	$\boldsymbol{A}$	$\boldsymbol{C}$	$\boldsymbol{D}$	$\boldsymbol{E}$	$\boldsymbol{K}$	$\boldsymbol{P}$	$\boldsymbol{W}$
0(a)	3	2	4	2	2	225	4
0(b)	3	2	4	2	2	476	4
0(c)	3	2	4	2	2	6,783	4

Table 16 Number of variables in different scenarios

	Variables					
Scenario nr	x_{adpw}	o_{ckpw}	m_{ew}	M_e	**Total**	**% increase**
0(a)	10,800	3,600	8	2	14,410	0%
0(b)	22,848	7,616	8	2	30,474	111%
0(c)	325,584	108,528	8	2	434,122	2,913%

Table 17 shows the maximum optimality gap and running time 99% confidence interval per scenario for n=200 runs. We see that case 0(b) has the largest maximum optimality gap of 0.0000753, which means that the solution is almost guaranteed to be near optimal at all times using the Gurobi solver. The largest running time found is 95.28 seconds for scenario 0(c), the scenario with the largest number of variables.

Table 17 Maximum optimality gap and confidence interval of running time for different P size scenarios

Scenario	**Max. gap**	**Max. running time**	**99% CI running time**	**Result**
0(a)	$1.93 * 10^{-16}$	10.1 sec	[3.79, 4.19]	€- 130,874.47
0(b)	$7.53 * 10^{-5}$	8.4 sec	[3.50, 3.86]	€- 126,170.53
0(c)	$1.40 * 10^{-5}$	95.3 sec	[76.83, 78.47]	€- 125,165,35

We conclude that an alternative solution algorithm is not necessary at this time, since we see that increasing the model size with 2,912.64% increases the maximum solution time to a very reasonable time still while maintaining a very small optimality gap. Additionally, the result stays approximately the same (within 5% of the original solution of scenario 0(a)). Therefore, aggregating the classification of patients does not significantly sacrifice the quality of the solutions. We expect that for other pharmacies, the sizes of sets K, E, P and W have the most risk of being different than the set sizes in the MA case presented in this paper. If a pharmacy wishes to apply the model presented in this paper and has many medication types k, employee types e, patient types p and periods w, such that the number of variables is significantly larger than the number of variables of scenario 0(c) (434,122), the model has a risk of being too slow, especially when the pharmacy wishes to run multiple scenarios. In this case, alternative solution methods may be considered, albeit this would be an extreme case that we do not expect to occur.

5. Conclusion

In this study, we addressed the Pharmaceutical Cold Supply Chain Management Considering Medication Synchronization and Different Delivery Modes (PCSCM-MDSM) problem. Our goal was to examine the effects of delivery methods, medication synchronization, and cooling requirements on distribution costs and revenues. To tackle this problem, we developed a Mixed-Integer Linear Programming (MILP) model. This model aims to optimize results by determining the optimal number and composition of orders, as well as the appropriate number of employees while considering patient demand, cooling restrictions, and employee constraints. To evaluate the effectiveness of our model, we utilized real-world data from the Maartensapotheek (MA), an outpatient pharmacy affiliated with a Dutch hospital. We implemented and solved the MILP model using the Gurobi 10.0 solver within the Python-MIP package. Our solver successfully provided near-optimal solutions for all instances of the MA case (an optimality gap of $1.83 * 10^{-15}$ for the base scenario), demonstrating the efficacy of our approach. Furthermore, we conducted tests with two variations of the model and explored two alternative model sizes. The maximum observed optimality gap across these experiments was $7.53 * 10^{-5}$. Computation times of alternative model sizes are never more than 100 seconds, which ensures the model runs within very reasonable time. These findings demonstrate the robustness and reliability of our model in addressing the PCSCM-MDSM problem and its ability to generate high-quality solutions in a reasonable time.

Despite the promising outcomes of this research, there exist certain limitations that warrant acknowledgment and present avenues for future investigation. Firstly, the current model overlooks dosage and package sizes. While package size seldom poses challenges for couriers in practice, variations in delivery modes may introduce packaging size issues. For instance, when patients order less frequently, such as every six months, the packages may become larger if the number of orders per period remains constant. Further research should explore the feasibility of potentially increasing order sizes for both the pharmacy and the chosen delivery methods.

Additionally, the model assumes an absence of stock shortages in the pharmacy, reflecting the infrequency of such shortages in the MA. However, this may not hold true for different pharmacies, where shortages could occur. In such cases, pharmacies often opt for more frequent patient orders to facilitate smaller batches. This adjustment would significantly influence the model's results, as it would generate a larger number of orders for certain medications. Consequently, investigating the impact of shortages on the model and incorporating appropriate adaptations becomes imperative for future research.

Moreover, the model's current formulation encompasses two types of cooling restrictions and three types of transportation cooling restrictions, one for each medication cooling restriction, as well as a combination type. Should the model be employed in a pharmacy with additional cooling types, the constraints outlined in Section 3.3 would require modification.

Another potential area for future research, as mentioned in Section 4.5, lies in exploring alternative solution methods that may prove advantageous for larger problem instances (it is not useful for our case as we could solve the problem to optimality in the matter of seconds).

Lastly, although not necessary for our case, expanding the number of scenarios tested in future research would provide a broader evaluation of the model's performance across diverse environments, enhancing its practical applicability.

We also note that the current model is of deterministic nature, as the variability of input data is deemed to be negligible by the problem owner. However, the problem can be imposed on stochastic elements corresponding to the input data. For instance, factors such as demand arrival patterns, frequency, and the composition of order batches may exhibit variability over time, influenced by different patient types. To address this dynamic environment more comprehensively, future research should consider incorporating stochastic models and exploring appropriate solution methods, such as simulation modeling. By adopting such approaches, decision-makers can obtain valuable insights and make informed decisions in the face of uncertainty.

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Appendix A. Data tables

This section contains the expanded versions of Table 5.

Table A.18 Complete values of q_{ckp}: the number of unique medicines with cooling type c, medication type k and for patient type p

	Nr unique meds q_{ckp}			
Patient type p	$c_0; k_0$	$c_0; k_1$	$c_1; k_0$	$c_1; k_1$
p_0	1	0	0	0
p_1	1	0	0	0
p_2	0	0	0	1
p_3	0	0	0	1
p_4	0	0	0	2
p_5	1	0	0	1
p_6	0	0	0	2
p_7	0	0	0	3
p_8	0	0	0	2
p_9	1	0	0	1
p_{10}	1	0	0	2
p_{11}	0	0	0	3
p_{12}	0	0	0	3
p_{13}	1	0	0	2

Continued on next page

Patient type p	$c_0; k_0$	$c_0; k_1$	$c_1; k_0$	$c_1; k_1$
p_{14}	0	0	0	4
p_{15}	0	0	0	4
p_{16}	2	0	0	0
p_{17}	1	0	0	3
p_{18}	0	0	0	4
p_{19}	1	0	0	1
p_{20}	1	0	0	1
p_{21}	2	0	0	0
p_{22}	1	0	0	3
p_{23}	1	0	0	2
p_{24}	2	0	0	0
p_{25}	0	0	0	2
p_{26}	1	0	0	3
p_{27}	1	0	0	2
p_{28}	0	0	0	5
p_{29}	1	0	0	3
p_{30}	0	0	0	5
p_{31}	1	0	0	4
p_{32}	1	0	0	4
p_{33}	0	0	0	5
p_{34}	1	0	0	1
p_{35}	0	0	0	3
p_{36}	1	0	0	2
p_{37}	1	0	0	4
p_{38}	1	0	0	2
p_{39}	0	0	0	3
p_{40}	0	0	0	6
p_{41}	0	0	0	4
p_{42}	1	0	0	2
p_{43}	0	0	1	0
p_{44}	0	0	0	5
p_{45}	2	0	0	1
p_{46}	1	0	0	5
p_{47}	2	0	0	1
p_{48}	1	0	0	3
p_{49}	0	1	0	0
p_{50}	1	0	0	5
p_{51}	0	0	0	6
p_{52}	1	0	0	3
p_{53}	0	0	0	4
p_{54}	1	0	0	5

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Patient type p	$c_0; k_0$	$c_0; k_1$	$c_1; k_0$	$c_1; k_1$
p_{55}	1	0	0	1
p_{56}	0	0	0	6
p_{57}	2	0	0	1
p_{58}	1	0	0	3
p_{59}	1	0	0	5
p_{60}	0	0	0	7
p_{61}	0	0	0	3
p_{62}	1	1	0	0
p_{63}	0	0	0	6
p_{64}	0	0	0	7
p_{65}	2	0	0	2
p_{66}	2	0	0	3
p_{67}	1	0	1	0
p_{68}	1	0	0	5
p_{69}	1	0	0	4
p_{70}	1	0	1	1
p_{71}	2	0	0	2
p_{72}	1	0	0	4
p_{73}	1	0	0	3
p_{74}	1	0	0	2
p_{75}	0	0	0	4
p_{76}	1	0	0	6
p_{77}	2	0	0	1
p_{78}	2	0	0	3
p_{79}	1	1	0	0
p_{80}	2	0	0	4
p_{81}	1	0	0	6
p_{82}	2	0	0	0
p_{83}	0	0	1	0
p_{84}	2	0	0	2
p_{85}	2	0	0	1
p_{86}	1	0	0	1
p_{87}	2	0	0	0
p_{88}	0	0	1	1
p_{89}	1	0	0	6
p_{90}	0	0	0	5
p_{91}	0	0	0	2
p_{92}	1	0	0	4
p_{93}	0	0	0	4
p_{94}	1	0	1	0
p_{95}	0	0	0	7

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Patient type p	$c_0; k_0$	$c_0; k_1$	$c_1; k_0$	$c_1; k_1$
p_{96}	2	0	0	3
p_{97}	2	0	0	1
p_{98}	1	0	0	2
p_{99}	0	0	0	5
p_{100}	2	0	0	1
p_{101}	1	0	0	6
p_{102}	1	0	0	7
p_{103}	2	0	0	2
p_{104}	1	0	1	1
p_{105}	1	0	0	3
p_{106}	0	0	0	3
p_{107}	2	0	0	1
p_{108}	1	0	0	7
p_{109}	0	0	0	7
p_{110}	0	0	1	2
p_{111}	2	0	0	4
p_{112}	0	0	0	9
p_{113}	2	0	0	5
p_{114}	2	0	0	5
p_{115}	2	0	0	3
p_{116}	2	0	0	2
p_{117}	2	0	0	4
p_{118}	0	0	0	8
p_{119}	1	0	0	4
p_{120}	1	0	1	0
p_{121}	1	0	0	2
p_{122}	0	0	1	2
p_{123}	1	0	0	1
p_{124}	1	0	0	5
p_{125}	0	0	0	8
p_{126}	2	0	0	3
p_{127}	0	0	0	5
p_{128}	2	0	0	4
p_{129}	2	0	0	0
p_{130}	0	0	1	1
p_{131}	0	0	1	3
p_{132}	2	0	0	0
p_{133}	1	0	0	2
p_{134}	1	0	0	5
p_{135}	1	0	1	2
p_{136}	2	0	0	6

Continued on next page

Patient type p	$c_0; k_0$	$c_0; k_1$	$c_1; k_0$	$c_1; k_1$
p_{137}	0	0	0	9
p_{138}	1	0	0	2
p_{139}	1	0	0	4
p_{140}	1	0	0	4
p_{141}	1	0	0	6
p_{142}	0	1	0	1
p_{143}	1	0	1	0
p_{144}	1	0	0	4
p_{145}	1	0	1	0
p_{146}	1	0	0	3
p_{147}	2	0	0	4
p_{148}	0	0	0	2
p_{149}	0	1	0	5
p_{150}	0	0	0	2
p_{151}	1	0	0	1
p_{152}	1	0	1	3
p_{153}	1	1	0	3
p_{154}	1	0	0	1
p_{155}	1	0	0	7
p_{156}	1	0	1	1
p_{157}	0	0	1	3
p_{158}	2	0	0	2
p_{159}	1	0	1	4
p_{160}	0	0	1	2
p_{161}	2	0	0	2
p_{162}	0	0	0	8
p_{163}	0	0	1	3
p_{164}	1	0	1	2
p_{165}	1	0	0	3
p_{166}	2	0	0	2
p_{167}	0	1	0	1
p_{168}	1	0	0	4
p_{169}	0	1	0	1
p_{170}	1	0	0	5
p_{171}	1	0	0	2
p_{172}	0	0	0	2
p_{173}	2	0	0	5
p_{174}	1	0	0	2
p_{175}	1	0	1	2
p_{176}	0	0	1	5
p_{177}	1	0	0	5

Continued on next page

Patient type p	$c_0; k_0$	$c_0; k_1$	$c_1; k_0$	$c_1; k_1$
p_{178}	1	0	0	8
p_{179}	1	1	0	0
p_{180}	1	1	0	0
p_{181}	1	0	1	3
p_{182}	2	0	0	3
p_{183}	1	0	0	7
p_{184}	1	0	0	5
p_{185}	2	0	0	5
p_{186}	0	0	1	4
p_{187}	1	0	0	6
p_{188}	1	0	0	9
p_{189}	1	0	0	7
p_{190}	0	0	1	1
p_{191}	0	0	0	8
p_{192}	1	0	1	2
p_{193}	1	0	0	14
p_{194}	2	0	0	3
p_{195}	1	0	0	8
p_{196}	1	0	0	9
p_{197}	0	0	1	1
p_{198}	2	0	0	2
p_{199}	1	1	0	1
p_{200}	2	0	0	3
p_{201}	1	0	0	7
p_{202}	0	0	1	3
p_{203}	0	0	0	10
p_{204}	1	0	1	2
p_{205}	2	0	0	1
p_{206}	1	1	0	0
p_{207}	2	0	0	6
p_{208}	1	0	1	0
p_{209}	1	0	0	8
p_{210}	0	0	0	9
p_{211}	1	1	0	2
p_{212}	2	0	0	4
p_{213}	0	0	1	4
p_{214}	1	1	1	5
p_{215}	0	1	0	2
p_{216}	0	2	0	0
p_{217}	0	0	1	5
p_{218}	1	0	1	1

Continued on next page

Patient type p	$c_0; k_0$	$c_0; k_1$	$c_1; k_0$	$c_1; k_1$
p_{219}	0	1	0	4
p_{220}	0	1	0	3
p_{221}	1	0	1	3
p_{222}	1	1	0	1
p_{223}	1	0	1	5
p_{224}	0	1	0	6
				End of table

Table A.19 Complete values of ρ_p: the number of patients of type p

Patient type $\boldsymbol{p}$	**Number of patients** $\boldsymbol{\rho_p}$
p_0	935
p_1	553
p_2	539
p_3	318
p_4	261
p_5	259
p_6	208
p_7	180
p_8	183
p_9	157
p_{10}	154
p_{11}	147
p_{12}	124
p_{13}	110
p_{14}	93
p_{15}	97
p_{16}	93
p_{17}	92
p_{18}	77
p_{19}	73
p_{20}	71
p_{21}	65
p_{22}	62
p_{23}	61
p_{24}	60
p_{25}	54
p_{26}	53
p_{27}	45
p_{28}	45

Continued on next page

Patient type p	**Number of patients ρ_p**
p_{29}	41
p_{30}	41
p_{31}	40
p_{32}	40
p_{33}	40
p_{34}	39
p_{35}	37
p_{36}	36
p_{37}	34
p_{38}	29
p_{39}	29
p_{40}	29
p_{41}	29
p_{42}	28
p_{43}	31
p_{44}	25
p_{45}	25
p_{46}	24
p_{47}	22
p_{48}	22
p_{49}	22
p_{50}	21
p_{51}	20
p_{52}	18
p_{53}	18
p_{54}	18
p_{55}	18
p_{56}	18
p_{57}	17
p_{58}	17
p_{59}	16
p_{60}	16
p_{61}	15
p_{62}	15
p_{63}	15
p_{64}	15
p_{65}	14
p_{66}	14
p_{67}	14
p_{68}	14
p_{69}	13

Continued on next page

Patient type p	**Number of patients ρ_p**
p_{70}	13
p_{71}	13
p_{72}	13
p_{73}	11
p_{74}	11
p_{75}	11
p_{76}	11
p_{77}	11
p_{78}	11
p_{79}	11
p_{80}	11
p_{81}	11
p_{82}	10
p_{83}	11
p_{84}	10
p_{85}	10
p_{86}	10
p_{87}	10
p_{88}	9
p_{89}	9
p_{90}	9
p_{91}	9
p_{92}	9
p_{93}	9
p_{94}	9
p_{95}	9
p_{96}	8
p_{97}	8
p_{98}	8
p_{99}	8
p_{100}	8
p_{101}	8
p_{102}	8
p_{103}	8
p_{104}	7
p_{105}	7
p_{106}	7
p_{107}	7
p_{108}	7
p_{109}	7
p_{110}	7

Continued on next page

Patient type p	Number of patients ρ_p
p_{111}	6
p_{112}	6
p_{113}	6
p_{114}	6
p_{115}	6
p_{116}	6
p_{117}	6
p_{118}	6
p_{119}	6
p_{120}	6
p_{121}	6
p_{122}	6
p_{123}	6
p_{124}	6
p_{125}	6
p_{126}	6
p_{127}	6
p_{128}	6
p_{129}	6
p_{130}	6
p_{131}	5
p_{132}	5
p_{133}	5
p_{134}	5
p_{135}	5
p_{136}	5
p_{137}	5
p_{138}	5
p_{139}	5
p_{140}	5
p_{141}	5
p_{142}	5
p_{143}	4
p_{144}	4
p_{145}	4
p_{146}	4
p_{147}	4
p_{148}	4
p_{149}	4
p_{150}	4
p_{151}	4

Continued on next page

Patient type p	**Number of patients ρ_p**
p_{152}	4
p_{153}	4
p_{154}	4
p_{155}	4
p_{156}	4
p_{157}	4
p_{158}	4
p_{159}	4
p_{160}	4
p_{161}	4
p_{162}	4
p_{163}	3
p_{164}	3
p_{165}	3
p_{166}	3
p_{167}	3
p_{168}	3
p_{169}	3
p_{170}	3
p_{171}	3
p_{172}	3
p_{173}	3
p_{174}	3
p_{175}	3
p_{176}	3
p_{177}	3
p_{178}	3
p_{179}	3
p_{180}	3
p_{181}	3
p_{182}	3
p_{183}	3
p_{184}	3
p_{185}	3
p_{186}	3
p_{187}	3
p_{188}	3
p_{189}	3
p_{190}	3
p_{191}	3
p_{192}	3

Continued on next page

Patient type $\boldsymbol{p}$	**Number of patients** $\boldsymbol{\rho_p}$
p_{193}	3
p_{194}	3
p_{195}	3
p_{196}	3
p_{197}	3
p_{198}	3
p_{199}	3
p_{200}	3
p_{201}	3
p_{202}	3
p_{203}	2
p_{204}	2
p_{205}	2
p_{206}	2
p_{207}	2
p_{208}	2
p_{209}	1
p_{210}	1
p_{211}	1
p_{212}	1
p_{213}	1
p_{214}	1
p_{215}	1
p_{216}	1
p_{217}	1
p_{218}	1
p_{219}	1
p_{220}	1
p_{221}	1
p_{222}	1
p_{223}	1
p_{224}	1
	End of table

Table A.20 Complete values of σ_p: the minimum number of orders per time horizon of patient type p

Patient type $\boldsymbol{p}$	**Minimum number of orders** $\boldsymbol{\sigma_p}$
p_0	1
p_1	1
p_2	1
	Continued on next page

Patient type $\boldsymbol{p}$	**Minimum number of orders $\boldsymbol{\sigma_p}$**
p_3	1
p_4	1
p_5	1
p_6	1
p_7	1
p_8	1
p_9	1
p_{10}	1
p_{11}	1
p_{12}	1
p_{13}	1
p_{14}	1
p_{15}	1
p_{16}	1
p_{17}	1
p_{18}	1
p_{19}	1
p_{20}	1
p_{21}	1
p_{22}	1
p_{23}	1
p_{24}	1
p_{25}	1
p_{26}	1
p_{27}	1
p_{28}	1
p_{29}	1
p_{30}	1
p_{31}	1
p_{32}	1
p_{33}	1
p_{34}	1
p_{35}	2
p_{36}	2
p_{37}	1
p_{38}	2
p_{39}	1
p_{40}	1
p_{41}	1
p_{42}	2
p_{43}	1

Continued on next page

Patient type p	Minimum number of orders σ_p
p_{44}	1
p_{45}	1
p_{46}	1
p_{47}	1
p_{48}	2
p_{49}	1
p_{50}	1
p_{51}	1
p_{52}	2
p_{53}	2
p_{54}	1
p_{55}	1
p_{56}	1
p_{57}	2
p_{58}	2
p_{59}	2
p_{60}	1
p_{61}	2
p_{62}	1
p_{63}	1
p_{64}	1
p_{65}	1
p_{66}	2
p_{67}	1
p_{68}	1
p_{69}	2
p_{70}	1
p_{71}	1
p_{72}	1
p_{73}	2
p_{74}	2
p_{75}	2
p_{76}	1
p_{77}	2
p_{78}	1
p_{79}	1
p_{80}	1
p_{81}	1
p_{82}	1
p_{83}	1
p_{84}	1

Continued on next page

Patient type p	Minimum number of orders σ_p
p_{85}	1
p_{86}	1
p_{87}	1
p_{88}	1
p_{89}	1
p_{90}	2
p_{91}	1
p_{92}	2
p_{93}	2
p_{94}	1
p_{95}	1
p_{96}	1
p_{97}	2
p_{98}	3
p_{99}	2
p_{100}	3
p_{101}	2
p_{102}	1
p_{103}	2
p_{104}	2
p_{105}	2
p_{106}	2
p_{107}	2
p_{108}	1
p_{109}	1
p_{110}	1
p_{111}	1
p_{112}	1
p_{113}	1
p_{114}	1
p_{115}	2
p_{116}	2
p_{117}	2
p_{118}	1
p_{119}	2
p_{120}	1
p_{121}	3
p_{122}	1
p_{123}	1
p_{124}	2
p_{125}	1

Continued on next page

Patient type p	**Minimum number of orders σ_p**
p_{126}	1
p_{127}	2
p_{128}	1
p_{129}	1
p_{130}	1
p_{131}	1
p_{132}	1
p_{133}	2
p_{134}	2
p_{135}	2
p_{136}	2
p_{137}	1
p_{138}	2
p_{139}	2
p_{140}	2
p_{141}	1
p_{142}	1
p_{143}	1
p_{144}	3
p_{145}	1
p_{146}	3
p_{147}	2
p_{148}	1
p_{149}	1
p_{150}	1
p_{151}	1
p_{152}	2
p_{153}	1
p_{154}	1
p_{155}	1
p_{156}	2
p_{157}	1
p_{158}	2
p_{159}	1
p_{160}	1
p_{161}	1
p_{162}	1
p_{163}	2
p_{164}	2
p_{165}	3
p_{166}	3

Continued on next page

Patient type p	Minimum number of orders σ_p
p_{167}	1
p_{168}	3
p_{169}	1
p_{170}	3
p_{171}	3
p_{172}	1
p_{173}	2
p_{174}	3
p_{175}	1
p_{176}	1
p_{177}	2
p_{178}	1
p_{179}	1
p_{180}	1
p_{181}	1
p_{182}	2
p_{183}	2
p_{184}	2
p_{185}	1
p_{186}	1
p_{187}	2
p_{188}	1
p_{189}	2
p_{190}	1
p_{191}	1
p_{192}	1
p_{193}	2
p_{194}	2
p_{195}	1
p_{196}	1
p_{197}	1
p_{198}	2
p_{199}	1
p_{200}	1
p_{201}	1
p_{202}	1
p_{203}	1
p_{204}	1
p_{205}	1
p_{206}	1
p_{207}	1

Continued on next page

Patient type $\boldsymbol{p}$	**Minimum number of orders $\boldsymbol{\sigma_p}$**
p_{208}	1
p_{209}	1
p_{210}	1
p_{211}	1
p_{212}	1
p_{213}	1
p_{214}	1
p_{215}	1
p_{216}	1
p_{217}	1
p_{218}	1
p_{219}	1
p_{220}	1
p_{221}	1
p_{222}	1
p_{223}	1
p_{224}	1
	End of table