THE FEASIBILITY AND IMPACT ON MOBILITY AND COSTS OF TRANSFERRING THE ADMINISTRATION OF PARENTERAL MEDICATION FROM THE HOSPITAL TO AN EXTERNAL OUTPATIENT SETTING

A DISCRETE-EVENT SIMULATION STUDY

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Table of Contents

Preface

Dear reader,

This report is the result of my master Industrial Engineering and Management and the execution of my graduation project at Isala. Completing this master's thesis marks the end of my master and therefore the end of my student life. I am thankful for all the opportunities I had over the past 6 years. These years were filled with growth and challenges.

I am grateful that I got the opportunity to perform my master graduation project at Isala. At Isala, I experienced what it is like to operate within a hospital. I want to thank the Connected Care Centre team for their help and input. During my time at Isala, they made me feel part of the team and made my experience enjoyable. A special thanks goes out to Jan Gerard Maring and Jedidja Lok-Visser, who guided me during my research at Isala. Through the detailed and in-depth discussions, I learned a lot from your insights and vision on healthcare. Furthermore, I want to thank the staff from the daycare department, who were always available for questions. They gave me the opportunity to join a home route for a day, visit an external outpatient clinic, and distributed the questionnaires among the patients.

Unquestionably, I want to express my sincere gratitude to my academic supervisors Erik Koffijberg and Xavier Pouwels, whose extensive feedback and guidance have been invaluable.
I enjoyed the meetings in which I learned to take a critical look at my research, which helped me to improve my project.

Furthermore, I would like to thank my family, boyfriend, and friends for their unconditional support, even in the most challenging moments.

I hope you enjoy reading this thesis!

Nina ten Broek,

Baak, June 2024

Management Summary

Problem Definition

This research is performed at Isala hospital, which is the largest top-clinical hospital in The Netherlands, with its main location in Zwolle. To cope with the growing demand and shortages in healthcare and to adhere to the agreements made in the Integral Care Agreement, Isala has the ambition to transfer the administration of parenteral medication from the hospital close to the patients' homes. It is expected that this shift will lead to a reduction in carbon dioxide emissions, by reducing the physical travels of patients and healthcare workers. This is of high importance since the government advocates the healthcare sector to be more sustainable (Rijksoverheid, n.d.). Secondly, it is expected that the costs associated with the different care pathways vary. Lastly, moving care from the hospital to the external outpatient setting leads to released capacity expressed in square metres in the hospital. This way, less complex care is moved to the external outpatient setting, which results in more capacity available for complex care in the hospital. Currently, Isala provides care close to home and at home by administering parenteral medication at patients' homes and in the external outpatient clinics (Heerde and Kampen) (Isala, n.d.-c, n.d.-a, n.d.-b). However, Isala does not know what the feasibility and the impact on mobility and costs of each care pathway is and which should therefore be implemented.

The objective of this study is to develop a model that assesses the feasibility and impact on mobility and costs of transferring the administration of parenteral medication from the hospital to an external outpatient setting for oncology and Immune-Mediated Inflammatory Diseases (IMID) patients. The analysis helps comparing the outcomes of the different care pathways. Thereby, giving insights into which care pathway or which combination of care pathways will improve the current situation based on the measured outcomes.

Given the objective of the study, the following main research question was defined:

"What is the feasibility and impact on mobility and costs of transferring the administration of parenteral medication from the hospital to an external outpatient setting for oncology and IMID patients?"

Methodology

The aim of the study was to estimate the feasibility and impact on mobility and costs of transferring the administration of parenteral medication from the hospital to an external outpatient setting. This led to modelling the complexity of the care pathway and at the same time generate different outcome measures, including the CO2 emissions. Two separate literature reviews were performed, on modelling techniques for modelling patient flow and on including carbon emissions as one of the outcome measures. Based on these reviews, we chose to develop a Discrete Event Simulation (DES) model to estimate the impact of transferring the administration of parenteral medication. The Key Performance Indicators (KPIs) *CO2 emissions*, *travel time*s and *travel distances* were selected to estimate the impact on mobility. The KPI *costs* was selected to estimate the impact on costs.

Historical patient data was used as input data for the simulation model. The dataset contained data of patients who had a parenteral administration between January 2019 and 13 November 2023. Furthermore, a questionnaire was distributed among patients to determine the travel modes used by patients to travel to and from their location of treatment. A data analysis was performed on the historical data and the data from the questionnaire.

Various experiments were performed with the model to observe the feasibility and impact on mobility and costs of different configurations. The experiments included closing different

locations, different population size growth rates, outsourcing the medicine administration in Heerde to the home care organisation, opening an external outpatient clinic in Steenwijk, implementing the procedures evaluated in the Minute Study (an ongoing study researching the effects of reducing the infusion time of the medicines Nivolumab, Pembrolizumab, Bevacizumab and Trastuzumab by 20 minutes) and making more medicines eligible for treatment at an external outpatient setting. Each experiment was replicated 100 times. Each replication consisted of 2555 days, including 1095 days of warm-up period. This resulted in 4 years of generated outcomes.

Results

From the experiments, we can conclude that offering at least two forms of treatment at an external outpatient setting (i.e. Kampen, Heerde or the home routes) leads to the lowest total CO2 emissions. Secondly, opening all external outpatient locations leads to the lowest travel times. Driving the home routes and opening at least one outpatient clinic leads to the lowest travel distances. Opening external outpatient clinic Steenwijk leads to an increase in the costs and CO2 emissions, without reducing the travel times and travel distances. The experiments in which different locations were closed, without hiring additional nurses in Zwolle, led to the lowest costs. However, it is important to keep in mind that for some of these experiments the percentage of feasible replications was relatively low (< 95%). Stopping the home routes led to a bigger cost reduction than closing one or both external outpatient clinics. Outsourcing the administration at Heerde to the home care organisation increased the costs, without reducing the average total CO2 emissions per day. Implementing the Minute study did not lead to a reduction in CO2 emissions. However, it led to a reduction in both the travel distances and travel times. Lastly, making more medicines eligible for treatment at an external outpatient setting did lead to a reduction in CO2 emissions and travel distances, but did not lead to a reduction in travel times and costs.

Recommendations

Table 1 shows the increase and reduction in costs, CO2 emissions, travel times and travel distances per year for opening and closing the different external outpatient clinics and the administration at home. Closing different combinations of external outpatient clinics and the home routes led to a reduction in costs compared to the current situation. However, it did not lead to a reduction in the CO2 emissions, travel times and travel distance. For all configurations, except for when both external outpatient clinics (Heerde and Kampen) were opened and the administration at home was stopped, the CO2 emissions increased. For all configurations the travel times and travel distances increased compared to the current situation. The more locations were closed, the bigger the reduction in costs was and the bigger the increase in CO2 emissions, travel times and travel distances was.

Table 1: Increase and reduction in costs, CO2 emissions, travel times and travel distances per year for opening and closing different external outpatient clinics and the administration at home

Experiment				Average number of patients per year	Change in KPIs										Feasibility (%)
	Description				Costs per year (€)	CO2 per year (kg)			Travel times per year (minutes)			Travel distances per year (km)			
	Heerde	Kampen	Home routes			Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	
1	✓	✓	✓	1035	0 (926 258.18)	0 (67 828.81)	0 (67 523.71)	0 (68 131.37)	0 (36 877.60)	0 (36 719.05)	0 (37 036.15)	0 (33 607.87)	0 (33 431.61)	0 (33 784.12)	100
11		✓	✓	1034	-20 568.83	+658.38	+208.93	+1107.82	+339.30	+138.31	+540.28	+629.83	+329.16	+930.50	100
12	✓		✓	1035	-40 502.03	+818.47	+319.06	+1317.87	+406.98	+191.12	+622.83	+1078.54	+815.51	+1341.57	89
13			✓	1035	-61 096.27	+1243.08	+812.22	+1673.94	+453.70	+269.97	+637.43	+1540.51	+1340.61	+1740.40	97
15	✓	✓		1034	-129 642.10	-89.55	-515.76	+336.67	+4300.17	+4093.58	+4506.77	+3656.65	+3438.12	+3875.18	96
17		✓		1033	-152 600.90	+1310.55	+846.283	+1774.81	+4605.58	+4381.15	+4830.01	+4547.74	+4215.98	+4879.51	99
16	✓			1034	-174 796.90	+1807.98	+1368.16	+2247.79	+4647.27	+4416.44	+4878.10	+4876.13	+4574.20	+5178.06	82
14				1034	-197 781.08	+2574.70	+2133.36	+3036.03	+5172.11	+4918.71	+5428.50	+5788.66	+5561.85	+6015.47	84

If Isala's main goal is to save costs compared to the current situation, then any of the configurations in which different locations were closed or home routes were stopped, can be chosen to implement. The cost-saving configurations were compared based on three perspectives (equally importance, climate perspective, patient perspective). If all KPIs have equal importance and are therefore assigned the same weight, closing Kampen and Heerde, and driving the home routes leads to the best outcomes. Secondly, when we look from a climate perspective, opening Heerde and Kampen, stopping the home routes leads to the best outcomes. Lastly, from a patient perspective, closing Kampen and Heerde, and driving the home routes leads to the best outcomes. Only offering administration at the hospitals leads to the biggest reduction in costs compared to the current situation. When it is more important to not increase the CO2 emissions, travel times and travel distances instead of saving costs, it is recommended to keep the current configuration. Not all experiments led to a feasibility percentage ≥ 95%. If Isala wants to ensure that all patients are successfully scheduled in the next four years, a feasibility percentage of 100% is required. The current situation (i.e. opening both external outpatient clinics and offering administration at home) and closing Heerde, opening Kampen and not offering administration at home both have a feasibility percentage of 100%.

It is not recommended to open external outpatient clinic Steenwijk, since it leads to an increase in costs and CO2 emissions, without reducing the travel times and travel distances of patients. The same applies to outsourcing the administration in Heerde to the home care organisation. This only leads to an increase in costs. Secondly, it is recommended to implement the procedures evaluated in the Minute study. The reduced infusion duration allows for more patients to be scheduled with the same capacity. As a result, more patients can be scheduled closer to home, reducing the travel times and travel distances of patients. Lastly, making more patients eligible for treatment at an external outpatient setting leads to a reduction in the CO2 emissions and travel times of patients. Therefore, we recommend Isala to make these medicines (Vedolizumab, Abatacept and Infliximab) eligible for treatment at an external outpatient setting as well.

1. Introduction

The population is ageing and the number of patients with comorbidities is increasing, leading to an increase in demand for care (RIVM, 2018; World Health Organization, 2022) Healthcare expenditure is expected to continue to grow and will have tripled by 2060, if no changes are made in the healthcare system (Wetenschappelijke Raad voor het Regeringsbeleid, 2021) At the same time, shortages of employees in healthcare are growing (World Health Organization, 2016). Currently, 16.7% of the Dutch working population works in healthcare. However, it is expected that in 2040 25% of the Dutch working population should be working in healthcare to maintain the current system (Rijksoverheid, 2022). This is not feasible. Therefore, to maintain the accessibility, affordability and quality of care, a shift in healthcare is required to create a sustainable system (Rijksoverheid, 2022).

1.1 Integral Care Agreement

To jointly take responsibility and to reorganise the healthcare system, the Integral Care Agreement (IZA) [Dutch: Integraal Zorgakkoord] was signed between the Dutch Ministry of Health, Welfare and Sports and 13 organisations active in healthcare (e.g., hospitals, patient federation, municipalities) in September 2022. The IZA states that healthcare should move towards appropriate care. This means that care should be value driven, more patient-centred and the right care should be provided at the right place. To realise this transition, regional and local cooperation between healthcare organisations is necessary. Moreover, digitalisation should be implemented widely to support patient care. And if possible, healthcare should be organised close to home. Additionally, sustainability in healthcare became a new agenda item. This implies that healthcare organisations should move towards more sustainable healthcare processes and reduce their carbon emissions (Rijksoverheid, 2022).

1.2 Isala

Isala is a regional hospital with locations in Zwolle, Meppel, Steenwijk, Kampen and Heerde, with its main location in Zwolle. It is the largest top clinical hospital in The Netherlands and offers neuro- and cardiac surgery and dialysis (Isala, n.d.-d). Isala is one of the seven top clinical hospitals that participates in the mProve network. The network aims to improve hospital care in The Netherlands (mProve, n.d.-b). To learn from each other, the results and experiences from projects are shared within the network. This way, innovations that are successful in one hospital can be easily implemented in the other hospitals (mProve, n.d.-a).

1.2.1 Connected Care Centre

In 2019, the Connected Care Centre (CCC) was established within Isala. The centre aims to realise that 25% of the patients will receive hospital care remotely, if needed with the help of e-health applications and/or with delivery of physical care at home The program consists of a team of professionals who try to deliver the best care to the patients. To do so, healthcare pathways are redesigned and optimized. This way, care becomes more patient-centred and more efficient (Isala, n.d.-b). The CCC contributes to improved healthcare delivery by focusing on four main goals:

- Improved healthcare outcomes
- Improved patient experience
- Improved experience for healthcare professionals
- Reduction in costs

1.2.2 Care at home and close to home

One of the running projects of the CCC is parenteral oncology and Immune-Mediated Inflammatory Diseases (IMID) treatment at an external outpatient setting. Forms of oncological treatment that can be administered parenteral are immunotherapy and chemotherapy. IMIDs are clinically diverse. However, the group of diseases is characterized by similar immune dysregulation and can be treated with parenteral medication (David et al., 2018). These treatments have a high impact on both the patient and the caregiver. For example, travelling to the treatment is time-consuming. In 2016, Isala started a pilot program in collaboration with the healthcare insurance company Zilveren Kruis to deliver short-term and non-complex systemic treatment or supportive treatment at home. Nowadays, the pilot expanded and became regular care (Isala, n.d.-c). There are two forms of treatment that are given outside of the hospital: treatment at home and treatment close to home (Isala, n.d.-c, n.d.-a).Treatment at home means that a specialised nurse administers the parenteral medication at the comfort of the patient's own home. As a result, the patient does not have to travel periodically to the hospital anymore. This results in no travel and waiting time and no parking costs. The nurse travels from patient home to patient home (Isala, n.d.-c). Another form of delivering treatment is treatment close to home. This means delivering care close to the patient's home in an external outpatient clinic. Isala has currently two external outpatient clinics where this is possible: one in Heerde and one in Kampen. The nurses and patients travel to the centrally located external outpatient clinic, where medication is administered (Isala, n.d.-c).

1.3 Problem context

1.3.1 Problem identification

To cope with the growing demand and shortages in healthcare and to adhere to the agreements made in the IZA, Isala has the ambition to transfer the administration of parenteral medication from the hospital to the external outpatient setting. Currently, Isala provides care close to home by administering parenteral medication at patients' home and in the external outpatient clinics (Isala, n.d.-c, n.d.-a, n.d.-b). However, Isala does not know what the feasibility and impact on mobility and costs is of each care pathway and which should therefore be implemented. It is expected that transferring the administration of parenteral medication from the hospital to an external outpatient setting will influence several outcome measures. Firstly, it is expected that this shift will lead to a reduction in carbon dioxide emissions, by reducing the physical travels of patients and healthcare workers. This is of high importance since the government advocates the healthcare sector to be more sustainable (Rijksoverheid, n.d.). Secondly, it is expected that the costs of property will be lower for the external outpatient clinics compared to the hospital. The regional cooperation within the external outpatient clinics, which is one of the goals of the Integral Care Agreement, leads to sharing of property between healthcare organisations. Lastly, moving care from the hospital to the home setting will lead to released capacity expressed in square metres in the hospital. This way, less complex care is moved to the external outpatient setting, which results in more capacity available for complex care in the hospital.

1.3.2 Core problem

Based on conversations with the program director of the Connected Care Centre Jan Gerard Maring, a problem cluster was established. Based on this, the following core problem was defined: *"It is unknown what the feasibility and impact on mobility and costs is of each care pathway for administering parenteral medication for oncology and IMID patients."*

1.4 Objective and research questions

The objective of this study is to develop a model that assesses the feasibility and impact on mobility and costs of transferring the administration of parenteral medication from the hospital to an external outpatient setting for oncology and IMID patients. The analysis will help comparing the outcomes of the different care pathways. Thereby, giving insights into which care pathway or which combination of care pathways may improve the current situation based on the measured outcomes.

Given the objective of the study, the following research question was defined:

"What is the feasibility and impact on mobility and costs of transferring the administration of parenteral medication from the hospital to an external outpatient setting for oncology and IMID patients?"

To answer the main research question, we divided the research question into sub-questions:

1. "*What are the care pathways for administering parenteral medication for oncology and IMID patients?"*

This first research question gives insights into the current situation at Isala. It helps mapping out the current care pathways for administering parenteral medication: at home, at the external outpatient clinic and in the hospital. In addition, the travel routes by both patients and nurses are explained in detail.

2. *"What modelling techniques for patient flow modelling exist in literature?"*

The second research question helps finding out what modelling techniques for modelling patient flow exists in literature. The research question is answered by conducting a literature review. The goal is to create an overview of modelling techniques that can be used for modelling patient flow. This helps to select a model for this research. Additionally, it helps to define the research gap and thus the scientific contribution of this study.

3. *"What modelling techniques can include carbon emission as an outcome measure?"*

The third research question helps finding out what type of models can include carbon emission as an outcome measure. The research question is answered by conducting a literature review. The goal is to create an overview of models that can include carbon emission as an outcome measure. By examining the literature, a suitable model for this specific problem context can be selected.

4. *"What travel modes are used by patients to travel to and from their location of administration?*

Before a model can be developed, the transportation types used by patients to travel to and from their location of administration need to be determined. Different travel modes have a different effect on the carbon dioxide emission. Therefore, a questionnaire is distributed among patients at the daycare department to determine the type of transport used.

5. *"How can the impact of the different care pathways be modelled?"*
    a. *What does the conceptual model look like?*
    b. *What data is required as input data to create a realistic model?*
    c. *What scenarios should be created and evaluated?*

Finally, a model is developed, and the feasibility and impact on mobility and costs of each care pathway is determined and compared. Answering the 5 research questions leads to an answer to the main research question.

2. Context analysis

This chapter answers the research question: "*What are the current care pathways for administering parenteral medication for oncology and IMID patients?*" In Section 2.1, the current care pathways, and the different travel routes of both the patients and nurses are introduced.

2.1 Current care pathways

In this section, we examine the current care pathways for administering parental medication for oncology and IMID patients. Currently, three care pathways exist: at home, at an external outpatient clinic and at the daycare department in the hospital. An overview of each is given. Figure 1 shows the current care pathways. The care pathways follow the same preparation phase. However, they differ in the actual administration of the medicine.

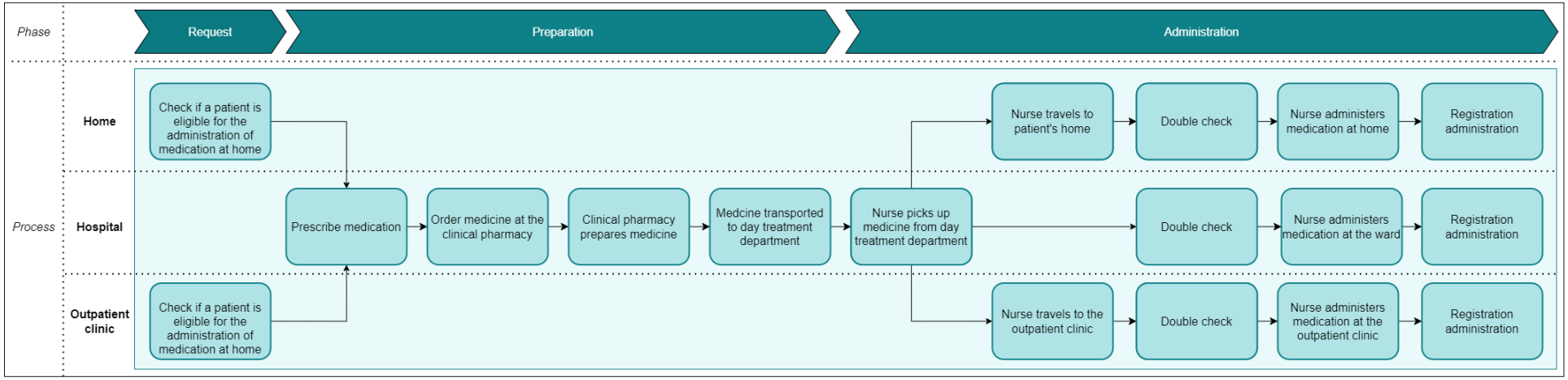

Figure 1: Chart of the current care pathway

2.1.1 Hospital

Originally, which is still the case for most patients, the administration of parenteral medicines takes place at the daycare department at the hospital. The process starts with a prescription for parenteral medication. The daycare department receives this prescription and orders the medicine from the clinical pharmacy. After that, the clinical pharmacy prepares the medicine and when finished transports the medicine to the daycare department, which is in the same wing of the hospital. Then, the patient visits the daycare department, and a nurse administers the medicine. After the administration, the nurse registers the administration in the Electronic Medical Record (EMR) of the hospital.

Figure 2 shows the travel routes for the administration at the daycare department in the hospital. During a normal day, multiple patients are scheduled to get treatment at the hospital. Each patient travels from home to the hospital to get treatment. After the medicine is administered, the patient returns home. This results in two travel movements each appointment. The carbon emission per patient depends on the travel distance and the travel mode. Nurses only travel from home to the hospital, and from the hospital back to home.

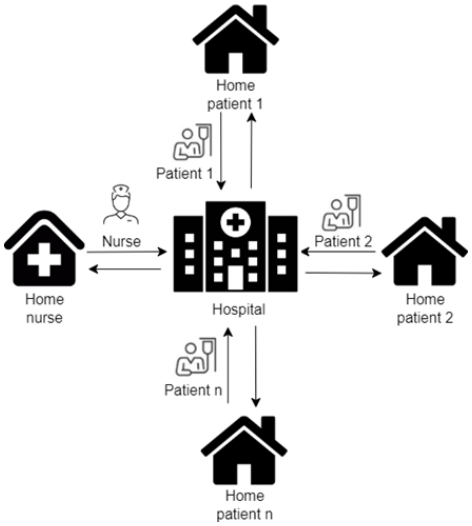

Figure 2: Travel routes care pathway administration at the hospital

2.1.2 At home

One of the care pathways for administering parenteral medication at an external outpatient setting is the administration at home. Before a patient can start with the treatment at home, it is first checked whether the patient is eligible for treatment at home. The inclusion criteria include that the patient's place of residence is not more than 30 km or 35 minutes away from the hospital and the infusion time of the medicine can be performed in at maximum 30 minutes. The criteria help to ensure safety and avoid too complex cases to be treated at home. Before the nurse starts the home route, the medicines of all patients for that day are checked and collected. Then, the route starts by travelling to the first patient and administering the medicine at home. To ensure safety, a double check is carried out prior to the medication administration to verify that the correct medication is given to the patient. This is done by calling the coordinator at the daycare department, who checks the identity of the patient and the medicine that will be administered. After the check is performed, the nurse starts administering the medicine. During the administration, the status of the patient is monitored. When the administration of the medicine is completed, the nurse registers the administration in the EMR of the hospital. Then, the nurse travels to the next patient. After the last patient of the day, the nurse travels back to the hospital. Figure 3 shows the travel routes of the care pathway for administration at home.

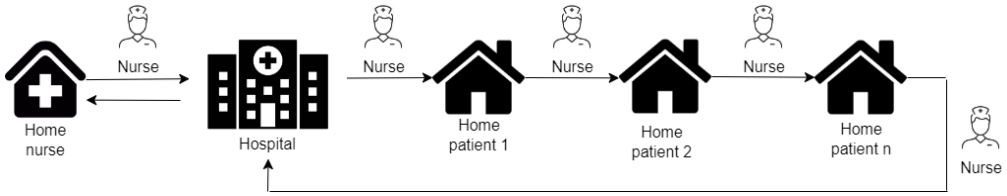

Figure 3: Travel routes care pathway administration at home

2.1.3 External outpatient clinic

Another care pathway for the administration of parenteral medication is the administration at an external outpatient clinic. Isala set up two rooms in two of her external outpatient clinics: one in Heerde and one in Kampen. The pathway for the administration at an external outpatient clinic follows the same pathway as the administration at home. However, instead of a nurse travelling to patients' homes the nurse now travels to the external outpatient clinic. Figure 4 shows the travel routes taken by patients and nurses within the care pathway of the external outpatient clinic. At the start of the day, the scheduled nurse travels from home to the hospital. After all medicines are checked and collected at the hospital, the nurse travels to the external outpatient clinic either in Heerde or Kampen. The nurse travels by car, owned by Isala. Patients who have an appointment at one of the external outpatient clinics travel from home to the external outpatient clinic and back. This results in two travel movements for patients each appointment. At the end of the day, the nurse travels from the external outpatient clinic back to the hospital. Prior to the medication administration, a similar double check as during the at home administration is done. After the administration, the nurse registers the administration in the EMR of the hospital. At the end of the day, the nurse travels back to the hospital.

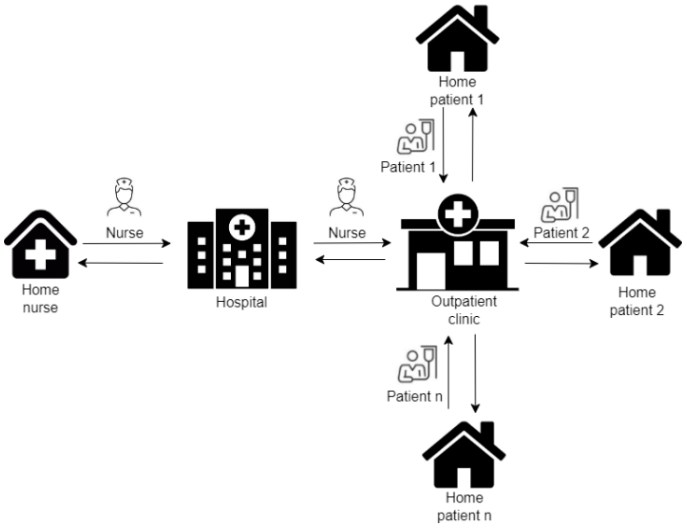

Figure 4: Travel routes care pathway administration at an external outpatient clinic

2.1.4 Medicine types

The target population of this research consists of oncology and IMID patients who receive parenteral medication. Table 2 shows a list of medicines that are currently administered to these patients at home, in the hospital and at an external outpatient clinic. Table 3 shows a list of medicines that are currently only administered at the hospital but have the potential to be administered in an external outpatient setting in the future.

Table 2: List of medicines currently administered at an external outpatient setting

Medicine	Type of medicine
Bortezomib	Chemotherapy
Trastuzumab	Onco-biological
Bevacizumab	Onco-biological
Nivolumab	Immunotherapy
Azacitidine	Chemotherapy
Pembrolizumab	Immunotherapy
Blinatumomab	Onco-biological
Carfilzomib	Chemotherapy
Zoledroninezuur	Bone strengthener
Daratumumab	Immunotherapy

Table 3: List of medicines with potential to be administered at an external outpatient setting

Medicine	Type of medicine
Vedolizumab	IMID
Abatacept	IMID
Immunoglobulins	IMID
Infliximab	IMID

3. Theoretical framework

In this section, we describe the findings of the literature review that was conducted on the different modelling techniques for modelling patient flow and including carbon emission as an outcome measure. The goal is to create an overview of the literature. This helps to define the research gap and select a suitable model for this research. The literature study gives an answer to the following two research questions: *"What modelling techniques for patient flow modelling exist in literature?"* and *"What modelling techniques can include carbon emission as an outcome measure?"*

First, Section 3.1 describes the steps followed to conduct the literature review. Section 3.2 gives an overview of modelling techniques for modelling patient flow. Then, Section 3.3 gives an overview of modelling techniques that can include carbon emission as an outcome measure. And lastly, Section 3.4 summarises the findings and outlines the selection process for a suitable model that can model the feasibility and impact on mobility and costs of the different care pathways for administering parenteral medication.

3.1 Search

To perform a literature review, the principles of the Grounded Theory were followed (Wolfswinkel et al., 2013). This method consists of five stages: define, search, select, analyse, and present. The first step is to define inclusion and exclusion criteria. Then, search strings are defined and inserted into the selected database. After that, articles are selected. To answer the research question, two separate searches were performed: one on patient flow and one on carbon emissions. The database Scopus was used during this review.

3.1.1 Patient flow search

The goal of the first search was to find suitable modelling techniques for modelling patient flow. Therefore, articles that included modelling techniques to model patient flow were sought. Studies that were published in any other language than English were excluded. The goal was to find reviews of different modelling techniques. Therefore, studies which focussed on the application of models were excluded. On top of that, only peer-reviewed academic articles were included, and book chapters were excluded. An overview of all the inclusion and exclusion criteria can be found in Table 4.

Table 4: Inclusion and exclusion criteria patient flow

Inclusion criteria	Exclusion criteria
Study should focus on patient flow	Study was not published in the English language
Study includes modelling techniques	Book chapters
Peer-reviewed academic articles	Studies which focus on the application of models
Reviews	

The following search string was used to conduct the literature review on modelling techniques for patient flow: ("Patient flow" AND "modelling" AND "techniques" OR "approaches"). The articles selected during this search were then used for forward and backward searching.

Figure 5 shows the selection procedure used. Inserting the search term into Scopus led to 162 articles found. First, we screened the articles on title and abstract. Based on this, 18 articles were selected. After that, a full text screening was performed, which led to the exclusion of 9 articles. 0 articles were selected based on forward and backward selection. Finally, resulting in a total number of 9 articles that were selected. Table 5 shows a concept matrix of the selected articles.

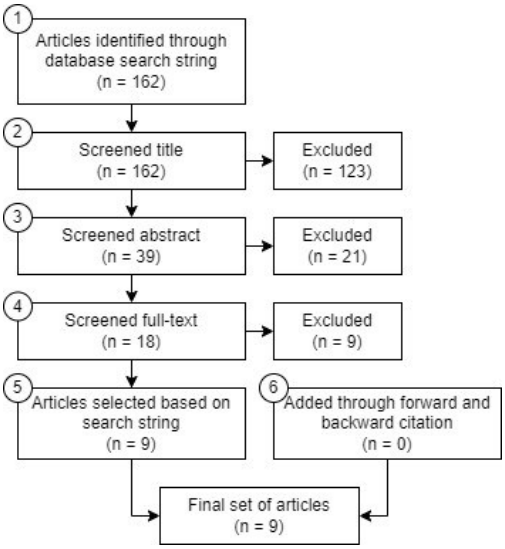

Figure 5: Selection procedure patient flow

Table 5: Concept matrix patient flow

Author's name	***Concepts***					
	Queuing models	*Markov chains*	*Mathematical modelling*	*Discrete Event Simulation*	*Agent-Based Modelling*	*System Dynamics*
(Bhattacharjee & Ray, 2014)	✓	✓		✓	✓	✓
(Bai et al., 2018)	✓	✓	✓	✓		
(Ahsan et al., 2019)	✓			✓	✓	
(Almagooshi, 2015)				✓	✓	
(Terning et al., 2022)				✓	✓	
(Demir et al., 2014)		✓				✓
(Ostermann, 2015)					✓	
(Davahli et al., 2020)						✓
(Vanderby & Carter, 2010)						✓

3.1.2 Carbon emissions search

The goal of the second search was to find suitable models for modelling carbon emissions in healthcare. Therefore, articles that included modelling techniques to model carbon emissions as an outcome measure in the healthcare sector were sought. Studies that were published in any other language than English were excluded. Since the inclusion of carbon emissions as an outcome measure in models is still relatively new, we did not only focus on reviews, but application and case studies were also included. An overview of all the inclusion and exclusion criteria can be found in Table 6.

Table 6: Inclusion and exclusion criteria carbon emissions

Inclusion criteria	Exclusion criteria
Study should focus on carbon emission	Study was not published in the English language
Study should focus on the healthcare sector	Book chapters
Study includes modelling techniques	

The following search string was used to conduct the literature review on modelling techniques for measuring carbon emissions:

(("routing" OR "transportation" OR "patient flow") AND ("carbon" OR "footprint" OR "emission" OR "electric") AND ("healthcare" OR "health care") AND ("modelling" OR "approach" OR "technique"))

The articles selected during this search were then used for forward and backward searching.

By conducting the literature review, we found articles that provide an overview of modelling techniques that can model carbon emissions. Figure 6 shows the selection procedure used. Inserting the search term into Scopus led to 252 articles found. First, we screened the articles on title and abstract. Based on this, 4 articles were selected. After that, a full text screening was performed, which led to the exclusion of 1 article. 5 articles were selected based on forward and backward selection. Finally, resulting in a total number of 8 articles that were selected. Table 7 shows a concept matrix of the selected articles.

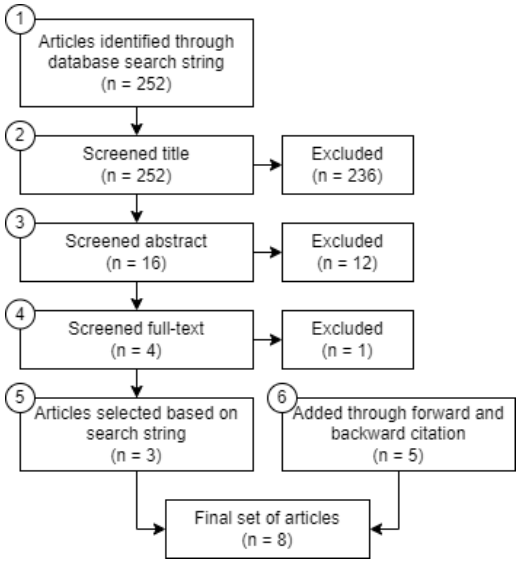

Figure 6: Selection procedure carbon emissions

Table 7: Concept matrix carbon emissions

Author's name	***Concepts***			
	Mathematical modelling	*Discrete Event Simulation*	*Agent-Based Modelling*	*System Dynamics*
(Bahri et al., 2021)	✓			
(Nasrollahi et al., 2018)	✓			
(Hilmola & Henttu, 2016)				✓
(Vali et al., 2022)		✓		
(Rodríguez Verjan et al., 2013)		✓		
(Loidl et al., 2016)				
(Peker et al., 2020)	✓			
(Ulusam Seçkiner & Koç, 2022)			✓	

3.2 Approaches for modelling patient flow

The first search focused on the modelling of patient flow. In this section, the following models that can model patient flow are described: Markov Chain, Queuing Models, Mathematical Programming, Discrete Event Simulation, Agent Based Modelling and System Dynamics. First, in Section 3.2.1, a short introduction is given about patient flow.

3.2.1 Patient flow modelling

To model the problem correctly, it is necessary to model the complete care pathway for the administration of parenteral medication. A way to model processes in healthcare is through patient flow modelling. Patient flow modelling encompasses the entire process of a patient moving through the healthcare system (Hall Randolph and Belson, 2006). The specific pathway a patient follows is determined by the patient's characteristics. However, segments of the pathways may be similar between patients. The patient enters the system at an entrance and leaves the system at an exit. Between these two points, single or multi servers exist where treatment is given (Bhattacharjee & Ray, 2014). Patient flows are complex, due to the different types of care pathways a patient can follow. On top of that, variability in characteristics leads to complexity. For example, service and arrival times might differ between patients (Bhattacharjee & Ray, 2014).

Patient flow modelling can help healthcare organisations to optimise their processes. It can help identifying bottlenecks and inefficiencies in care pathways. Since patient flow modelling recreates processes in detail, it can give insights in resource allocation and scheduling (Bhattacharjee & Ray, 2014).

A patient flow model consists of 3 main aspects: the arrival distribution, transition probabilities and service time distributions. The arrival distribution describes the arrival of patients to the system. Arrivals can be either scheduled or unscheduled. For scheduled arrivals, the distribution for the time that patients arrive earlier to their appointment needs to be determined as well. In literature, unscheduled arrivals are commonly described by Poisson arrivals. The transition probabilities describe the probabilities of a patient transitioning from one state to another. The transition probabilities may differ between patients based on patient characteristics. They can be determined based on historical data. The service time distribution represents the time a patient is in service. For example, when the medicine is administered to the patient by a nurse (Bhattacharjee & Ray, 2014).

3.2.2 Markov chains

A technique to model patient flow in hospitals, is by Markov chains. A Markov chain is a stochastic model that describes the process of transitioning from one state to another state with

a certain probability. The state space and the number of transitions is finite. A Markov chain satisfies the Markov property (memoryless property), which means that the probability of transitioning to a state only depends on the current state (Bhattacharjee & Ray, 2014).

In a Markov chain, patients transfer from one state to another. This can be used to model the transition of patients through treatment. Markov chains can be applied in healthcare to optimise the resource allocation and estimate the patient movement through a system. On top of that, it can estimate the number of patients that are present in a state at a specific point in time. In literature, Markov chain models were used to model the length of stay and waiting times of patients in a hospital.

However, there are a few disadvantages of using Markov chains for modelling patient flow. Firstly, Markov chains require assumptions and are therefore simplified models. For example, the Markov property assumes that the probability of transitioning to a state only depends on the current state. However, this might not be the case. As a result, complex systems are difficult to model. Lastly, Markov chains cannot distinguish between patients based on their characteristics. Patients in the same state are identical. This might influence the patient flow (Bai et al., 2018; Bhattacharjee & Ray, 2014; Demir et al., 2014).

3.2.3 Queueing models

Queuing models can model the flow of patients through different medical services in the hospital. Adding queuing theory to the model gives the ability to model uncertain arrival times and service times, while considering limited resources. This way, outcome measures such as length of stay, waiting times and congestion can be measured (Ahsan et al., 2019; Bai et al., 2018; Bhattacharjee & Ray, 2014).

Queuing models can determine the efficiency of the patient flow. It can assess the waiting times, service times and the utilisation of resources. This way, bottlenecks can be detected, and resources can optimally be allocated. Outcome measures of a queuing model in healthcare include the average queue length and average waiting time.

Queuing models are an efficient way of modelling patient flow for moderate complex systems. However, as the complexity increases, queuing models become less suitable (Bhattacharjee & Ray, 2014). In addition, queuing models are stationary. This means that parameters do not change over time. However, in a dynamic healthcare context this might not be the case. As a result, the model might not represent the real-world correctly. Lastly, queuing models cannot model the impact of limited capacity correctly. Shortages of staff and beds are difficult to model in a queuing model. This might influence the outcome measures.

3.2.4 Mathematical programming

Mathematical models try to look for the optimal solution to a given objective. The model includes constraints, variables, and equations/inequalities. Types of mathematical models are linear programming, integer programming and mixed-integer programming. In healthcare, mathematical modelling is often used for scheduling and resource allocation problems. The optimisation of scheduling and resource allocation can help to ensure an efficient patient flow (Bai et al., 2018). An advantage of using mathematical programming to model patient flow is that it can model complex scenarios. For example, multiple objective functions can be defined.

However, using mathematical programming to model patient flow has some disadvantages as well. First, the computation time for mathematical models is rather long, especially when modelling large and complex systems as the healthcare system. Secondly, the quality of the model depends on the accuracy of the constraints and assumptions made to develop the model.

Lastly, mathematical models are deterministic and therefore can often not model the dynamic changes in the healthcare system correctly (Bai et al., 2018).

3.2.5 Discrete Event Simulation

Simulation is a suitable method for gaining insights into processes. This is because various processes can be simulated and evaluated, without affecting real projects and incurring high investment costs. Discrete Event Simulation (DES) is a simulation technique that models a system over time. Events occur at specific point in time. Between the events, the entity's state does not change. Thus, the model jumps from event to event. In literature, DES is widely used for process modelling to support optimisation studies in healthcare (Bhattacharjee & Ray, 2014).

There are many studies available in literature that simulate patient flow in hospitals. Most of these studies focus on optimising patient flow. DES is often used to identify the bottlenecks in the process. The modelling process starts with a simulation model that represents the current situation. Then, various experiments are performed. For example, changing the number of staff members who are available or including unscheduled maintenance in machines in the model. The outcome measures of the experiments are then compared to the current situation.

An advantage of using a DES model to model patient flow is the ability to model a system in detail. Individual patients and nurses can be modelled into the simulation. On top of that, a DES can model a network of interlinked services. This leads to a realistic representation of the real-world system and its behaviour. Compared to the other models mentioned above, a DES model has more flexibility and freedom in selecting distributions for arrival processes (Bai et al., 2018). Additionally, by using a DES model several scenarios can be analysed. This allows decision makers to explore the potentially most optimal process, without the need for prior implementation.

3.2.6 Agent-Based modelling

Agent-Based Modelling (ABM) is a simulation technique that allows for the modelling of behaviour. It models the interactions between agents in a complex system (Ostermann, 2015). The entities in the system, which are autonomous and interact within the system, are called agents. Agents can interact with each other within the environment. Moreover, agents can base their next activities on the state of the environment. Agents can interact, learn, and move through space and time. Furthermore, agents and the environment can change, develop, and evolve (Ostermann, 2015; Terning et al., 2022).

ABM can model the decision-making of individual patients. It can model behaviour, preferences, and characteristics. Agents are autonomous. Therefore, they can make their own decisions. For example, which healthcare location they want to go to. However, to accurately model this, ABM requires data on patient behaviour (Ostermann, 2015; Terning et al., 2022).

3.2.7 System Dynamics

System Dynamics (SD) is a modelling technique that can model a complex system dynamically. It models the dynamic behaviour of a system over time. The structure of the system determines the behaviour of a system, instead of external factors causing specific behaviour. SD models cannot model individual patients. Instead, populations are accumulated (Bhattacharjee & Ray, 2014; Davahli et al., 2020; Vanderby & Carter, 2010).

A SD model consists of feedback loops, stocks, and flow. It models nonlinearity. Through the flow the entities move, they are aggregated in stocks and the feedback loops create a dynamic system. Usually, SD models are visualised by a casual loop diagram. This diagram shows the relationships and feedback loops within the system (Bhattacharjee & Ray, 2014; Vanderby & Carter, 2010).

In healthcare, SD models are often used to optimise patient flow. When modelling patient flow, SD can model the different stages of a process. However, SD cannot model individual patients. SD modelling is a suitable method to model high-level problems in healthcare. These problems often include strategy and policy decisions (Davahli et al., 2020).

3.3 Approaches for modelling carbon emissions

The second search focused on the inclusion of carbon emissions as one of the outcome measures in models. Adding carbon emissions as one of the outcome measures in a model is still relatively new and not widely described in literature. Especially in the healthcare sector, not many studies include carbon emissions.

3.3.1 Mathematical Programming

Mathematical Programming can be used to model carbon emissions. Mathematical models try to look for the optimal solution to a given objective. For example, the Vehicle Routing Problem (VRP). VRP is a traditional problem in Operations Research. The problem calculates the optimal route for a fleet of vehicles. The objective is to minimise the total costs. The problem consists of a given set of vehicles, which are operated by a set of drivers. These vehicles can drive within a given network of routes to deliver goods or services to a set of customers. This way, the problem represents, for example, a delivery service.

Several studies proposed variants of the VRP, by introducing carbon emissions to the problem (Bahri et al., 2021; Peker et al., 2020).The goal of this extended VRP is not to only minimise the travel costs, but also minimise the carbon emissions. The vehicles start from a distribution centre and return to the distribution centre after travelling to all customers. VRP can be applied to optimisation problems in healthcare. For example, Bahri et al. (2021) used multi-objective optimisation methods and VRP to optimise the routing of nurses who drive electric vehicles and make home visits to patients.

Another example of mathematical programming to model carbon emissions, is the study performed by Nasrollahi et al. (2018). They developed a multi-objective mathematical programming model to measure the transport related carbon emissions in a healthcare supply network.

3.3.2 Simulation models

In literature, simulation modelling is widely used for process modelling to support optimisation studies in healthcare. However, only a few studies include carbon emissions in their simulation model. Both DES, ABM and SD can include carbon emissions into their model.

Discrete Event Simulation

For example, Vali et al. (2022) used DES to improve patient flow while minimising carbon emissions. The model simulates the patient flow, by simulating how patients move through the hospital and which activities they undergo. When a patient arrives, a certain category is given to the patient based on the patient's condition. Each category follows its own specific care pathway, resulting in different outcomes. The emission is then calculated based on the duration that specific equipment is used for the treatment.

Rodríguez Verjan et al. (2013) performed an economic comparison between Hospital at Home (HAH) and hospital care. A DES was developed to compare various scenarios. The economic comparison included various costs, including patient transportation. Patient transportation covers all costs related to the transportation of a patient from home to the hospital. For example, when a patient needs to be transported to the hospital by ambulance in case of an accident.

However, Rodríguez Verjan et al. (2013) did not consider any emissions related to the transportation. Only costs were included.

System Dynamics

Hilmola & Henttu (2016) also studied the transportation of patients to hospitals. They developed a SD model to estimate the total costs of transportation. The carbon dioxide emissions resulting from transportation were studied. The kilometres travelled by different travel modes were converted into carbon dioxide emissions, resulting in a total sum of carbon dioxide emission. To distinguish between the different travel modes, specific values of carbon dioxide emissions were given to each travel mode.

Agent-Based Modelling

Ulusam Seçkiner & Koç (2022) used ABM to manage multi-energy systems. Forms of energy that were studied were electricity, heating, gas, and converters. According to Ulusam Seçkiner & Koç (2022), hospitals are a multi-energy system. In their agent-based model, carbon emissions were used as an outcome measure to optimise the multi-energy system.

3.4 Conclusion

To find a suitable model for our specific problem context, the model must meet a few conditions. First, the model must be able to properly model the complexity of healthcare pathways. Secondly, the model must be able to include carbon emissions as an outcome measure. This concerns the emissions caused by the travel movements of both patients and nurses. Lastly, it is important to be able to model the individual characteristics of patients. Each patient uses a different type of medicine. The type of medicine determines the care pathway the patient follows. Additionally, each patient has a different home address, resulting in different travel distances and type of transportation between patients.

From literature, we can conclude that the use of simulation is a common technique for modelling patient flow in healthcare. Queuing models, Markov chains and mathematical programming are efficient ways of modelling patient flow for moderate complex systems. However, as the complexity increases, simulation becomes a better approach to model patient flow (Bhattacharjee & Ray, 2014). Simulations can model the complexity of healthcare pathways. Studies that use simulation models are often used for the optimisation of healthcare processes. For example, common outcome measures of simulation models in healthcare are length of stay, access time and service utilisation (Bai et al., 2018; Bhattacharjee & Ray, 2014; Kulkarni et al., 2021).

Including carbon emissions as one of the outcome measures of a model is still relatively new in healthcare. Only a few studies included carbon emissions into their models. These studies used mathematical programming and simulation models (Bahri et al., 2021; Hilmola & Henttu, 2016; Loidl et al., 2016; Peker et al., 2020; Rodríguez Verjan et al., 2013; Vali et al., 2022). A mathematical programming model often used in healthcare is the Vehicle Routing Problem (VRP). VRP is used to minimise the carbon emissions of routing problems. For example, to calculate the optimal routing of healthcare professionals. At first glance, this seems to be a suitable model for this specific problem context since we focus on mobility. However, for this problem the optimisation of routing is only required for the home routes. The travelling of patients and nurses between the hospital and external outpatient clinics are fixed routes. Therefore, the VRP is not a suitable model to answer the research question. On top of that, VRP cannot model the individual characteristics of patients. Simulation models on the other hand seem to be a suitable model to answer the research question. Simulation models can model both the complexity of patient flow and include carbon emissions as an outcome measure.

Discrete Event Simulation, Agent-Based Modelling and System Dynamics are simulation models that can model both patient flow and include carbon emissions as an outcome measure. However, the extent to which they are suitable for this problem context varies. First, we can conclude that SD simulation is not suitable for this problem context, as SD models cannot model individual patient characteristics. In contrast, ABM and DES can model individual characteristics. The main difference between a DES model and an ABM model is that ABM models can model behaviours and interactions in a system. When looking at our problem context, possible interactions are, for example, patients having social interactions with each other. These social interactions can influence patients' preferred treatment location, which can lead to a form of behavioural action (preference) caused by interaction. However, since patients are not allowed to choose the location of treatment themselves, these interactions are not relevant for this problem context. Another form of behavioural action is the fact that the distance between a patient's home and the location where the treatment is provided could influence the type of transportation that is chosen by a patient to travel to the location. Locating a treatment location X km closer or further away from a patient's home might influence the choice of transportation. However, the locations where treatment is given (hospital, external outpatient clinic or at home) are fixed locations. The issue of where to locate a treatment location and the influence this will have on the behaviour of patients with regards to the type of transportation chosen is not relevant to this problem context. However, it is relevant to know what type of transportation different patients choose to travel to a specific location. For example, what type of transportation is used when a patient had to travel X km. On top of that, patients that are treated at the hospital might choose another type of transportation compared to patients treated at an external outpatient clinic. Since the behavioural actions and interactions between patients is limited in this problem context, it is not required to use a model that can model complex behaviour and interactions. The focus of the problem is to get insights into the different care pathways and their feasibility and impact on mobility and costs. A DES is a suitable model to model this impact. A DES model can improve patient flow while minimising carbon emissions. The model can simulate the patient flow, by simulating how patients move through their care pathway and which activities they undergo. Therefore, it can properly model patients' travels, the administration of medicines and at the same time generate outcomes, such as carbon emissions. Since DES models can model individual characteristics, a certain medicine type can be given to the patient based on the patient's condition. Each medicine type follows its own specific care pathway and service time can depend on the type of medicine. Lastly, DES models can model less complex behaviour, for example, data on travel mode selection based on distance and age can easily be inserted into the model.

To conclude, DES is the most suitable model to model this specific problem context. A DES model allows to model the complexity of healthcare processes and patient flow. On top of that, it can model individual characteristics. The ability to model behavioural actions in a DES model is limited. However, since locations where treatment is given are fixed and patients cannot schedule themselves at preferred locations, the modelling of complex behaviour and interactions is not required.

4. Methodology

This chapter outlines the development of the simulation model. Based on the performed literature review, we selected a Discrete Event Model as our simulation model (Section 3.4). Section 4.1 explains how we performed the data analysis of the historical dataset. Section 4.2 describes how we performed the data analysis of the questionnaire. The data analysis of the historical data and the questionnaire were used as input data for the simulation model. Section 4.3 outlines the development of the simulation model. It explains the input data used and the experiments that were performed.

4.1 Data analysis of the historical data

Historical patient data was used as input data for the simulation model. The dataset contains data of patients who had an administration with one of the medicines described in Section 2.1.4 between January 2019 and 13 November 2023. Patient data collected before 2019 was stored differently and therefore not available to the researcher. The following data was extracted from the electronic health records: appointment dates, type of medicine that was administered during the appointment, appointment duration, appointment location, age, gender, and postal code. For privacy reasons, it was not acceptable to use the exact addresses of patients. Instead, the postal codes of patients were used. This section discusses all input data in detail.

4.1.1 Number of new patients and number of appointments

The number of new patients consists of the patients who have their first appointment. The dataset provided by Isala does not contain any appointment data before the year 2019. On top of that, the number of the appointment is not specified. As a results, patients who had an appointment in 2019 were automatically seen as new patients in the dataset. However, these patients may have already had appointments in the years before 2019. This means that these patients are new in the dataset but may not be new to the hospital. To ensure that the patients who have their first appointment in the dataset, are new patients to the hospital, a certain amount of data must be excluded. However, excluding too much data leads to major data loss. Therefore, a trade-off needed to be made. First, we determined the number of days between two consecutive appointments of all the appointments in the historical data. This showed us the range and maximum number of days that can occur between two consecutive appointments. Based on this, we could determine the latest possible date for a second appointment of a patient who had their first appointment on December 31, 2018 (which represents the earliest date preceding the data available in the dataset). And therefore, determine the chance of misidentifying a patient as a new patient in the dataset, by assuming it is the first appointment, while in reality it the patient's second appointment. In total 0.7% of the appointments in the historical dataset had more than 365 days between two consecutive appointments. When we exclude the data from the year 2019 (365 days), there is a 0.7% chance that a patient who had their appointment on December 31, 2018, is misidentified as a new patient. We chose to consider this percentage small enough. It is expected that many patients had their appointments before December 31, 2018, which increases the number of 365 days and therefore lowers the percentage of 0.7%. To conclude, data from the year 2019 was excluded for the analysis of the new number of patients. The number of appointments consists of all the appointments patients had during the years 2019-2023.

Data of the year 2023 was not complete. The month November was incomplete, and the month December was missing. Therefore, we extrapolated the number of patients and appointments based on the monthly increase of the previous years. To see if there were any seasonal fluctuations which may influence the extrapolation, the number of patients and appointments over the seasons were plotted.

4.1.2 Appointment duration

We checked if the appointment durations in the dataset were valid data points. The daycare department is open 10.25 hours per day. However, 4 points (0.01%) in the data had an appointment duration longer than 10.25 hours. These data points were seen as invalid and were removed.

Type of medicine

To see if the appointment duration varies per medicine, the appointment durations for each medicine were plotted separately. The median, mean, standard deviation and accompanying confidence intervals were determined. By examining the confidence intervals of the means, it was determined whether there was a significant difference between the appointment durations. If two confidence intervals overlapped, we assumed that there was no significant difference between the appointment durations over the years.

Location of administration

The protocol used within Isala says that the infusion time of medicines administered at an external outpatient clinic or home cannot be longer than 30 minutes. This does not apply to the administrations at Zwolle and Meppel. Based on this, it is expected that the appointment duration is shorter at an external outpatient setting compared to the hospitals. To analyse this, the appointment durations were divided by the five separate locations. To eliminate the effect of the medicine type on appointment duration, the appointment durations were divided by the medicine types. Again, by examining the confidence intervals of the means, it was estimated whether there was a significant difference between the appointment durations of the appointments at the different locations.

First three appointments

When a patient is eligible for treatment at an external outpatient setting, the first three appointments are always given at the daycare department in the hospital to ensure safety and to make sure no unexpected reaction to the medicine occurs. This can be either in Zwolle or Meppel. Because of this, these first three appointments take longer than the other appointments. To see if the first three appointments differ from the other appointments in duration, the data was divided into the first, second and third appointment and all the other appointments. Since the year 2019 cannot give accurate information about whether an appointment is the first appointment, data from 2019 was excluded for this analysis. The appointments were excluded to the locations Zwolle and Meppel. At these locations, both the first three and the other administrations are provided. This way, the effect the location of administration has on the appointment duration was eliminated. Again, by examining the confidence intervals of the means, it was estimated whether there was a significant difference between the appointment durations.

4.1.3 Postal codes

To calculate the travel times and travel distances between the postal codes of the patients and the different locations of administration, the postal codes of patients were used. Both the four numbers and the two letters were used.

When observing the postal codes and the accompanying travel distances, we can see that a few patients live far away from Isala. This is because Isala provides specialised care. However, most patients do not live this far away from Isala. The travel distances by car from the postal codes to Isala Zwolle were determined. A boxplot was created to find the outliers in the data. The IQR rule was used to remove the outliers. All postal codes with a driving distance larger than 69.4 km to Isala Zwolle were excluded from the data. This resulted in the removal of 137 (0.04%) postal codes, resulting in a total of 3564 unique postal codes.

In the simulation model, the postal codes were split from the other data in the historical dataset. This way patients could be stratified from all the postal codes areas. However, this split only leads to correct results if there is no relation present between the postal codes, age, gender, and appointment duration. Therefore, the data was analysed to see if there was a relation between these variables. The age, gender and appointment duration were all separately plotted in a heatmap that showed the postal codes. After that, it was examined if patterns could be discovered in specific areas. For example, whether there were areas that stood out in, for example, a high age group. The Cramer's V between each of the three variables (age, gender, and appointment duration) and the postal codes were calculated to see if there was any correlation between the variables. A Cramer's V of 1 indicates there is a high correlation between the variables and a Cramer's V of 0 indicates there is no correlation between the variables.

4.2 Data analysis of the questionnaire

To calculate the carbon emissions caused by travel movements, data about the travel mode patients use to travel to and from the location of administration is necessary. A questionnaire was distributed among patients who were administered medication. In addition to the travel mode used by patients, the questionnaire provides insight into patients' preferences regarding the different locations.

4.2.1 Participants

Patients who visited the hospital (Zwolle and Meppel) and the currently opened external outpatient clinics (Kampen and Heerde) for the administration of parenteral medication received an invitation to participate in an online questionnaire. At Zwolle, the planners at the department distributed the invitations among the patients. While in Meppel, Heerde and Kampen, the nurses distributed the invitations.

4.2.2 Design

The surveys were developed in the online tool *Qualtrics* (Qualtrics, n.d.).Because all patients were Dutch, the language of the surveys was in Dutch. The questionnaires were divided into 4 sections. Before respondents could start with the questionnaires, informed consent needed to be given. After this was completed, the respondent was shown the first questions. If a respondent did not agree with the informed consent, the respondent was referred to the end of the questionnaire. The first questions were about the demographics of the patients. Next, questions were asked about the type of transportation used to travel to and from the location of administration. Then, questions were asked about the behavioural choices concerning the travel modes of the respondents. Lastly, the questions related to the preferences of the respondents for a location. The complete questionnaires for the hospitals and the external outpatient clinics can be found in Appendix A.

4.2.3 Data analysis

Missing data

The Multivariate Imputation by Chained Equations (MICE) technique was used to deal with the missing data. The package *mice* in R was used to perform the MICE (Buuren & Groothuis-Oudshoorn, 2011). For numeric missing data, the predictive mean matching method was used. For binary missing data, logistic regression was used. And for factor missing values with more than two unordered levels, polytomous regression was used. A single imputation was then imputed into the original dataset.

Nonresponse bias

The patients who responded and filled out the questionnaire might differ from the entire population, which could bias the results. This is called nonresponse bias (Berg, 2005). A t-test

was performed to see if there was a statistically significant difference between the characteristics of the two groups (gender, age, location of administration).

Data visualisation

After the missing values were imputed and the nonresponse bias was identified, data could be visualised. The data visualisation allowed patterns and relationships between the data to be recognised. For the data visualisation, Tableau Software 2023.3 (*Tableau 2023.3*, n.d.) was used. For visualisation purposes, we categorised the variables age, distance travelled maximum travel time, and the five factors (costs, convenience, physical exercise, sustainability, and travel time) into groups. This transformation allows for a more condensed representation of the data, while remaining the patterns present in the data. The five factors had a scale from 0 to 100, with 0 being hardly important and 100 being very important. Patients also had the option to not give a value to the factor, indicating that the factor was of non-importance. We converted this to a 0 to 5 scale, where 0 indicates non-importance, 1 hardly important and 5 very important. The scales are evenly distributed. This means that an increment on the 0 to 5 scale represents 20 values on the 0 to 100 scale. The ages were clustered into 5 age groups: young adult (18 – 34), early middle-age (35 – 49), middle-age (50 – 64), senior (65- 75) and older senior (75+). The distances travelled by patients were also clustered into 5 groups: very close (0 – 5), close (5 – 15), moderate (15 – 25), far (25 – 40) and very far (40+). The maximum travel time was clustered into groups of 30 minutes, since most patients defined their answer to the question in increments of 30 minutes.

4.3 Model design

This chapter outlines the developed simulation model. First, we describe the structure of the model by showing the conceptual model and the assumptions. Then, the Key Performance Indicators are described. After that, we show the input data of the DES model. Lastly, we explain the experiment design. The DES model was built in Plant Simulation version 16.1 (*Plant Simulation*, n.d.) A screenshot of the control panel of the simulation model can be found in Appendix C.

4.3.1 Conceptual model

Figure 7 illustrates the conceptual model of the simulation model. A more comprehensive flow chart of the appointment scheduling (grey coloured box) can be found in Appendix D.

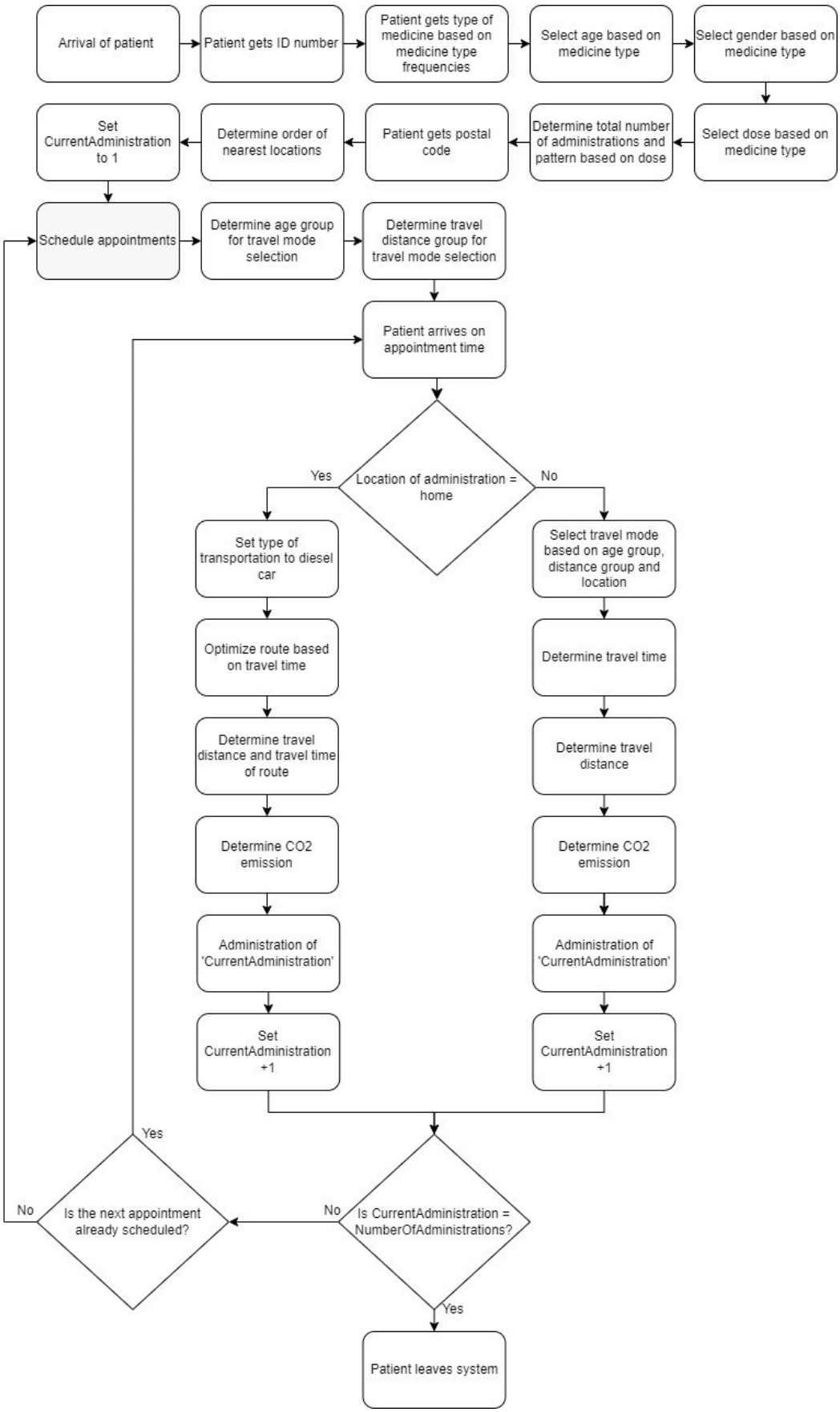

Figure 7: Conceptual model

Patients arrive at a certain time in the model. First, the patient gets an ID number, to easily track the patient within the model. After that, a medicine type is given to the patient based on predetermined probabilities. The age, gender, and the dose of the patient is selected by randomly selecting a patient from all the patients in the historical dataset that had their first appointment with the corresponding medicine type. The total number of administrations the patient needs to have and the days between these administrations were randomly selected from all the patients who had an administration with the corresponding medicine type and dose. This way, the patterns in the historical data are recreated. Then, the postal code of the patient is randomly selected from the list of all the postal codes that were present in the historical dataset. Based on the postal code, the order of nearest location of administration for the patient is determined. This is done by determining the travel distances by car from the postal code of the patient to the different locations of administration. Lastly, the current administration is set to 1.

After the arrival of the patient and the initialisation of its characteristics, the first appointments can be scheduled. In the case the patient can only be scheduled at a hospital, it is first checked whether the patient can be scheduled at the nearest hospital for the same day. If so, the patient receives its appointment time and moves to the location of administration. If not, it is checked whether the patient can be scheduled at the other hospital for the same day. If the patient can be scheduled for that day, the patient receives its appointment time and moves to the location of administration. If both hospitals do not have room for the patient that same day, it is checked whether the patient can be scheduled at the nearest hospital for the next day and otherwise it is checked whether the patient can be scheduled at the other hospital for the next day. This is done until the patient is scheduled or until maximum number of days a patient can be rescheduled is exceeded. The maximum number of days an appointment can be rescheduled is 3 days. When the maximum number of days a patient can be rescheduled was exceeded, we checked whether the patient could be scheduled a day earlier or later than the 3 days. In some cases, the patient could still not be scheduled. If this was the case, the simulation automatically stopped, and a warning message was given. This meant that with the current settings and capacity of the model we could not schedule and treat all patients, leading to an infeasible replication.

In the case the patient can be scheduled at all the locations, it is first determined whether a patient will be treated at home. This is done based on the probability for at home treatment and no at home treatment. When a patient will not be treated at home, it is checked whether a patient can be scheduled at the nearest location of administration for the same day. If the patient can be scheduled for that day, the patient receives its appointment time and moves to the location of administration. If not, it is checked if the patient can be scheduled at the second nearest location and so on. If the patient cannot be scheduled at any location for the same day, it is checked whether the patient can be scheduled at any of the locations in the order of nearest location for the next day. This is done until the patient is scheduled or until maximum number of days a patient can be rescheduled is exceeded.

If a patient has treatment at home, it is checked whether a patient can be scheduled on a route for the next day. If not, it is checked whether the patient can be scheduled any other day until the patient is scheduled or until the maximum number of days a patient can be rescheduled is exceeded. Each day, the optimal route is determined. If a patient could not be scheduled on a home route within the maximum number of days, we checked whether the patient could be scheduled at the nearest location, until the patient was scheduled.

After the first appointment is scheduled, a few subsequent appointments are planned, depending on the medicine type. The subsequent appointments are scheduled the same way as the first scheduled appointment. However, if there is no room for the patient on the same day, they can be scheduled on preceding days as well.

After the appointments are scheduled, the patient arrives at the appointment time at the location of administration. The type of transportation used by the patient is then determined based on the travel distance and age of the patient. Based on this, the travel distance, travel time and CO_2 emission can be determined as well. The time the patient is at the location equals the appointment duration. After the appointment, the patient leaves the location. Statistics about the patient and the appointment are stored (e.g. travel distance, travel time, age, travel mode and CO2 emission). It is then checked whether a patient has had all its appointments. If so, the patient leaves the system. If not, it is checked whether the next appointment is already scheduled or not. If so, the patient arrives at the appointment time at the corresponding location. If there is no appointment scheduled upfront, new appointments will be planned. After each day, the patient statistics of that day are combined and written as day statistics. This results in data about, for example, mean travel distances, average costs, average CO2 emissions, etc.

4.3.2 Assumptions

To deal with the complexity of the system, assumptions and simplifications were made. It was important that despite these assumptions and simplifications, the model still generates accurate and valid results that represent the real-world situation.

First, we assumed that patients only arrive between specific opening hours. These opening hours are general opening hours of the daycare department and not location related. This means, for example, that patients do not arrive during the night.

Secondly, the CO2 emission factor of the travel mode 'other', which represents a mobility scooter, is equal to the emission factor of an electric bicycle. In addition, we assumed that half of the patients who travelled by bicycle, travelled by an electric bicycle. Therefore, the emission factor for bicycles was set to 0.0015.

We assumed that patients cannot choose the location of their next appointment themselves. An appointment is scheduled for the patient at one of the opened locations. Patients are scheduled at the nearest location. If a patient cannot be scheduled at the nearest location, patients are scheduled at the second nearest location, and so on.

In addition, we assumed that the ratio *select patient group : total patient population* equals the ratio of the surface of the daycare department per patient group. This means that 32.06% of the size of the daycare department is used by our select patient group. Additionally, we assumed that the released capacity by transferring care from the hospital to the outpatient locations can be put to good use. This allowed us to calculate square meter prices for real estate costs.

To calculate the order of the nearest locations, the travel distance from the centre of the postal code to the exact location by car was used.

The protocol states that a patient cannot live more than 30 km or 35 minutes from Zwolle to be eligible for administration at home. We assumed that similar criteria are used in practice for the eligibility for administration at an external outpatient clinic. A patient cannot live more than 30 km or 35 mins from the external outpatient clinic.

Lastly, we assumed that on days when the external outpatient clinic is not used by the daycare department, it is used by another department. This allowed us to share the locations costs.

4.3.3 Key Performance Indicators

The model tries to assess the feasibility and impact on mobility and costs of transferring the administration of parenteral medication from the hospital to the external outpatient setting. Based on these impact factors, the following Key Performance Indicators (KPIs) were selected.

CO_2 emission
The CO_2 emission are the emissions emitted by the patients who travel to their appointments and the nurses who drive the home routes and travel to the external outpatient clinics. The CO_2 emission is defined in kg CO2. For illustration, 1 kg of CO2 is equivalent to producing 150 plastic bags, driving a car for 4.5 km, taking a 12-minute shower, or flying for 4 km (Hoeveel Is 1 Kilo CO2?, n.d.). It is therefore important to keep this in mind when interpreting the results. The KPI CO2 emission indicates the environmental impact of each scenario.

Costs
The costs include the real estate costs of the locations opened, the salary of the nurses and the costs of the car used for the home routes and to drive to the external outpatient clinics. The costs of the car include the costs for the lease contract and the diesel. All costs are expressed in euros.

Mean travel time
The mean travel time represents the average time a patient had to travel to their location of administration. This tells us something about whether people had a long or short journey to their appointment. A longer journey might negatively affect patient satisfaction. Therefore, it is an important factor to measure.

Mean travel distance
The mean travel distance represents the mean distance patients had to travel to their location of administration. As with the travel time, a longer journey might negatively affect patient satisfaction.

4.3.4 Input data

Postal codes
The 3564 unique postal codes were used as input data in the model. The postal codes consisted of 4 digits and 2 letters. The travel times and travel distances between the postal codes of the patients and the locations of administration were calculated. Within this research, we were not interested in Euclidian distances, because this does not represent the actual route a patient or nurse takes. Therefore, a distance matrix Application Programming Interface (API) was used. An API allows computer programs to communicate with each other. As a result, one program can send a request for data or services to another program, which then can respond back. A distance matrix API can determine the most efficient travel route between an origin and destination for a given travel mode and returns the travel distance and travel time. The centres of the coordinates of the postal codes were used as origin and the coordinates of the different locations of administrations as destination. The travel distances and travel times for the following modes of transport were calculated: car, bicycle, and public transport. To calculate the travel distances and travel times for the car, the Bing Maps API was used (Bing Maps API, n.d.). And to calculate the travel distances and travel times for the bicycle and public transport, the Google Maps API was used (*Google Maps API*, n.d.). To minimise the effects of traffic congestions on the travel distance and travel time, the APIs were called after 7 pm and before 6 am.

Appointment duration
For some of the locations, there was little appointment data available. For example, Kampen has only been open since 2023, resulting in only a few appointments. Therefore, to have more data to select appointment durations from, the locations were clustered into two categories. The three external outpatient clinics (Heerde, Kampen and Steenwijk) and the administration at home were clustered into the category *external outpatient*. The two hospitals (Zwolle and Meppel) were clustered into the category *hospital*.

We also found that the appointment duration is dependent on whether the appointment is one of the first three appointments or another appointment. Therefore, the appointment duration was clustered into two categories: first three appointments and the other appointments.

For some medicine types, we saw a change in the appointment duration over the years. Table 8 shows the change in appointment duration for these medicine types. For our model, we aim to reflect the current situation and the possible future most accurately. If the appointment duration has changed over the years, the older years will no longer properly represent the current time. Therefore, more recent data was used, and older data about the appointment durations was excluded. Table 8 shows which years were included as input data for the medicine types that changed in appointment duration over the years.

Table 8: Change in appointment duration per medicine type and years used

Medicine type	Change	Data used
Infliximab	Appointment duration decreased in 2022 and 2023	2022 + 2023
Abatacept	Appointment duration decreased in 2023	2023
Vedolizumab	Appointment duration decreased in 2023	2023
Azacitidine	Appointment duration decreased in 2023	2023
Nivolumab	Appointment duration decreased in 2022 and 2023	2022 + 2023

Dose

After analysing the historical data, it turned out that certain doses were not administered in the year 2023 anymore, only in the years before. This was presented to Jan Gerard Maring, the program director of the Connected Care Centre and a clinical pharmacologist. After this, it was decided to exclude doses that are no longer administered today and will no longer be administered in the future. Trial and compassionate use doses were also excluded. These doses represent only a small share of the total number of doses administered (17.4% of the appointments between January 2019 and November 2023) and it is uncertain whether these doses will be given in the future. Therefore, we excluded them as input data for our model. As a result, only relevant doses for administration in the current time and the future were included. Appendix B shows an overview of the doses that were included and excluded.

Frequency of administration

The days between two consecutive appointments differ per medicine type. Some medicine types are given every 2 weeks, while others are given every 4 weeks. For some medicines there does not exist solely one treatment guideline. To get the most accurate representation of reality, historical data about the days between two consecutive appointments per medicine type and dose was used. This way, the different patterns present in the dataset were recreated in the model. Since the days between the appointments depend on the medicine type and the dose, the frequencies of treatment were stratified by the different medicine types and doses.

Admission of patients

In practice, one patient can be admitted every 30 minutes per nurse, resulting in the admission of 2 patients per hour. The nurse admits the patient and starts the treatment. While the treatment is running via the IV, the nurse can admit the next patient. The model recreates this, whereby a new patient can be admitted per nurse every half hour for the hospital locations and the external outpatient clinics. Break time is excluded from the total hours during which a nurse can admit new patients. In practice, nurses working at an external outpatient clinic take their 15-minute breaks before and after the time patients can be admitted. However, they take their 30-minute break at the external outpatient clinic during the time patients can be admitted. Therefore, 30-minutes are extracted from the total time new patients can be admitted at an external outpatient clinic. For the home routes, in practice, nurses take their breaks before and

after they start their route and while driving from one patient to another. Therefore, 0-minutes break time is extracted from the total time of a home route. The hospital in Zwolle works with 2 shifts, which partly overlap. During a period of 6 hours (10 am – 4 pm), a double number of nurses work at the same time. This allows double the number of patients to be admitted per hour. Therefore, a patient can be admitted every 15 minutes. However, the nurses also take breaks, which influences the number of patients being admitted. We assume that nurses working the same shift take a break at the same time. Nurses who work the first shift take a 15-minute break before 10 am and a 30-minute and 15-minute break between 10 am and 4 pm. Nurses who work the second shift take a 15-minute and 30-minute break between 10 am and 4 pm and a 15-minute break after 4 pm. As a result, during a period of 1.5 hours, half of the nurses take a break between 10 am and 4 pm. This means they no longer work with the double number of nurses between this time. On average, this results in a new patient being admitted every 24 minutes by 2 nurses of which one works the first shift, and one works the second shift. We used every 24 minutes as input data for our model for the admission of patients at Zwolle.

Eligibility administration at an external outpatient setting

For patients to be eligible for administration at home, a patient cannot live more than 30 km or 35 minutes from the hospital in Zwolle. In addition, the infusion time of the medicine cannot be more than 30 minutes. For the external outpatient clinics, a similar criterion was used. For a patient to be eligible for administration at an external outpatient clinic, the patient cannot live more than 30 km or 35 mins from the external outpatient clinic.

Carbon dioxide emission

The CO2 emissions caused by the travel movements of patients and nurses are tracked. To calculate the CO2 emissions, the following formula was used:

$$CO_2\ emission = travel\ distance * emission\ factor$$

The travel distance is the distance travelled in km. The emission factor is a factor that quantifies the average CO2 output per unit of distance, in this case km. The size of the factor depends on the type of transportation used. CO2 emission is measured in kg. The emission factors provided by the Green Deal were used. The Green Deal provides one uniform list of CO2 emission factors per travel mode for The Netherlands. The website is managed by Rijkswaterstaat on behalf of the Ministry of Economic Affairs and Climate (Lijst Emissiefactoren - Personenvervoer, 2024). Table 9 gives an overview of the emission factors per type of transportation. The Green Deal list divided the cars into three different weight classes: small, medium, and large. Since we have no information about the weight class of the cars used by patients, we took the average of the emission factors of the three different classes. For the hybrid cars, we did not have information on the type of fuel used by the patients. Therefore, we took the average of the emission factors of the hybrid diesel, hybrid gasoline and hybrid plug-in gasoline car. The bicycle has an emission factor of 0, while the electric bicycle has an emission factor of 0.003. We assumed that half of the cycling patients would use an electric bicycle. Therefore, the emission factor for bicycles was set to 0.0015. For the taxies, we did not have information about the type of fuel of the car. Therefore, we used the 'Unknown fuel type' emission factor as the emission factor for the taxi. Patients who indicated to travel by other means of transportation, came by mobility scooter. We assumed that the emission factor for a mobility scooter is equal to an electric bicycle. Therefore, the emission factor for the travel mode 'Other' was set to 0.003.

Table 9: Emission factors per travel mode

Travel mode	Emission factor
Gasoline car	0.199
Diesel car	0.183
Hybrid car	0.139
Electric car	0.067
Bicycle	0.0015
Train	0.003
Taxi	0.193
Other	0.003

Travel mode probabilities

After visualising the results of the questionnaire, we saw that the type of transportation used by a patient depends on the distance to the location of administration and the age of the patient. Within the model, the probabilities of a patient selecting a certain travel mode depends on the travel distance and age of the patient as well. The travel distances and ages were each clustered into the same five groups as used in the questionnaire, see Table 10 and Table 11. The distances used to determine into which distance group a patient fell, are the travel distances from the patient's postal code to the different locations by car. The distances by car were chosen, because this travel mode was mostly used by the patients in the questionnaire.

Table 10: Age groups

Age group	Age
Young adult	18 - 34
Early middle age	35 - 49
Middle age	50 - 64
Senior	65 - 75
Older senior	75 +

Table 11: Distance groups

Distance group	Distance
Very close	0 – 5
Close	5 – 15
Moderate	15 – 25
Far	25 – 40
Very far	40 +

Table 12 shows the probability of a patient being assigned to a certain travel mode. The probabilities were based on the results of the questionnaire.

Table 12: Probability of a patient receiving a certain travel mode

	Young adult					Early middle age					Middle age				
	Very close	Close	Moderate	Far	Very far	Very close	Close	Moderate	Far	Very far	Very close	Close	Moderate	Far	Very far
(Electric) bicycle	0.33	0.00	0.00	0.00	0.00	0.00	0.17	0.00	0.00	0.00	0.14	0.00	0.00	0.00	0.00
Diesel car	0.00	0.25	0.00	0.00	0.00	0.00	0.17	0.29	0.50	0.00	0.14	0.00	0.00	0.00	0.22
Electric car	0.00	0.00	0.00	0.00	0.00	0.50	0.17	0.00	0.00	0.00	0.00	0.08	0.00	0.00	0.00
Gasoline car	0.67	0.50	0.67	1.00	1.00	0.50	0.50	0.57	0.00	1.00	0.71	0.83	0.67	0.83	0.78
Hybrid car	0.00	0.25	0.00	0.00	0.00	0.00	0.00	0.14	0.50	0.00	0.00	0.00	0.33	0.17	0.00
Other	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.08	0.00	0.00	0.00
Taxi	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Train	0.00	0.00	0.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

	Senior					Older senior				
	Very close	Close	Moderate	Far	Very far	Very close	Close	Moderate	Far	Very far
(Electric) bicycle	0.29	0.00	0.00	0.00	0.00	0.25	0.00	0.00	0.00	0.00
Diesel car	0.14	0.14	0.14	0.14	0.00	0.00	0.00	0.00	0.00	0.33
Electric car	0.00	0.00	0.00	0.14	0.00	0.00	0.25	0.00	0.00	0.00
Gasoline car	0.43	0.71	0.78	0.57	0.60	0.75	0.75	0.67	0.00	0.67
Hybrid car	0.14	0.14	0.00	0.00	0.20	0.00	0.00	0.33	1.00	0.00
Other	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Taxi	0.00	0.00	0.14	0.14	0.20	0.00	0.00	0.00	0.00	0.00
Train	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Number of newly arriving patients

New patients are generated within a certain time interval. In the historical dataset, we saw an increasing trend in the number of new patients. When excluding the decrease in patients from 2020-2021 and the extra increase in patients from 2021-2022, to eliminate the effect caused by the COVID-19 lockdowns, the increase in newly arriving patients is 10.2% per year. The number of new patients per month is not a constant number and differs over the months, with a high number of patients arriving in some months and a low number of patients arriving in other months. To keep the pattern of patients over the different months, it was decided to determine the number of patients per month instead of over a whole year. For example, to calculate the number of patients in month 1 in 2024, the number of patients in month 1 in 2023 is increased with 10.2%. The number of new patients that arrived each day was then divided by the number of days the daycare department was opened that month. Which led to a constant time interval between newly arriving patients per day, based on the total number of patients arriving per month. It was also checked whether patterns in arrival could be found for certain days of the month. This was done by determining the number of patients per day for 4 consecutive months. The months of August, September, October, and November were chosen because there were no major holidays during these months that could have affected the number of newly arriving patients. The year 2022 was chosen, because this year had no missing data and COVID-19 had no longer an effect on the newly arriving patients. Table 13 shows the number of patients over the days of the weeks over these four months.

Table 13: Number of new patients per day of the week

	Number of new patients																				
	August 2022					September 2022					October 2022					November 2022					
	Week																				
Day	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	Average
Monday	2	1	0	4	4		7	6	2	1	8	2	7	5	4		2	1	2	1	*3.69*
Tuesday	2	1	2	0	3		3	2	2	6	3	6	4	2		2	3	6	4	3	*3.54*
Wednesday	3	1	1	2	2		3	1	4	3	2	1	6	5		5	7	3	3	0	*3.58*
Thursday	1	6	1	2		3	2	4	1	6	1	3	2	1		0	4	4	0		*2.38*
Friday	3	3	1	5		4	1	1	3	5	3	5	7	1		5	3	3	5		*3.54*

A one-way ANOVA test was performed to determine whether there was a statistically significant difference between the means of the days of the week. Table 14 shows the results of the ANOVA test. The p-value is bigger than 0.05, which means there is no statistically significant difference between the means of the days the weeks.

Table 14: One-way ANOVA test days of the week

	Df	*Sum Sq*	*Mean sq*	*F value*	*Pr (>F)*
Day	4	10.4	2.594	0.678	0.609
Residuals	83	317.6	3.827		

Costs

Appendix I shows an overview of the different costs. The costs are divided into 5 categories: general, hospital, external outpatient clinic, home care and home route costs.

Room size per location

To calculate the costs per location, information about the sizes of the rooms utilised by the daycare department per location is required, as real estate costs are expressed in euro per square meter. In Zwolle and Meppel, the daycare department treats a larger group of patients than solely the select patient group we focus on in our research. Therefore, the sizes of these locations were adjusted based on the percentages of the sizes of the two patient groups. Between January 2019 and November 2023, a total of 13610 patients visited the daycare department, of which 4364 are patients we focus on in our research. This results in a total of 32.06% of the total patient population at the daycare department. Table 15 shows the sizes of the different locations used by the daycare department, before and after correction of patient group sizes.

Table 15: Sizes in m² per location

Location	**Size in m²**	**Size in m² for selected patient group**
Zwolle	818.94	262.55
Meppel	70.00	22.44
Heerde	27.44	27.44
Kampen	31.72	31.72
Steenwijk	29.58	29.58

Opening hours

Table 16 shows an overview of the opening hours of the different locations and the working hours of the nurses. The opening and closing times are the times during which appointments can be scheduled. The daycare department is closed during the weekends and public holidays. Nurses start and end their days at different times. The hospital in Zwolle works with 2 shifts. Shift 1 starts at 7:30 and ends at 16:00. Shift 2 starts at 10:00 and ends at 18:30. The collective labour agreement describes that a nurse has 3 breaks: 15 minutes in the morning, 30 minutes for lunch and 15 minutes in the afternoon. This results in a total of 1 hour for breaks. The break time is considered as personal time and is therefore not included in the calculation for the nurse's salary costs per day.

During a shift, 10 nurses work in Zwolle at the daycare department, of which 8 are specialised oncology nurses and 2 are general nurses. These nurses are available for the entire patient population at the daycare department. Since we only focus on a select group of patients, we do not have the full amount of 10 nurses to our availability. Our patient group needs specialised nurses, of which there are 8 available. The select patient group we focus on consist of 32.06% of the total patient population, which results in a total of 3 nurses available in Zwolle per shift for our select patient group. There are two shifts in a day, resulting in 6 nurses a day. In Meppel, there are 2-3 nurses available each day, resulting in 1 nurse available for our select patient group. In Kampen and Heerde, there is one nurse available for our patient group every day the external outpatient clinic is open. For the administration at home, there is one nurse available every day, with one extra nurse on Thursdays. Table 16 shows an overview of the number of nurses available per location.

Table 16: Opening hours, shifts and number of nurses per location

Location	Opening time	Closing time	Start shift nurse	End shift nurse	Number of nurses per day
Zwolle	8:15	18:30	7:30 / 10:00	16:00 / 18:30	6
Meppel	8:30	16:30	8:00	16:30	1
Heerde	9:15	15:30	8:00	16:30	1
Kampen	9:15	15:30	8:00	16:30	1
Home	8:00	16:00	7:30	16:30	2
Steenwijk	9:15	15:30	8:00	16:30	1

Medicine types

The first time a patient enters the model, a specific medicine type is assigned to the patient. The probabilities for assigning a specific medicine type to a patient are based on the frequencies of the various medicine types present in the historical dataset. Since the data of 2019 does not give accurate information about newly arriving patients and the year 2023 is not complete, the years 2019 and 2023 were excluded from the calculation. Table 17 shows the probabilities per medicine type.

Table 17: Probabilities medicine types (2020-2022)

Medicine type	Probability
Bortezomib	0.04
Trastuzumab	0.06
Bevacizumab	0.07
Nivolumab	0.1
Azacitidine	0.02
Pembrolizumab	0.22
Blinatumomab	0
Carfilzomib	0.01
Zoledroninezuur	0.28
Daratumumab	0.04
Vedolizumab	0.04
Abatacept	0.01
Immunoglobulins	0.02
Infliximab	0.09

Number of appointments scheduled upfront
A few appointments are scheduled upfront. The number of appointments that are scheduled upfront depends on the medicine type. Every 3 months, there is a medical check with the healthcare professional. The appointments between these checks are scheduled upfront. For example, if a patient needs an appointment every 3 weeks, a total of 6 appointments are scheduled upfront.

Optimal home route
The travelling salesman problem (TSP) algorithm was used to find the optimal home route. Within the TSP, the travelling salesman must visit several cities and must start and end at a starting point. The distances between the cities are known and described in a distance matrix. TSP solves this problem and returns the shortest possible route (Jünger et al., 1995).The problem of optimising the home route is like the TSP. Nurses start and end at their route at the hospital in Zwolle. During the route they must visit several patients (cities). The distances between the patients are known, by calculating the distances between the postal codes. This way, the route that returns the shortest possible route can be determined. To calculate the distances between all the postal codes of the patients, only the four digits of the postal codes were used.

4.3.5 Validation and verification
To ensure the correctness and the accuracy of the model, the verification and validation of the model is an important step.

Both white-box and black-box verification was performed. White-box verification was performed by checking the flow of the model. During the development of the model, the model was debugged several times. Each component of the model (administration at the different locations, appointment scheduling and arrival of the patient) was debugged separately, and the animation was observed. The journey of a patient throughout the system was tracked, from the arrival of the patient till the departure from the system. For example, it was checked if a patient was scheduled correctly and at the nearest location. For the home routes, it was checked if the optimisation of the route led to the shortest travel time. In addition, it was checked whether the separate costs were calculated correctly and if they were summed up correctly. Black-box verification was performed by changing the settings of the model and checking whether the expected outcomes were achieved. Costs and CO_2 emissions were set to 0, to see if the total costs and total emissions changed to 0 as well.

We validated the model by consulting the project leader of the Medication@home project within Isala, who had in-depth knowledge of the simulated care pathways. During this session, the model was explained and reviewed in depth by going through the model and the associated conceptual model step by step. Besides the validation of an expert, the outcomes of the simulation model were compared to the historical dataset. A t-test was performed to see if there was a statistically significant difference between the ages and the total number of administrations of the simulation outcomes and the historical dataset. A chi-squared test was performed to determine if there was a statistically significant difference between the ratio men and female in the two sets. QQ-plots and boxplots were created to visualise the spread of the appointment duration in the two sets. For the results of the statistic tests and a more detailed explanation of the validation process, we refer to Appendix E. Based on the comparison between the historical dataset and the simulation model, we can conclude that the patient group in the simulation model aligns with the patients and their characteristics of the historical dataset.

4.3.6 Experimental design

This section describes the experiments performed. Table 19 shows all the experiments and their configurations. For all experiments, a warm-up period of 1095 days was used, and 100 independent replications were run.

Current situation [experiment 1]

In the current situation, the hospitals Zwolle and Meppel and the external outpatient clinics Heerde and Kampen are opened. Heerde is open on Wednesday and Kampen is open on Monday and Friday. Steenwijk is not open for administration. Each day, there is one home route, with one extra route on Thursdays. In Zwolle, six nurses work per day, while in Meppel, Heerde, and Kampen, one nurse works per day at each location. Additionally, two nurses cover the home routes. One works daily, while the other only works on Thursdays. Only the medicines described in Table 2 in Section 2.1.4. can be administered at an external outpatient setting. The increase in newly arriving patients is 10.2% per month. Isala nurses work at all the locations. The effect of the Minute study (an ongoing study researching the effects of reducing the infusion time of the medicines Nivolumab, Pembrolizumab, Bevacizumab and Trastuzumab by 20 minutes) on the appointment duration is not considered. Experiment 1 is the experiment that represents the current situation.

Steenwijk open [experiment 2 – 6]

In these five experiments, Steenwijk is open for one day during the work week (Monday - Friday). Each experiment represents a different day of the week. One nurse from Isala works at the external outpatient clinic. We assumed that the opening hours of Steenwijk are the same as the opening hours of the other external outpatient clinics.

Home care Heerde [experiment 7 and 15]

In this experiment, the administration in Heerde is no longer carried out by an Isala nurse, but by an external party, a home care organisation. The hourly wage of a specialised home care nurse is higher than an Isala nurse. The costs of real estate of the external outpatient clinic Heerde are paid by the home care organisation and then charged to Isala. Since the service is now provided by the home care organisation, the trip from Zwolle to Heerde and back is omitted when calculation the total emissions. In experiment 15, the administration is outsourced to the home care organisation as well, but in this experiment the costs of real estate and the salary of the nurses are equal to the costs for Isala.

Minute study [experiment 8]

Currently, an ongoing study called the Minute study is researching the effects of reducing the infusion time of the following medicines by 20 minutes: Nivolumab, Pembrolizumab, Bevacizumab and Trastuzumab. In experiment 8, we reduced the infusion time of these medicines with 20 minutes. Resulting in an infusion time of 10 minutes.

Eligible outpatient [experiment 9]

In the current situation, not all medicines are eligible for administration at an external outpatient setting. In experiment 9, we made the medicines Vedolizumab, Abatacept, and Infliximab eligible for outpatient administration as well.

Increase and decrease number of new patients [experiment 10 and 25-28]

Based on the historical data, we determined that the annual growth rate of the number of newly arriving patients 10.2% per year is. Isala determined an average demographic growth rate based on diagnosis of 2% between the years 2019 and 2030. The specific growth rate differs per diagnoses. Since we do not have any data about the diagnoses of patients, we chose not to use this average percentage for our base experiment (experiment 1). However, to still see what the

effect of a lower growth rate in patients per year is on the outcome measures, we included this in an experiment. Experiment 10 represents the current situation, but with an annual growth rate of 2%. In experiments 25- 28 we increased the growth rate and set it to 12%, 15%, 17.5% and 20%, respectively, to see under which growth rate the current capacity can still treat all patients.

CBS travel mode probabilities [experiment 24]

In experiment 24, instead of the data from the questionnaire, data from CBS was used to determine the probability of selecting a certain travel mode. For the different distance groups, data about the percentages of travel modes used to travel to and from work by distance class in 2016 was used (Centraal Bureau Statistiek, 2018). For the different age groups, data about the percentages of travel modes used to travel to and from work by age groups in 2022 was used (Centraal Bureau Statistiek, 2022a). In our questionnaire, no patient walked to their appointment. However, in the data published by CBS, walking was one of the travel modes. Therefore, we included this new travel mode in our model. Table 18 shows the probabilities for travel mode selection based on the data published by CBS.

Table 18: Probabilities travel mode selection based on CBS data

	Young adult					Early middle age					Middle age				
	Very close	Close	Moderate	Far	Very far	Very close	Close	Moderate	Far	Very far	Very close	Close	Moderate	Far	Very far
(Electric) bicycle	0.24	0.07	0.00	0.00	0.00	0.22	0.07	0.00	0.00	0.00	0.25	0.08	0.00	0.00	0.00
Diesel car	0.03	0.04	0.04	0.04	0.04	0.03	0.04	0.05	0.05	0.05	0.03	0.04	0.05	0.05	0.05
Electric car	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Gasoline car	0.64	0.80	0.84	0.84	0.84	0.68	0.85	0.91	0.91	0.91	0.64	0.84	0.91	0.91	0.91
Hybrid car	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other	0.01	0.01	0.01	0.01	0.01	0.02	0.02	0.01	0.01	0.01	0.02	0.02	0.01	0.01	0.01
Taxi	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Train	0.03	0.08	0.10	0.10	0.10	0.01	0.02	0.03	0.03	0.03	0.01	0.02	0.02	0.02	0.02
Walking	0.04	0.00	0.00	0.00	0.00	0.04	0.00	0.00	0.00	0.00	0.05	0.00	0.00	0.00	0.00

	Senior					Older senior				
	Very close	Close	Moderate	Far	Very far	Very close	Close	Moderate	Far	Very far
(Electric) bicycle	0.38	0.13	0.01	0.01	0.01	0.38	0.14	0.01	0.01	0.01
Diesel car	0.03	0.04	0.05	0.05	0.05	0.03	0.04	0.05	0.05	0.05
Electric car	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Gasoline car	0.53	0.80	0.92	0.92	0.92	0.52	0.80	0.93	0.93	0.93
Hybrid car	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.00	0.00
Taxi	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Train	0.00	0.01	0.02	0.02	0.02	0.00	0.00	0.01	0.01	0.01
Walking	0.05	0.00	0.00	0.00	0.00	0.06	0.00	0.00	0.00	0.00

Closing external outpatient locations [experiments 11 –17, 20 – 23, and 29 – 31]

In experiments 11 – 17, 20 -23 and 29 – 31, we closed several external outpatient locations. In experiment 14, all administration at an external outpatient setting was stopped (Heerde, Kampen and Home). In the other experiments one or more locations were closed

Closing an external outpatient clinic or stopping the administration at home, results in a nurse being available to work at another location. However, for most locations, closing the location does not result in a nurse being available to work at another location full-time. This is because these locations are not open all week. For example, closing external outpatient clinic Heerde will only lead to 1 extra nurse on Wednesdays. As this makes the model too complex, it has been

decided to not automatically transfer released capacity in the form of nurses to other locations. To still evaluate the impact of the released capacity, experiments where additional nurses were working in Zwolle were run. In Zwolle there are two shifts per day, which partly overlap. This affects the number of patients that can be admitted, and it affects when nurses take their breaks. Therefore, to correctly model this, only multiples of 2 nurses (a nurse who works the first shift and a nurse who works the second shift) can be working in Zwolle. Experiments where 6 and 8 nurses were working in Zwolle were run. In some experiments, this increase of 2 nurses will be close to the size of the released capacity. For example, closing all external outpatient clinics and stopping the home routes leads to released capacity in the form of nurses. One nurse will be available full-time, and one nurse will be available 3 days a week to work at another location. This leads to an increase of 1.6 nurses working in Zwolle. However, it is up to Isala to determine whether it is possible to hire the additional nurses in Zwolle and therefore if these experiments are feasible in practice.

Fewer nurses Zwolle [experiment 18]

In experiment 18 we reduced the number of nurses in Zwolle from 6 to 4. This scenario could be the case when not only our select patient group increases over the years, but when also the other patient groups treated at the day care treatment department increases but at a faster rate. A larger group of patients must then be treated with the same number of nurses, which means that there are fewer nurses available for our select patient group.

Table 19: Experiments

Experiment	*Number of nurses*						*Home care Heerde*	*Minute study*	*All eligible outpatient*	*Travel modes based on*	*Increase new patients per year*
	Zwolle	*Meppel*	*Heerde*	*Kampen*	*Home*	*Steenwijk*					
1	6	1	1	1	2	0	No	No	No	Questionnaire	10.2%
2	6	1	1	1	2	1	No	No	No	Questionnaire	10.2%
3	6	1	1	1	2	1	No	No	No	Questionnaire	10.2%
4	6	1	1	1	2	1	No	No	No	Questionnaire	10.2%
5	6	1	1	1	2	1	No	No	No	Questionnaire	10.2%
6	6	1	1	1	2	1	No	No	No	Questionnaire	10.2%
7	6	1	1	1	2	0	Yes	No	No	Questionnaire	10.2%
8	6	1	1	1	2	0	No	Yes	No	Questionnaire	10.2%
9	6	1	1	1	2	0	No	No	Yes	Questionnaire	10.2%
10	6	1	1	1	2	0	No	No	No	Questionnaire	2%
11	6	1	0	1	2	0	No	No	No	Questionnaire	10.2%
12	6	1	1	0	2	0	No	No	No	Questionnaire	10.2%
13	6	1	0	0	2	0	No	No	No	Questionnaire	10.2%
14	6	1	0	0	0	0	No	No	No	Questionnaire	10.2%
15	6	1	1	1	0	0	No	No	No	Questionnaire	10.2%
16	6	1	1	0	0	0	No	No	No	Questionnaire	10.2%
17	6	1	0	1	0	0	No	No	No	Questionnaire	10.2%
18	4	1	1	1	2	0	No	No	No	Questionnaire	10.2%
19	6	1	1	1	2	0	Yes	No	No	Questionnaire	10.2%
20	8	1	0	0	0	0	No	No	No	Questionnaire	10.2%
21	8	1	1	1	0	0	No	No	No	Questionnaire	10.2%
22	8	1	1	0	0	0	No	No	No	Questionnaire	10.2%
23	8	1	0	1	0	0	No	No	No	Questionnaire	10.2%
24	6	1	1	1	2	0	No	No	No	CBS	10.2%
25	6	1	1	1	2	0	No	No	No	Questionnaire	12%
26	6	1	1	1	2	0	No	No	No	Questionnaire	15%
27	6	1	1	1	2	0	No	No	No	Questionnaire	17.5%
28	6	1	1	1	2	0	No	No	No	Questionnaire	20%
29	8	1	0	1	2	0	No	No	No	Questionnaire	10.2%
30	8	1	1	0	2	0	No	No	No	Questionnaire	10.2%
31	8	1	0	0	2	0	No	No	No	Questionnaire	10.2%

Run length and number of replications

We ran the model for 2555 days, including 1095 days of warm-up period, starting on January 1, 2021. This resulted in 4 years of generated outcomes (2024 – 2027). Running the model for more years reduces the accuracy of the outcomes, as several parameters and variables become more and more uncertain in the future. For example, the percentage of patients who travel by an electric car might increase in the future or the patient growth might change. On top of that, in our model we cannot change the number of nurses working at each location between the years. The number of nurses working at the department might change in the future, resulting in different capacity available. For our KPIs, at least 10 replications were needed until the width of the confidence interval, relative to the average, was smaller than 5%, see Appendix F. However, instead of 10 replications, we chose to run 100 replications for each experiment in total. Running 100 replications led to smaller confidence intervals for the KPIs and ensured a more accurate representation of the infeasibility. Only running 10 replications results in a small sample, running more replications increases the sample and reduces the likelihood of random variation in the (in)feasibility. Appendix F explains the selection of the warm-up period and the number of replications in more detail.

4.3.7 Summary

Table 20 summarises the input data of our model and what type of data analysis was used to collect this data.

Table 20: Input data for DES per data analysis

Data analysis	***Input data model***	***Used for the calculation of …***
Questionnaire analysis	Travel mode probabilities	CO2 emissions
Historical data analysis	Postal codes	Travel distance
		Travel time
		CO2 emissions
		Optimal home route
	Medicine type	Eligibility administration at an external outpatient setting
		Number of appointments scheduled upfront
	Dose	
	Appointment duration	
	Patient growth	
	Number of newly arriving patients	
	Number of days rescheduled	
Context analysis	Opening hours and days	
	Costs	
	Room size per location	
	Number of nurses per location	
	Working hours nurses	

5. Results

In this chapter, the results of the data analyses and the simulation model are described. Section 5.1 shows the results of the data analysis of the historical dataset. In Section 5.2, we show the results of the data analysis of the questionnaire. Lastly, Section 5.3 shows the results of the simulation model.

5.1 Data analysis of the historical dataset

5.1.1 Dataset

The dataset contains of 4364 oncology and IMID patients, who had an administration at the daycare department between 2019 and 2023. Together, they had a total of 53 723 appointments. The average age was 63 years old. Of the patients, 57.7% were female and 42.3% male. The locations Zwolle and Meppel were opened during all the years (starting from 2019). External outpatient clinics Heerde and Kampen opened in 2022 and 2023 respectively. The administration at home has been offered since 2020. The percentage of patients visiting the locations Zwolle, Meppel, Kampen, Heerde and at home were 63.1%, 23.5%, 1.9%, 1.2% and 10.2%, respectively, in the year 2023. Thus, most of the appointments were scheduled in Zwolle.

5.1.2 Number of new patients

There were no seasonal fluctuations in the number of new patients. The average increase in the number of patients per month from January 2020 until October 2023 is 3.67% per month. Based on the 3.67% increase, we assumed that the number of patients in November 2023 and December 2023 will be 76 and 78 respectively. Table 21 shows the number of patients per month, including the estimation of the months November and December in 2023. The number of patients decreased a bit between 2020 and 2021. This might be due to the lockdowns caused by COVID-19 in 2020 and 2021, when care that was given at the daycare department was scaled down. During this time, patients might have postponed treatment due to COVID-19 (Meijer et al., 2021). After the lockdowns caused by COVID-19 in 2022, the number of newly arriving patients increased again.

Table 21: Number of new patients who start treatment over the months (estimation of 2023) (all medicines)

	Number patients				***Absolute increase***			***Increase percentage***		
Month	*2020*	*2021*	*2022*	*2023*	*2020-2021*	*2021-2022*	*2022-2023*	*2020-2021*	*2021-2022*	*2022-2023*
1	62	47	76	76	-15	29	0	-24.2	61.7	0
2	57	54	57	57	-3	3	0	-5.3	5.6	0
3	41	53	78	87	12	25	9	29.3	47.2	11.5
4	29	51	60	53	22	9	-7	75.9	17.6	-11.7
5	34	31	69	69	-3	38	0	-8.8	122.6	0
6	49	59	58	86	10	-1	28	20.4	-1.7	48.3
7	56	53	68	70	-3	15	2	-5.4	28.3	2.9
8	63	47	49	78	-16	2	29	-25.4	4.3	59.2
9	59	53	70	69	-6	17	-1	-10.2	32.1	-1.4
10	76	50	78	73	-26	28	-5	-34.2	56	-6.4
11	63	66	66	76	3	0	10	4.8	0	15.2
12	50	67	53	78	17	-14	25	34	-20.9	47.2
Total	639	631	782	872	-8	151	90	-1.3	23.9	11.5

5.1.3 Number of appointments

There were no seasonal fluctuations in the number of appointments. The average increase in the number of appointments per month from January 2019 until October 2023 is 0.81%. Based on this increase of 0.81%, we assumed that the number of appointments in November 2023 and December 2023 will be 1104 and 1113, respectively. Table 22 shows the number of appointments over the months, including the estimation of the months November and December

in 2023. We can see an increasing trend in the number of appointments. However, the increase in 2022 is exceptionally high. This might also be due to the lockdowns caused by COVID-19 in 2020 and 2021. When excluding the increase in appointments from 2021-2022, the average increase in number of appointments over the years is 4.4% per year.

Table 22: Number of appointments over the months (estimation of 2023) (all medicines)

	Number appointments					***Absolute increase***				***Increase percentage***			
Month	*2019*	*2020*	*2021*	*2022*	*2023*	*2019-2020*	*2020-2021*	*2021-2022*	*2022-2023*	*2019-2020*	*2020-2021*	*2021-2022*	*2022-2023*
1	872	899	843	942	1078	27	-56	99	136	3.1	-6.2	11.7	14.4
2	780	818	809	875	910	38	-9	66	35	4.9	-1.1	8.2	4
3	822	726	964	1010	1147	-96	238	46	137	-11.7	32.8	4.8	13.6
4	848	728	846	947	939	-120	118	101	-8	-14.2	16.2	11.9	-0.8
5	870	816	799	1022	1066	-54	-17	223	44	-6.2	-2.1	27.9	4.3
6	772	868	893	1030	1096	96	25	137	66	12.4	2.9	15.3	6.4
7	841	955	882	1010	1022	114	-73	128	12	13.6	-7.6	14.5	1.2
8	793	831	906	1037	1118	38	75	131	81	4.8	9	14.5	7.8
9	807	848	880	1078	1027	41	32	198	-51	5.1	3.8	22.5	-4.7
10	826	927	885	978	1095	101	-42	93	117	12.2	-4.5	10.5	12
11	799	918	909	1100	1104	119	-9	191	4	14.9	-1	21	0.36
12	820	957	978	993	1113	137	21	15	20	16.7	2.2	1.5	2.01
Total	9850	10291	10594	12022	12715	441	303	1428	693	4.5	2.9	13.5	5.8

5.1.4 Appointment duration

Figure 8 shows the appointment duration of all the medicine types. Table 23 shows the accompanying mean, standard deviation and 95% confidence interval. The density plot has several peaks. This may be explained by the fact that this plot is not divided into different medicine types, which might all have their own distribution of appointment duration. The plot has a few outliers (high appointment durations). These data points were verified by an expert in the hospital (program director of the Connected Care Centre and clinical pharmacist), to see if these data points were valid observations. In practice, a patient can be scheduled for the entire day to reserve a bed or chair. However, the actual administration of the medicine will not take the entire day. Because we look at capacity, we do include these reservations in our model because another patient cannot be scheduled during this reservation. Based on this, we verified that these data points are valid observations and were therefore not removed from the data.

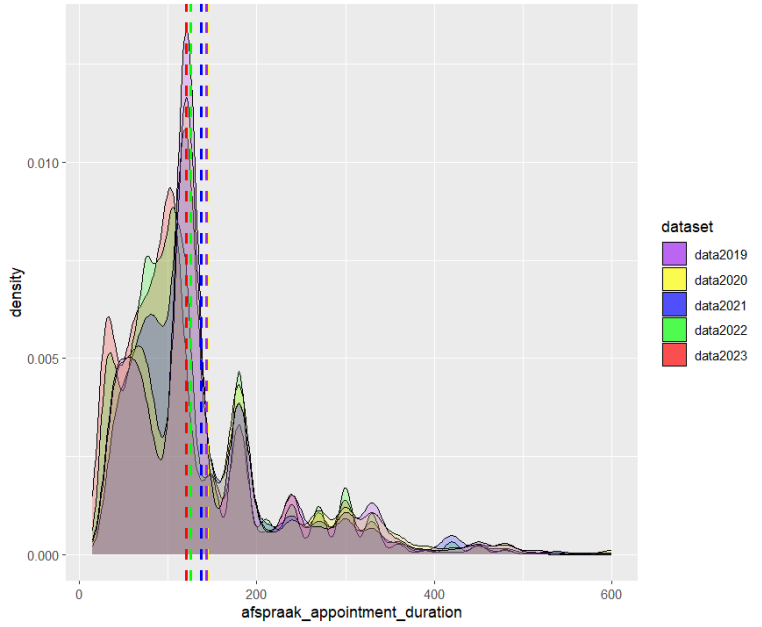

Figure 8: Density plot of appointment duration (all medicines)

Table 23: Mean, SD, 95% CI of appointment duration (all medicines)

			95% CI	
Year	Mean	Standard deviation	Lower CI	Upper CI
2019	143.6	93.4	92.2	95.8
2020	144.5	96.0	93.7	96.3
2021	137.5	88.0	86.8	89.2
2022	126.0	84.9	83.8	86.0
2023	121.0	85.0	83.9	86.1

Medicine types

Since the different medicine types have different appointment durations, we plotted each medicine type separately in a density plot. The separate density plots of the appointment duration for each medicine type all have their own distribution of appointment duration. For the medicines Infliximab, Abatacept, Vedolizumab, Azacitidine and Nivolumab, the appointment duration decreased over the years. The density plots and the median, mean, and standard deviation of the appointment duration per medicine type can be found in Appendix E.

Location of administration

The appointment durations for all medicine types at the external outpatient setting (Heerde Kampen and home) are similar and are shorter compared to the appointment durations at Zwolle and Meppel. This means that the appointment duration depends on whether the medicine is administered in an external outpatient setting. As an example, Table 24 shows the mean and 95% confidence interval of the appointment duration of Trastuzumab per location of administration. In 2023, all the 5 locations were opened. By looking at the confidence intervals of the year 2023, we can see that the appointment duration differs between the outpatient locations (Home, Kampen and Heerde) and the hospitals (Zwolle and Meppel) since these confidence intervals do not overlap. The results of the other medicine types can be found in Appendix E.

Table 24: Appointment duration per location (Trastuzumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	189.2	179.7	198.6	192.7	175.5	209.9	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	211.3	200.9	221.6	183.9	168.9	199	66.2	64.1	68.4	NA	NA	NA	NA	NA	NA
2021	232.2	221.8	242.7	182	167.3	196.7	65.5	62.4	68.6	NA	NA	NA	NA	NA	NA
2022	179.5	170.8	188.1	163.9	152.3	175.5	69.3	66.4	72.2	NA	NA	NA	NA	NA	NA
2023	183.8	174.8	192.7	148	136.9	159	67.8	62.5	73.1	61.8	50.9	72.6	74.5	73.4	75.6

First three appointments

The protocol states that the first three appointments are scheduled at the hospitals to ensure safety and to make sure there is no unexpected reaction to the medicine, resulting in longer appointment durations. A difference was found in the appointment duration between the first three appointments and all the other appointments. The appointment duration for the first three appointments was longer than the appointment duration of all the other appointments. As an example, Table 25 shows the mean and the accompanying 95% confidence interval of the first, second, third and all the other appointment at Zwolle and Meppel for Trastuzumab. By looking at the confidence intervals of the year 2023, we can see that the appointment duration differs between the first three appointments and the other appointments. The results of the other medicine types can be found in Appendix E.

Table 25: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Trastuzumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	302.7	273.3	332	247.2	222.2	272.2	226.5	200.3	252.7	156.1	147.4	164.8
2020	413.3	386.2	440.3	317.9	295.3	340.5	298.9	271.2	326.5	175.3	166.9	183.6
2021	443.5	413.7	473.2	330.3	299.6	361	321.4	294.1	348.7	188.8	180.4	197.1
2022	391.2	360.9	421.6	272.3	247.2	297.3	274.5	250.1	299	148.1	141.7	154.5
2023	384.7	357.9	411.4	290.1	268.9	311.4	289.9	270.8	309	148.3	141.9	154.8

5.1.5 Postal codes

Figure 9 shows a heatmap of the postal codes of patients after the removal of the outliers. We can see that most patients live nearby one of the locations of Isala. With most patients living in Zwolle. Other postal areas where many patients live are Kampen, Meppel, Heerde, Hattem and Wezep.

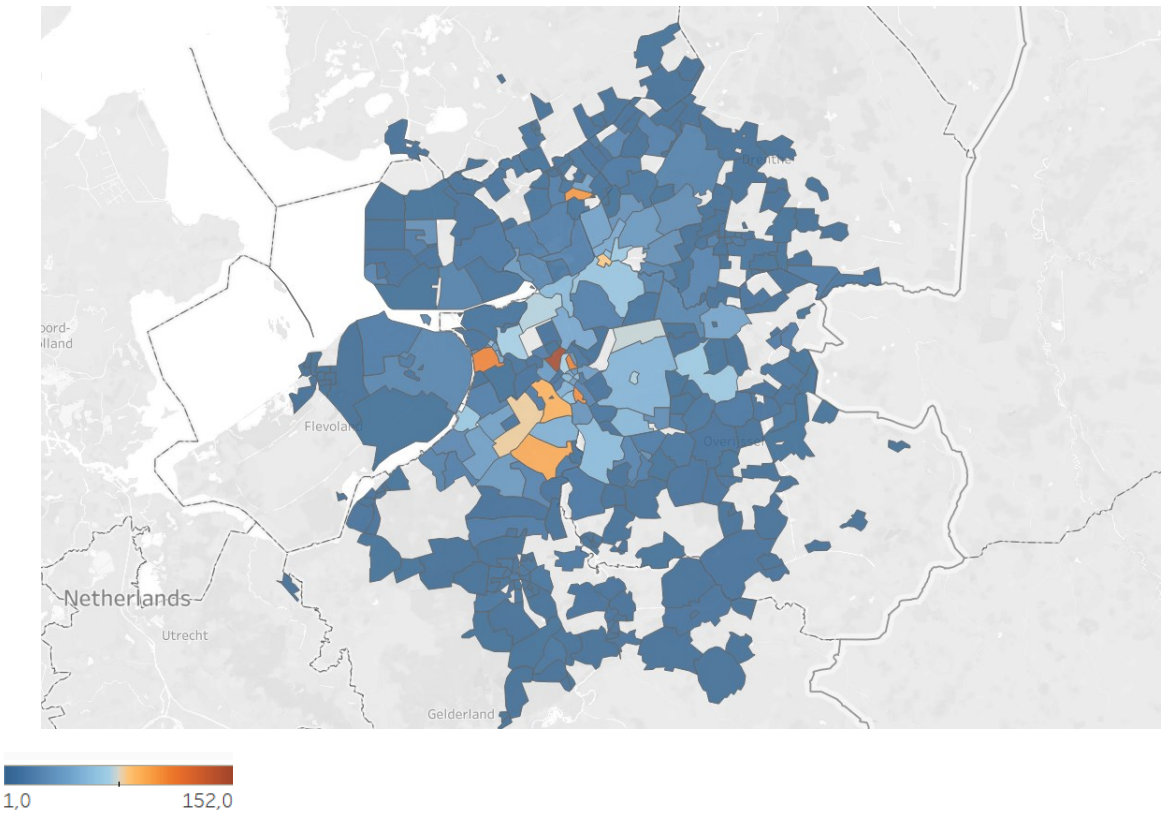

Figure 9: Heat map postal codes

After examining the heat maps that show the relation between the postal codes and the variables age, gender and appointment duration, no relation was found between the variables and the postal codes. The corresponding heatmaps can be found Appendix E. Table 26 shows the Cramer's V of the variables postal codes, age, gender, and appointment duration. All have a low Cramer's V, indicating there is no correlation between the three variables and the postal codes.

Table 26: Cramer's V of the variables postal code, age, gender, and appointment duration

Variables	**Cramer's V**
Postal codes – Age	0.104
Postal codes – Gender	0.061
Postal codes – Appointment duration	0.085

5.2 Data analysis of the questionnaire

5.2.1 Missing data

Table 27 shows the number of missing data per variable. Most missing data was present in the numeric variables (age and maximum travel time). For the further analysis of the questionnaire and for visualisation purposes, we converted the numeric variables into categorical variables.

Table 27: Number of missing data per variable

Variable	Type of variable	Number missing values (%)
Age	Numeric	16 (13.4)
Residential area	Categorical	2 (1.7)
Extra km	Categorical	3 (2.5)
Less km	Categorical	2 (1.7)
Maximum travel time	Numeric	13 (10.9)

5.2.2 Characteristics

A total of 119 patients filled out the questionnaire. Table 28 shows the characteristics of the patients. Out of the 119 respondents, 61 were male and 58 were female. Most patients fell into the age groups 55-64 and 65-74 years old (48.7%). Most patients lived in a town (40.2%) or the suburb of a city (38.7%). Only a few respondents had their administration at an external outpatient clinic (Kampen and Heerde), with 6 (5.0%) respondents in Heerde and 5 (4.2%) in Kampen. Most respondents (78.2%) had their administration in Zwolle. Because the number of respondents at some locations was so low, the responses from the different locations were combined for the majority of the analysis.

Table 28: Characteristics respondents

Characteristics	**Responses n (%)**
Gender	
Male	61 (51.3)
Female	58 (48.7)
Residential area	
City centre	14 (11.8)
Suburb of a city	48 (38.7)
Town	46 (40.2)
Countryside	11 (9.2)
Age	
18 – 24	3 (2.5)
25 – 34	10 (8.4)
35 - 44	12 (10.1)
45 - 54	18 (15.1)
55 – 64	26 (21.8)
65 – 74	32 (26.9)
75 - 84	17 (14.3)
85+	1 (0.8)
Mean (SD)	58.6 (15.9)
Location of administration	
Zwolle	93 (78.2)
Meppel	15 (12.6)
Heerde	6 (5.0)
Kampen	5 (4.2)

By examining the percentages in Table 29, we see a similar distribution of demographics between the respondents and the patients in the historical dataset, resulting in a presumably minimal nonresponse bias. The t-test shows that there is no statistically significant difference

for the male/female ratio and the location of administration. However, we found a difference in the age distribution.

Table 29: Estimation of the nonresponse bias

Characteristics	Respondents n (%)	Historical dataset	P-value t-test
Gender			*0.1982*
Male	61 (51.3)	1178 (42.1)	
Female	58 (48.7)	2447 (57.9)	
Age			*0.0158*
18 – 24	3 (2.5)	93 (2.2)	
25 – 34	10 (8.4)	156 (3.7)	
35 - 44	12 (10.1)	256 (6.1)	
45 - 54	18 (15.1)	530 (12.5)	
55 – 64	26 (21.8)	914 (21.6)	
65 – 74	32 (26.9)	1212 (28.7)	
74 - 85	17 (14.3)	932 (22.1)	
85+	1 (0.8)	132 (3.1)	
Mean (SD)	58.6 (15.9)	63.2 (15.0)	
Location of administration			*0.2094*
Zwolle	93 (0.78)	3000 (0.75)	
Meppel	15 (0.12)	898 (0.23)	
Heerde	6 (0.04)	45 (0.01)	
Kampen	5 (0.05)	42 (0.01)	

5.2.3 Type of transportation

The first questions regarded the type of transportation used by patients or their informal caregiver to travel to and from the hospital or external outpatient clinic. Table 30 shows the type of transportation that was used to travel to and from the hospital. Most of the respondents (90.7%) travelled by car, in particular by gasoline car (67.2%). Only a few respondents travelled by hybrid car (8.4%), electric car (4.2%), (electric) bicycle (5.0%), taxi (2.5%) or train (0.8%). Not a single patient walked to their appointment. One respondent used another means on transport, namely a mobility scooter. Only 4 respondents did not have a driver's license.

Table 30: Type of transportation used to travel to and from the hospital

Type of transportation	Respondents n (%)
Gasoline car	80 (67.2)
Diesel car	13 (10.9)
Hybrid car	10 (8.4)
Electric car	5 (4.2)
(Electric) bicycle	6 (5.0)
Taxi	3 (2.5)
Train	1 (0.8)
Other	1 (0.8)

Figure 10 shows whether there is any difference between the type of transportation used to travel to and from the location of administration and the different residential areas of the respondents. In all residential area's respondents travelled by gasoline car, with the percentage of respondents living in a town being the highest (80.4%). Only respondents living in a suburb of the city travelled by (electric) bicycle. The respondents living in a town all travelled by car, no other travel modes were used. The electric car was only used by respondents living in the city centre or a suburb of a city.

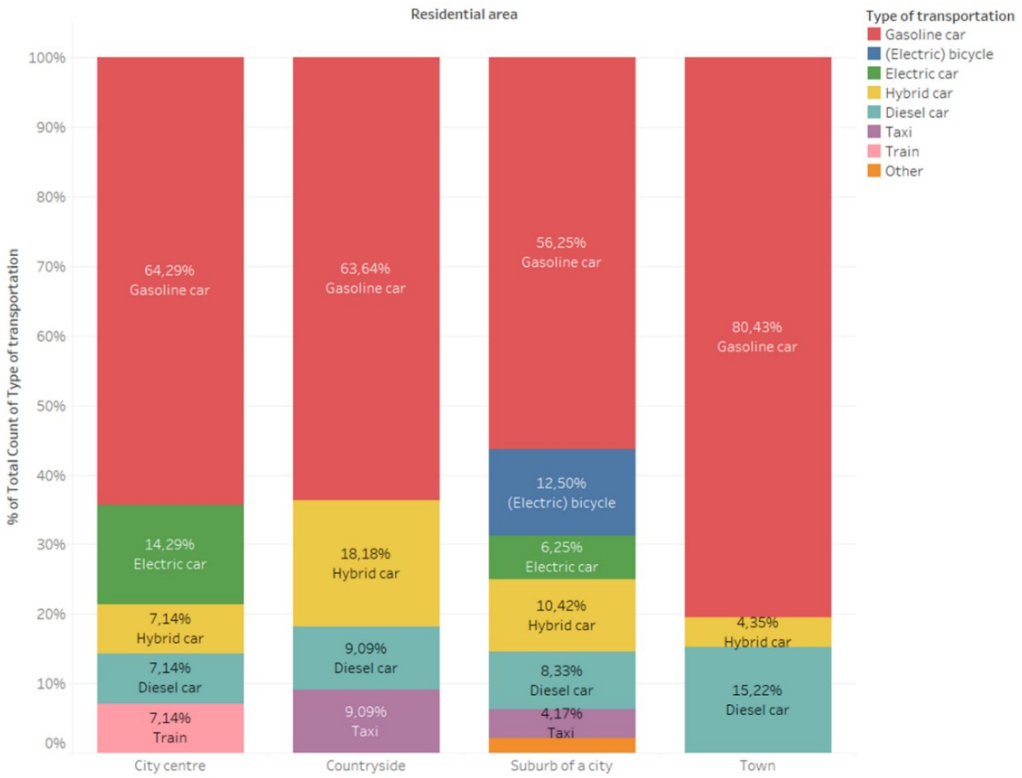

Figure 10: Type of transportation used per residential area

Figure 11 shows the type of transportation used to travel to the location of administration per age group. In most age groups, all different types of transportation were used to travel to and from the location of administration. In all age groups, the gasoline car was used most often.

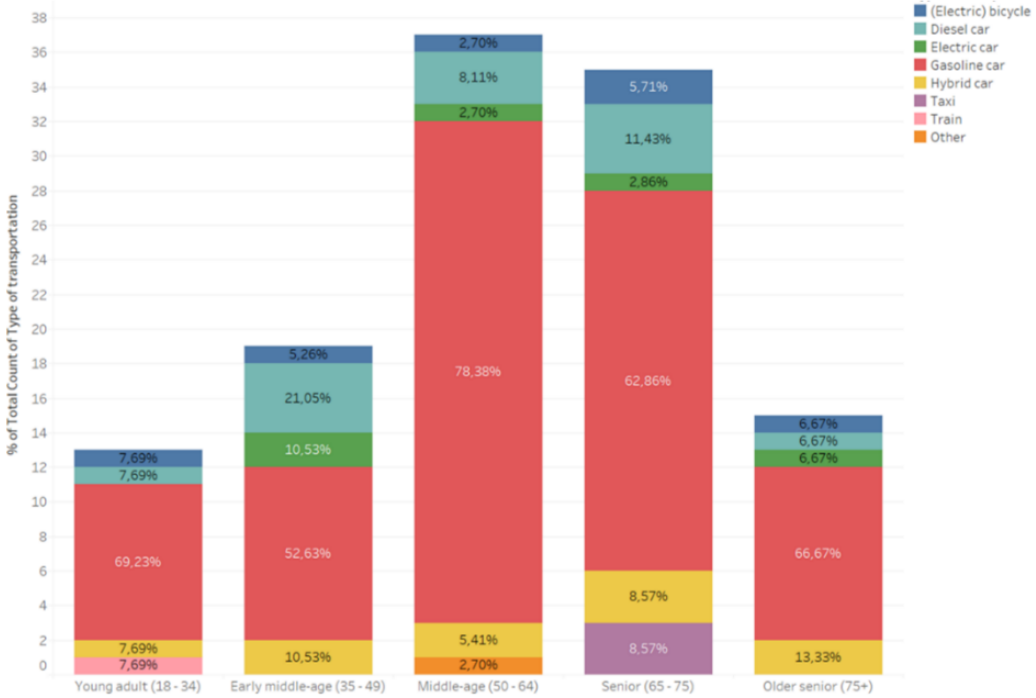

Figure 11: Type of transportation used per age group

In total 38 (31.9%) respondents indicated that they were dependent on an informal caregiver. So they may have travelled to the hospital with their informal caregiver. Figure 12 divided the age groups into two groups: dependent on an informal caregiver (yes) and not dependent on an informal caregiver (no). When looking at the group that is not dependent on an informal caregiver, we see that only the age group 35 - 64 years old used an electric car to travel to and from the hospital.

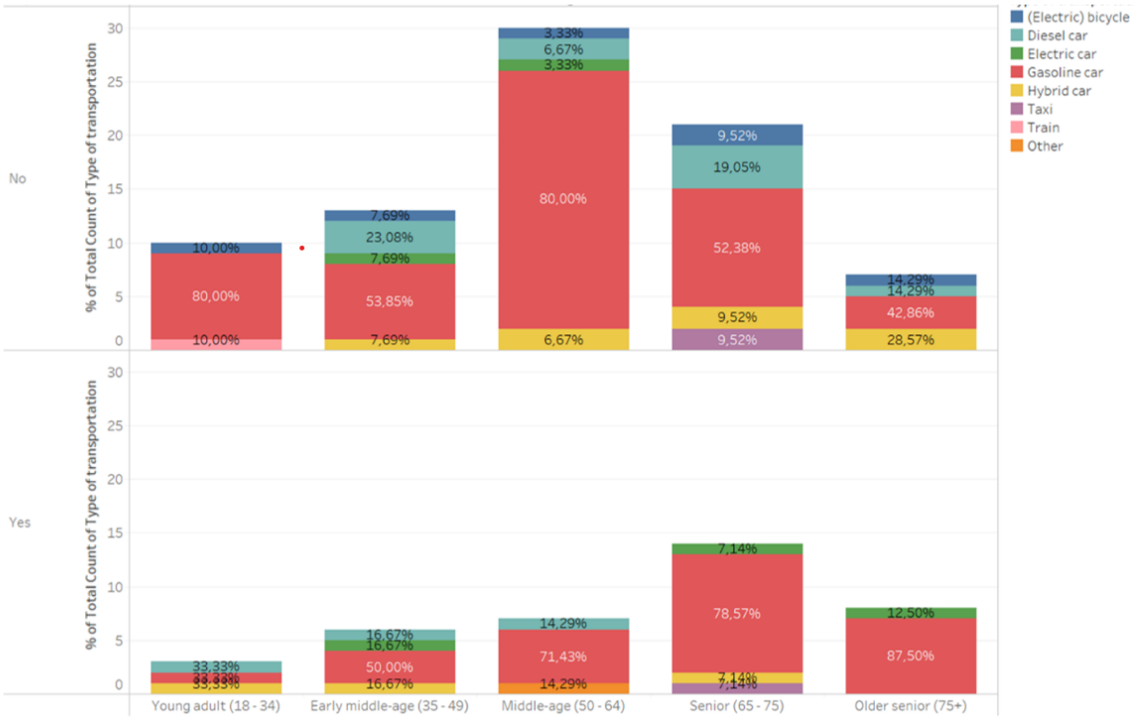

Figure 12: Type of transportation per age group, divided into two groups: dependent or not dependent on informal caregiver

5.2.4 Travel distance

The distance a respondent had to travel to and from the location of administration may have influenced the choice transportation. Figure 13 shows the type of transportation used by patients for the different distances the respondents had to travel. The distance represents a one-way trip to the location where the medicine was administered (Zwolle, Meppel, Heerde or Kampen). Only respondents who had to travel less than 15 km chose to cycle. Electric cars were mostly used by respondents who had to travel short distances. Respondents that had to travel very far travelled all by car.

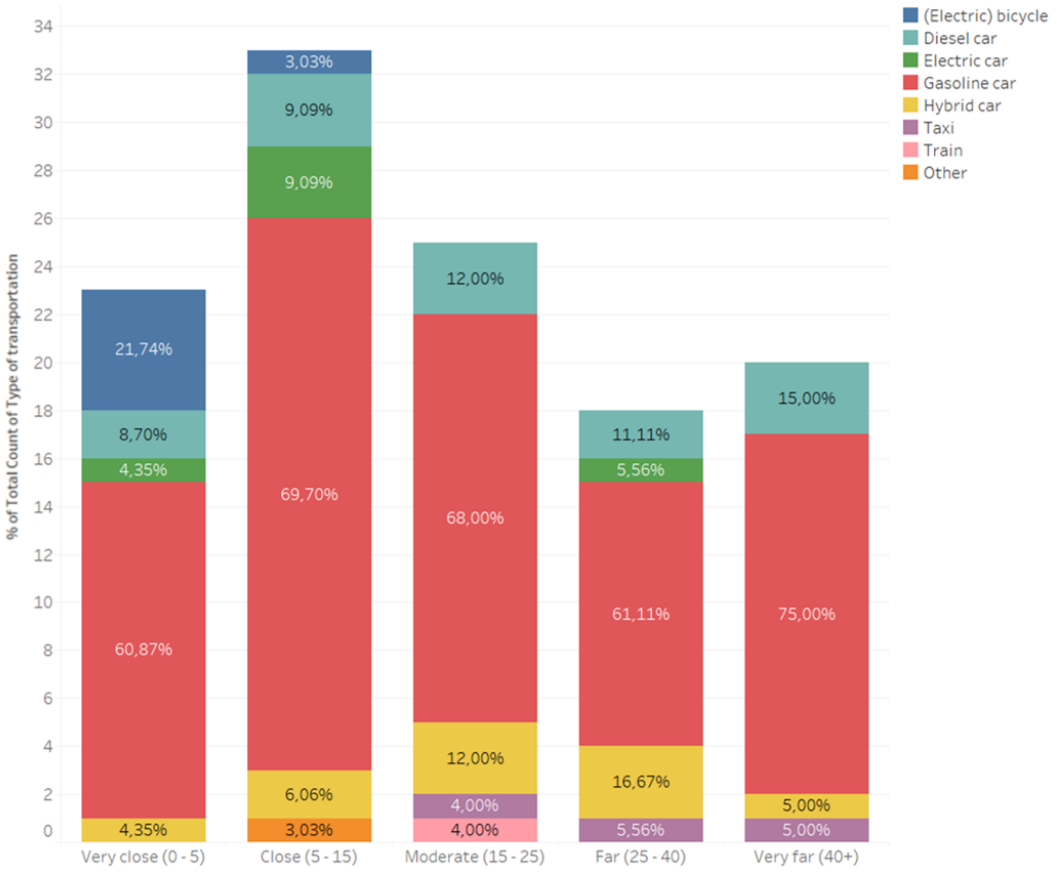

Figure 13: Type of transportation divided over the distance travelled to the hospital (one-way trip)

Figure 14 shows whether there was a difference between the different locations of administration in the choice of mode of transport. The figure shows that for all locations the gasoline car was used most often as a mode of transport.

Figure 14: Type of transportation per location of administration

Figure 15 shows the distance respondents had to travel to their locations of administration for a one-way trip. Respondents who had to go to Zwolle or Meppel covered all the different distances. Respondents who had to go to Kampen only travelled 0 -5 km or 25 km. Respondents who had to go to Heerde travelled all distances, except moderate distances (15 – 25 km).

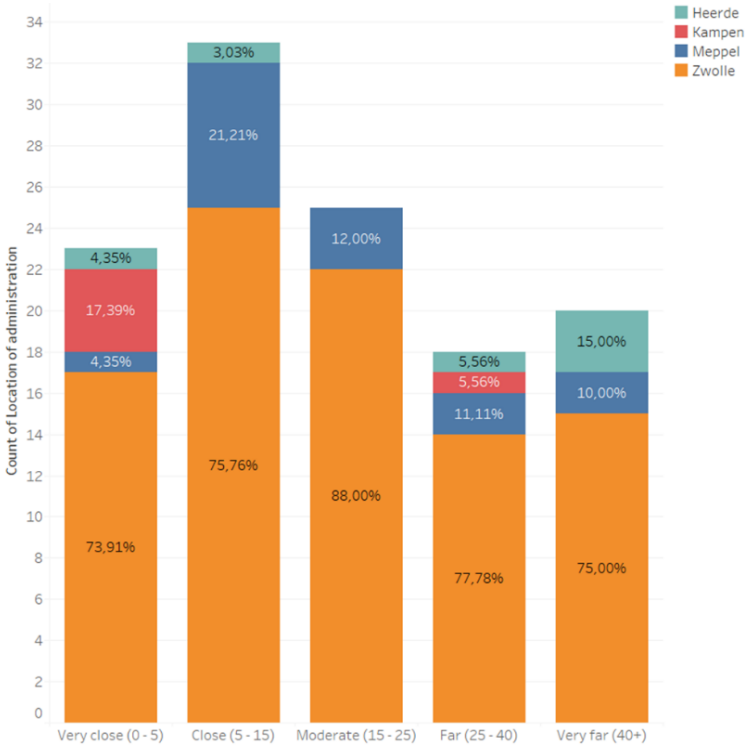

Figure 15: Distance (one-way trip) respondents had to travel to their location of administration

Figure 16 shows the maximum minutes a respondent was willing to travel for treatment (a round way trip).

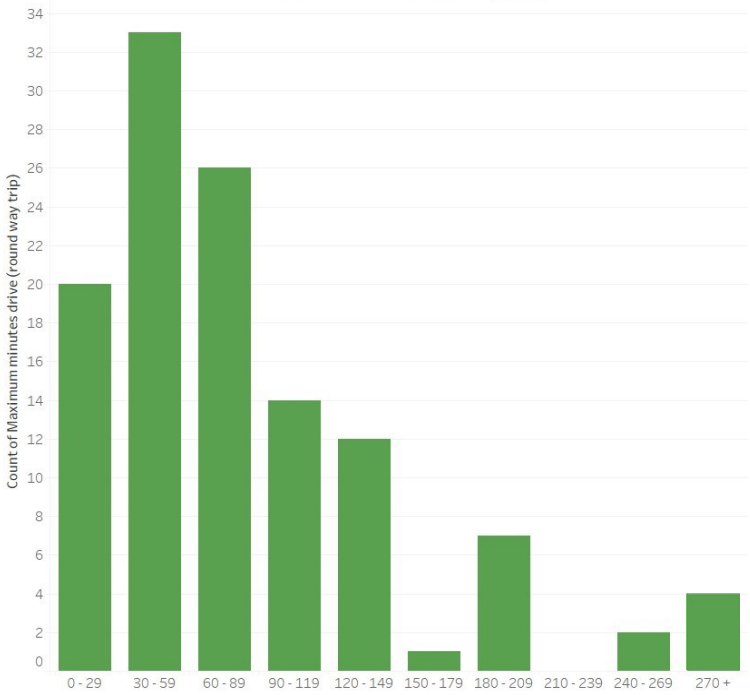

Figure 16: Maximum minutes willing to travel for a round-way trip

Figure 17 shows the results of the question: *"I can easily travel for shorter distances (< 5km) without the need of a car"* per type of transportation used. As can be seen, all patients who cycled to and from the hospital indicated that they can easily travel short distances without the need of a car. On the other hand, patients who used the taxi cannot travel short distances without the need of a car. The same applies to the train and mobility scooter. For the other transportation modes, some respondents indicated they can easily travel short distances without the need for a car, while others do not. Therefore, some were dependent on a transportation mode like a car, while others could have chosen a different mode of transportation.

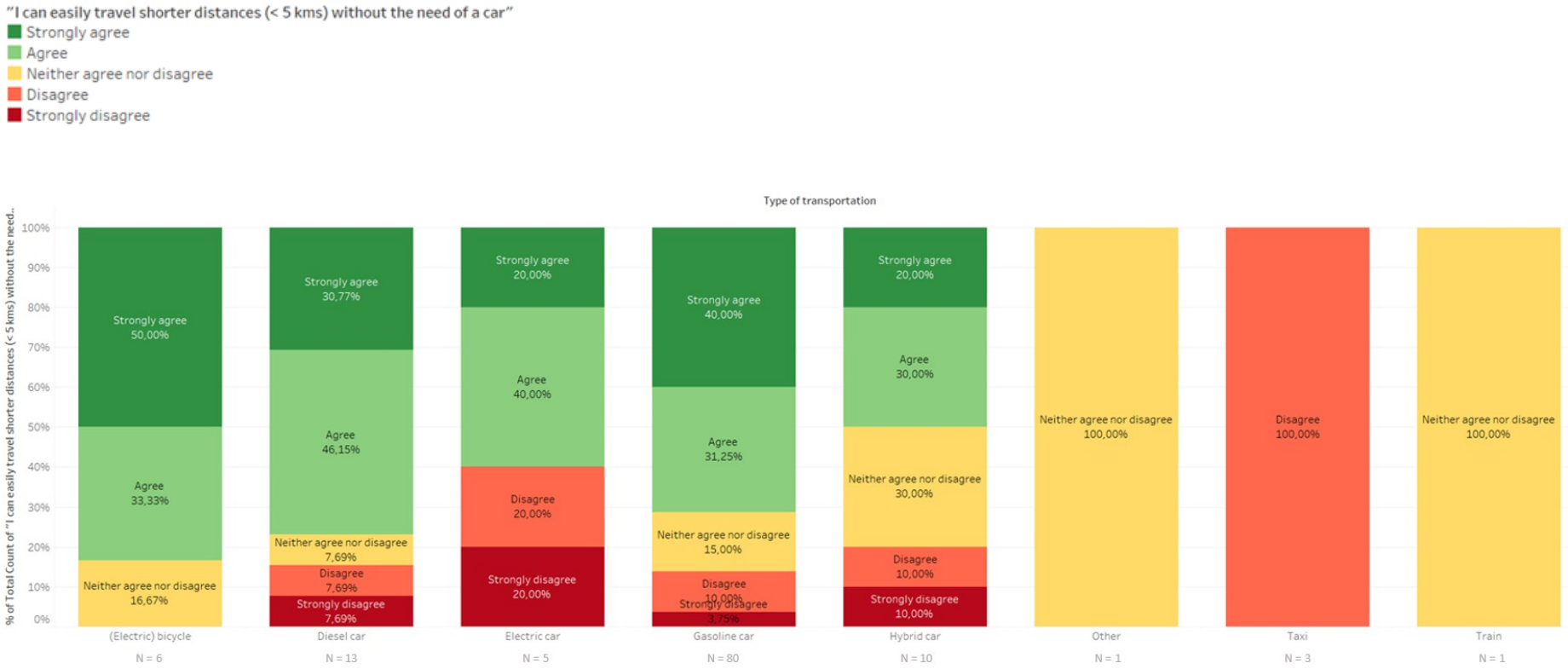

Figure 17: "I can easily travel for shorter distances (< 5km) without the need of a car" per type of transportation used

5.2.5 Preferences

Respondents were asked to order the different treatment locations, from 1 being the most preferred to 5 being the least preferred. Figure 18 shows the results. Respondents who had their administration at Zwolle, indicated that Zwolle is also their preferred location. The location where they least wanted to be treated is at home. The same applies to respondents who had their administration at Meppel, their preferred location is Meppel and their least preferred location is at home. Respondents who had their administration at one of the two external outpatient clinics (Heerde or Kampen), indicated the external outpatient clinic where they had administration as their preferred location. For respondents at Kampen, the locations Meppel and Heerde were considered as least preferred locations. For respondents at Heerde, the locations Meppel and Kampen were considered as least preferred locations.

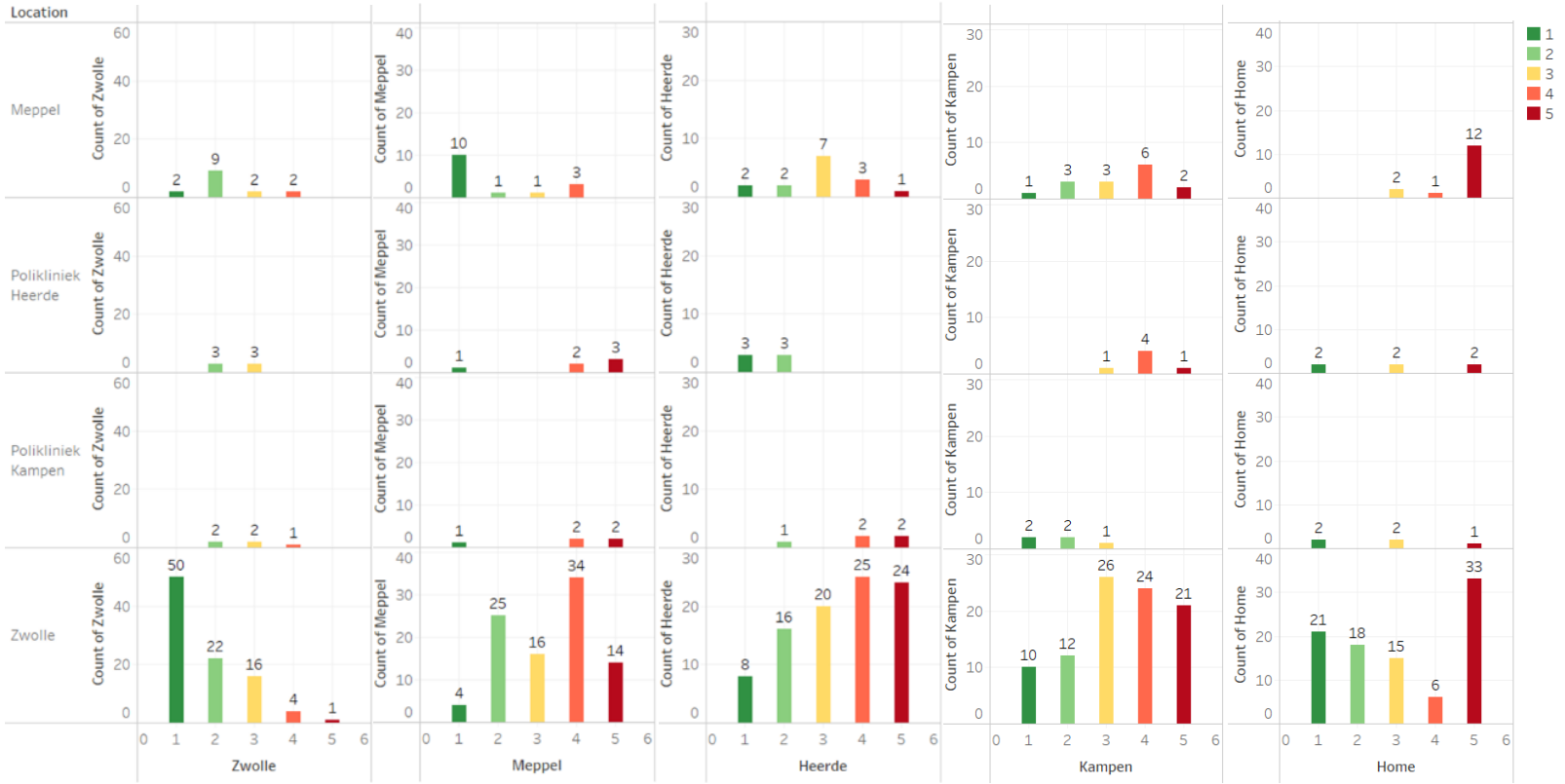

Figure 18: Preference location (1 = preferred) per location of administration

Respondents were asked to score the 5 factors (costs, convenience, physical exercise, sustainability, and travel time) on a scale from 0 to 100, with 0 being non important and 100 being very important when choosing a mode of transport. Figure 19 shows the results. The value 0 indicates that a respondent did not find the factor important in their decision. If a respondent indicated that they considered the factor important, the values 1 to 5 in the figures indicate its importance. Where 1 is hardly important and 5 is very important. The figure shows that travel time and convenience are important factors for respondents when choosing a mode of transport. Costs are moderately important. Physical exercise and sustainability are not important factors when choosing a mode of transport. Besides the predetermined factors, respondents were also given the opportunity to indicate a factor themselves. Four respondents mentioned that weather conditions are the most important factor when choosing a mode of transport.

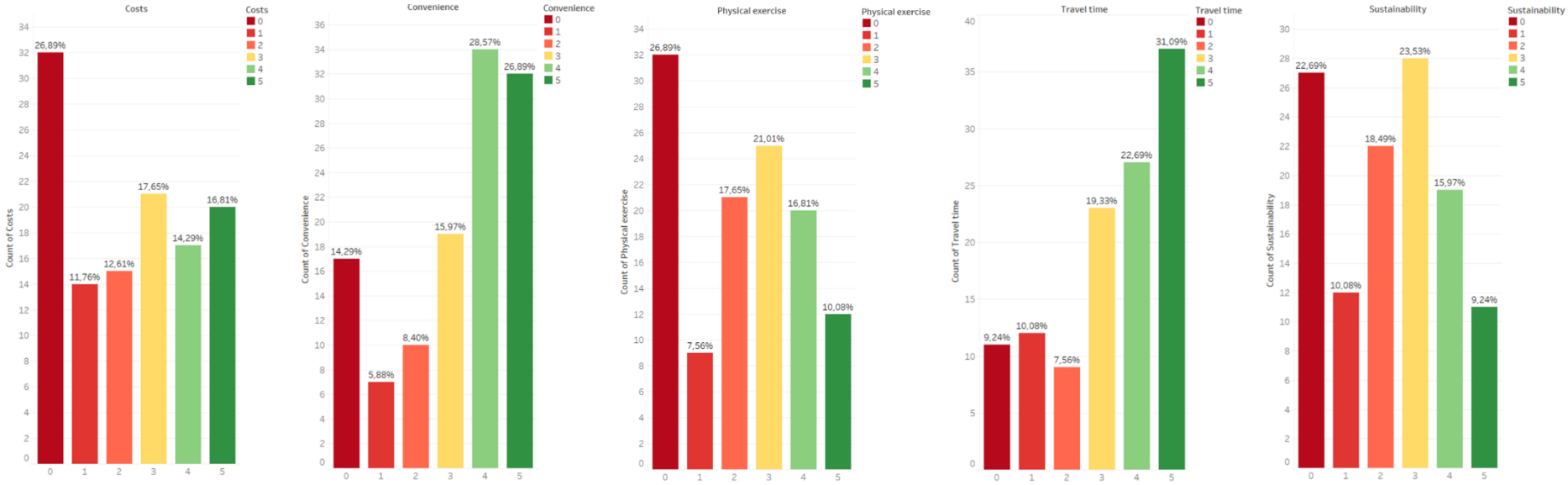

Figure 19: Importance of costs, convenience, physical exercise, travel time and sustainability on choice of a travel mode

5.3 Experiment results

In this section, we present the results of the 31 different experiments. Detailed results (mean, 95% CI, SD) per experiment for each KPI can be found in Appendix H.

5.3.1 Feasibility experiments

Not all replications led to feasible solutions. Table 31 shows the number of patients that had to be rescheduled an extra day earlier or later, the percentage of feasible replications, and the number of patients for each experiment. The patients that were rescheduled an extra day in the feasible replications were all rescheduled successfully, making the replication feasible. The patients that were rescheduled an extra day in the infeasible replications were not all rescheduled successfully. In this case, rescheduling the last patient was not possible, making the replication infeasible. An experiment with the highest feasibility did not have to reschedule any patients and had a feasibility percentage of 100%. In Table 31, we marked the experiments that led to infeasibility in more than 5%, 10% and 25% of the replications with a *, ** and *** respectively.

Table 31: Feasibility of each replication and accompanying data

Experiment	*Average number of patients rescheduled an extra day in the feasible replications*			*Number of patients rescheduled an extra day in the infeasible replications*			*Percentage feasible replications (%)*	*Percentage infeasible replications (%)*	*Number of patients in the feasible replications*			*Number of patients in the infeasible replications*		
	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI			Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
1	0	0	0.1	-	-	-	100	0	4138.9	4132.3	4145.5	-	-	-
2	0	0	0	-	-	-	100	0	4140.8	4134.1	4147.5	-	-	-
3	0	0	0.1	-	-	-	100	0	4141.5	4133.9	4149.2	-	-	-
4	0	0	0.1	2	-	-	99	1	4141.1	4134.2	4148	3361	-	-
5	0	0	0.1	-	-	-	100	0	4139.6	4133	4146.1	-	-	-
6	0	0	0	2	2	2	98	2	4137.1	4131.3	4142.9	3354.5	3259.2	3449.8
7	0	0	0.1	-	-	-	100	0	4138.3	4131.7	4144.8	-	-	-
8	0.1	0	0.1	2	-	-	99	1	4139.7	4132.5	4146.9	3376	-	-
9	0.1	0	0.1	2	-	-	99	1	4139.6	4132.8	4146.3	3463	-	-
10	0	0	0	-	-	-	100	0	3143.1	3137.2	3149	-	-	-
11	0	0	0.1	-	-	-	100	0	4135.2	4129.1	4141.3	-	-	-
*12***	0.3	0.1	0.5	2	2	2	89	11	4139.7	4132.3	4147.1	3382.9	3354.6	3411.2
13	0.4	0.1	0.7	2	2	2	97	3	4139	4132	4146.1	3379.7	3316.5	3442.8
*14***	0.4	0.2	0.6	2.8	2	3.5	84	16	4135.8	4128.4	4143.1	3270	3105.8	3434.2
15	0.3	0.1	0.5	2	2	2	96	4	4134.7	4127.6	4141.9	3380.8	3320.8	3440.7
*16***	0.5	0.3	0.7	2.3	2	2.6	82	18	4136	4129.1	4142.8	3385.1	3376.9	3393.3
17	0.2	0.1	0.3	2	-	-	99	1	4132.9	4125.2	4140.6	3282	-	-
*18****	7	3.1	10.9	4.7	4.2	5.2	8	92	4135.8	4113.2	4158.3	2865.3	2687.5	3043

19	0	0	0.1	-	-	-	100	0	4138.4	4131.8	4144.9	-	-	-
20	0	0	0	-	-	-	100	0	4134.7	4128.2	4141.3	-	-	-
21	0	0	0	-	-	-	100	0	4131.1	4124.6	4137.6	-	-	-
22	0	0	0	-	-	-	100	0	4131.5	4125.1	4137.9	-	-	-
23	0	0	0	-	-	-	100	0	4138.1	4130.7	4145.6	-	-	-
24	0	0	0.1	2	-	-	99	1	4135.2	4128.3	4142.1	3380	-	-
*25***	0.6	0.3	0.8	2	2	2	89	11	4519.2	4512.4	4526.1	3546.7	3288	3805.5
*26***	1	0.5	1.5	2.2	2	2.4	83	17	4840.2	4832.5	4847.8	3906.6	3894.1	3919.1
*27****	2.2	1.5	2.9	2.4	2.1	2.8	57	43	5236	5226.7	5245.3	4175.4	4145.7	4205.2
*28****	6.5	5.1	7.9	3.4	2.9	3.9	17	83	5635.8	5617.9	5653.8	4435.1	4378.9	4491.3
29	0	0	0	-	-	-	100	0	4138.1	4132.2	4144	-	-	-
30	0	0	0	-	-	-	100	0	4132	4124.7	4139.2	-	-	-
31	0	0	0	-	-	-	100	0	4137.7	4130.8	4144.5	-	-	-

** ≥ 5% and < 10% infeasibility, ** ≥ 10% and < 25% infeasibility, *** ≥ 25 % infeasibility*

Table 31 shows that of the experiments in which we set the growth to 10.2%, the number of patients in the feasible experiments is on average around 4137. Thus, in these replications, all 4137 patients could be scheduled. In most infeasible replications, we could still schedule around 3000 patients. This means that the simulation does not immediately stop in the first year, but around 3 years. Therefore, with the current capacity, patients can still be scheduled for some time. In experiment 18, we set the number of nurses in Zwolle to 4. On average 2865 patients can successfully be scheduled in the experiment, before the simulation stops. This means that in the current situation, with the only difference that there were only 4 nurses working in Zwolle, patients were successfully scheduled for approximately 2.5 years. In experiments 24-28 we increased the percentage of growth in the new number of patients per year to 12%, 15%, 17.5% and 20% respectively, while the other settings remained the same. With the current capacity, a growth in the number of patients leads to more and more infeasible replications. On top of that, in the feasible replications, more patients are rescheduled an extra day earlier or later. This might have an impact on the quality of care provided to patients. In experiment 10 we decreased the percentage of growth to 2%. As expected, in this experiment, no patients had to be rescheduled an extra day earlier or later. There is sufficient capacity to schedule and treat these patients.

5.3.2 Selection relevant experiments

In experiment 24, we did not use the probabilities for the selection of a travel mode from the questionnaire. Instead, data provided by the CBS was used. The experiment led to statistically significant higher CO2 emissions, travel distances and travel times compared to the other experiments. For the further analysis of the results, we only compare the experiments that used the data from the questionnaire for the travel mode selection since this was the best available input data, we had for the travel mode selection.

5.3.3 Distribution of CO2 emissions

Table 32 shows the distribution of the CO2 emissions for each experiment. The current situation led to an average total CO2 emission per day of 266.8 kg. Of this, 84.5% consisted of travel movements of the patients, 12.4% of home routes and 2.9% of nurses travelling to the external outpatient clinics. In all the experiments, the travel movements caused by patients causes the largest emissions. Reducing these emissions will therefore have the greatest impact on total emissions.

Experiments 14 and 20 represent the situation in which administration of the medicines is no longer provided at an external outpatient setting. In experiment 14, 6 nurses work in Zwolle and in experiment 20, 8 nurses work in Zwolle. One nurse remains employed in Meppel. To analyse what the effect is of opening an external outpatient location or stopping the administration at home on CO2 emissions, we must compare these experiments with either experiment 14 or 20, depending on the number of nurses in Zwolle.

Table 32: Distribution of CO2 emissions per experiment

Experiment	CO2 emission															
	Home route 1			*Home route 2*			*Total home routes*			*Travel to clinic by nurse*	*Travel movements by patients*			*Total*		
	Mean	*Lower CI*	*Upper CI*	*Mean*	*Lower CI*	*Upper CI*	*Mean*	*Lower CI*	*Upper CI*	*Mean*	*Mean*	*Lower CI*	*Upper CI*	*Mean*	*Lower CI*	*Upper CI*
1	18	18	18.1	15.1	14.9	15.2	33.1	32.9	33.3	7.7	225.9	224.8	227.1	266.8	265.6	268
2	21	20.9	21.1	17.4	17.3	17.5	38.4	38.3	38.6	12.4	221.2	220.2	222.3	272	270.9	273
3	21	20.9	21	17.3	17.2	17.4	38.3	38.1	38.4	9.4	222.3	221.3	223.4	270	268.9	271
4	21	20.9	21.1	17.2	17.1	17.4	38.2	38.1	38.4	12.6	221.8	220.8	222.8	272.6	271.6	273.6
5	20.9	20.8	21	17.3	17.2	17.5	38.2	38.1	38.4	9.4	225.1	224.1	226.2	272.7	271.6	273.8
6	20.9	20.8	21	17.3	17.2	17.5	38.3	38.1	38.4	12.5	220.5	219.4	221.7	271.3	270.2	272.5
7	18.1	18	18.1	15.1	14.9	15.2	33.1	32.9	33.3	8.2	224.1	222.9	225.2	265.4	264.2	266.6
8	19.6	19.5	19.7	16.4	16.3	16.6	36.1	35.9	36.2	7.7	222	220.8	223.1	265.8	264.6	266.9
9	16.7	16.7	16.8	14.7	14.6	14.8	31.4	31.3	31.5	7.7	223.5	222.4	224.5	262.6	261.5	263.7
10	18.1	18	18.2	14.8	14.6	14.9	32.8	32.7	33	7.7	175.9	174.9	177	216.5	215.4	217.6
11	18.1	18	18.2	15	14.9	15.1	33	32.9	33.2	8.2	228.1	226.8	229.4	269.4	268	270.7
12**	18.1	18	18.2	15.6	15.5	15.7	33.7	33.5	33.8	6.8	229.4	227.9	230.9	269.9	268.4	271.5
13	18	18	18.1	15.5	15.4	15.7	33.6	33.4	33.8	-	238.2	237	239.4	271.8	270.6	273
14**	-	-	-	-	-	-	-	-	-	-	277.2	276	278.4	277.2	276	278.4
15	-	-	-	-	-	-	-	-	-	7.7	258.8	257.7	259.9	266.5	265.4	267.6
16**	-	-	-	-	-	-	-	-	-	6.8	267.4	266.3	268.5	274.3	273.2	275.4
17	-	-	-	-	-	-	-	-	-	8.2	263.8	262.6	265	272	270.8	273.2

18***	18.1	17.8	18.5	15.3	14.7	15.9	33.5	32.7	34.3	7.7	225.5	222.4	228.6	266.7	263.5	269.9
19	18.1	18	18.2	15.1	15	15.2	33.1	33	33.3	8.2	224.1	223	225.3	265.5	264.3	266.7
20	-	-	-	-	-	-	-	-	-	-	277.2	276	278.5	277.2	276	278.5
21	-	-	-	-	-	-	-	-	-	7.7	259	258	260.1	266.8	265.7	267.8
22	-	-	-	-	-	-	-	-	-	6.8	267.2	265.9	268.4	274	272.8	275.3
23	-	-	-	-	-	-	-	-	-	8.2	264.1	263	265.2	272.3	271.2	273.4
24	18.1	18	18.1	15.1	15	15.2	33.2	33	33.3	7.7	300.5	299.2	301.8	341.4	340.1	342.7
25**	18.1	18.1	18.2	15.1	15	15.2	33.3	33.2	33.4	7.7	248.1	246.8	249.4	289.1	287.9	290.4
26**	18.2	18.1	18.2	15.2	15.1	15.3	33.4	33.2	33.5	7.7	263	261.4	264.7	304.1	302.5	305.8
27***	18.2	18.1	18.3	15.2	15.1	15.4	33.5	33.2	33.7	7.7	287.5	286.2	288.8	328.7	327.4	330
28***	18.3	18.1	18.4	15.1	14.8	15.4	33.4	33	33.7	7.7	311.5	308	314.9	352.5	349.2	355.9
29	18.1	18	18.1	15	14.9	15.1	33	32.9	33.2	8.2	227.8	226.5	229.1	269	267.7	270.3
30	18	18	18.1	15.5	15.4	15.7	33.6	33.4	33.7	6.8	229	227.6	230.3	269.4	268	270.7
31	18.1	18	18.1	15.6	15.5	15.7	33.6	33.5	33.8	-	238.4	237.3	239.5	272	270.9	273.2

** ≥ 5% and < 10% infeasibility, ** ≥ 10% and < 25% infeasibility, *** ≥ 25 % infeasibility*

Impact of external outpatient clinics on CO2 emissions

In experiments 16 and 22, only Heerde is opened. In experiments 17 and 23, only Kampen is opened. And in experiments 15 and 21 both external outpatient clinics are opened. Opening the external outpatient clinics leads to a statistically significant difference in total CO2 emissions compared to not opening any external outpatient clinic at all. There is no difference in total CO2 emissions between opening either Kampen or Heerde. There is a difference between the CO2 emissions caused by the travel movements of patients, Kampen has lower CO2 emission than Heerde. However, the emissions caused by the nurse travelling to the outpatient clinics is larger for Kampen than Heerde, resulting in no difference in total CO2 emissions. Opening both external outpatient clinics leads to the lowest CO2 emissions. The reduction in total CO2 emissions is caused by a reduction in travel movements of patients. This reduction is smaller than the additional CO2 emissions caused by the nurse travelling to and from the external outpatient clinic.

Opening external outpatient clinic Steenwijk on any day of the working week (Monday – Friday), except on Thursdays, leads to a small reduction in the average CO2 emissions caused by travel movements per day. However, this reduction in travel movements is smaller than the additional CO2 emissions of a nurse travelling to and from Steenwijk. Therefore, opening Steenwijk does lead to an increase in total CO2 emissions compared to the current situation. This can be explained by the fact that most patients live in the areas of Zwolle or south or south-west of Zwolle, see Figure 9 in Section 5.1.5. In addition, there is already a hospital in the north, namely Meppel. The nearest location of administration for most patients living in the north is Meppel instead of Steenwijk.

Impact of administration at home on CO2 emissions
In experiments 13 and 31, administration at an external outpatient setting is only given at home. Driving the home routes leads to a statistically significant difference in total CO2 emissions compared to not driving the home routes. Patients who have their administration at home do not have to travel to and from the hospital anymore, which results in a reduction in the CO2 emissions caused by travel movements of patients. This reduction (38.8 and 39 kg CO2) in CO2 emissions caused by travel movements is bigger than the increase (33.6 kg CO2) in CO2 emissions caused by driving the home routes. There is no statistically significant difference between opening either Kampen, Heerde or driving the home routes in total CO2 emissions.

5.3.4 Costs
Table 33 shows the average total costs per day for each experiment in euros.

Table 33: Average costs per day in euros per experiment

Experiment	Mean
1	3643.1
2	3720.5
3	3724.1
4	3724.1
5	3722.1
6	3723.7
7	3801.4
8	3643.1
9	3643.1
10	3643.1
11	3562.2
12	3483.8
13	3402.8
14	2865.2
15	3133.2
16	2955.6
17	3042.9
18	2888.5
19	3630.3
20	3619.9
21	3887.9
22	3710.2
23	3797.6
24	3643.1
25	3643.1
26	3643.1
27	3643.1
28	3643.1
29	4316.8
30	4238.4
31	4157.5

Impact of external outpatient clinics on costs
Opening Heerde led to the lowest average additional costs per day (90.4 euros), followed by Kampen (177.7 euros). This can be explained by the fact that Heerde is only opened one day a week, while Kampen is opened two days a week. Opening both external outpatient clinics led to an average increase in costs of 268 euros per day, compared to not opening any external outpatient clinic at all.

Impact of administration at home on costs
Offering administration at home costs on average an additional of 537.6 euros per day, compared to not offering administration at home. These costs consist of the salaries of the nurses and the

cars used, including fuel. Driving the home routes leads to more average additional costs per day than opening both external outpatient clinics (268 euros). This can be explained by the fact that administration at home is given 5 days a week, with an extra route on Thursdays. While the external outpatient clinics are only opened 3 days a week in total.

5.3.5 Costs and CO2 emissions compared to current situation

Figure 20 shows a quadrant plot of the average total costs per day and the average total CO2 emissions per day of all the experiments, compared to the current situation (experiment 1). Behind each experiment, the type of experiment, the outpatient locations which were opened and the number of nurses working in Zwolle are described. The zero point of the x-axis represents the average total costs of the current situation per day, namely 3643.1 euros. The zero point of the y-axis represents the average total CO2 emission of the current situation, namely 266.8 kg CO2. The dashed vertical lines around the y-axis represent the confidence interval around the mean. There are no confidence intervals around the mean for the costs because the costs remain the same every replication and is therefore one consistent value. Figure 20 shows that no configuration led to both lower costs and lower CO2 emissions.

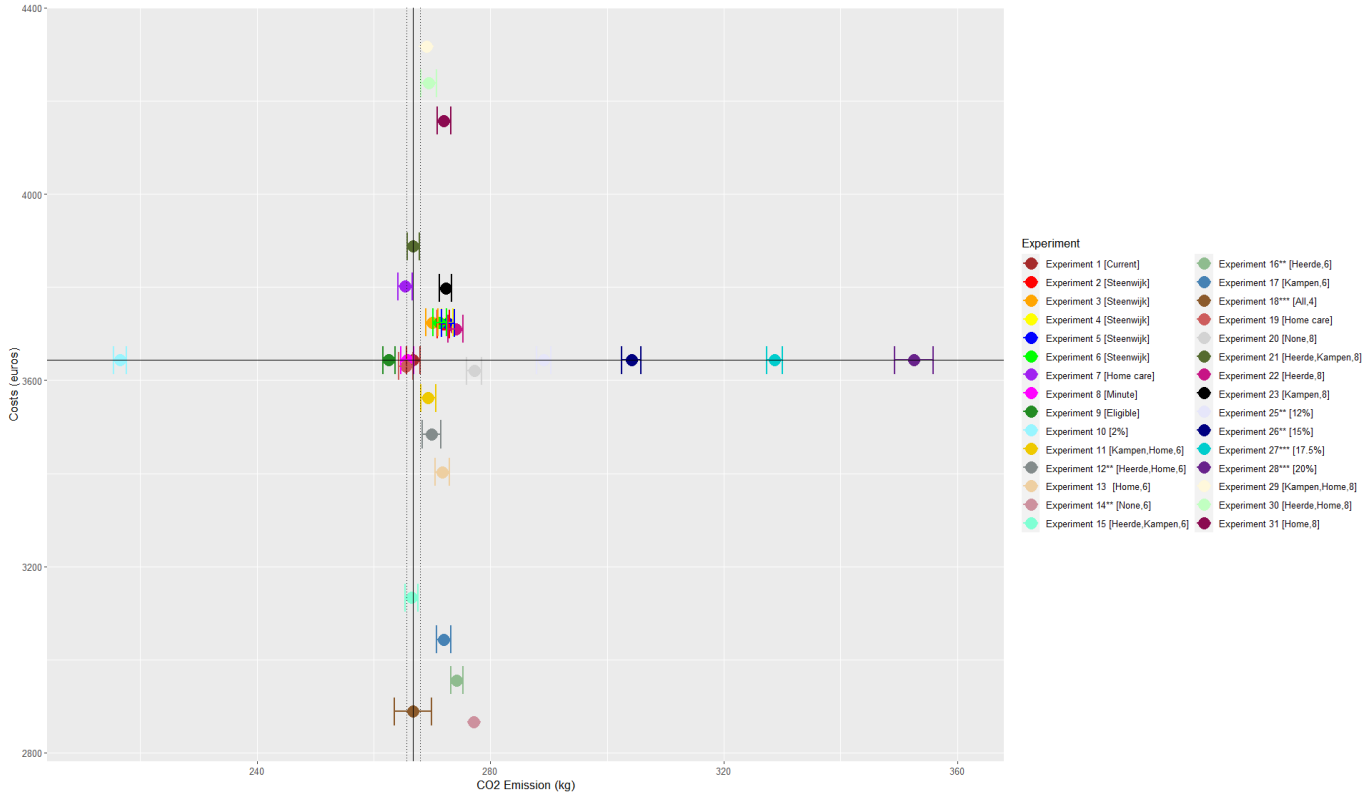

Figure 20: Quadrant plot of the CO2 emissions and costs

Lower costs

Experiments 11 – 20 resulted in lower average total costs per day, compared to the current situation. For the experiments 11-18 and 20, this can be explained because several locations were closed, without extra nurses being hired in Zwolle. Closing these locations resulted in lower real estate costs. In addition, there were no more salaries of the nurses who worked at these locations. In experiment 19, the administration in external outpatient clinic Heerde was outsourced to the home care organisation. However, different from experiment 7, the hourly wage of the home care nurse was equal to the hourly wage of an Isala nurse. In addition, the costs

of real estate represent the costs when the location is managed by Isala. As a result, the only difference in costs is that a car was no longer needed to travel to and from Heerde. Experiment 18 resulted in the lowest costs. In this experiment, we set the number of nurses in Zwolle to 4. However, it is important to keep in mind that only 8% of the replications of experiment 18 were feasible. As a result, the capacity used in experiment 18 was too low to treat all patients in the upcoming four years in most replications. Additional nurses may need to be hired, resulting in additional costs.

Higher costs
Experiments 2 – 7, 22, 23 and 29 – 31 led to higher average total costs per day, compared to the current situation. Experiments 2 – 6 represent the opening of the external outpatient clinic in Steenwijk, on different days of the week. The higher costs can be explained by the extra real estate costs of Steenwijk and the salary costs for a nurse one day a week. In experiment 7, the medicine administration at external outpatient clinic Heerde was outsourced to the home care organisation. The home care organisation charges a higher hourly wage for a specialised nurse. In addition, the costs of real estate charged by the home care organisation are higher. In experiments 22, 23 and 29 – 31, different locations were closed. To cover up this closure, 2 additional nurses were hired in Zwolle. However, closing some locations or stopping the home routes did not lead to a large enough cost reduction to compensate for the extra costs caused by hiring two additional nurses in Zwolle. Experiment 29, in which only Heerde is closed, and two additional nurses were hired in Zwolle, led to the highest costs.

Similar costs
Experiments 8 – 10 and 24 – 28 led to the exact same costs as in the current situation. The same number of nurses were deployed at each location, resulting in similar salary costs, 2 cars were leased, and the same locations were in use.

Lower CO2 emission
The confidence intervals of experiment 9 and 10 do not overlap with the confidence interval of experiment 1. Therefore, the total CO2 emissions of these experiments are statistically significantly lower than the total CO2 emissions of the current situation. In experiment 10, we set the growth in the number of new patients 2%, which resulted in less travel movements by patients. In experiment 9, more patients were eligible for treatment at an external outpatient setting. As a result, more patients could be treated closer to home, which resulted in lower CO2 emissions.

Higher CO2 emission
The confidence intervals of the experiments 2 – 6, 12 – 14, 16, 17, 20, 22 – 28 and 31 do not overlap with the confidence intervals of experiment 1. Therefore, the total CO2 emissions of these experiments are statistically significantly higher than the total CO2 emissions of the current situation. In experiment 2 – 6, we opened external outpatient clinic Steenwijk. Opening Steenwijk led to a small reduction in travel movements caused by patients but led to a bigger increase in CO2 emissions caused by the travels of the nurses to the external outpatient clinic. In experiments 12 – 14, 16, 17, 20, 22 and 23 we closed different combinations of the external outpatient clinics and the home routes. Closing the external outpatient clinics or stopping the home routes led to an increase in the CO2 emissions caused by the travel movements of patients. In experiments 25 – 28, the growth in patients was increased, leading to more patients travels and therefore an increase in the CO2 emissions.

Similar CO2 emissions
Experiments 7, 8, 11, 15, 18, 19, 21, 29 and 30 led to no difference in the total CO2 emissions, compared to the current situation. In experiment 7 and 19 we outsourced the medicine

administration in Heerde to the home care organisation. In experiment 8, the procedures evaluated in the Minute Study were implemented. In experiment 11 and 29, external outpatient clinic Heerde was closed. In experiment 15 and 21, the home routes were stopped. In experiment 30, external outpatient clinic Kampen was closed. In experiment 18, we set the number of nurses working in Zwolle to 4. Thus, closing at least one external outpatient setting (i.e. Heerde, Kampen or the home routes) did not lead to an increase in CO2 emissions compared to the current situation.

5.3.6 Travel time and travel distance

Figure 21 shows a quadrant plot of the average travel time and travel distance of a patient for each experiment.

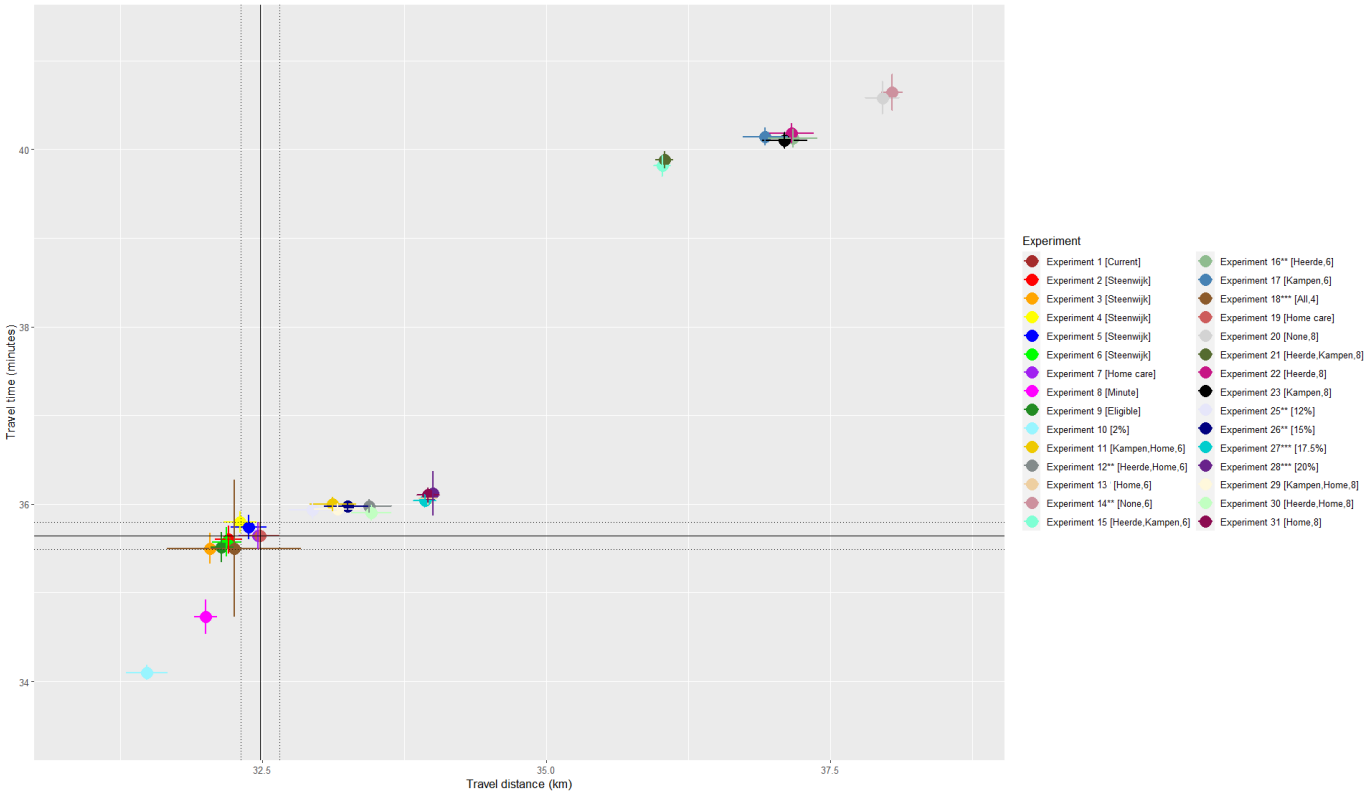

Figure 21: Quadrant plot of the travel distances and travel times

Travel time

The experiments 11, 13 – 17, 20 – 24, 26, 27 and 31 led to higher average travel times per patient compared to the current situation. In experiments 11, 13 – 17, 20 – 23 and 31, different combinations of the external outpatient clinics and the home routes were closed. The more locations were closed, the higher the travel times got. Closing the external outpatient clinics meant that patients had to travel to another location for treatment, which may have been further away. In addition, stopping the home routes meant that patients who were previously treated at home and therefore had a travel of 0 km, now had to travel to a location for their treatment. In experiments 26 and 27, the growth rate of the population size was increased, while the capacity available remained the same. This resulted in fewer feasible experiments, because there was not enough capacity to schedule all patients, which increased the sizes of the confidence intervals. The limited capacity may have caused that patients could not be scheduled at the nearest location, resulting in longer travel times.

The experiments 8 and 10 led to shorter travel times, compared to the current situation. In experiment 8, the procedures evaluated in the Minute study were implemented, which reduces the duration of the infusion. This meant that more patients could be scheduled on the home routes or at the external outpatient clinics in one day, reducing the travel times of patients. In experiment 10, we set the growth in the number of new patients to 2%. This meant that less patients had to be scheduled with the same capacity. As a result, more patients could be scheduled at the nearest location, resulting in a reduction in the travel times.

There was no statistically significant difference between the travel times of experiments 2 – 7, 9, 12, 18, 19, 25 and the current situation.

Travel distance
The KPI travel distances gave similar results as the travel times. This was expected since these two were correlated. As with the travel distances, the experiments 11 – 17 and 20 – 31 led to higher travel times. The experiments 3 and 8 – 10 led to a reduction in the travel distances. In experiment 3, we opened external outpatient clinic Steenwijk on Tuesdays. For some patients, Steenwijk was closer than the other locations, resulting in shorter travel distances. In experiment 9, more medicines came eligible for the administration at an external outpatient setting. As a result, more patients could be scheduled closer to home, resulting in lower travel distances. In the experiments 2, 4 – 7, 9 and 18 – 19 there was no statistically significant difference between the travel distances of the current situation and these experiments.

Impact of the external outpatient clinics on travel times and travel distances
Opening the external outpatient clinics led to a statistically significant reduction in both the travel times and the travel distances of patients. There was no statistically significant difference found between the travel distances and travel times of the two external outpatient clinics, both led to a similar reduction. Opening both external outpatient clinics led to the lowest reduction in both travel time and travel distance.

Impact of administration at home on travel times and travel distances
Offering administration at home ensured that a certain patient group did not have to travel to a location for their treatment. Therefore, compared to not offering any administration at home, driving the home routes led to a reduction in both the average travel times and travel distances of patients.

5.3.7 More medicines eligible for outpatient administration
In experiment 9, more medicine types became eligible for treatment at an external outpatient setting. In this experiment, the costs remained the same. When looking at the travel distances, there is a statistically significant difference between the current situation and experiment 9. As a result, the total CO2 emissions of experiment 9 compared to the current situation are lower as well. However, no statistically significant difference is present between the travel times of the current situation and experiment 9.

5.3.8 Home care organisation
Outsourcing the administration at Heerde to the home care organisation increased the costs, without resulting in a statistically significant difference in the average total CO2 emissions per day. When outsourcing the administration at Heerde to the home care organisation, Isala nurses did not have to travel to and from Heerde anymore. This results in a CO2 reduction. However, since the CO2 emission caused by the travel to and from Heerde is only a small part of the total CO2 emissions and Heerde is only opened on Wednesdays, the reduction in CO2 emissions is small. As a result, there is no significant difference between the average total CO2 emissions per when the administration at Heerde is outsourced to the home care organisation or not.

5.3.9 Minute study

No statistically significant difference was found between the total CO2 emissions of the current situation and the implementation of the Minute study. However, a statistically significant difference between both the travel times and travel distances of the current situation and the implementation of the Minute study was found. The implementation meant that more patients could be scheduled on the home routes or at the external outpatient clinics in one day, reducing the travel times of patients.

6. Conclusion

This study answered the research question: *"What is the feasibility and impact on mobility and costs of transferring the administration of parenteral medication from the hospital to an external outpatient setting for oncology and IMID patients?"*

We developed a discrete event simulation model to simulate the complex system of transferring the administration of parenteral medication from the hospital to an external outpatient setting. In total, 31 experiments were performed. The KPIs costs, CO2 emissions, travel distance and travel time of each experiment were analysed and compared to the current situation.

From the experiments, we can conclude that opening at least two external outpatient locations (i.e. Kampen, Home or the home routes) leads to the lowest total CO2 emissions. Opening all external outpatient clinics and offering administration at home leads to the lowest travel times. Driving the home routes and opening at least one outpatient clinic leads to the lowest travel distances. Opening external outpatient clinic Steenwijk leads to an increase in the costs and CO2 emissions, without reducing the travel times and travel distances. The experiments in which different locations were closed, without hiring additional nurses in Zwolle, led to the lowest costs. However, it is important to keep in mind that for some of these experiments the percentage of feasible replications was low (< 95%). Closing the home routes led to a bigger cost reduction than closing one or both external outpatient clinics. Outsourcing the administration at Heerde to the home care organisation increases the costs, without reducing the average total CO2 emissions per day. Implementing the Minute study does not lead to a reduction in CO2 emissions. However, it leads to a reduction in both the travel distances and travel times. Lastly, making more medicines eligible for treatment at an external outpatient setting does lead to a reduction in CO2 emissions and travel distances on average per patient per year, but does not lead to a reduction in travel times and costs.

7. Discussion

7.1 Scientific contribution

The aim of our study was to estimate the feasibility and impact on mobility and costs of transferring the administration of parenteral medication from the hospital to an external outpatient setting for oncology and IMID patients. This meant that we had to model the complexity of the care pathway and at the same time generate different outcome measures, including CO2 emissions. Literature showed that simulation models are suitable models for this purpose. However, we found that including carbon emissions as one of the outcome measures of a model is still relatively new in healthcare. Only a few studies included carbon emissions into their models (Bahri et al., 2021; Hilmola & Henttu, 2016; Peker et al., 2020; Rodríguez Verjan et al., 2013; Vali et al., 2022). Vali et al. (2022) used a DES model to improve patient flow while minimising carbon emissions. The emissions were calculated based on the duration that specific equipment was used for treatment. However, Vali et al. (2022) did not investigate the effect of travel movements by patients on these emissions. Another study that included carbon emissions

was done by Rodríguez Verjan et al. (2013). They developed a DES model to make an economic comparison between Hospital at Home (HAH) and hospital care. Carbon emissions were calculated based on the transportation of patients from home to the hospital (e.g. by ambulance). However, Rodríguez Verjan et al. (2013) did also not consider the travel movements by patients to and from their appointments. Besides that, they only considered hospital care at home and did not study the effect of external outpatient clinics on transportation. Hilmola & Henttu (2016) did study the transportation of patients and their visitors to the hospitals by developing a SD model. However, a SD model is not able to model the individual characteristics present in our complex context. In our research, we combined the results of both separate literature studies on modelling techniques for modelling patient flow and including carbon emissions as one of the outcomes measures and chose to develop a discrete event simulation model. Our research contributes a novel addition to existing literature, by developing a model that reflects a complex and dynamic patient flow and includes carbon emissions as an outcome measure. Besides that, little is currently known about the transfer of care to external outpatient clinics. Studies have mainly been conducted into the concept of Hospital at Home (HaH), instead of external outpatient clinics (Rodríguez Verjan et al., 2013). Our research provides new scientific insights into the potential broader impact of this relocation of care.

Our research contributes to existing literature by confirming, contrasting, and expanding upon findings from prior research. Rodríguez Verjan et al. (2013) found that HaH leads to a significant reduction in healthcare costs compared to providing traditional hospital care. This is mainly due to the lower overhead costs. The results of our study contrast with the findings of this research. In our research, we found that transferring care from the hospital to an external outpatient setting leads to extra expenses, as external outpatient clinics must be opened and a car to drive the home routes with must be purchased or leased. The costs for real estate do not differ between the external outpatient clinics and the hospital's outpatient departments, which means that moving care does not lead to a reduction in costs. When you administer treatments at an external outpatient setting, you still need to maintain the outpatient clinic in the hospital, which prevents any cost reduction in the form of real estate. A study done by Hilmola & Henttu (2016) found that the placement of the hospital plays a critical role in the transportation of patients. This is important when reaching the population from a shorter proximity. In our study, we also found that the placement of the hospital and external outpatient clinics determines the travel modes of patients. The results of the questionnaire showed that the travel distance a patient had to travel to and from the location of treatment determines the choice of travel mode. In most cases, as soon as the patient must travel a longer distance, the CO2 emissions emitted by the patient increases. Therefore, it is important to consider the placement of an (external) outpatient clinic, as confirmed in the study done by Hilmola & Henttu (2016). Devarakonda (2016) studied the implementation of the Hub and Spoke Model (HSM) in healthcare, which was used to provide high quality care to rural areas. The HSM is a structure where there is a central point (the hub) and smaller locations (the spokes). The central point serves as the primary location. From this central point, resources and services are distributed to the smaller locations. In healthcare, the hub often represents the hospital location, and the spokes represent the external outpatient clinics. In our study context, a similar structure was present. Devarakonda (2016) showed that the HSM eliminates the need for unnecessary travels to larger central points, by ensuring that the spokes offered basic treatment. Patients would only need to travel to the hub for more complex care. In line with our findings, the HSM saves the patient travel time.

7.2 Practical contribution

Besides the scientific contribution, this research is also relevant to practice. Within this research, the feasibility and impact on mobility and costs of different configurations were analysed. This helps Isala to implement a certain configuration for the administration of parenteral medication for oncology and IMID patients and determine the feasibility and impact of the transfer of care from the hospital to the home-setting. Therefore, this study helps Isala to contribute to the reorganisation of the healthcare system as stated in the Integral Care Agreement. This is important, since the government advocates for more sustainability in the healthcare sector (Rijksoverheid, n.d.). In addition, the Integral Care Agreement states that, when possible, care should be given close to the patient's home (Rijksoverheid, 2022). Because Isala is one of the hospitals that participates in the mProve network, the results and experiences from this research can easily be shared within the network to benefit other hospitals (mProve, n.d.-a).

The results of this study are not directly generalisable to similar healthcare organisations. Our research was conducted for Isala. As a result, the results are based on the specific input data and parameters provided by Isala and are therefore only applicable to the specific context within Isala. However, when changing the input data, the model could be generalised to similar healthcare organisations within and outside The Netherlands. When applying the model to other healthcare organisations, it is important to verify, for example, whether patients live at similar distances from the different administration locations. Our research was conducted for Isala, which is in the northern region. In general, the travel distances in the northern region are greater than in, for example, the Randstad area (Centraal Bureau Statistiek, 2022b). Additionally, patients at other healthcare organisations might make different choices in the means of transport, resulting in different emission factors and therefore different CO2 emissions. Besides the input data for the CO2 emissions, other healthcare organisations might have different salary and real estate costs and opening hours. In our research, we ran experiments based on the current capacity within Isala (square meters per location and number of nurses available). However, the capacity might be different at other healthcare organisations. This can be easily adjusted per location in the model. Within our model, other locations can be opened by simply adjusting the postal codes of the locations and the associated distance matrices. In our research, we focussed on specific medicine types. However, different medicine types could be easily inserted into the model, resulting in different patient characteristics, appointment durations and total number of administrations. Input data that can be easily adjusted within the model are costs, number of nurses working per location, opening hours and days, patient growth, percentage of patients per medicine type, medicine types and their eligibility for treatment at an external outpatient setting, time between admissions, travel distances, travel times, postal codes, addresses and sizes of the different locations and maximum travel distance and travel time for treatment at an external outpatient setting. However, there are a few restrictions to the generalisability of the model. In the model, a maximum of 2 hospitals, 3 external outpatient clinics and 10 home routes can be opened. Besides that, only the travel modes we specified in our model can be used by the patient ((electric) bicycle, diesel, electric, hybrid and gasoline car, taxi, train, mobility scooter and walking). There is no limit to the number of nurses working per location. To conclude, our model has a high generalisability for healthcare organisations that have a similar number of locations as Isala and whose patients do not use other means of transport than we specified in our model.

7.3 Limitations

A first limitation of our research is that we assumed that the growth in the other patient groups, who also receive treatment at the daycare department, was no bigger than the growth in our select patient group. This allowed us to assume that the 6 nurses who were working in Zwolle and the 1 nurse working in Meppel, were completely available to our select patient group. This also allowed us to assume that 32.06% of the square metres in Zwolle and Meppel were available to our select patient group. However, it may be the case that these other patient groups will grow faster in the future. This would affect the ratio of capacity available for the different patient groups. As a result, the current capacity might no longer be sufficient. This would mean that additional nurses would have to be hired and additional space would be needed to treat all these patients.

A second limitation is that we assumed that the current capacity of the daycare department is sufficient to treat all patients in the upcoming 4 years. When there is a shortage of capacity expressed in square metres, transferring the administration from the hospitals to external outpatient clinics can be a good solution to this problem. The external outpatient clinics are existing buildings, in which a treatment room is used by the daycare treatment. Another solution would be to expand the daycare department in Zwolle and Meppel. However, this will lead to high investment costs because a new building would have to be built. The square meter price or rental price of an external outpatient clinic will always be lower than the investment costs of expanding the daycare department. As a result, opening the external outpatient clinics when there is a shortage of capacity expressed in square metres, avoids high investment costs of new construction.

A third limitation is that only 9% (11) of the respondents of the questionnaire had their administration at an external outpatient clinic. This small group of patients might not represent the patients who receive treatment at the external outpatient clinics correctly. As a result, the probabilities used in the model might not entirely correctly reflect the whole patient group. Additionally, no questionnaires were distributed among patients who had administration at home. The physical condition of most of these patients is not optimal and often the treatment guideline for the medicines administered to these patients demands a short period between two consecutive administrations. They may therefore prefer administration at home or a short travel time to and from their location of administration. The results of the questionnaire showed that 40% of the respondent did not have a high preference (gave at home administration a score of 4 and 5, on a scale from 1 to 5, with 1 being the most preferred to 5 being the least preferred) for administration at home. However, these patients may have never had an experience with administration at home or might differ from the patients who have their administration at home. However, despite these limitations, it was still decided to use the data from the questionnaire as input data for the model since this was the best available data concerning this patient population. We performed an experiment with the data published by CBS. The results of this experiment led to greater CO2 emissions, longer travel times and travel distances. This was primarily due to fewer people travelling by bicycle and electric car. The data published by CBS contains data from 2016 and 2022. It is expected that between these years and the present year, there has been an increase in the number of individuals utilizing electric travel modes (electric car or bicycle), which are characterised by low emissions factors. This trend is caused by the yearly increase in the number of people owning an electric car or electric bicycle (Kampert et al., 2023; RAI Vereniging & BOVAG, 2023). There is also a difference between the population described in the CBS data and our patient group, which makes the CBS data less representative. Patients undergoing oncological treatment are often weaker than those who are working. This physical condition can affect their choice of transport. Additionally, in some cases these patients are

dependent on an informal caregiver, who might have to travel to the patient first and then travel to and from the hospital. This may result in a different choice of travel mode. For example, taxis are more frequently used in the questionnaire data than the CBS data.

Another limitation is that not all replications led to feasible solutions. In our research we only examined an extra day of rescheduling for when it was not possible to schedule a patient within the maximum range of days of rescheduling. However, the hospital may resolve the inability to schedule the patient in other ways. For example, a solution is to hire a nurse from the flex pool. Further research could look at other possible solutions to be able to treat the patient within the set timeframe. Besides that, in Operations Research a lot of research has been done into the optimal scheduling of oncology treatments (Hooshangi-Tabrizi et al., 2020; Liang et al., 2015; Sadki et al., 2011). These studies could be used as a basis for the efficient and optimal scheduling of oncology treatment and thus make the most optimal use of limited capacity. This might result in the ability to schedule all patients, resulting in a now feasible solution. Further research could investigate the possibility of implementing these optimal scheduling techniques and rules and therefore make the most optimal use of the limited capacity.

A limitation of our study was that we only used one imputation to fill in the missing data of our questionnaire. This may have underestimated the uncertainty in our data. A better approach would have been to generate multiple imputations and then pool them. For example, Rubin's Rules could have been used to pool the imputations.

Lastly, from Isala's perspective, outsourcing the administration in Heerde led to fewer travel movements and therefore less CO2 emissions, since no Isala nurse had to travel from Zwolle to Heerde and back. However, in reality, a travel movement to and from Heerde still takes place, because a home care nurse must travel to and from Heerde. In the current situation, the Isala nurse who is deployed at Heerde takes the medication for Heerde with her from Zwolle. When the medicine administration in Heerde is outsourced to the home care organisation, the medication administered in Heerde must be collected by the home care organisation in Zwolle or delivered to Heerde, resulting in a travel movement. However, it is unknown how large these travel movements are and the amount of CO2 emissions it results in. In this case, a shift takes place in the CO2 emissions between the two organisations. The CO2 emissions of the nurses travelling to the external outpatient clinic Heerde are eliminated for Isala but are added to the home care organisation. The same applies to the capacity. Because the administration in Heerde is outsourced to the home care organisation, an Isala nurse becomes available (i.e. the capacity of Isala increases) who can be deployed at another Isala location. However, the home care organisation then needs to deploy a specialised nurse in Heerde, where they previously did not deploy a nurse (i.e. their capacity decreases). Consequently, applying a regional perspective, only a shift takes place in CO2 emissions and capacity between organisations, without leading to a reduction in CO2 emissions or released capacity.

7.4 Further research

First of all, in our research we only included patient satisfaction by looking at the travel distances and travel times patients had to travel to their location of administration However, there are many more factors that influence patient satisfaction. For example, patients may value personal contact, which is often more extensive at the external outpatient clinics and at home because fewer patients are present at the same time. In the Hospital at Home model, it was already found that patients experienced more personal contact with the HaH model compared to traditional hospital care (Wilson et al., 2002). In addition, parking at the external outpatient clinics is free and right in front of the entrance. Therefore, it is interesting for further research to examine the effect of other factors on patient satisfaction.

Secondly, in our research we did not examine employee satisfaction. Nurses may prefer providing treatment at a certain location or at home. They may also value personal contact, which is often more extensive at the external outpatient clinics and at home. On top of that, at the external outpatient clinic and during the administration at home, a nurse works alone. As a result, there is little contact with colleagues during this time. This might influence the employee's satisfaction. Further research could examine the effect of the different configurations on employee satisfaction. In the Hospital at Home model, it was already observed that the employee satisfaction is higher with HaH compared to traditional hospital care. Vaartio-Rajalin et al. (2020) found that staff perceive a deeper patient-nurse relationship. They experience independence and feel more motivated to work. Additionally, Albarello et al. (2019) showed that nurses working under a HSM structure, felt highly independent. They were more satisfied with their job and had a higher work engagement than nurses who did not work under a HSM structure.

Further research could investigate the potential impact of opening a different external outpatient clinic than Steenwijk. Opening another location than Steenwijk may lead to better outcomes. This will be the case when the external outpatient clinic is opened in an area where many patients live, such as a suburb of Zwolle, which reduces the travel distances and travel times. As a result, the CO2 emissions caused by travel movements are reduced. In addition, opening an external outpatient clinic closer to the hospital will lead to shorter travel distances and travel times for the nurses, which also reduces CO2 emissions. Besides that, it is interesting to look at external outpatient clinics that have lower real estate costs. In further research, it is therefore recommended to look at other outpatient locations to open in the future. It is important to first investigate in which areas most patients live. It is also important to consider the real estate costs for these new locations.

In the current situation, a diesel car is used to drive the home routes and to travel to and from the external outpatient clinics by nurses. A diesel car has a CO2 emission factor of 0.183. Every kilometre driven results in 183 grams of CO2 emissions. Replacing the car with an electric car will reduce CO2 emissions of the home routes and the travel to and from the external outpatient clinics by nurses by 63.9% (assuming the emission factor of an electric car is 0.067). However, replacing the cars means that a new lease contract must be entered. Early termination of a lease contract may lead to additional costs or a fine. On top of that, the purchase cost of an electric car is generally higher than a diesel car. However, the costs for maintenance and driving an electric car are lower than for a gasoline or diesel car (Milieu Centraal, n.d.). It is important to consider that this replacement might negatively or positively influence the monthly costs for the car. In further research, it is interesting to analyse the impact of replacing the current cars with electric cars on the different KPIs.

In our research, we mainly focused on opening and closing the existing locations, to limit the number of experiments. We only looked at expanding by opening external outpatient clinic Steenwijk. In addition to the experiments performed, there are more experiments that could be performed in further research. For example, the impact of opening more treatment rooms in the external outpatient clinics can be studied. In our research, we found that opening the external outpatient clinics led to a reduction in CO2 emissions, travel times and travel distances. It is therefore expected that opening an additional treatment room within these clinics will lead to an additional reduction. For further research, it is interesting to investigate at what point expanding the capacity at the external outpatient clinics no longer leads to a reduction in the KPIs. And thus, at which point there are no longer enough patients living in the areas around the external outpatient clinics. This may be the case because a large proportion of the patients live around Zwolle, thereby making the hospital in Zwolle closer. The impact of travelling an additional home route can also be examined. Besides that, experiments can be performed on the

impact of solely providing administration at an external outpatient setting (i.e. either only at home, only at the external outpatient clinics or a combination of both). However, the first three appointments must still be administered at the hospital. Again, it is interesting to investigate at what point expanding the capacity at the external outpatient setting no longer leads to a reduction in CO2 emissions, travel times and travel distances. It is expected that a major increase in capacity will be required to only drive the home routes. This is because fewer patients can be treated on a home route compared to the (external) outpatient clinics.

In some of the experiments where different locations were closed and no extra nurses were hired in Zwolle to cover up this closure, there was insufficient capacity to treat all patients. The Minute study explores the impact of reducing the duration of infusion. As soon as there is a capacity shortage or when there is an increase in the number of patients, a reduction in appointment duration will have an impact on the system, because more patients can be treated with the same capacity. For further research, it might be interesting to analyse the effect of the Minute study on these experiments that resulted in a low percentage of feasible replications. It could be that these experiments become feasible. This will mainly lead to a reduction in costs. Because no additional nurses have to be hired in Zwolle to cover up the reduced capacity due to the closure of the locations.

Lastly, in addition to the KPIs we focused on in our research there are several factors that can be taken into consideration when deciding on which configuration to implement. A framework often used in healthcare for the delivery of high value care is the Quadruple Aim model. The model focuses on four objectives: improving the patient experience, improving population health, reducing costs, and improving employee satisfaction. From this framework's perspective, it is also valuable to consider the patient and employee satisfaction. For example, patients and nurses may value personal contact, which is often more extensive at the external outpatient clinics and at home because fewer patients are present at the same time. Secondly, the population is ageing and the number of patients with comorbidities is increasing, leading to an increase in demand for care the upcoming years (RIVM, 2018; World Health Organization, 2022). At the same time, shortages of employees are growing (World Health Organization, 2016). Therefore, the efficiency of the different configurations should be considered when making a decision. For example, driving the home routes is less efficient because fewer patients can be treated. On top of that, when there is a shortage of capacity expressed in square metres, transferring the administration from the hospitals to external outpatient clinics can be a good solution. This is because expanding the daycare department in Zwolle and Meppel would mean constructing a new building, which leads to high investment costs. There are currently options available to open more external outpatient clinics. As soon as there is insufficient capacity, it is interesting to look at these options and take them in consideration when deciding. Lastly, possible collaborations with home care organisations, different from the one we studied, can be considered at the external outpatient clinics. External outpatient clinics can be rented together, which may result in lower real estate costs.

8. Recommendations

8.1 Opening and closing external outpatient locations

Table 34 shows the impact of the different experiments in which different combinations of the external outpatient clinics and the administration at home were offered. Which configuration leads to the most optimal configuration depends on the importance of the different KPIs. Closing different forms of external outpatient locations and stopping the administration at home leads to a reduction in costs compared to the current situation. However, it does not lead to a reduction in the CO2 emissions, travel times and travel distance. For all configurations, except for when both external outpatient clinics (Heerde and Kampen) are opened and the administration at home is stopped, the CO2 emissions increased. For all configurations the travel times and travel distances increased compared to the current situation.

The more locations are closed, the bigger the reduction in costs is and the bigger the increase in CO2 emissions, travel times and travel distances is. We therefore recommend Isala to determine which trade-off is desired and what weight each KPI gets, before implementing one of the configurations.

Table 34: Increase and reduction in costs, CO2 emissions, travel times and travel distances per year for opening and closing different external outpatient locations

Experiment				Average number of patients per year	Change in KPIs										Feasibility (%)
	Description				Costs per year (€)	CO2 per year (kg)			Travel times per year (minutes)			Travel distances per year (km)			
	Heerde	Kampen	Home routes			Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	
1	✓	✓	✓	1035	0 (926 258.18)	0 (67 828.81)	0 (67 523.71)	0 (68 131.37)	0 (36 877.60)	0 (36 719.05)	0 (37 036.15)	0 (33 607.87)	0 (33 431.61)	0 (33 784.12)	100
11		✓	✓	1034	-20 568.83	+658.38	+208.93	+1107.82	+339.30	+138.31	+540.28	+629.83	+329.16	+930.50	100
12	✓		✓	1035	-40 502.03	+818.47	+319.06	+1317.87	+406.98	+191.12	+622.83	+1078.54	+815.51	+1341.57	89
13			✓	1035	-61 096.27	+1243.08	+812.22	+1673.94	+453.70	+269.97	+637.43	+1540.51	+1340.61	+1740.40	97
15	✓	✓		1034	-129 642.10	-89.55	-515.76	+336.67	+4300.17	+4093.58	+4506.77	+3656.65	+3438.12	+3875.18	96
17		✓		1033	-152 600.90	+1310.55	+846.283	+1774.81	+4605.58	+4381.15	+4830.01	+4547.74	+4215.98	+4879.51	99
16	✓			1034	-174 796.90	+1807.98	+1368.16	+2247.79	+4647.27	+4416.44	+4878.10	+4876.13	+4574.20	+5178.06	82
14				1034	-197 781.08	+2574.70	+2133.36	+3036.03	+5172.11	+4918.71	+5428.50	+5788.66	+5561.85	+6015.47	84

Table 35 shows the increase in CO2 emissions, travel times and travel distances for every euro reduction in costs per year for the different configurations. Offering administration at home and opening both external outpatient clinics (Heerde and Kampen) leads to the lowest increase in CO2 emissions for every euro reduction in costs, namely an increase of 0. Solely offering administration at home leads to the lowest increase in travel times and travel distances for every euro reduction in costs.

Table 35: increase in CO2 emissions, travel times and travel distances for every 1 euro reduction in costs per year

Experiment				Ratio		
	Description			Increase in CO2 emissions (kg) for every 1 euro reduction in costs (€) per year	Increase in travel times (minutes) for every 1 euro reduction in costs (€) per year	Increase in travel distance (minutes) for every 1 euro reduction in costs (€) per year
	Heerde	Kampen	Home routes			
1	✓	✓	✓	0	0	0
11		✓	✓	0.032	0.016	0.031
12	✓		✓	0.020	0.010	0.027
13			✓	0.020	0.007	0.025
15	✓	✓		0.000	0.033	0.028
17		✓		0.009	0.030	0.030
16	✓			0.010	0.027	0.028
14				0.013	0.026	0.029

8.1.1 Save costs

If Isala's main goal is to save costs compared to the current situation, then any of the configurations different from the current situation can be chosen to implement. However, saving costs always leads to an increase in CO2 emissions, except for when Isala stops offering administration at home and both external outpatient clinics (Heerde and Kampen) are opened, which does not lead to an increase nor reduction in CO2 emissions. On the other, saving costs always leads to an increase in travel time and travel distance. The size of the increase and the feasibility of the configuration differs between the configurations. To analyse the impact on CO2 emissions, travel times and travel distances of the configurations that lead to a cost saving, a Multi-Criteria Decision Analysis (MCDA) was performed. MCDA is an approach to evaluate multiple conflicting attributes in decision making (Stewart, 1992). Table 36 shows the results of the MCDA. The results were examined from three different perspectives: equally importance (i.e. CO2 emissions, travel times and travel distances are equally important), climate perspective (i.e. CO2 emissions are more important), and a patient's perspective (i.e. travel time and travel distance are more important).

Table 36: Multi-Criteria Decision Analysis

Experiment				Normalized scores			Aggerated scores		
	Description			Increase in CO2 emissions (kg) for every 1 euro reduction in costs (€) per year	Increase in travel times (minutes) for every 1 euro reduction in costs (€) per year	Increase in travel distance (minutes) for every 1 euro reduction in costs (€) per year	Equally importance	Climate perspective	Patient's perspective
	Heerde	Kampen	Home routes				Equal weights (0.33, 0.33, 0.33)	CO2 emissions (0.5, 0.25, 0.25)	Travel time and travel distance (0.2, 0.4, 0.4)
1	✓	✓	✓	0	0	0	0	0	0
11		✓	✓	1.00	0.50	1.00	0.83	0.87	0.80
12	✓		✓	0.63	0.30	0.87	0.60	0.61	0.60
13			✓	0.64	0.22	0.82	0.56	0.58	0.55
15	✓	✓		0.00	1.00	0.92	0.64	0.48	0.77
17		✓		0.27	0.91	0.97	0.72	0.60	0.81
16	✓			0.32	0.80	0.91	0.68	0.59	0.75
14				0.41	0.79	0.96	0.72	0.64	0.78

Equally importance

If all KPIs have equal importance and are therefore assigned the same weight, experiment 13 (i.e. closing Kampen and Heerde and driving the home routes) leads to the best outcomes. The configuration leads to an average increase of 0.020 kg CO2 emissions, 0.007 minutes of travel time and 0.025 km of travel distance for every euro reduction per year.

Climate perspective

When we look from a climate perspective, experiment 15 leads to the best outcomes (i.e. opening Heerde and Kampen, stopping the home routes). The configuration does not lead to an increase in kg CO2 emissions for every euro reduction. The travel times increases with 0.033 minutes and the travel distances with 0.028 km for every euro reduction per year.

Patient perspective

From a patient perspective, experiment 13 (i.e. closing Kampen and Heerde and driving the home routes) leads to the best outcomes. The configuration leads to an average increase of 0.020 kg CO2 emissions, 0.007 minutes of travel time and 0.025 km of travel distance for every euro reduction per year.

Lowest costs

Experiment 14 resulted in the lowest costs. In this case, both external outpatient clinics (Kampen and Heerde) are closed, and the home routes are stopped. This reduction in costs is a result of the decrease in total real estate expenses and the absence of vehicle-related costs.

8.1.2 Reduce CO2 emissions, travel time and travel distance

If Isala's main goal is not to save costs compared to the current situation, but when it is more important not to increase the CO2 emissions, travel times and travel distances, it is recommended to keep the current configuration. This is because none of the configurations led to a reduction in CO2 emissions, travel times and travel distances. Most even led to an increase in CO2 emissions, travel times and travel distances compared to the current situation.

8.1.3 Feasibility

The percentage of feasible replications various between the experiments. Not all experiments led to a feasibility percentage ≥ 95%. If Isala wants to ensure that all patients are successfully scheduled in the next four years, a feasibility percentage of 100% is required. The experiments 1 (i.e. the current situation) and 11 (i.e. closing Heerde, opening Kampen, and stopping the home routes) both had a feasibility percentage of 100%

8.2 Other experiments

Table 37 shows the recommendations regarding opening Steenwijk, outsourcing the medicine administration in Heerde to the home care organisation, implementing the procedures evaluated in the Minute study and making more patients eligible for treatment at an external outpatient setting. First, we do not recommend Isala to open external outpatient clinic Steenwijk, since it leads to an increase in costs and CO2 emissions, without reducing the travel times and travel distances of patients. The same applies to outsourcing the administration in Heerde to the home care organisation. This only leads to an increase in costs. Secondly, we do recommend Isala to implement the procedures evaluated in the Minute study. The reduced infusion duration allows for more patients to be scheduled with the same capacity. As a result, more patients can be scheduled closer to home, reducing the travel times and travel distances. Lastly, making more patients eligible for treatment at an external outpatient setting leads to a reduction in the CO2 emissions and travel times. Therefore, we recommend Isala to make these medicines (Vedolizumab, Abatacept and Infliximab) eligible for treatment at an external outpatient setting as well.

Table 37: Recommendations for Steenwijk, home care, Minute study and making more patients eligible

Experiment					Change in KPIs			
Number	Description				Costs per day (€)	CO2 per day (kg)	Travel times per patient (minutes)	Travel distances per patient (km)
	Steen wijk	Home care	Minute study	More eligible				
2 - 6	✓				Increase	Increase	Same	Same
7		✓			Increase	Same	Same	Same
8			✓		Same	Same	Reduction	Reduction
9				✓	Same	Reduction	Reduction	Same

8.3 The magnitude of the impact

To put the impact in perspective, the patient group we focused on in our research consists of 32.06% of the entire population that receives treatment at the daycare department. This means that when all the medicines we focused on in our research are eligible for treatment at an external outpatient setting, in total 32.06% of the population at the daycare department is eligible for treatment at an external outpatient setting. In the experiment that represents the current situation, an average of 27.3% of the patients was scheduled at an external outpatient setting (8.0% Heerde, 9.6% Kampen, and 9.6% at home). We did not estimate the impact of transferring the administrations of the other 67.94% of the patient population at the daycare department from the hospital to an external outpatient setting. In our research, we found that

transferring care from the hospital to an external outpatient setting leads to a reduction in CO2 emissions, travel times and travel distances. Additionally, we found that making more medicines eligible for treatment at an external outpatient setting leads to a reduction in CO2 emissions and travel times. Therefore, it is expected that expanding the group of medicines that is eligible for treatment at an external outpatient setting, thus encompassing a larger portion of the overall patient population at the daycare department, could result in a greater positive impact. In our study, we found that there is sufficient capacity to treat the patients groups we focused on for at least the next three years. For certain configurations, with lower feasibility percentages, there might be a shortage in capacity after these three years. Nevertheless, it is possible that within the other patient groups which we did not include in our research, there may already be a shortage in capacity. When there is a shortage of capacity expressed in square metres, transferring the administration from the hospitals to external outpatient clinics can be a good solution. This is because expanding the daycare department in Zwolle and Meppel would mean constructing a new building, which leads to high investment costs. There are currently options available to open more external outpatient clinics. As soon as there is insufficient capacity, it is interesting to look at these options and take them in consideration when deciding. To conclude, it is expected that a comparable impact will be observed when offering treatment at an external outpatient setting to a larger portion of the patient population at the daycare department. It is expected that the costs will increase when opening new external outpatient clinics and driving more home routes, but it will reduce the CO2 emissions, travel times and travel distances of patients.

8.4 Conclusion

Closing different external outpatient clinics and stopping the administration at home leads to a reduction in costs compared to the current situation. However, it does not lead to a reduction in the CO2 emissions, travel times and travel distance. If Isala's main goal is to save costs compared to the current situation, then any of the configurations in which different locations were closed or the administration at home was stopped, can be chosen to implement. If all KPIs have equal importance, closing Kampen and Heerde, and driving the home routes leads to the best outcomes. Secondly, when we look from a climate perspective, opening Heerde and Kampen, stopping the home routes leads to the best outcomes. Lastly, from a patient perspective, closing Kampen and Heerde, and driving the home routes leads to the best outcomes. Only offering administration at the hospitals leads to the biggest reduction in costs compared to the current situation. When it is more important to not increase the CO2 emissions, travel times and travel distances instead of saving costs, it is recommended to keep the current configuration. If Isala wants to ensure that all patients are successfully scheduled in the next four years, a feasibility percentage of 100% is required. The current situation (i.e. opening both external outpatient clinics and offering administration at home) and closing Heerde, opening Kampen and not offering administration at home have both a feasibility percentage of 100%. It is not recommended to open external outpatient clinic Steenwijk, since this leads to an increase in costs and CO2 emissions, without reducing the travel times and travel distances of patients. The same applies to outsourcing the administration in Heerde to the home care organisation. This only leads to an increase in costs. Secondly, it is recommended to implement the procedures evaluated in the Minute study, since it reduces the travel times and travel distances of. Lastly, making more patients eligible for treatment at an external outpatient setting leads to a reduction in the CO2 emissions and travel times of patients. Therefore, we recommend Isala to make these medicines (Vedolizumab, Abatacept and Infliximab) eligible for treatment at an external outpatient setting as well.

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Appendix A: Questionnaires

Questionnaire External outpatient clinics

Informed Consent
U wordt uitgenodigd om deel te nemen aan een onderzoek genaamd *"Het verplaatsen van parenterale medicatie van het ziekenhuis naar de buitenpoli"*. Dit onderzoek wordt uitgevoerd in opdracht van Isala door Nina ten Broek van de Universiteit Twente.

Het doel van het onderzoek is om inzicht te krijgen in de vervoerskeuzes van patiënten om van en naar de buitenpoli te reizen, en zal ongeveer 5 minuten in beslag nemen. De data zal worden gebruikt om de invloed van vervoerskeuzes op de CO2 uitstoot te bepalen.

Uw deelname aan dit onderzoek is volledig vrijwillig, en u kunt zich elk moment terugtrekken zonder reden op te geven. U bent vrij om vragen niet te beantwoorden.

We zijn van mening dat er geen bekende risico's verbonden zijn aan dit onderzoek. Zoals bij elke onlineactiviteit is het risico op een databreuk echter altijd mogelijk. Wij doen ons best om uw antwoorden vertrouwelijk te houden. We minimaliseren deze risico's door de vragenlijst anoniem af te nemen.

Voor verdere informatie kan u contact opnemen met:

Nina ten Broek
n.b.m.a.tenbroek@student.utwente.nl

Ik heb de informatie gelezen en begrepen en ik geef toestemming om deel te nemen aan dit onderzoek.

- ○ Akkoord
- ○ Niet akkoord

Demografische informatie

Wat is uw leeftijd?
_____

Ik ben een ...

- ○ Man
- ○ Vrouw
- ○ Anders
- ○ Wil ik liever niet zeggen

Wat zijn de 4 cijfers van uw postcode?
_____

Waar woont u?

- ○ Stadscentrum
- ○ Een buitenwijk van een stad
- ○ Dorp
- ○ Platteland

Welk vervoersmiddel heeft u (of uw mantelzorger) vandaag gebruikt om naar de buitenpoli te gaan?

- ○ Benzine auto
- ○ Diesel auto
- ○ Elektrische auto
- ○ (Elektrische) fiets
- ○ Lopend
- ○ Taxi
- ○ Bus
- ○ Trein
- ○ Scooter
- ○ Elektrische scooter
- ○ Brommer
- ○ Elektrische brommer
- ○ Motor
- ○ Anders, _____

Welk vervoersmiddel gaat u (of uw mantelzorger) vandaag gebruiken om naar huis te gaan?

- ○ Benzine auto
- ○ Diesel auto
- ○ Elektrische auto
- ○ (Elektrische) fiets
- ○ Lopend
- ○ Taxi
- ○ Bus
- ○ Trein
- ○ Scooter
- ○ Elektrische scooter
- ○ Brommer
- ○ Elektrische brommer
- ○ Motor
- ○ Anders, _____

Heeft u een autorijbewijs?

- ○ Ja
- ○ Nee

Ik ben afhankelijk van een mantelzorger om van en naar het ziekenhuis te reizen

- ○ Ja
- ○ Nee

Ik kan mij voor korte afstanden (minder dan 5 km) gemakkelijk zonder auto verplaatsen

- ○ Helemaal mee eens
- ○ Eens
- ○ Neutraal
- ○ Oneens
- ○ Helemaal oneens

Vanaf welk aantal extra kilometers op uw huidige reisafstand zou u een andere keuze hebben gemaakt voor vervoersmiddel?

- ○ Vanaf _____
- ○ Dit heeft geen invloed op mijn keuze

Zo ja, wat zou deze keuze zijn?

- ☐ Dan zou ik eerder bewust met een duurzaam vervoersmiddel reizen (bijvoorbeeld: (elektrische) fiets, elektrische auto, lopend)
- ☐ Dan zou ik met een benzine auto reizen
- ☐ Dan zou ik met een diesel auto reizen
- ☐ Dan zou ik met een elektrische auto reizen
- ☐ Dan zou ik met de bus reizen
- ☐ Dan zou ik met de trein reizen
- ☐ Dan zou ik met de (elektrische) fiets gaan
- ☐ Dan zou ik lopend gaan
- ☐ Dan zou ik met de taxi gaan
- ☐ Anders, _____

Vanaf welk aantal verminderde kilometers op uw huidige reisafstand zou u een andere keuze hebben gemaakt voor vervoersmiddel?

○ Vanaf _____

○ Dit heeft geen invloed op mijn keuze

Zo ja, wat zou deze keuze zijn?

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☐ Dan zou ik met een elektrische auto reizen

☐ Dan zou ik met de bus reizen

☐ Dan zou ik met de trein reizen

☐ Dan zou ik met de (elektrische) fiets gaan

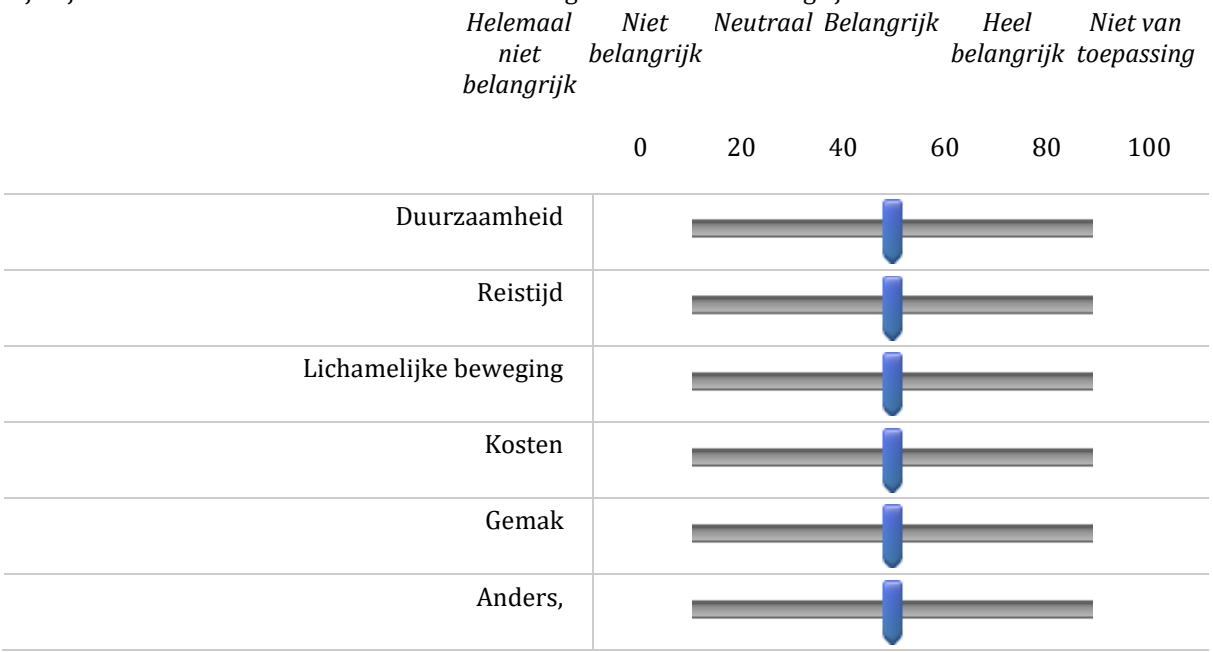
☐ Dan zou ik lopend gaan

☐ Dan zou ik met de taxi gaan

☐ Anders, _____

Hoeveel minuten bent u maximaal bereid om te reizen voor uw behandeling (heen- en terugreis)?
_____

Bij mijn keuze voor vervoersmiddel vind ik de volgende factoren belangrijk



Voorkeuren
Op welke locatie zou u het liefst behandeld willen worden?
(Zet de locaties door te slepen in volgorde van voorkeur, waarbij 1 de locatie is waar u het liefst behandeld zou willen worden)

_____ Polikliniek Heerde
_____ Polikliniek Kampen
_____ Isala Zwolle
_____ Thuis

Opmerkingen
Heeft u verder nog opmerkingen?
_____

Questionnaire Hospital

Informed Consent
U wordt uitgenodigd om deel te nemen aan een onderzoek genaamd *"Het verplaatsen van parenterale medicatie van het ziekenhuis naar de buitenpoli"*. Dit onderzoek wordt uitgevoerd in opdracht van Isala door Nina ten Broek van de Universiteit Twente.

Het doel van het onderzoek is om inzicht te krijgen in de vervoerskeuzes van patiënten om van en naar het ziekenhuis te reizen, en zal ongeveer 5 minuten in beslag nemen. De data zal worden gebruikt om de invloed van vervoerskeuzes op de CO2 uitstoot te bepalen.

Uw deelname aan dit onderzoek is volledig vrijwillig, en u kunt zich elk moment terugtrekken zonder reden op te geven. U bent vrij om vragen niet te beantwoorden.

We zijn van mening dat er geen bekende risico's verbonden zijn aan dit onderzoek. Zoals bij elke onlineactiviteit is het risico op een databreuk echter altijd mogelijk. Wij doen ons best om uw antwoorden vertrouwelijk te houden. We minimaliseren deze risico's door de vragenlijst anoniem af te nemen.

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Waar woont u?

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Welk vervoersmiddel heeft u (of uw mantelzorger) vandaag gebruikt om naar het ziekenhuis te gaan?

- ○ Benzine auto
- ○ Diesel auto
- ○ Elektrische auto
- ○ (Elektrische) fiets
- ○ Lopend
- ○ Taxi
- ○ Bus
- ○ Trein
- ○ Scooter
- ○ Elektrische scooter
- ○ Brommer
- ○ Elektrische brommer
- ○ Motor
- ○ Anders, _____

Welk vervoersmiddel gaat u (of uw mantelzorger) vandaag gebruiken om naar huis te gaan?

- ○ Benzine auto
- ○ Diesel auto
- ○ Elektrische auto
- ○ (Elektrische) fiets
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- ○ Taxi
- ○ Bus
- ○ Trein
- ○ Scooter
- ○ Elektrische scooter
- ○ Brommer
- ○ Elektrische brommer
- ○ Motor
- ○ Anders, _____

Heeft u een autorijbewijs?

- ○ Ja
- ○ Nee

Ik ben afhankelijk van een mantelzorger om van en naar het ziekenhuis te reizen

- ○ Ja
- ○ Nee

Ik kan mij voor korte afstanden (minder dan 5 km) gemakkelijk zonder auto verplaatsen

- ○ Helemaal mee eens
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- ○ Helemaal oneens

Vanaf welk aantal extra kilometers op uw huidige reisafstand zou u een andere keuze hebben gemaakt voor vervoersmiddel?

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- ○ Dit heeft geen invloed op mijn keuze

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- ☐ Dan zou ik met een elektrische auto reizen
- ☐ Dan zou ik met de bus reizen
- ☐ Dan zou ik met de trein reizen
- ☐ Dan zou ik met de (elektrische) fiets gaan
- ☐ Dan zou ik lopend gaan
- ☐ Dan zou ik met de taxi gaan
- ☐ Anders, _____

Vanaf welk aantal verminderde kilometers op uw huidige reisafstand zou u een andere keuze hebben gemaakt voor vervoersmiddel?

○ Vanaf _____

○ Dit heeft geen invloed op mijn keuze

Zo ja, wat zou deze keuze zijn?

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☐ Dan zou ik met een benzine auto reizen

☐ Dan zou ik met een diesel auto reizen

☐ Dan zou ik met een elektrische auto reizen

☐ Dan zou ik met de bus reizen

☐ Dan zou ik met de trein reizen

☐ Dan zou ik met de (elektrische) fiets gaan

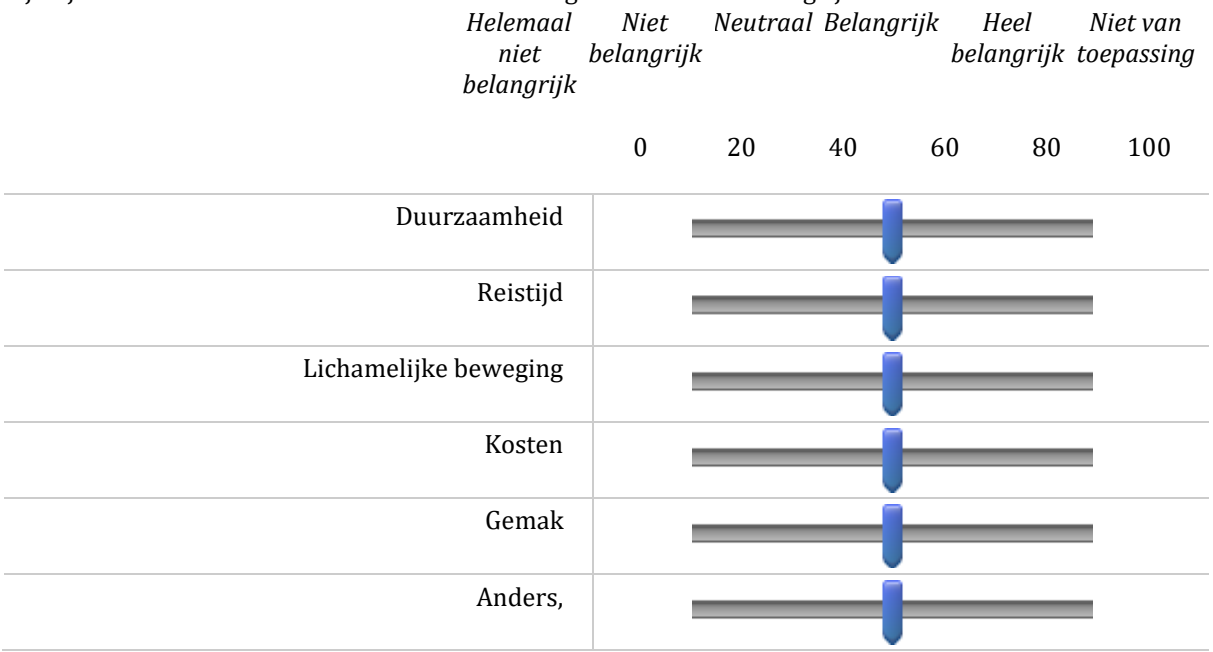
☐ Dan zou ik lopend gaan

☐ Dan zou ik met de taxi gaan

☐ Anders, _____

Hoeveel minuten bent u maximaal bereid om te reizen voor uw behandeling (heen- en terugreis)?
_____

Bij mijn keuze voor vervoersmiddel vind ik de volgende factoren belangrijk



Voorkeuren
Op welke locatie zou u het liefst behandeld willen worden?
(Zet de locaties door te slepen in volgorde van voorkeur, waarbij 1 de locatie is waar u het liefst behandeld zou willen worden)

_____ Polikliniek Heerde
_____ Polikliniek Kampen
_____ Isala Zwolle
_____ Thuis

Opmerkingen
Heeft u verder nog opmerkingen?
_____

Appendix B: Doses inclusion and exclusion

ZOLEDRONINEZUUR

Dose	Years administered in historical dataset	Included or excluded
INFVLST 0,04MG/ML FL 100ML	All	Included
INFVLST 0,05MG/ML FL 100ML	All	Included
INFOPL CONC 0,8MG/ML FL 5ML	2019, 2020, 2021	Excluded (years)

INFLIXIMAB

Dose	Years administered in historical dataset	Included or excluded
INFUSIEPOEDER 100MG FL	All	Included

VEDOLIZUMAB

Dose	Years administered in historical dataset	Included or excluded
INFUSIEPOEDER 300MG FL	All	Included

NIVOLUMAB

Dose	Years administered in historical dataset	Included or excluded
INFOPL CONC 10MG/ML FL 4ML	All	Included
NADINA (NIVOLUMAB) 100MG=10ML (TRIAL)	2022, 2023	Excluded (trial)
CHECKMATE (NIVOLUMAB) 100 MG=10 ML INFVL (TRIAL)	2019, 2020, 2021	Excluded (years + trial)
DRUP (NIVOLUMAB) 100 MG=10 ML INFVL (TRIAL)	2019, 2021, 2022, 2023	Excluded (trial)
NEKTAR (NIVOLUMAB) INJVLST 100MG=10ML (TRIAL)	2021, 2022	Excluded (years + trial)
NIVOLUMAB INFVLST 100MG=10ML (COMP USE)	2019	Excluded (years + comp)

AZACITIDINE

Dose	Years administered in historical dataset	Included or excluded
PDR V INJSUSP 100MG FL	All	Included

BEVACIZUMAB

Dose	Years administered in historical dataset	Included or excluded
INFOPL CONC 25MG/ML FL 16ML	All	Included
DRUP (BEVACIZUMAB) INFVLS 100MG=4ML (TRIAL)	2022	Excluded (years + trial)
TASCO1 (BEVACIZUMAB) INFVLS 100MG=4ML (TRIAL)	2019, 2020	Excluded (years + trial)

TRASTUZUMAB

Dose	Years administered in historical dataset	Included or excluded
INF 150MG F(HER/KAN/OGI/ONT/TRA/ZER)	All	Included
EMTANSINE INFPDR 100MG FL (KADCYLA)	All	Included
INJVLST 120MG/ML FL 5ML (HERCEPTIN)	All	Included
DRUP (TRASTUZUMAB) INFUSIEPDR 150MG (TRIAL)	2022, 2023	Excluded (trial)
DERUXTECAN INFPDR 100MG (COMP USE)	2022, 2023	Excluded (comp)
TRAIN3 (TRASTUZUMAB) INFPDR 150 MG (TRIAL)	2019, 2020, 2021, 2022	Excluded (trial + years)

PEMBROLIZUMAB

Dose	Years administered in historical dataset	Included or excluded

INFOPL CONC 25MG/ML FL 4ML	All	Included
INFVLSTCONC 100MG=4ML (COMP USE)	2019	Excluded (years + comp)
DRUP (PEMBROLIZUMAB) INFVLSTCONC 100MG=4ML (TRIAL)	All	Excluded (trial)
ZEAL1L (PEMBROLIZUMAB) INFVLS 100MG=4ML (TRIAL)	2021, 2022	Excluded (years + trial)

BORTEZOMIB

Dose	Years administered in historical dataset	Included or excluded
INJVLST 2,5MG/ML FL 1,4ML	All	Included
INJECTIEPOEDER 3,5MG FL	2019	Excluded (years)

DARATUMUMAB

Dose	Years administered in historical dataset	Included or excluded
INJVLST 120MG/ML FL 15ML	2020, 2021, 2022, 2023	Included
INFOPL CONC 20MG/ML FL 5ML	2019, 2020	Excluded (years)
INFOPL CONC 20MG/ML FL 20ML	2019	Excluded (years)
MAJESTEC3 INJVL FL 1800MG=15ML(TRIAL)	2022, 2023	Excluded (trial)
DARZALEX INJVLST 120MG/ML FLACON 15ML (COMP USE)	2023	Excluded (comp)

IMMUNOGLOBULINES

Dose	Years administered in historical dataset	Included or excluded
PRIVIGEN INFVLST 100MG/ML FLACON 50ML	All	Included
OCTAGAM INFUSIEVLOEISTOF 50MG/ML FLACON 200ML	All	Included
OCTAGAM INFUSIEVLOEISTOF 100MG/ML FLACON 50ML	2021, 2022, 2023	Included
OCTAGAM INFUSIEVLOEISTOF 100MG/ML FLACON 200ML	2021, 2023	Included
NANOGAM INFUSIEVLOEISTOF 100MG/ML FLACON 25ML	2021, 2022, 2023	Included
NANOGAM INFUSIEVLOEISTOF 50MG/ML FLACON 50ML	2019, 2020, 2021	Excluded (years)
NANOGAM COVID19 INFVL 100MG/ML FLACON 200ML	2021	Excluded (years)
NORMAAL INFVLST 50MG/ML FL 400ML	2019, 2022	Excluded (years)
NORMAAL INFVLST 100MG/ML FL 200ML	2019, 2021, 2022, 2023	Included
NORMAAL INFVLST 100MG/ML FL 100ML	2019, 2020, 2022, 2023	Included
NORMAAL INFVLST 100MG/ML FL 50ML	2019, 2020, 2021, 2022	Excluded (years)
NORMAAL INFVLST 50MG/ML FL 100ML	2019, 2023	Included
NORMAAL INFVLST 50MG/ML FL 50ML	2019, 2023	Included
NORMAAL INFVLST 100MG/ML FL 25ML	2019, 2021	Excluded (years)
NORMAAL INFVLST 100MG/ML FL 10ML	2020	Excluded (years)
KIOVIG INFUSIEVLOEISTOF 100MG/ML FLACON 100ML	2019, 2020	Excluded (years)
KIOVIG INFUSIEVLOEISTOF 100MG/ML FLACON 50ML	All	Included

ABATACEPT

Dose	Years administered in historical dataset	Included or excluded
INFUSIEPOEDER 250MG FL	All	Included

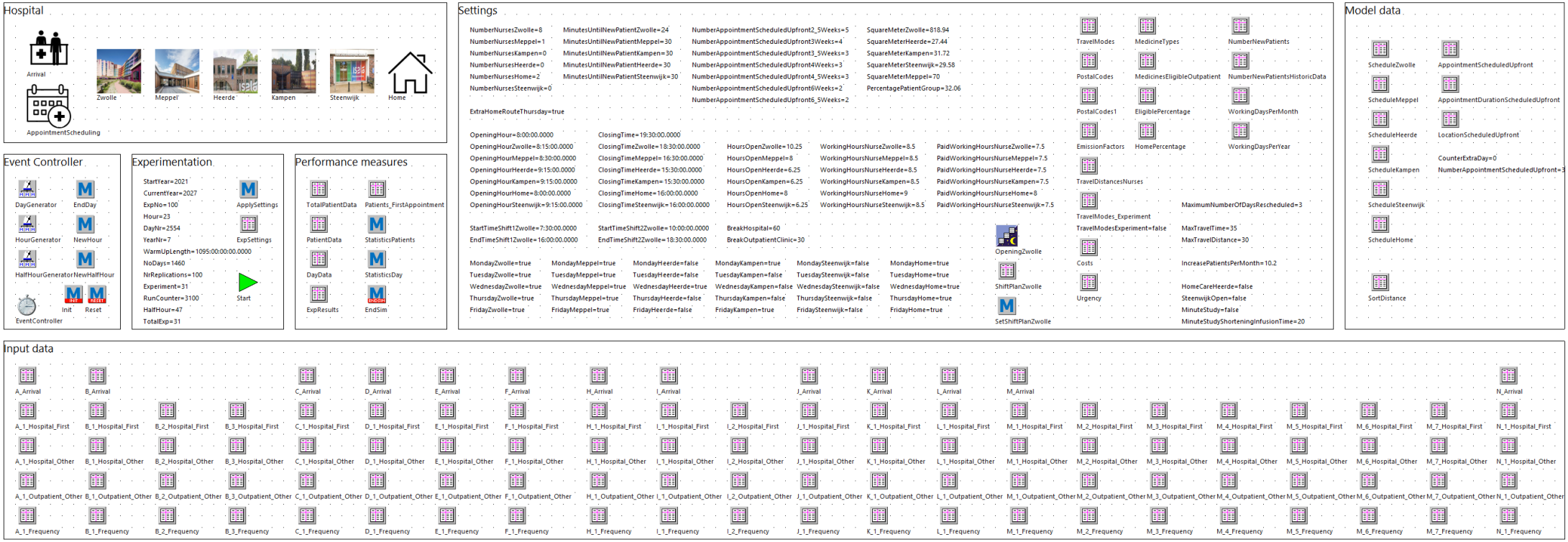
CARFILZOMIB

Dose	Years administered in historical dataset	Included or excluded
INFUSIEPOEDER 60MG FL	All	Included

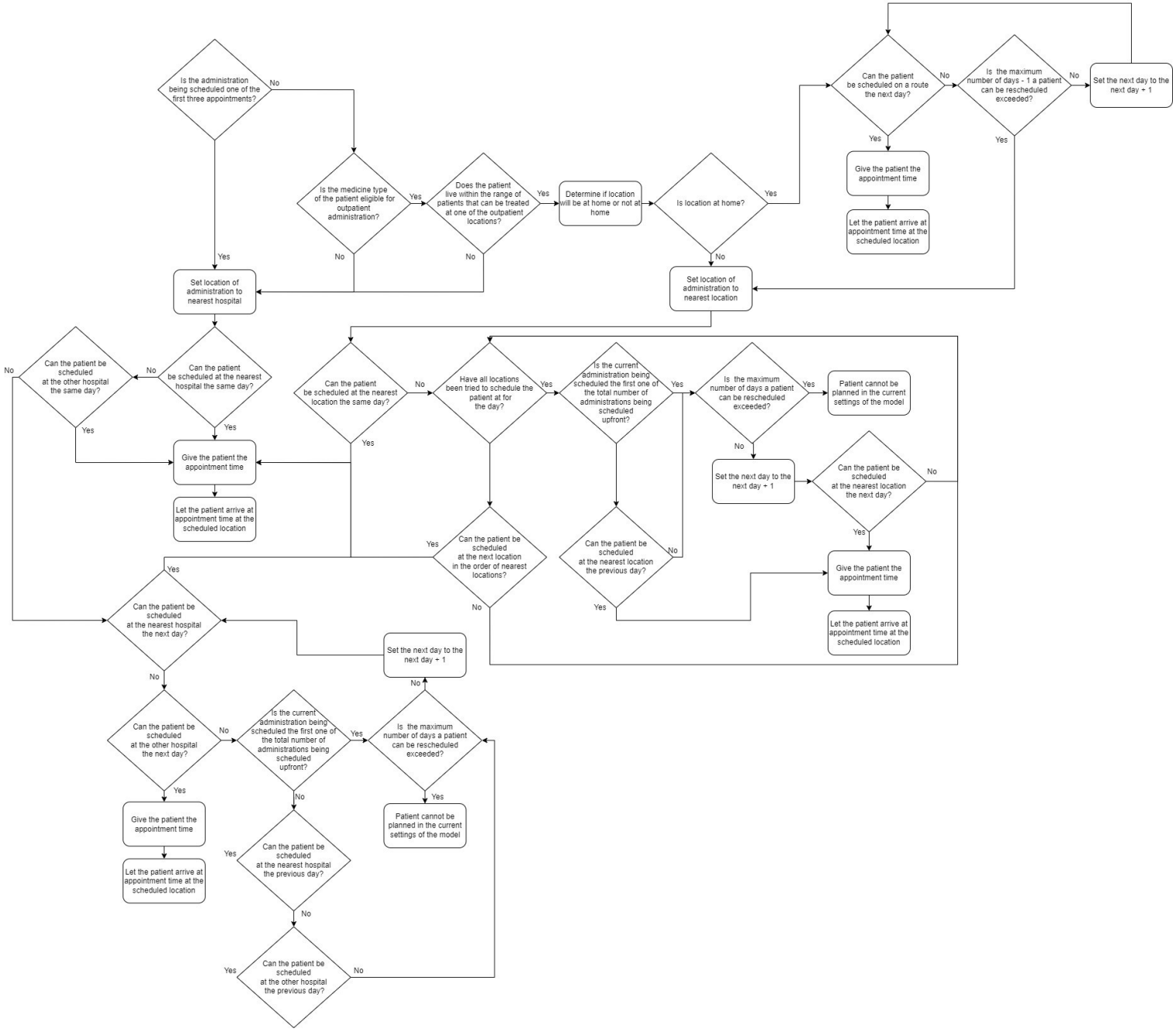
BLINATUMOMAB

Dose	Years administered in historical dataset	Included or excluded
HOVON146 (BLINATUMOMAB) INFPDR 38,5MCG (TRIAL)	2019, 2020	Excluded (trial + years)

Appendix C: Control panel Plant Simulation model



Appendix D: Flow chart appointment scheduling



Appendix E: Validation of the model

1. Age

Table 38 shows the results of the t-tests that were performed to determine if there was a statistically significant difference between the historical data and the simulation data. All p-values are greater than 0.05, indicating that there is no statistically significant difference between the ages in the historical data and the simulation data.

Table 38: T-tests on age for all medicine types

Medicine type	*T*	*df*	*P-value*	*Mean Historical*	*Mean Simulation*
Bortezomib	-1.40	92.06	0.16	66.8	68.5
Trastuzumab	1.08	374.33	0.28	60.0	58.9
Bevacizumab	0.57	408.48	0.57	65.5	65.0
Nivolumab	0.92	708.40	0.35	66.7	66.0
Azacitidine	-0.71	138.82	0.48	73.8	74.5
Pembrolizumab	0.53	1186.50	0.60	68.1	67.9
Blinatumomab	-	-	-	-	-
Carfilzomib	-1.06	2.28640	0.39	64.0	66.3
Zoledroninezuur	-0.86	2168.90	0.39	66.6	66.9
Daratumumab	0.87	166.49	0.39	72.5	71.7
Vedolizumab	0.74	227.44	0.46	48.6	47.3
Abatacept	0.88	90.33	0.38	62.7	60.2
Immunoglobulins	-0.18	308.32	0.86	65.0	65.2
Infliximab	1.54	919.77	0.13	43.9	42.3

2. Total number of administrations

Table 39 shows the results of the t-tests that were performed to determine if there was a statistically significant difference between the total number of administrations in the historical data and the simulation data. All p-values are greater than 0.05, except a dose of Zoledroninezuur. This means that for those doses there is no statistically significant difference between the total number of administrations in the historical data and the simulation data. The small p-value for the dose of Zoledroninezuur can be explained by the limited data. In addition, the days between the appointments are long for the dose of Zoledroninezuur, namely 1-2 years. T tests could not be performed for dose Blinatumomab and two doses of Immunoglobulins (5 and 6) due to limited data.

Table 39: T-test on total number of administrations for all doses

Medicine type	*T*	*df*	*p-value*	*Mean Historical*	*Mean Simulation*
Bortezomib	-0.64	232.34	0.53	14.2	14.8
Trastuzumab 1	-0.24	680.40	0.81	13.8	13.9
Trastuzumab 2	0.31	93.82	0.76	9.6	9.2
Trastuzumab 3	-0.15	56.42	0.88	11.4	11.9
Bevacizumab	1.14	487.41	0.26	8.2	7.5
Nivolumab	-0.34	1088.10	0.73	8.6	8.8
Azacitidine	1.06	166.52	0.29	37.1	33.4
Pembrolizumab	-0.13	1324.60	0.90	8.6	8.6
Blinatumomab	-	-	-	-	-
Carfilzomib	1.09	43.59	0.28	20.7	17.0
Zoledroninezuur 1	-1.72	1932.50	0.09	4.4	4.7
Zoledroninezuur 2	-14.60	890.96	$2.2e^{-16}$	1.6	2.4
Daratumumab	0.20	232.93	0.84	16.5	16.3
Vedolizumab	0.53	251.14	0.60	13.5	12.9

Abatacept	-0.83	106.48	0.60	17.9	19.6
Immunoglobulins 1	-0.47	85.768	0.64	21.0	22.6
Immunoglobulins 2	0.23	35.98	0.82	15.3	13.9
Immunoglobulins 3	-0.31	32.18	0.76	12.0	13.6
Immunoglobulins 4	0.02	45.06	0.99	19.3	19.3
Immunoglobulins 5	-	-	-	-	-
Immunoglobulins 6	-	-	-	-	-
Immunoglobulins 7	0.04	15.37	0.97	17.6	17.1
Infliximab	-0.87	1376.50	0.39	19.2	19.8

3. Female and male ratio

Table 40 shows the results of three different tests that were performed to see if there was a statistically significant difference between the female/male ratio of the historical data and the simulation data. Three different types of tests were performed, since not all tests always gave a good approximation due to sample sizes. For all medicine types, there was no statistically significant difference between the historical data and the simulation data.

Table 40: Statistics test on the female and male ratio in the historical and simulation data

Medicine type	*Chi-squared*	*Fisher*	*G-test*
Bortezomib	0.88	0.81	0.69
Trastuzumab	-	0.27	0.29
Bevacizumab	0.56	0.51	0.48
Nivolumab	0.09	0.08	0.06
Azacitidine	0.81	0.78	0.60
Pembrolizumab	0.61	0.59	0.56
Blinatumomab	-	-	-
Carfilzomib	-	1.00	0.31
Zoledroninezuur	0.66	0.60	0.60
Daratumumab	0.59	0.54	0.46
Vedolizumab	0.30	0.26	0.23
Abatacept	-	0.51	0.45
Immunoglobulins	0.20	0.17	0.14
Infliximab	0.85	0.85	0.78

4. Appointment duration

For both the appointments at the hospital and appointments at an external outpatient setting, separate boxplots and QQ plots were created to visualise the difference between the appointment duration of the historical data and the simulation data. In general, the simulation data represents the historical data accurately. However, when there was limited data in the historical data, the simulation model automatically represented the historical data less accurately.

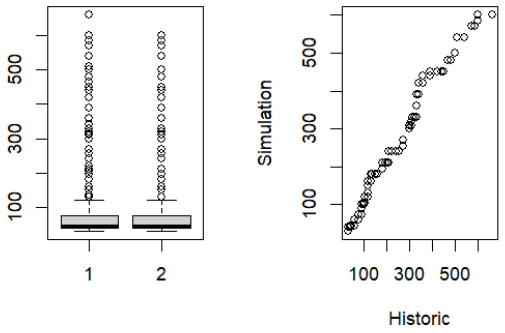


Figure 22: Box & QQ plot appointment duration, hospital Bortezomib

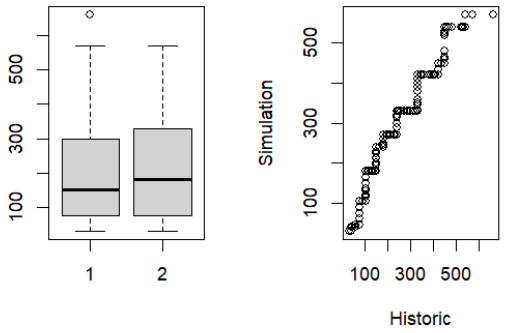


Figure 23: Box &QQ plot appointment duration hospital, Trastuzumab

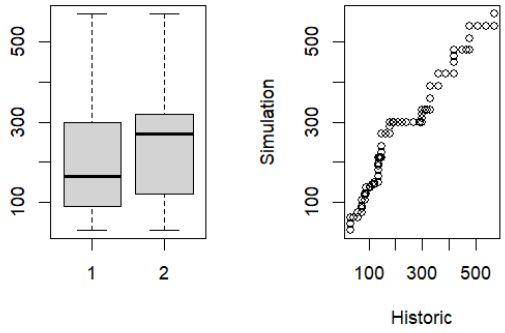


Figure 24: Box & QQ plot appointment duration, hospital Bevacizumab

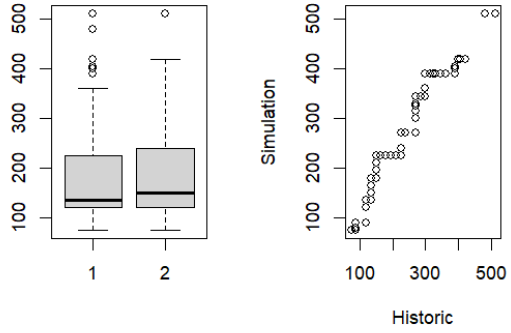


Figure 25: Box & QQ plot appointment duration, hospital Nivolumab

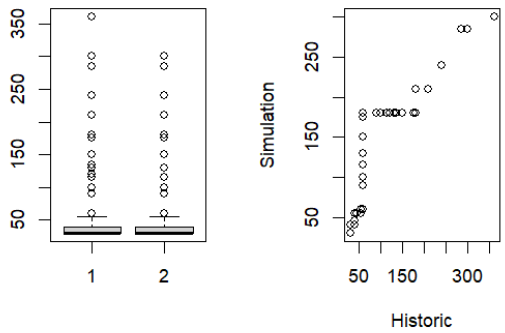


Figure 26: Box & QQ plot appointment duration, hospital Azacitidine

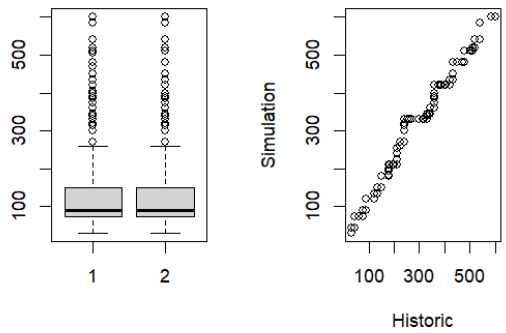


Figure 27: Box & QQ plot appointment duration, hospital Pembrolizumab

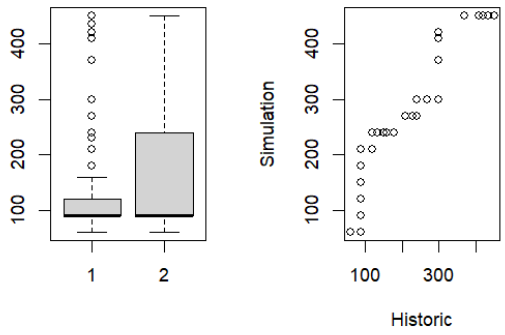


Figure 28: Box & QQ plot appointment duration, hospital Carfilzomib

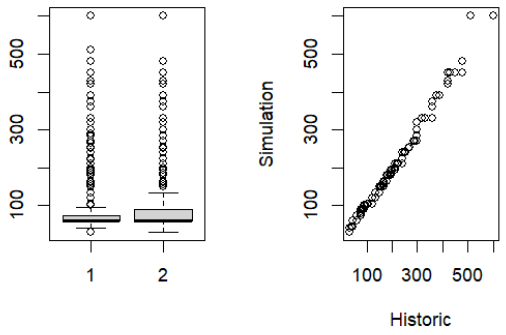


Figure 29: Box & QQ plot appointment duration, hospital Zoledroninezuur

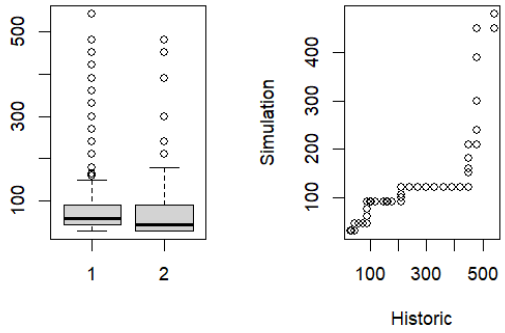


Figure 30: Box & QQ plot appointment duration, hospital Daratumumab

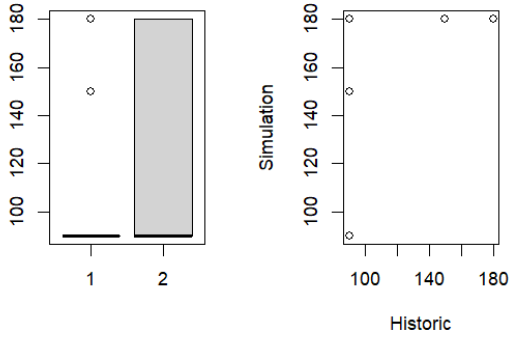


Figure 31: Box & QQ plot appointment duration, hospital Vedolizumab

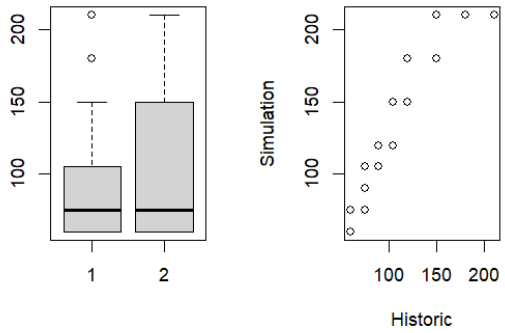


Figure 32: Box & QQ plot appointment duration, hospital Abatacept

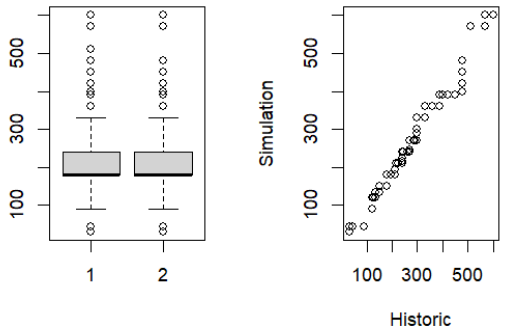


Figure 33: Box & QQ plot appointment duration, hospital Immunoglobulins

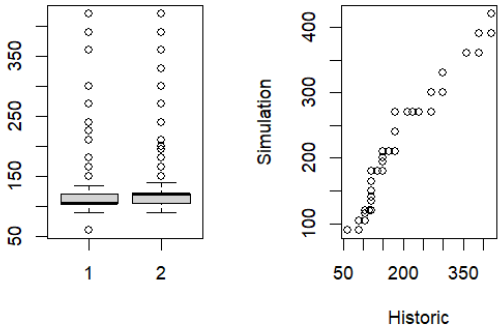


Figure 34: Box & QQ plot appointment duration, hospital Infliximab

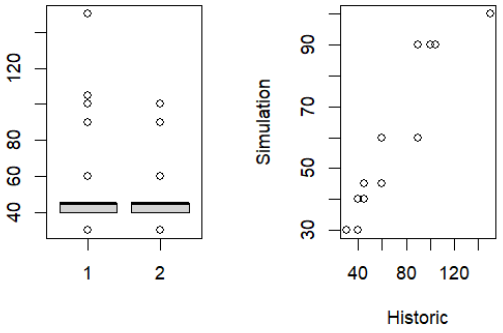


Figure 35: Box & QQ plot appointment duration, outpatient Bortezomib

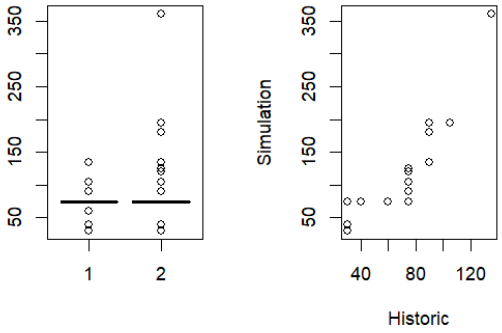


Figure 36: Box & QQ plot appointment duration, outpatient Trastuzumab

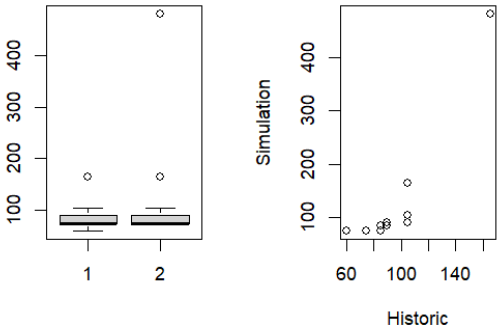


Figure 37: Box & QQ plot appointment duration, outpatient Bevacizumab

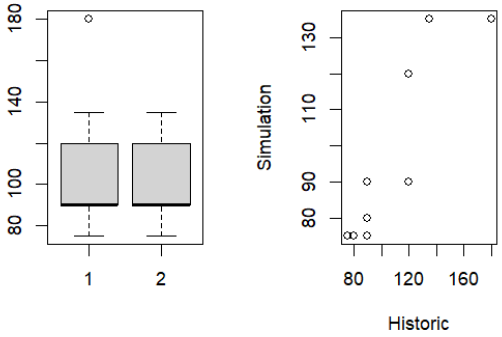


Figure 38: Box & QQ plot appointment duration, outpatient Nivolumab

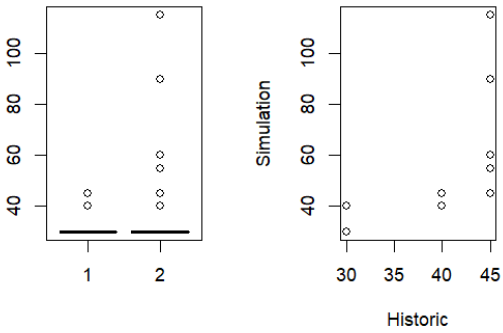


Figure 39: Box & QQ plot appointment duration, outpatient Azacitidine

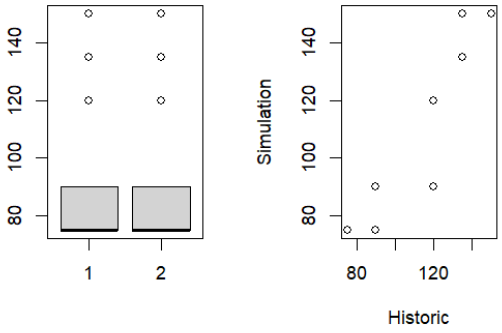


Figure 40: Box & QQ plot appointment duration, outpatient Pembrolizumab Carfilzomib

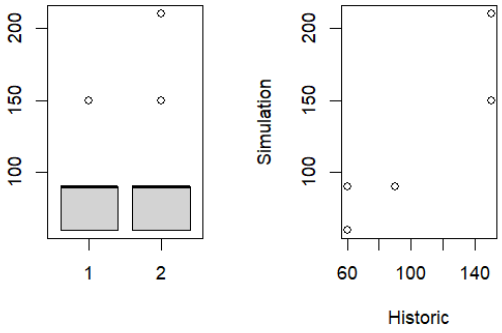


Figure 41: Box & QQ plot appointment duration, outpatient

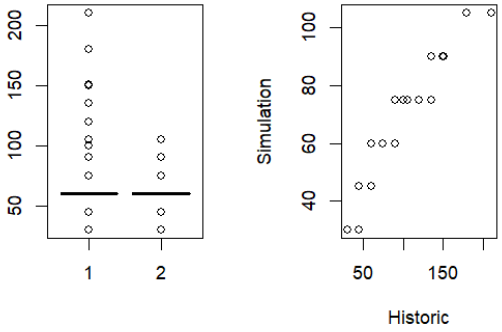


Figure 42: Box & QQ plot appointment duration, outpatient Zoledroninezuur Daratumumab

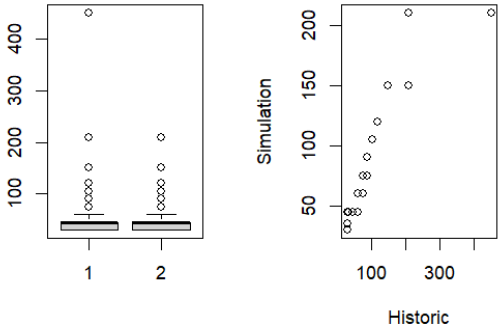


Figure 43: Box & QQ plot appointment duration, outpatient

Appendix F: Warm-up period and number of replications

1. Warm-up period

The simulation is a non-termination simulation. This means that there is no natural event in the simulation that determines the end of the simulation. We start our model with an empty system. There are no patients in the model who return every so often for treatment. To represent the current situation at Isala as best as possible, the model must first run for several days to reach a steady state behaviour, the so-called warm-up period.

Welch's method was used to determine the warm-up period. The Welch's method calculates the moving average over a window to smooth out high-frequency oscillations. The moving averages are then plotted. The warm-up period is the point beyond which the model reaches a steady state (Welch, 1983). To determine the warm-up period, we ran the current situation scenario for 3285 days (9 years). The moving averages of different windows were plotted, see Figure 44.

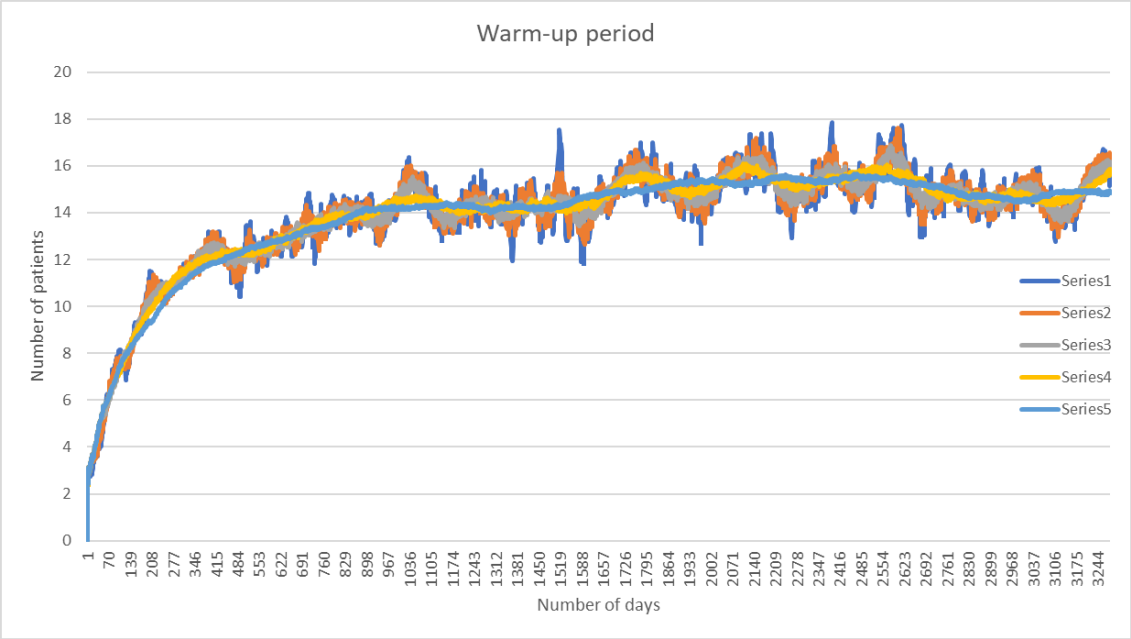


Figure 44: Welch's method for warm-up period

Based on Figure 44, a warm-up period of at least 904 days is needed, which is 2.48 years. To ensure that the model can run properly, and data is stored correctly, the warm-up period is set to 1095 days, which is 3 years. The model starts running in 2021 and generates outcomes from the year 2024.

1. Number of replications

To determine the number of replications needed, the approach by Law (2015) was used. We ran 10 independent replications. Each replication had a warm-up period of 1095 days and were run for an additional 2555 days. Each replication used a different seed value. After that, we calculated how many replications were needed until the width of the confidence interval, relative to the average, was smaller than 5%. For the KPI CO2 emission, travel distance, travel time and number of patients at Zwolle 3 replications were sufficient. For the KPI costs and number of patients at home only 2 replications were sufficient. For the number of patients at Meppel, the number of patients at Kampen and the number of patients at Heerde were 5, 9 and 10 replications sufficient respectively. Based on this. we set the minimum number of replications to 10.

Appendix G: Data analysis

1. Descriptive statistics dataset

1.1 Age

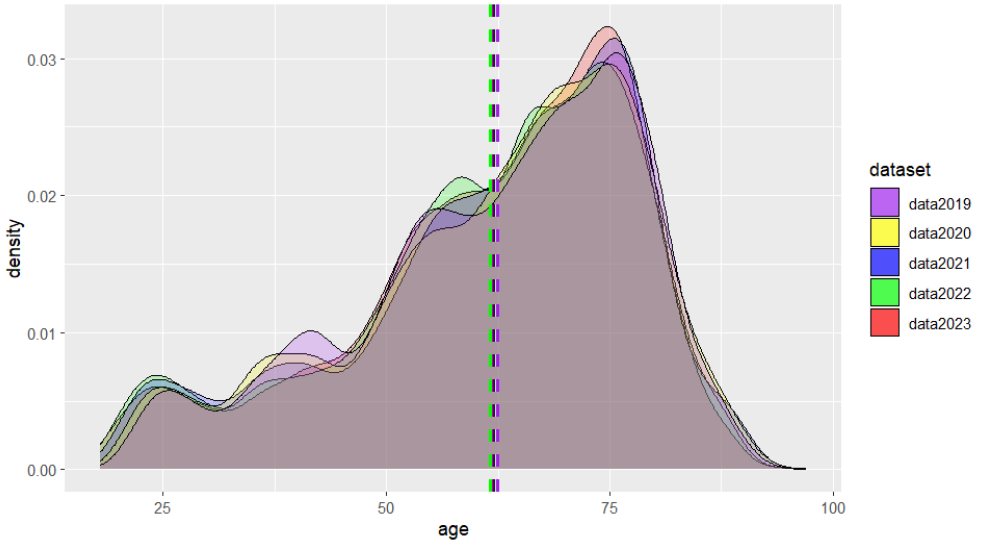


Figure 45: Density plot of the ages (all medicines)

Table 41: Median, Mean and 95% CI of age (all medicines)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	66	62.39	62.08	62.70
2020	66	62.31	62.00	62.62
2021	66	62.06	61.75	62.37
2022	65	61.56	61.27	61.85
2023	66	61.88	61.58	62.17

1.2 Gender

Table 42: Number of females and males (all medicines)

Year	Female	Male	Percentages female	Percentages male
2019	5185	4665	52.6	47.4
2020	5394	4897	52.4	47.6
2021	5481	5113	51.7	48.3
2022	6129	5893	51	49
2023	5558	5407	50.7	49.3

1.3 Location of administration

Table 43: Number of appointments per location (all medicines)

Year	Thuis	Zwolle	Meppel	Heerde	Kampen	% Thuis	% Zwolle	% Meppel	% Heerde	% Kampen
2019	0	8002	1848	0	0	0	81.2	18.8	0	0
2020	1100	7125	2066	0	0	10.7	69.2	20.1	0	0
2021	1180	7252	2162	0	0	11.1	68.5	20.4	0	0
2022	1230	8137	2588	67	0	10.2	67.7	21.5	0.6	0
2023	1120	6923	2576	212	134	10.2	63.1	23.5	1.9	1.2

2. All medicine types

2.1 Number of patients

Table 44: Number of patients (all medicines)

Year	Number of patients	Absolute increase	Increase in percentages
2019	1558		
2020	1658	100	6.4
2021	1755	97	5.9
2022	1996	241	13.7
2023	2046	50	2.5

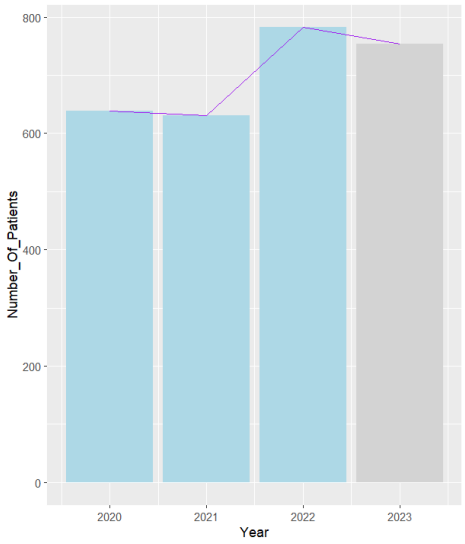


Figure 46: Histogram number of patients (all medicines)

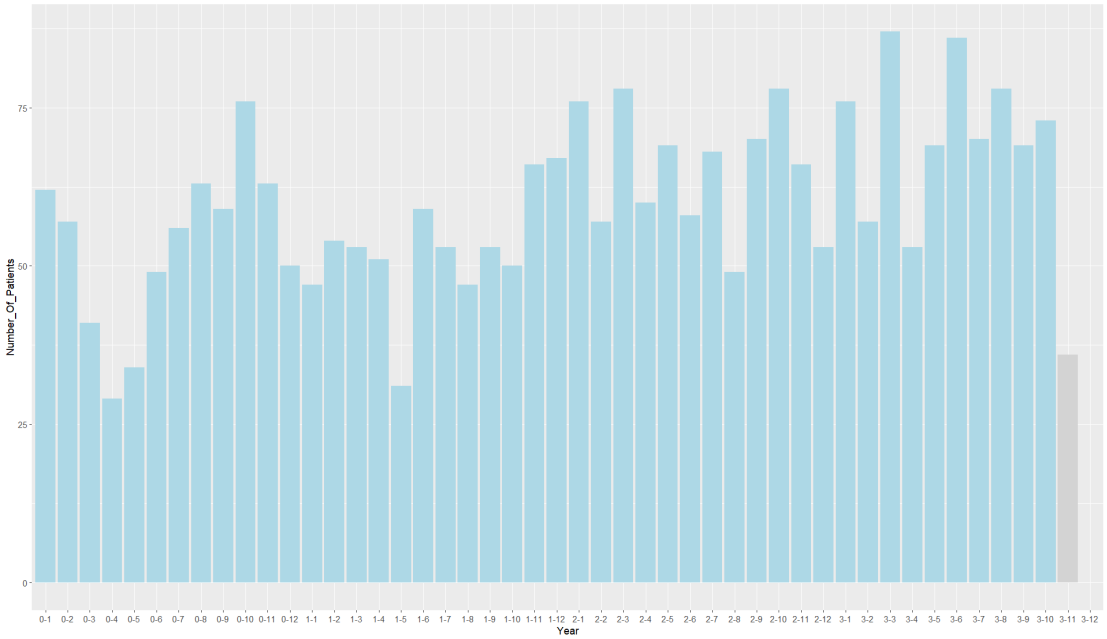


Figure 47: Number of patients per month (all medicines)

Table 45: Number of patients per month (all medicines)

	Number patients				***Absolute increase***			***Increase percentage***		
Month	*2020*	*2021*	*2022*	*2023*	*2020-2021*	*2021-2022*	*2022-2023*	*2020-2021*	*2021-2022*	*2022-2023*
1	62	47	76	76	-15	29	0	-24.2	61.7	0
2	57	54	57	57	-3	3	0	-5.3	5.6	0
3	41	53	78	87	12	25	9	29.3	47.2	11.5
4	29	51	60	53	22	9	-7	75.9	17.6	-11.7
5	34	31	69	69	-3	38	0	-8.8	122.6	0
6	49	59	58	86	10	-1	28	20.4	-1.7	48.3
7	56	53	68	70	-3	15	2	-5.4	28.3	2.9
8	63	47	49	78	-16	2	29	-25.4	4.3	59.2
9	59	53	70	69	-6	17	-1	-10.2	32.1	-1.4
10	76	50	78	73	-26	28	-5	-34.2	56	-6.4
11	63	66	66	36	3	0	-30	4.8	0	-45.5
12	50	67	53	0	17	-14	-53	34	-20.9	-100

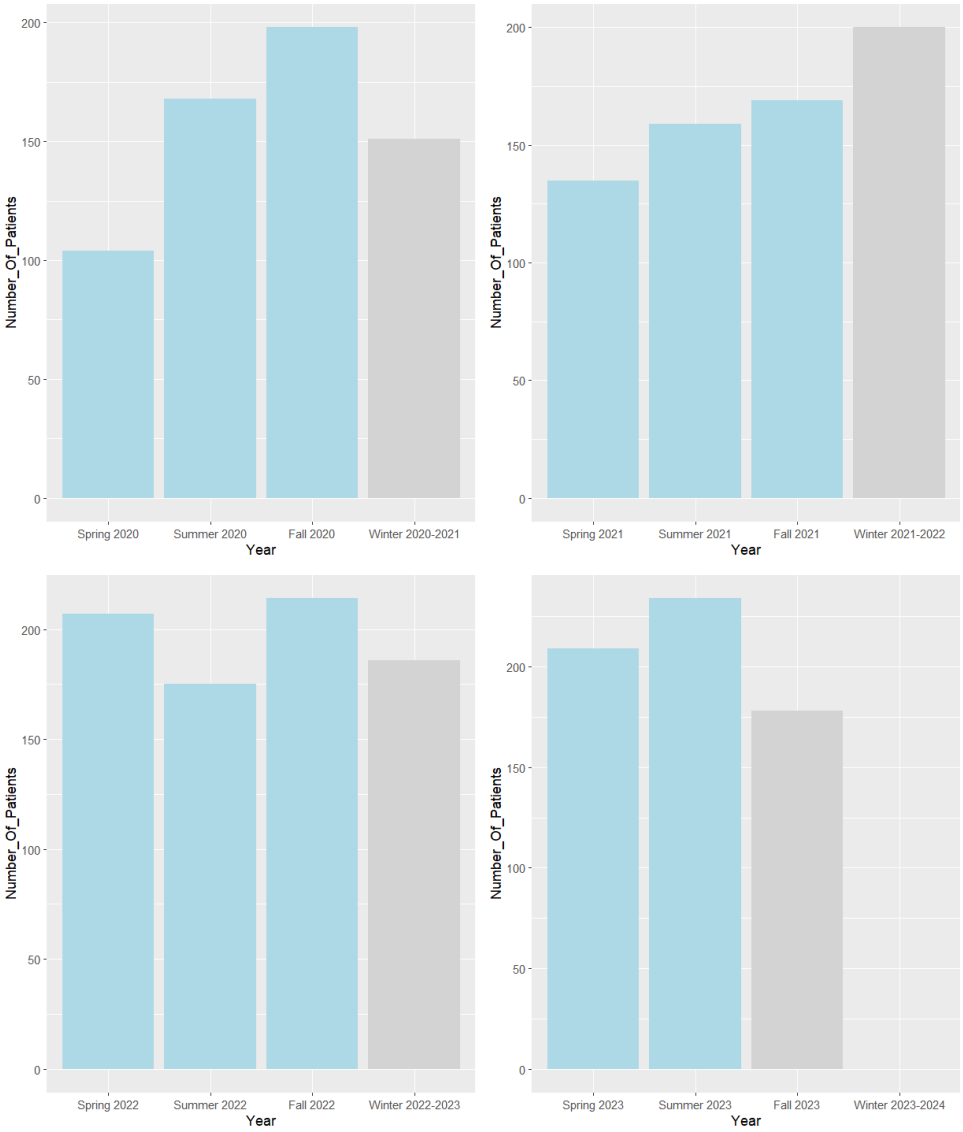


Figure 48: Number of patients over the seasons (all medicines)

Table 46: Number of patients over the months (estimation of 2023) (all medicines)

	Number patients				***Absolute increase***			***Increase percentage***		
Month	*2020*	*2021*	*2022*	*2023*	*2020-2021*	*2021-2022*	*2022-2023*	*2020-2021*	*2021-2022*	*2022-2023*
1	62	47	76	76	-15	29	0	-24.2	61.7	0
2	57	54	57	57	-3	3	0	-5.3	5.6	0
3	41	53	78	87	12	25	9	29.3	47.2	11.5
4	29	51	60	53	22	9	-7	75.9	17.6	-11.7
5	34	31	69	69	-3	38	0	-8.8	122.6	0
6	49	59	58	86	10	-1	28	20.4	-1.7	48.3
7	56	53	68	70	-3	15	2	-5.4	28.3	2.9
8	63	47	49	78	-16	2	29	-25.4	4.3	59.2
9	59	53	70	69	-6	17	-1	-10.2	32.1	-1.4
10	76	50	78	73	-26	28	-5	-34.2	56	-6.4
11	63	66	66	76	3	0	10	4.8	0	15.2
12	50	67	53	78	17	-14	25	34	-20.9	47.2

Table 47: Number of patients per year (estimation of 2023) (all medicines)

Year	Number of patients	Absolute increase	Increase in percentages
2019			
2020	639		
2021	631	-8	-1.3
2022	782	151	23.9
2023	872	90	11.5

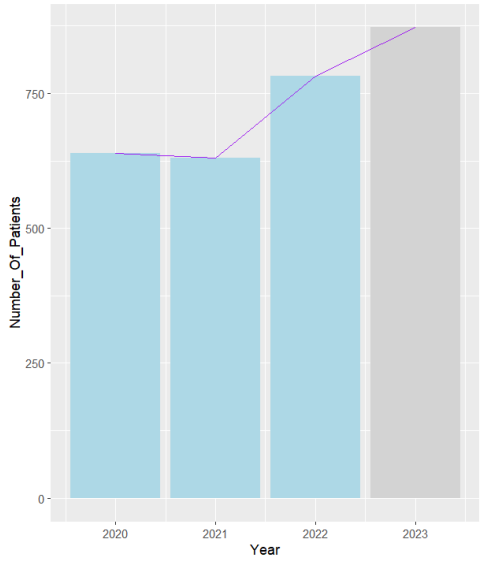


Figure 49: Histogram number of patients per year (estimation of 2023) (all medicines)

2.2 Number of appointments

Table 48: Number of appointments (all medicines)

Year	Number of appointments	Absolute increase	Increase in percentages
2019	9850		
2020	10291	441	4.5
2021	10594	303	2.9
2022	12022	1428	13.5
2023	10965	-1057	-8.8

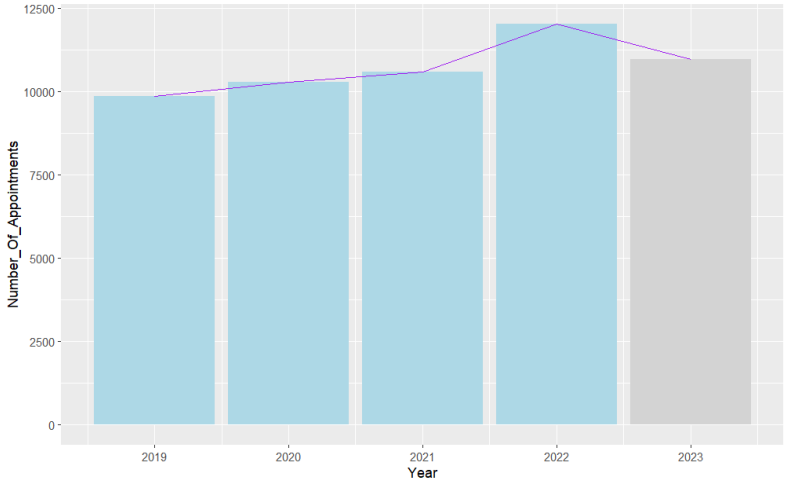


Figure 50: Histogram number of appointments over the years (all medicines)

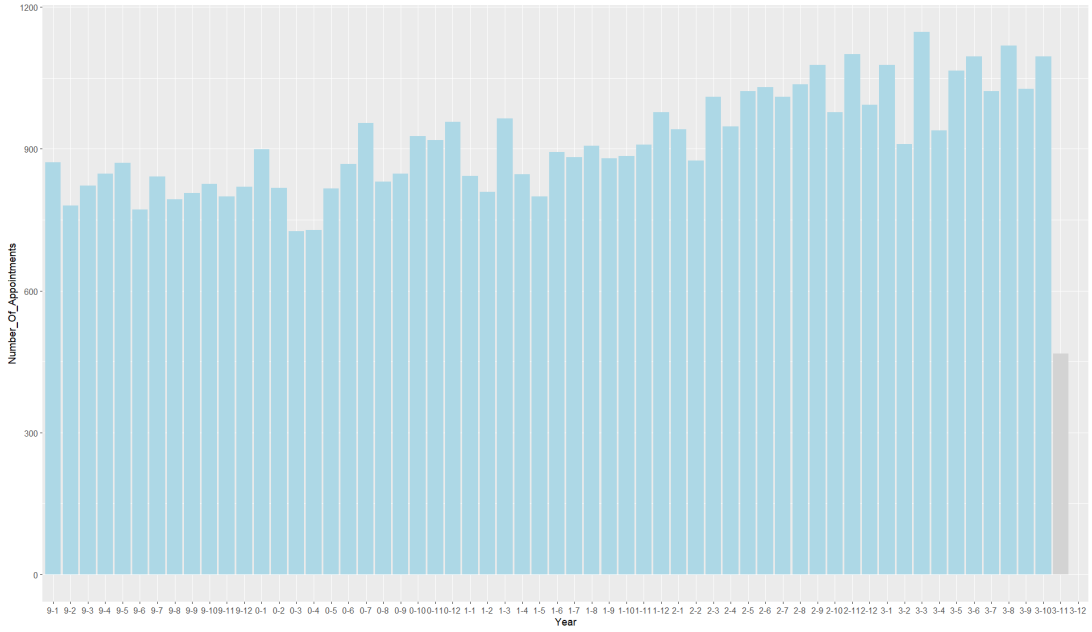


Figure 51: Histogram number of appointments per month (all medicines)

Table 49: Number of appointments over the months (all medicines)

	Number appointments					***Absolute increase***				***Increase percentage***			
Month	*2019*	*2020*	*2021*	*2022*	*2023*	*2019-2020*	*2020-2021*	*2021-2022*	*2022-2023*	*2019-2020*	*2020-2021*	*2021-2022*	*2022-2023*
1	872	899	843	942	1078	27	-56	99	136	3.1	-6.2	11.7	14.4
2	780	818	809	875	910	38	-9	66	35	4.9	-1.1	8.2	4
3	822	726	964	1010	1147	-96	238	46	137	-11.7	32.8	4.8	13.6
4	848	728	846	947	939	-120	118	101	-8	-14.2	16.2	11.9	-0.8
5	870	816	799	1022	1066	-54	-17	223	44	-6.2	-2.1	27.9	4.3
6	772	868	893	1030	1096	96	25	137	66	12.4	2.9	15.3	6.4
7	841	955	882	1010	1022	114	-73	128	12	13.6	-7.6	14.5	1.2
8	793	831	906	1037	1118	38	75	131	81	4.8	9	14.5	7.8
9	807	848	880	1078	1027	41	32	198	-51	5.1	3.8	22.5	-4.7
10	826	927	885	978	1095	101	-42	93	117	12.2	-4.5	10.5	12
11	799	918	909	1100	467	119	-9	191	-633	14.9	-1	21	-57.5
12	820	957	978	993	0	137	21	15	-993	16.7	2.2	1.5	-100

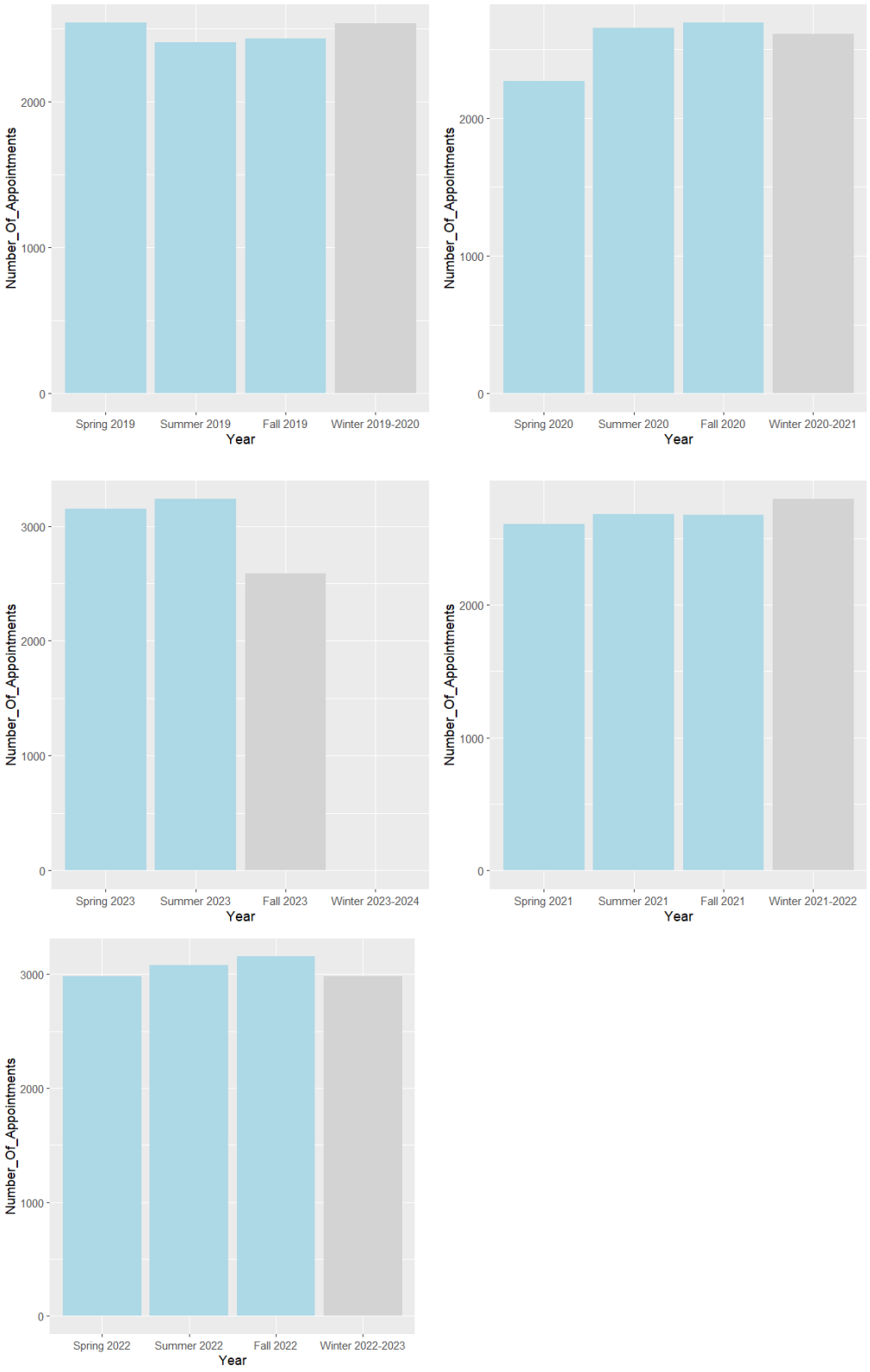


Figure 52: Number of appointments over the seasons (all medicines)

Table 50: Number of appointments over the months (estimation of 2023) (all medicines)

	Number appointments					***Absolute increase***				***Increase percentage***			
Month	*2019*	*2020*	*2021*	*2022*	*2023*	*2019-2020*	*2020-2021*	*2021-2022*	*2022-2023*	*2019-2020*	*2020-2021*	*2021-2022*	*2022-2023*
1	872	899	843	942	1078	27	-56	99	136	3.1	-6.2	11.7	14.4
2	780	818	809	875	910	38	-9	66	35	4.9	-1.1	8.2	4
3	822	726	964	1010	1147	-96	238	46	137	-11.7	32.8	4.8	13.6
4	848	728	846	947	939	-120	118	101	-8	-14.2	16.2	11.9	-0.8
5	870	816	799	1022	1066	-54	-17	223	44	-6.2	-2.1	27.9	4.3
6	772	868	893	1030	1096	96	25	137	66	12.4	2.9	15.3	6.4
7	841	955	882	1010	1022	114	-73	128	12	13.6	-7.6	14.5	1.2
8	793	831	906	1037	1118	38	75	131	81	4.8	9	14.5	7.8
9	807	848	880	1078	1027	41	32	198	-51	5.1	3.8	22.5	-4.7
10	826	927	885	978	1095	101	-42	93	117	12.2	-4.5	10.5	12
11	799	918	909	1100	1104	119	-9	191	4	14.9	-1	21	0.36
12	820	957	978	993	1113	137	21	15	20	16.7	2.2	1.5	2.01

Table 51: Number of appointments per year (estimation of 2023) (all medicines)

Year	Number of appointments	Absolute increase	Increase in percentages
2019	9850		
2020	10291	441	4.5
2021	10594	303	2.9
2022	12022	1428	13.5
2023	12715	693	5.8

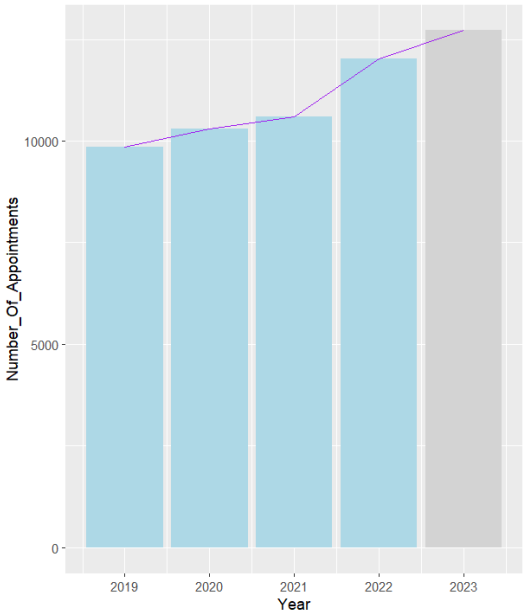


Figure 53: Histogram number of appointments per year (estimation of 2023) (all medicines)

2.3 Appointment duration

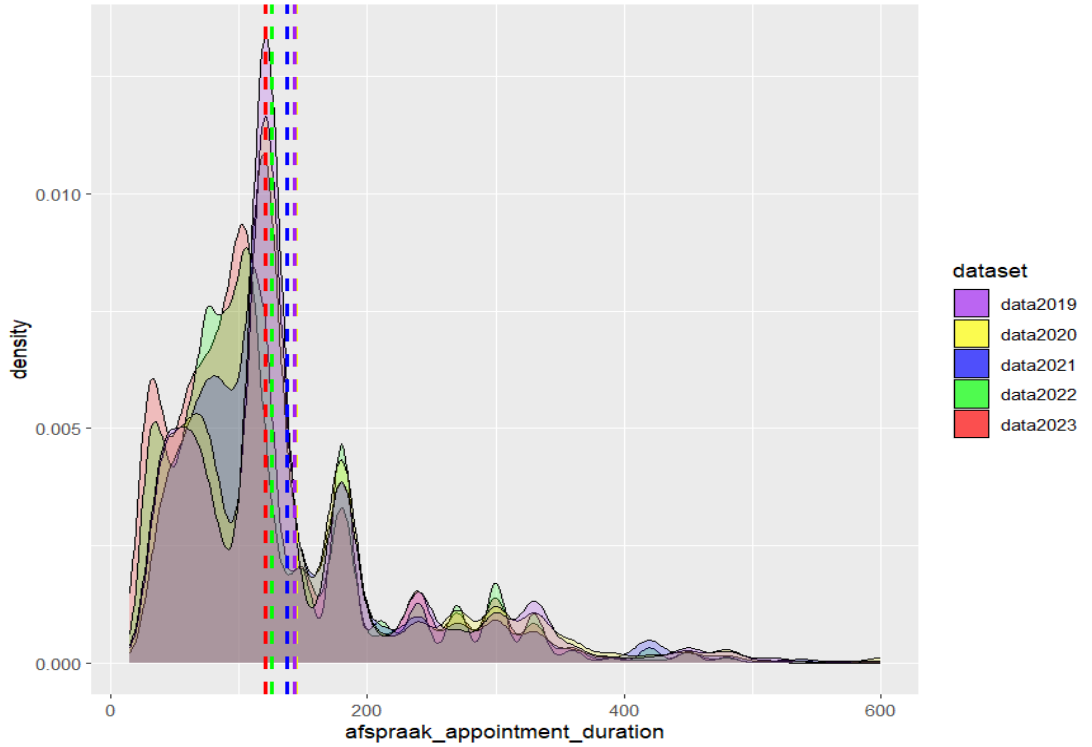


Figure 54: Density plot of appointment duration (all medicines)

Table 52: Median, Mean, 95% CI of appointment durations (all medicines)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	120	143.6	141.8	145.5
2020	120	144.5	142.6	146.3
2021	120	137.5	135.8	139.2
2022	105	126.0	124.4	127.5
2023	105	121.0	119.4	122.6

Table 53: Median, SD, 95% CI of appointment durations (all medicines)

			95% CI	
Year	Median	Standard deviation	Lower CI	Upper CI
2019	120	93.4	92.2	95.8
2020	120	96.0	93.7	96.3
2021	120	88.0	86.8	89.2
2022	105	84.9	83.8	86.0
2023	105	85.0	83.9	86.4

2.4 Postal codes

Figure B1: Heat map postal codes

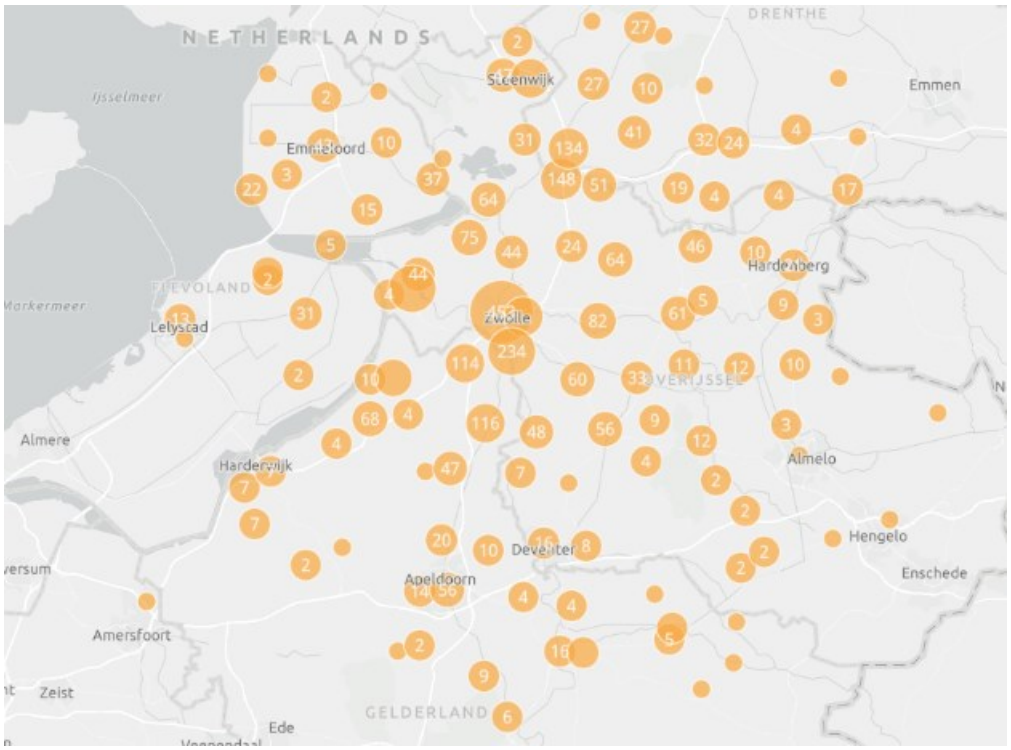


Figure B2: Heat map postal codes (outliers removed)

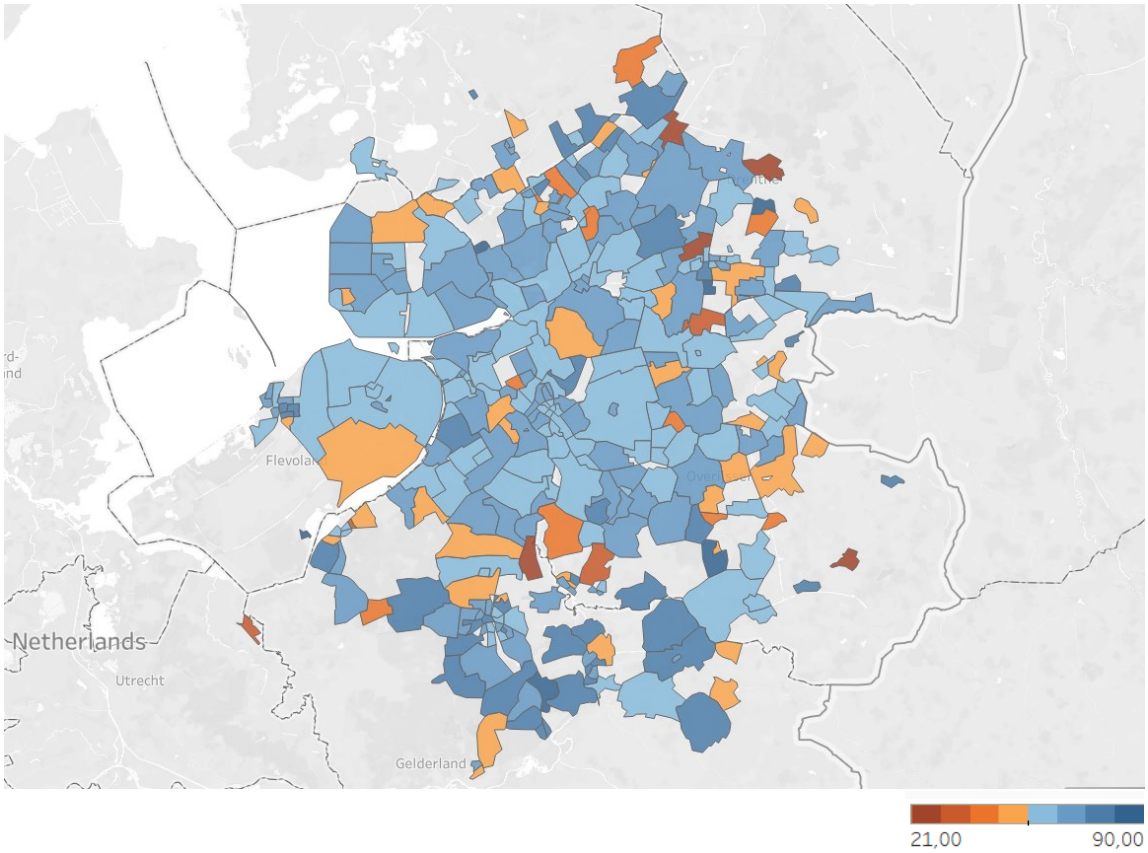


Figure 55: Relation between postal codes and average age

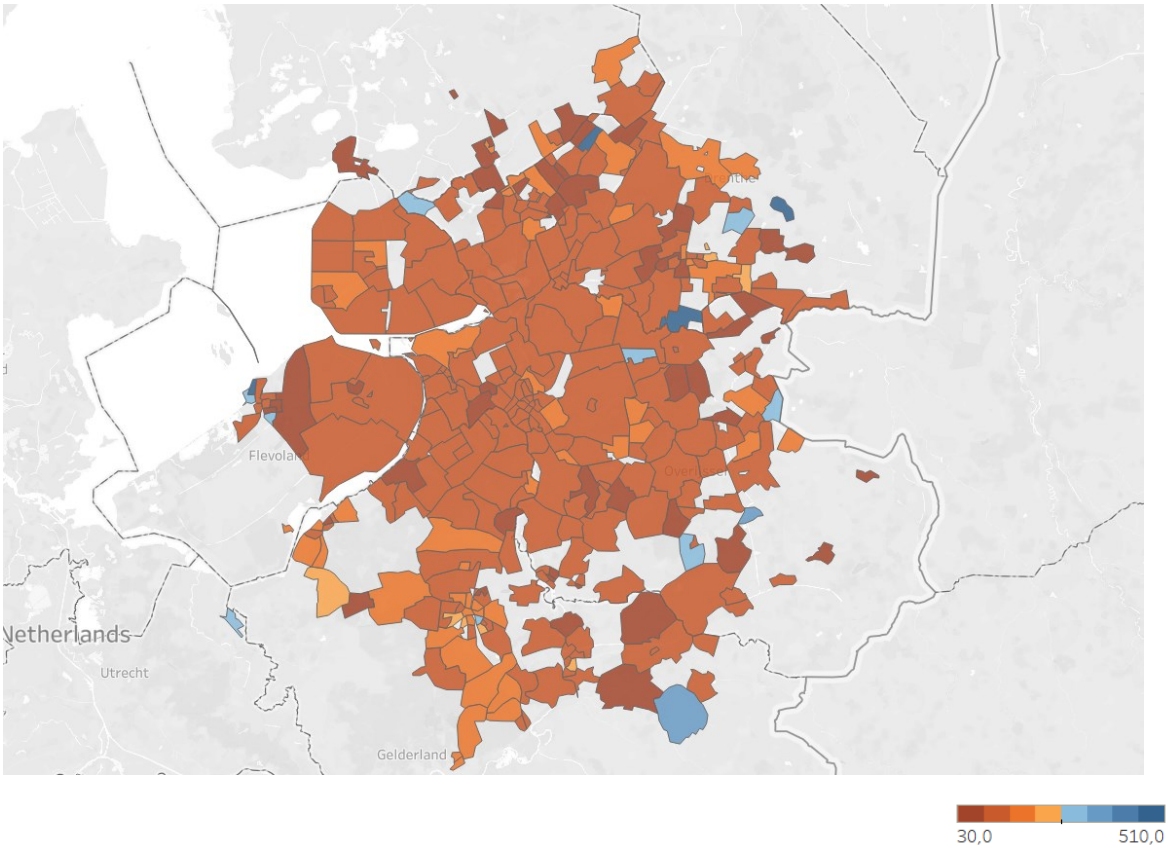


Figure 56: Relation between postal code and appointment duration

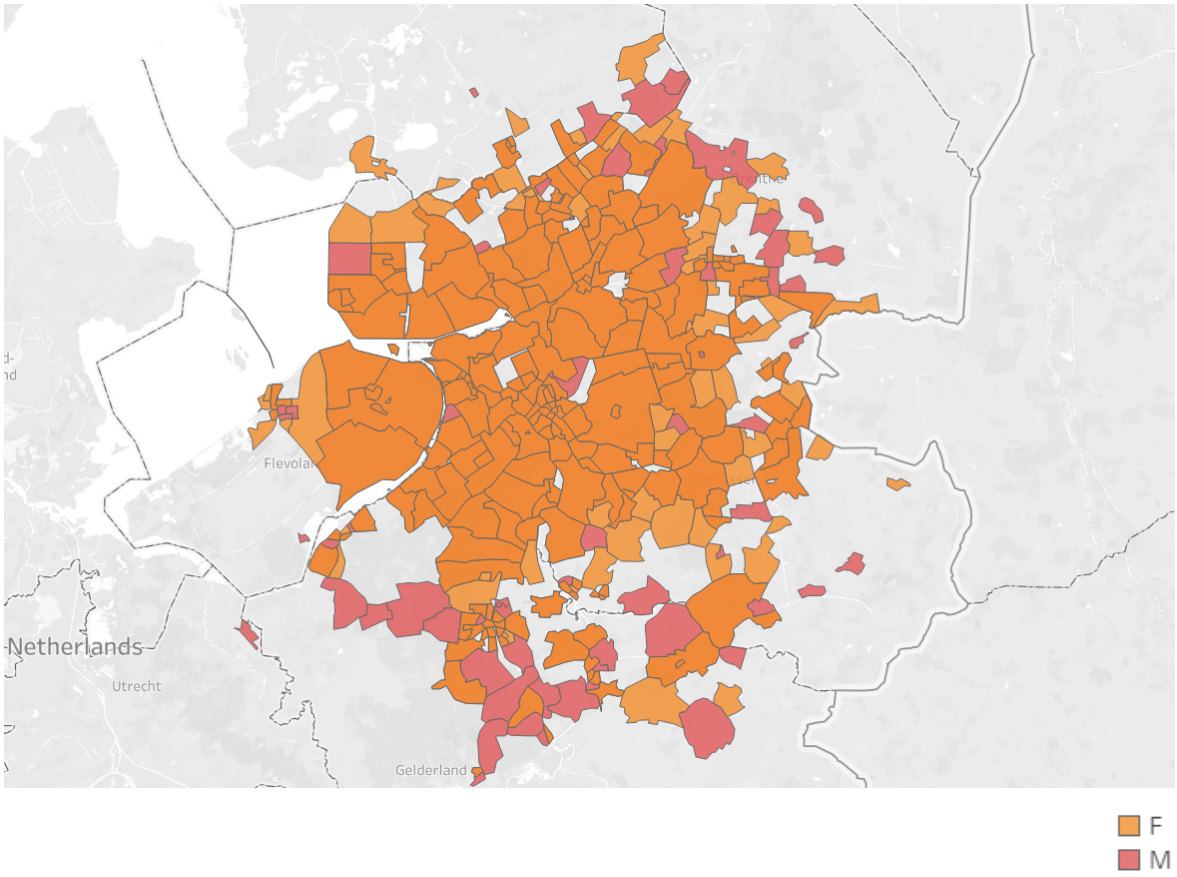


Figure 57: Relation between postal code and gender

3. Bortezomib

3.1 Appointment duration

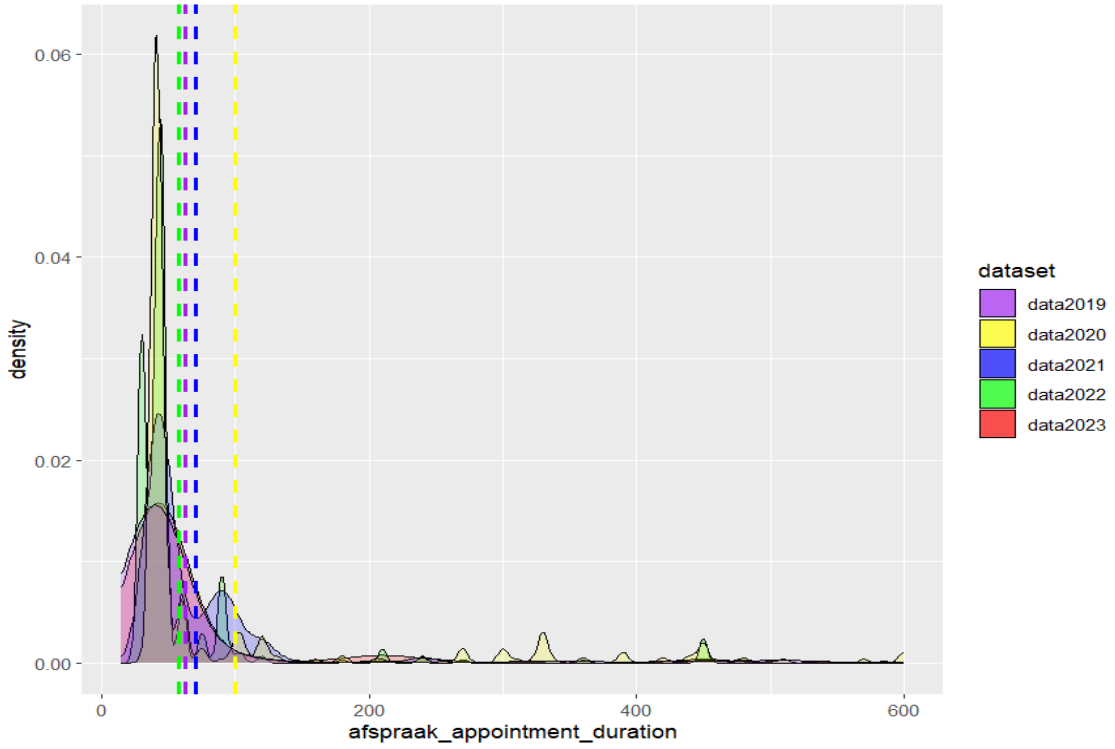


Figure 58: Density plot of the appointment duration (Bortezomib)

Table 54: Median, Mean, 95% CI of appointment duration (Bortezomib)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	40	62.7	55.0	70.4
2020	40	100.1	89.9	110.3
2021	40	70.2	64.2	76.2
2022	45	57.5	51.1	63.9
2023	45	62.6	54.1	71.1

Table 55: SD, 95% CI of appointment duration (Bortezomib)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	89.4	84.3	95.2
2020	126.7	119.9	134.3
2021	64.1	60.2	68.6
2022	63.5	59.4	68.4
2023	69.3	63.8	75.9

3.1.1 Location of administration

Table 56: Median appointment duration per location (Bortezomib)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	40	40	NA	NA	NA
2020	45	40	40	NA	NA
2021	45	45	45	NA	NA
2022	45	40	45	NA	NA
2023	45	45	45	30	30

Table 57: Mean and 95% CI appointment duration per location (Bortezomib)

Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Zwolle			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
70.5	59.7	81.3	44	41.7	46.3	NA	NA	NA	NA	NA	NA	NA	NA	NA
144.7	124.6	164.8	87.6	72.9	102.4	43.9	42.5	45.2	NA	NA	NA	NA	NA	NA
74.2	64.5	83.8	74.3	62.9	85.7	58.2	53.8	62.5	NA	NA	NA	NA	NA	NA
63.5	53.7	73.3	55.8	39.6	72.1	44.9	41.5	48.2	NA	NA	NA	NA	NA	NA
81.3	64.8	97.8	50.7	42	59.5	43.1	40.5	45.7	33.3	28.2	38.4	30	30	30

3.1.2 First three appointments

Table 58: Median appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Bortezomib)

	Appointment			
Year	First	Second	Third	Others
2019	40	40	40	40
2020	45	40	45	45
2021	45	45	45	45
2022	45	45	45	45
2023	255	45	210	45

Table 59: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Bortezomib)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	94	43.5	144.4	52.9	30.8	75.1	71	37.3	104.7	59.8	52	67.5
2020	145.2	68.7	221.6	81.7	34.8	128.5	111.4	41.8	180.9	121.8	107.4	136.1
2021	128.3	59.5	197.2	63.6	40.6	86.6	58.1	37.8	78.4	71.5	64.2	78.8
2022	178.8	62.9	294.8	111.1	43.1	179.1	68.1	29.7	106.4	51.7	46.2	57.2
2023	290	161	419	46.2	43.5	49	201.7	167.5	235.8	53.6	45.9	61.3

4. Trastuzumab

4.1 Appointment duration

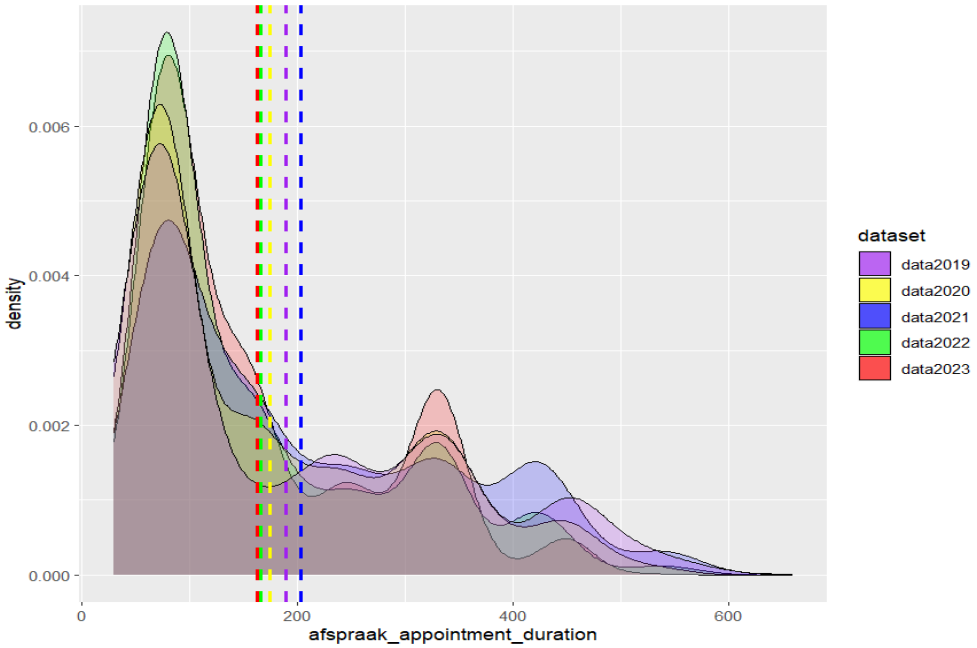


Figure 59: Density plot of the appointment duration (Trastuzumab)

Table 60: Median, Mean, 95% CI of appointment duration (Trastuzumab)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	120	189.9	181.6	198.2
2020	135	174.8	167.2	182.4
2021	150	202.7	194.5	211.0
2022	105	165.8	159.2	172.4
2023	105	163.1	156.3	169.8

Table 61: SD, 95% CI of appointment duration (Trastuzumab)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	142.7	137.1	148.8
2020	126.3	121.2	131.9
2021	138.1	132.5	144.2
2022	118.5	114.0	123.4
2023	109.7	105.2	114.7

4.1.1 Location of administration

Table 62: Median appointment duration per location (Trastuzumab)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	105	150	NA	NA	NA
2020	180	150	75	NA	NA
2021	180	150	75	NA	NA
2022	135	105	75	NA	NA
2023	150	105	75	75	75

Table 63: Mean and 95% CI appointment duration per location (Trastuzumab)

Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Zwolle			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
189.2	179.7	198.6	192.7	175.5	209.9	NA	NA	NA	NA	NA	NA	NA	NA	NA
211.3	200.9	221.6	183.9	168.9	199	66.2	64.1	68.4	NA	NA	NA	NA	NA	NA
232.2	221.8	242.7	182	167.3	196.7	65.5	62.4	68.6	NA	NA	NA	NA	NA	NA
179.5	170.8	188.1	163.9	152.3	175.5	69.3	66.4	72.2	NA	NA	NA	NA	NA	NA
183.8	174.8	192.7	148	136.9	159	67.8	62.5	73.1	61.8	50.9	72.6	74.5	73.4	75.6

4.1.2 First three appointments

Table 64: Median appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Trastuzumab)

	Appointment			
Year	First	Second	Third	Others
2019	330	242.5	240	75
2020	450	330	330	150
2021	450	330	330	150
2022	420	270	300	105
2023	450	330	330	105

Table 65: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Trastuzumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	302.7	273.3	332	247.2	222.2	272.2	226.5	200.3	252.7	156.1	147.4	164.8
2020	413.3	386.2	440.3	317.9	295.3	340.5	298.9	271.2	326.5	175.3	166.9	183.6
2021	443.5	413.7	473.2	330.3	299.6	361	321.4	294.1	348.7	188.8	180.4	197.1
2022	391.2	360.9	421.6	272.3	247.2	297.3	274.5	250.1	299	148.1	141.7	154.5
2023	384.7	357.9	411.4	290.1	268.9	311.4	289.9	270.8	309	148.3	141.9	154.8

5. Bevacizumab

5.1 Appointment duration

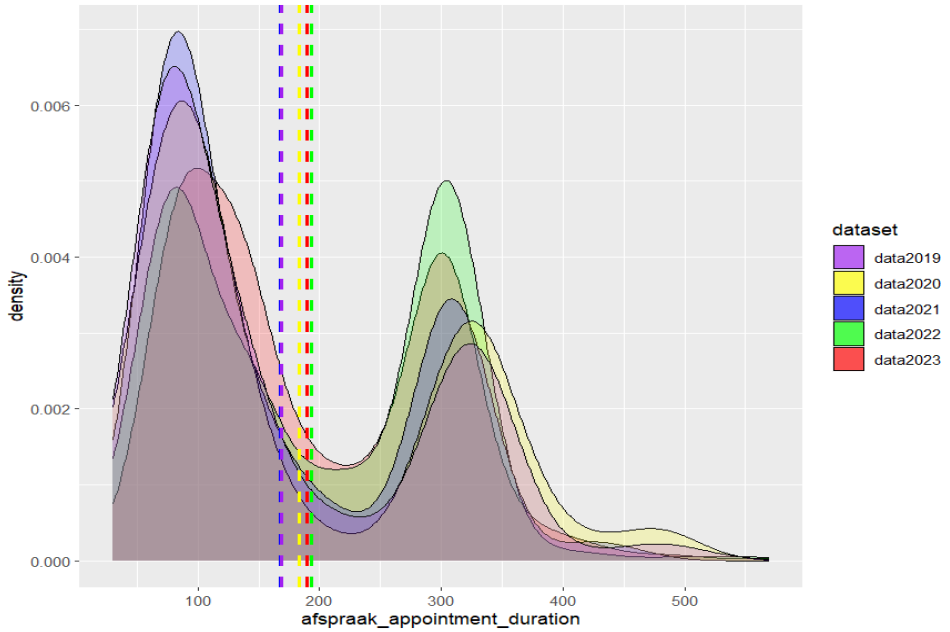


Figure 60: Density plot of the appointment duration (Bevacizumab)

Table 66: Median, Mean, 95% CI of appointment duration (Bevacizumab)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	120	168.4	158.4	178.3
2020	105	183.2	171.2	195.2
2021	105	167.7	157.8	177.5
2022	165	193.1	182.2	201.9
2023	150	189.5	181.3	197.6

Table 67: SD, 95% CI of appointment duration (Bevacizumab)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	115.4	108.8	122.9
2020	124.8	116.9	133.9
2021	106.2	99.7	113.6
2022	107.3	101.5	114.0
2023	101.5	96.0	107.6

5.1.1 Location of administration

Table 68: Median appointment duration per location (Bevacizumab)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	135	75	NA	NA	NA
2020	150	95	75	NA	NA
2021	195	105	75	NA	NA
2022	225	150	75	NA	75
2023	150	190	85	90	75

Table 69: Mean and 95% CI appointment duration per location (Bevacizumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	175.6	164.3	186.9	139.9	119.7	160.1	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	214.6	198.9	230.2	152.6	129.6	175.5	87.5	83.8	91.3	NA	NA	NA	NA	NA	NA
2021	202.2	188.5	215.8	149.6	132	167.2	84.4	81	87.8	NA	NA	NA	NA	NA	NA
2022	211.4	201.3	221.5	185.4	163.5	207.2	80.5	77.7	83.3	NA	NA	NA	78.3	64	92.7
2023	196.5	186.9	206.1	202.3	184.7	219.8	84.2	81.6	86.9	82.5	58.6	106.4	75	75	75

5.1.2 First three appointments

Table 70: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Bevacizumab)

	Appointment			
Year	First	Second	Third	Others
2019	240	205	135	75
2020	330	330	330	105
2021	300	300	300	105
2022	300	300	300	135
2023	300	270	240	135

Table 71: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Bevacizumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	231.4	203	259.8	217.8	189.3	246.4	195.7	166	225.5	134.3	123.6	145.1
2020	283.4	252.4	314.4	277.8	243.5	312.1	278.5	237.9	319.2	163.7	148.3	179.1
2021	284	256.7	311.2	280	252.3	307.7	263.5	231.5	295.6	150.6	138.8	162.4
2022	287.6	266.7	308.5	271.4	248.9	293.8	253.2	232	274.4	170.8	160.1	181.6
2023	265.3	244.9	285.7	241.7	214.4	269.1	223.4	197	249.8	174.7	165.1	184.3

6. Nivolumab

6.1 Appointment duration

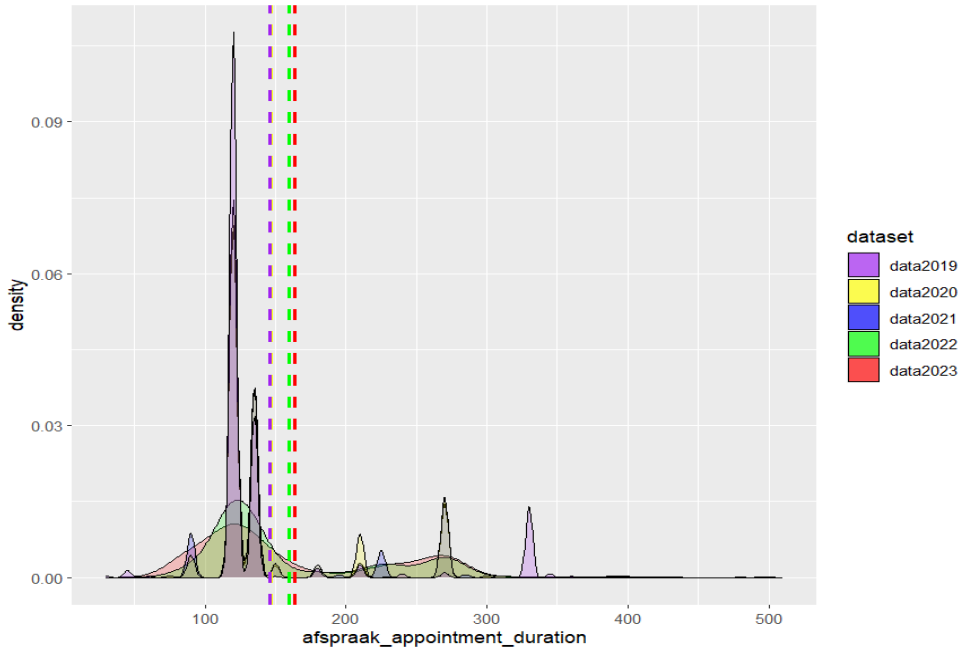


Figure 61: Density plot of the appointment duration (Nivolumab)

Table 72: Median, Mean, 95% CI of appointment duration (Nivolumab)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	120	145.9	142.4	149.4
2020	120	147.0	143.5	150.6
2021	120	147.0	143.1	150.9
2022	120	160.0	155.6	164.6
2023	120	163.3	158.9	167.7

Table 73: Median, Mean, 95% CI of appointment duration of the selected doses (Nivolumab)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	120	146.9	143.4	150.4
2020	120	147.5	143.9	151.0
2021	120	146.9	143.0	150.9
2022	120	160.3	155.8	164.7
2023	120	163.0	158.6	167.4

Table 74: SD, 95% CI of appointment duration (Nivolumab)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	64.3	61.9	66.8
2020	52.6	50.2	55.2
2021	54.2	51.6	57.1
2022	61.8	58.9	65.0
2023	71.6	68.7	74.9

Table 75: SD, 95% CI of appointment duration of the selected doses (Nivolumab)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	64.0	61.6	66.5
2020	52.9	50.5	55.6
2021	53.3	51.7	57.3
2022	62.1	59.1	65.4
2023	71.4	68.4	74.7

6.1.1 Location of administration

Table 76: Median appointment duration per location (Nivolumab)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	120	120	NA	NA	NA
2020	135	120	120	NA	NA
2021	135	120	120	NA	NA
2022	135	135	120	NA	90
2023	135	135	90	90	90

Table 77: Mean and 95% CI appointment duration per location (Nivolumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	147.4	143.7	151.1	130	122.7	137.4	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	153.7	149.2	158.3	137.5	128.2	146.8	124.8	123.6	126	NA	NA	NA	NA	NA	NA
2021	159	153.5	164.4	128.7	121.7	135.8	124	121.6	126.4	NA	NA	NA	NA	NA	NA
2022	168.2	162.9	173.4	154.4	144.4	164.4	113.1	108.7	117.5	NA	NA	NA	95	82.1	107.9
2023	170.4	165.4	175.3	154.9	144.4	165.4	96.7	92.4	100.9	88.3	84	92.6	91.9	88	95.8

6.1.2 First three appointments

Table 78: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Nivolumab)

	Appointment			
Year	First	Second	Third	Others
2019	120	120	120	120
2020	210	210	180	120
2021	225	225	217.5	120
2022	240	225	225	120
2023	240	225	225	120

Table 79: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Nivolumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	183.8	169.8	197.7	173.9	159.8	187.9	164.7	150.4	179	130.5	128	133.1
2020	200.6	184	217.1	202.4	183.1	221.6	184.5	166.3	202.8	135	131.7	138.3
2021	215.8	198.6	233.1	208.3	189.8	226.8	201.2	182.3	220.1	132.4	128.8	136.1
2022	223.2	210.6	235.8	207.6	193.3	222	212	196.9	227.2	138.6	134.6	142.5
2023	232.4	218.9	246	212.3	198.7	226	211.2	198.4	224.1	141.1	136.8	145.4

7. Azacitidine

7.1 Appointment duration

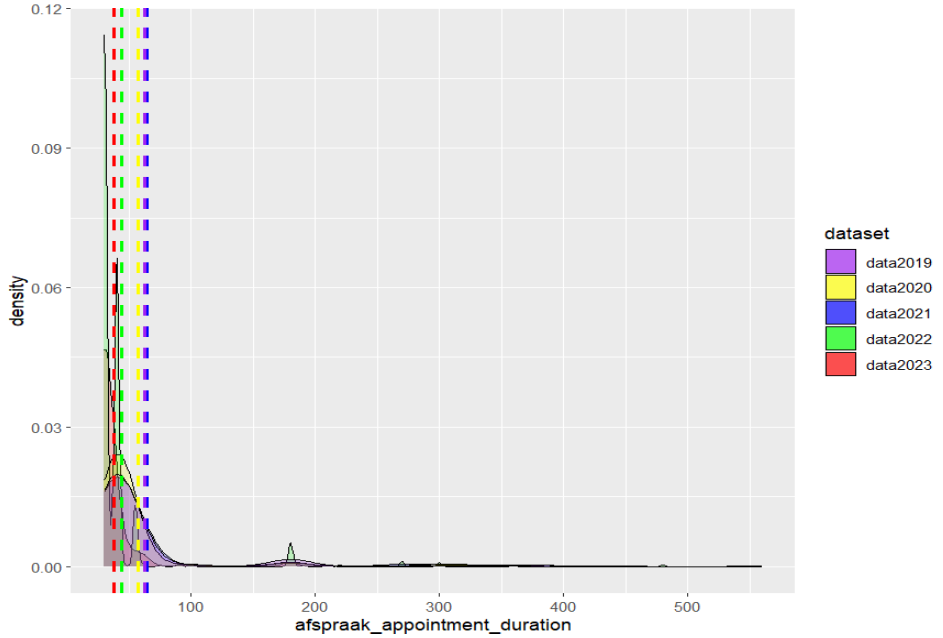


Figure 62: Density plot of the appointment duration (Azacitidine)

Table 80: Median, Mean, 95% CI of appointment duration (Azacitidine)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	40	62.7	57.1	68.4
2020	40	57.4	53.0	61.9
2021	40	63.9	58.1	69.8
2022	30	43.5	40.6	46.5
2023	30	38.0	36.0	40.0

Table 81: SD, 95% CI of appointment duration (Azacitidine)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	68.2	64.4	72.5
2020	59.0	56.0	62.3
2021	71.5	67.6	75.9
2022	41.5	39.5	43.7
2023	32.3	30.9	33.8

7.1.1 Location of administration

Table 82: Median appointment duration per location (Azacitidine)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	40	40	NA	NA	NA
2020	40	40	40	NA	NA
2021	55	40	40	NA	NA
2022	40	35	30	NA	30
2023	30	30	30	30	30

Table 83: Mean and 95% CI appointment duration per location (Azacitidine)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	63.3	56.2	70.3	62	52.7	71.3	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	76.8	67.3	86.3	59.8	45	74.6	40.1	39.9	40.3	NA	NA	NA	NA	NA	NA
2021	97.9	82.6	113.2	67.9	55	80.9	40.1	40	40.2	NA	NA	NA	NA	NA	NA
2022	55	48.4	61.6	42.6	35.7	49.4	33.5	33	34	NA	NA	NA	30	30	30
2023	42.3	38.4	46.1	49.4	40.8	58	30.8	30.6	31.1	30.4	29.6	31.3	31.2	29.5	32.9

7.1.2 First three appointments

Table 84: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Azacitidine)

	Appointment			
Year	First	Second	Third	Others
2019	120	40	40	40
2020	180	180	55	40
2021	180	180	55	40
2022	180	180	55	30
2023	110	45	55	30

Table 85: Mean and 95% CI appointment duration for the first, second, third and all other appointments (Azacitidine)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	127.3	78.8	175.8	93.8	64.9	122.6	57.5	39.6	75.4	58.3	52.6	64
2020	189.4	144.9	233.8	166.3	99	233.6	68.3	32.7	104	63	55.4	70.5
2021	144.3	100.8	187.9	187.9	122.8	253	71.8	37	106.6	76.3	65.6	87
2022	129.3	90.1	168.5	128.7	76.9	180.5	64.3	32.5	96.2	45.1	40.4	49.8
2023	113.4	67.5	159.4	83.2	47.6	118.9	48.3	38.4	58.3	40.5	37.2	43.9

8. Pembrolizumab

8.1 Appointment duration

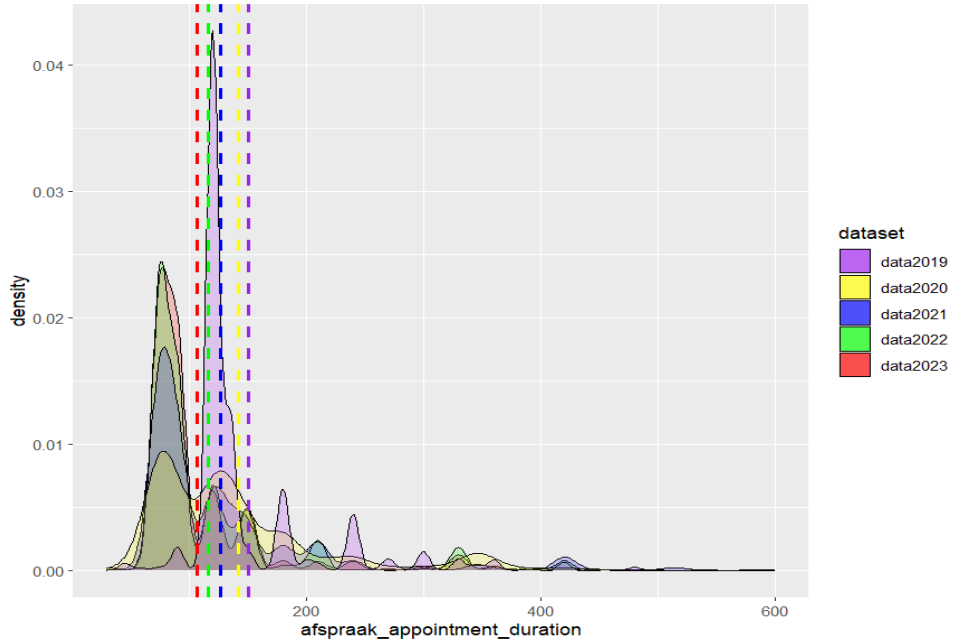


Figure 3:Density plot of the appointment duration (Pembrolizumab)

Table 86: Median, Mean, 95% CI of appointment duration (Pembrolizumab)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	120	150.9	146.8	155.0
2020	120	142.4	138.1	146.8
2021	90	127.0	123.0	131.0
2022	90	116.0	112.6	119.4
2023	90	107.2	104.2	110.2

Table 87: SD, 95% CI of appointment duration (Pembrolizumab)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	64.5	61.7	67.6
2020	82.2	79.3	85.5
2021	80.0	77.3	83.0
2022	71.4	69.1	73.9
2023	55.7	53.6	57.9

Table 88: Median, Mean, 95% CI of appointment duration for selected doses (Pembrolizumab)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	120	151.5	147.4	155.7
2020	120	143.1	138.7	147.6
2021	90	127.5	123.5	131.6
2022	90	116.4	112.9	119.8
2023	90	107.4	104.3	110.5

Table 89: SD, 95% CI of appointment duration for selected doses (Pembrolizumab)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	63.9	61.1	66.9
2020	82.6	79.6	85.8
2021	80.5	77.7	83.4
2022	71.9	69.5	74.4
2023	55.9	53.6	58.2

8.1.1 Location of administration

Table 90: Median appointment duration per location (Pembrolizumab)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	120	120	NA	NA	NA
2020	120	120	90	NA	NA
2021	90	120	75	NA	NA
2022	90	90	75	NA	90
2023	90	90	75	75	90

Table 91: Mean and 95% CI appointment duration per location (Pembrolizumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	150.5	146.1	154.8	155.1	141.7	168.4	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	148.1	143	153.2	134.7	122.8	146.7	101.9	97.3	106.6	NA	NA	NA	NA	NA	NA
2021	133.2	128.1	138.3	134.8	124.5	145.1	91.8	89.1	94.5	NA	NA	NA	NA	NA	NA
2022	120.5	116.2	124.8	117	109.1	124.8	85.3	82.5	88	NA	NA	NA	83.6	81	86.2
2023	112.7	108.6	116.8	104.8	98.7	110.9	80.2	78.6	81.7	77.9	75.1	80.6	91.9	87.7	96

8.1.2 First three appointments

Table 92: Median appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Pembrolizumab)

	Appointment			
Year	First	Second	Third	Others
2019	135	135	120	120
2020	135	135	135	120
2021	120	120	120	90
2022	120	135	90	90
2023	90	90	90	90

Table 93: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Pembrolizumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	165.8	153.5	178.1	170.6	156.3	184.8	164.3	150.1	178.6	140.2	135.8	144.6
2020	159.8	144.8	174.9	165.5	148.4	182.6	177.5	158.3	196.7	134.5	129.7	139.2
2021	159.6	142.5	176.8	161.7	142.8	180.7	167.7	145.8	189.6	119.9	115.7	124.1
2022	157.7	141.8	173.7	157.5	141.8	173.3	150.3	133.8	166.9	104.8	101.5	108.1
2023	134.7	120.7	148.7	127.9	114.7	141.2	132.1	117.2	147	101	97.8	104.2

9. Blinatumomab

9.1 Appointment duration

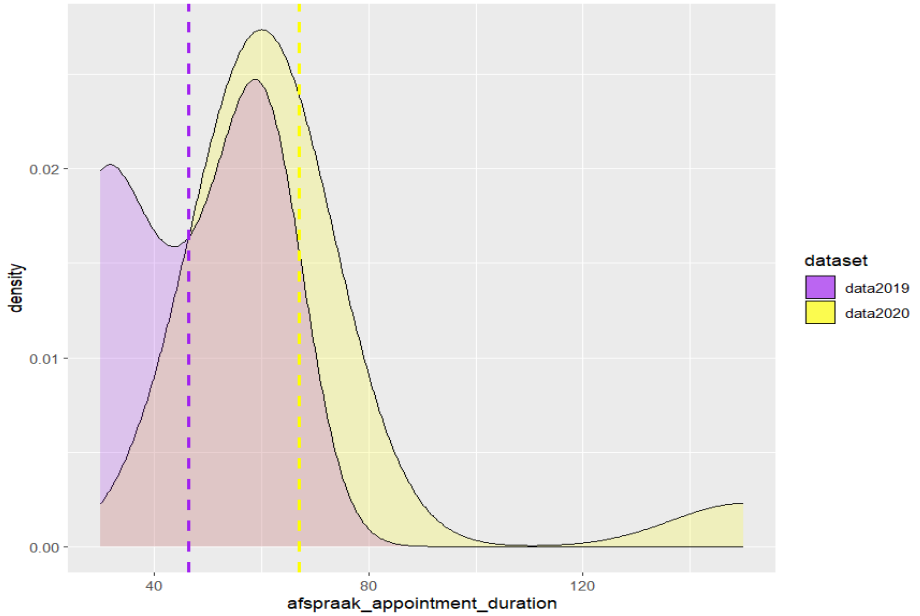


Figure 63: Density plot of the appointment duration (Blinatumomab)

Table 94: Median, Mean, 95% CI of appointment duration (Blinatumomab)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	45	46.4	36.9	55.9
2020	60	66.9	51.8	82.0
2021	NA	NA	NA	NA
2022	NA	NA	NA	NA
2023	NA	NA	NA	NA

Table 95: SD, 95% CI of appointment duration (Blinatumomab)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	14.2	9.9	24.8
2020	25.0	17.9	41.2
2021	NS	NA	NA
2022	NA	NA	NA
2023	NA	NA	NA

9.1.1 Location of administration

Table 96: Median appointment duration per location (Blinatumomab)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	45	NA	NA	NA	NA
2020	150	NA	60	NA	NA
2021	NA	NA	NA	NA	NA
2022	NA	NA	NA	NA	NA
2023	NA	NA	NA	NA	NA

Table 97: Mean and 95% CI appointment duration per location (Blinatumomab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	46.4	36.9	55.9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	150	NA	NA	NA	NA	NA	60	60	60	NA	NA	NA	NA	NA	NA
2021	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2022	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2023	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

9.1.2 First three appointments

Table 98: Median appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Blinatumomab)

	Appointment			
Year	First	Second	Third	Others
2019	45	30	30	60
2020	NA	NA	NA	150
2021	NA	NA	NA	NA
2022	NA	NA	NA	NA
2023	NA	NA	NA	NA

Table 99: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Blinatumomab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	45	NA	NA	30	NA	NA	30	NA	NA	50.6	39.1	62.1
2020	NA	NA	NA	NA	NA	NA	NA	NA	NA	150	NA	NA
2021	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2022	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2023	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

10. Carfilzomib

10.1 Appointment duration

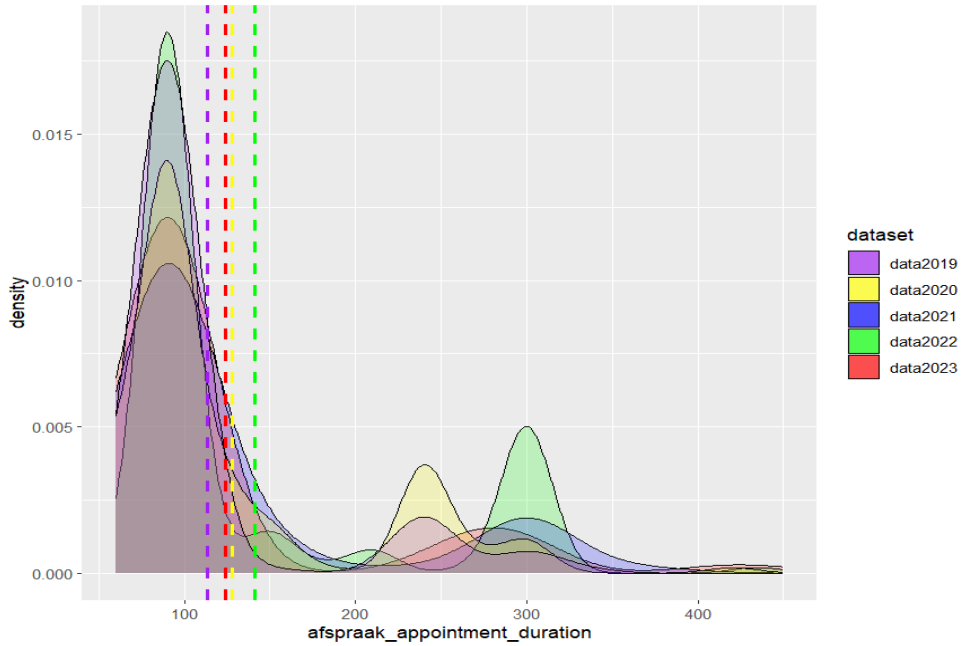


Figure 64: Density plot of the appointment duration (Carfilzomib)

Table 100: Median, Mean, 95% CI of appointment duration (Carfilzomib)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	90	113.2	103.6	122.7
2020	90	127.7	115.9	139.5
2021	90	128.2	110.7	145.6
2022	90	141.0	126.4	155.6
2023	90	123.7	109.6	137.8

Table 101: SD, 95% CI of appointment duration (Carfilzomib)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	59.1	53.1	66.7
2020	72.8	65.4	82.2
2021	78.4	67.8	92.8
2022	86.8	77.6	98.4
2023	80.2	71.4	91.5

10.1.1 Location of administration

Table 102: Median appointment duration per location (Carfilzomib)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	90	NA	NA	NA	NA
2020	90	165	90	NA	NA
2021	90	NA	NA	NA	NA
2022	90	90	NA	NA	NA
2023	90	90	90	NA	NA

Table 103: Mean and 95% CI appointment duration per location (Carfilzomib)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	113.2	103.6	122.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	140.1	124.2	156	165	120.1	209.9	85.5	75.7	95.3	NA	NA	NA	NA	NA	NA
2021	128.2	110.7	145.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2022	141.7	126.5	156.9	132	68.7	195.3	NA	NA	NA	NA	NA	NA	NA	NA	NA
2023	118.8	97.5	140	131.6	110.3	152.9	90	90	90	NA	NA	NA	NA	NA	NA

10.1.2 First three appointments

Table 104: Median appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Carfilzomib)

	Appointment			
Year	First	Second	Third	Others
2019	90	165	90	90
2020	270	240	240	90
2021	300	300	300	90
2022	300	300	300	90
2023	NA	NA	NA	90

Table 105: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Carfilzomib)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	157.5	76.2	238.8	165	108.4	221.6	156	93.8	218.2	102.4	94.2	110.6
2020	270	NA	NA	240	NA	NA	240	NA	NA	140.3	125.5	155.1
2021	300	NA	NA	300	NA	NA	300	NA	NA	121.5	105.2	137.8
2022	300	NA	NA	300	NA	NA	300	NA	NA	137.4	123.1	151.8
2023	NA	NA	NA	NA	NA	NA	NA	NA	NA	126.3	111.2	141.4

11. Zoledroninezuur

11.1 Appointment duration

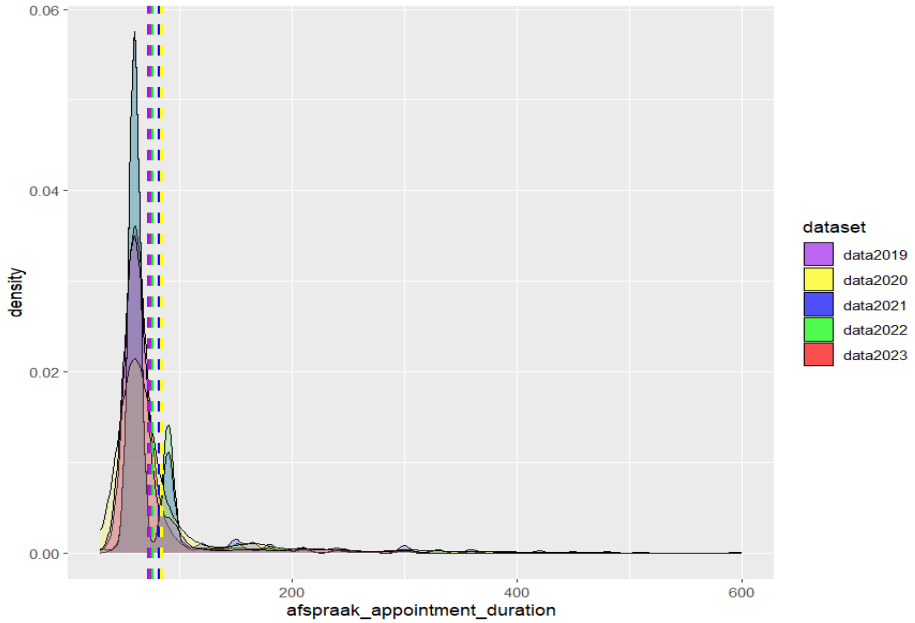


Figure 65: Density plot of the appointment duration (Zoledroninezuur)

Table 106: Median, Mean, 95% CI of appointment duration (Zoledroninezuur)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	60	73.1	70.5	75.7
2020	60	83.9	79.9	87.9
2021	60	81.6	78.0	85.2
2022	60	75.8	73.2	78.4
2023	60	72.5	70.2	74.9

Table 107: SD, 95% CI of appointment duration (Zoledroninezuur)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	41.9	40.2	43.9
2020	63.1	60.4	66.1
2021	58.6	56.1	61.2
2022	43.2	41.4	45.1
2023	39.1	37.5	40.8

11.1.1 Location of administration

Table 108: Median appointment duration per location (Zoledroninezuur)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	60	60	NA	NA	NA
2020	60	60	60	NA	NA
2021	60	60	60	NA	NA
2022	60	60	60	NA	60
2023	60	60	60	60	60

Table 109: Mean and 95% CI appointment duration per location (Zoledroninezuur)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	73.8	70.8	76.8	70.2	64.9	75.5	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	82	77.4	86.5	91.2	81.7	100.7	75.3	62.8	87.8	NA	NA	NA	NA	NA	NA
2021	84.2	79.5	88.8	86.3	77.1	95.5	64.3	61.4	67.1	NA	NA	NA	NA	NA	NA
2022	78.8	75.3	82.3	75.7	70.7	80.8	61.3	58.3	64.4	NA	NA	NA	60	60	60
2023	75.8	72.4	79.3	71.8	67.6	76	60.4	58.9	61.9	60	60	60	59	57.1	61

11.1.2 First three appointments

Table 110: Median appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Zoledroninezuur)

	Appointment			
Year	First	Second	Third	Others
2019	60	60	60	60
2020	60	60	60	60
2021	60	60	60	60
2022	60	60	60	60
2023	60	60	60	60

Table 111: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Zoledroninezuur)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	72.5	69.1	75.9	67.2	62.4	72.1	79.6	67.3	91.8	78.7	72.1	85.2
2020	93.4	81	105.8	84.5	75.7	93.3	70.4	64.5	76.2	86.3	79.9	92.7
2021	81.9	74.6	89.2	73.4	68.5	78.4	82.8	71.1	94.5	88.8	82.2	95.3
2022	82	76.3	87.8	79.7	71.6	87.8	73.7	67.4	80	76.7	72.3	81.2
2023	76.1	70.2	82	73.5	67.4	79.7	67	62	72.1	76	71.9	80.1

12. Daratumumab

12.1 Appointment duration

Figure 66: Density plot of the appointment duration (Daratumumab)

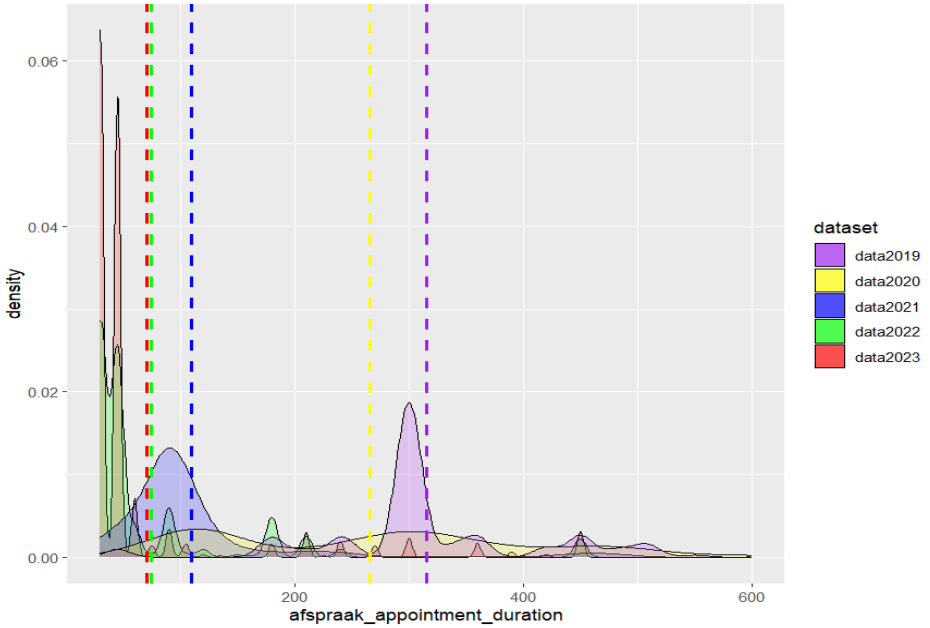


Table 112: Median, Mean, 95% CI of appointment duration (Daratumumab)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	300	315.1	300.2	329.9
2020	300	265.9	250.8	281.1
2021	90	109.3	102.5	116.1
2022	45	74.8	69.2	80.4
2023	45	70.7	64.9	76.5

Table 113: SD, 95% CI of appointment duration (Daratumumab)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	92.8	83.4	104.6
2020	137.6	127.7	149.2
2021	77.9	73.4	83.0
2022	84.0	80.2	88.2
2023	90.7	86.7	94.9

Table 114: Median, Mean, 95% CI of appointment duration for selected doses (Daratumumab)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	-	-	-	-
2020	120	190.8	170.7	210.9
2021	90	109.3	102.5	116.1
2022	45	67.0	61.2	72.7
2023	45	57.2	52.5	61.9

Table 115: SD, 95% CI of appointment duration for selected doses (Daratumumab)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	-	-	-
2020	132.5	119.7	148.3
2021	77.9	73.4	83.0
2022	82.2	78.3	86.5
2023	71.2	68.0	74.7

12.1.1 Location of administration

Table 116: Median appointment duration per location (Daratumumab)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	300	240	NA	NA	NA
2020	300	240	120	NA	NA
2021	90	90	90	NA	NA
2022	45	45	30	NA	30
2023	45	45	30	30	30

Table 117: Median, Mean, 95% CI of appointment duration per location (Daratumumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	328.4	318.2	338.6	251.9	228.2	275.6	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	281.2	263.6	298.8	216.6	189.3	244	120	NA	NA	NA	NA	NA	NA	NA	NA
2021	91.2	88.4	93.9	90	90	90	79.1	74.8	83.5	NA	NA	NA	NA	NA	NA
2022	75.8	69.9	81.7	45.5	42.2	48.9	37.3	36.2	38.5	NA	NA	NA	30	30	30
2023	48.6	45.5	51.7	44.5	41.8	47.3	37.5	36.6	38.4	30	30	30	30	30	30

12.1.2 First three appointments

Table 118: Median appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Daratumumab)

	Appointment			
Year	First	Second	Third	Others
2019	480	450	435	300
2020	510	420	272.5	275
2021	450	180	120	90
2022	450	210	45	45
2023	450	120	45	45

Table 119: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Daratumumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	443.3	123	763.7	424	310.7	537.3	403.3	292.7	513.9	304.5	290.1	318.9
2020	531.4	470	592.9	365	279.6	450.4	267.5	170.7	364.3	256.6	241.3	271.8
2021	357.5	170.6	544.4	197.5	43.1	351.9	139.5	86.4	192.6	110.9	103.4	118.5
2022	378.8	308.7	448.8	195	145.5	244.5	79.3	51.4	107.2	76.9	70.1	83.7
2023	306.4	224.8	388	160.3	98.3	222.2	115.6	47.1	184	80.9	72.6	89.2

13. Vedolizumab

13.1 Appointment duration

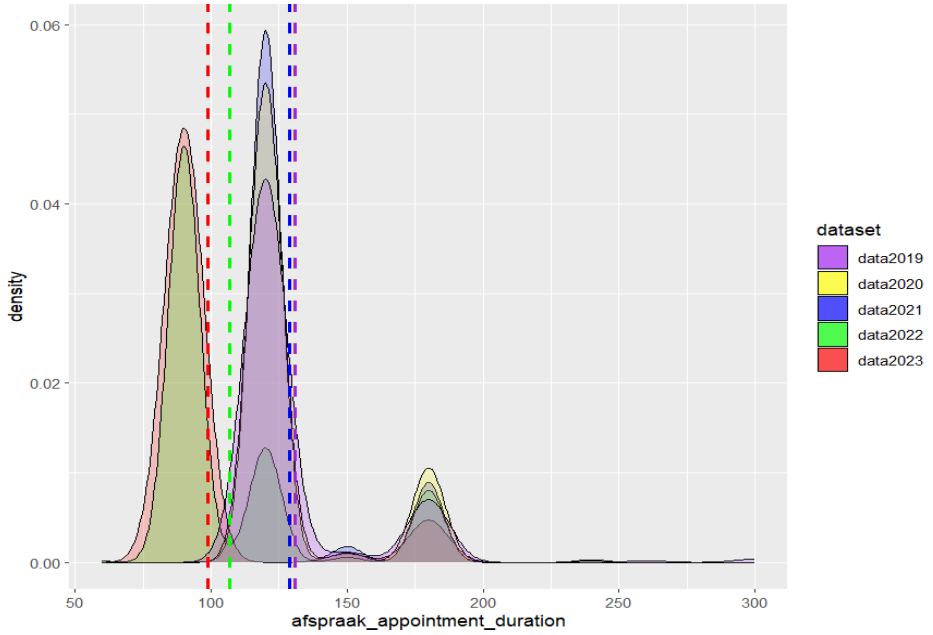


Figure 67: Density plot of the appointment duration (Vedolizumab)

Table 120: Median, Mean, 95% CI of appointment duration (Vedolizumab)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	120	130.6	127.5	133.8
2020	120	130.5	128.3	132.6
2021	120	128.8	126.9	130.8
2022	90	106.7	104.1	109.4
2023	90	98.9	96.1	101.7

Table 121: SD, 95% CI of appointment duration (Vedolizumab)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	26.8	24.5	28.9
2020	22.8	21.4	24.5
2021	21.5	20.2	23.0
2022	29.6	27.9	31.7
2023	36.3	24.5	28.4

13.1.1 Location of administration

Table 122: Median appointment duration per location (Vedolizumab)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	120	180	NA	NA	NA
2020	120	120	NA	NA	NA
2021	120	120	NA	NA	NA
2022	90	90	NA	NA	NA
2023	90	90	NA	NA	NA

Table 123: Mean and 95% CI appointment duration per location (Vedolizumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	130	126.9	133.1	168	134.7	201.3	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	129.3	127	131.5	135.8	129.8	141.7	NA	NA	NA	NA	NA	NA	NA	NA	NA
2021	130.1	127.8	132.4	122.9	120.1	125.8	NA	NA	NA	NA	NA	NA	NA	NA	NA
2022	106.2	103.3	109	109.2	102.4	116.1	NA	NA	NA	NA	NA	NA	NA	NA	NA
2023	96.4	93.6	99.2	107.5	99.9	115.2	NA	NA	NA	NA	NA	NA	NA	NA	NA

13.1.2 First three appointments

Table 124: Median appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Vedolizumab)

	Appointment			
Year	First	Second	Third	Others
2019	120	120	120	120
2020	180	180	120	120
2021	180	180	120	120
2022	180	180	180	90
2023	180	180	180	90

Table 125: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Vedolizumab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	148	136.5	159.4	144.7	133.6	155.8	123.7	119.3	128	122.3	120.5	124.1
2020	174.5	166.7	182.4	177	170.7	183.3	132.5	119.6	145.4	125.1	123.5	126.8
2021	176.5	163.2	189.7	170.5	159.7	181.4	133.8	117.9	149.7	124.9	123.4	126.5
2022	175.4	165.3	185.4	171.7	159.3	184	148.1	127.5	168.7	100.6	98.6	102.7
2023	171	150.6	191.4	180	180	180	180	180	180	93.4	91.6	95.1

14. Abatacept

14.1 Appointment duration

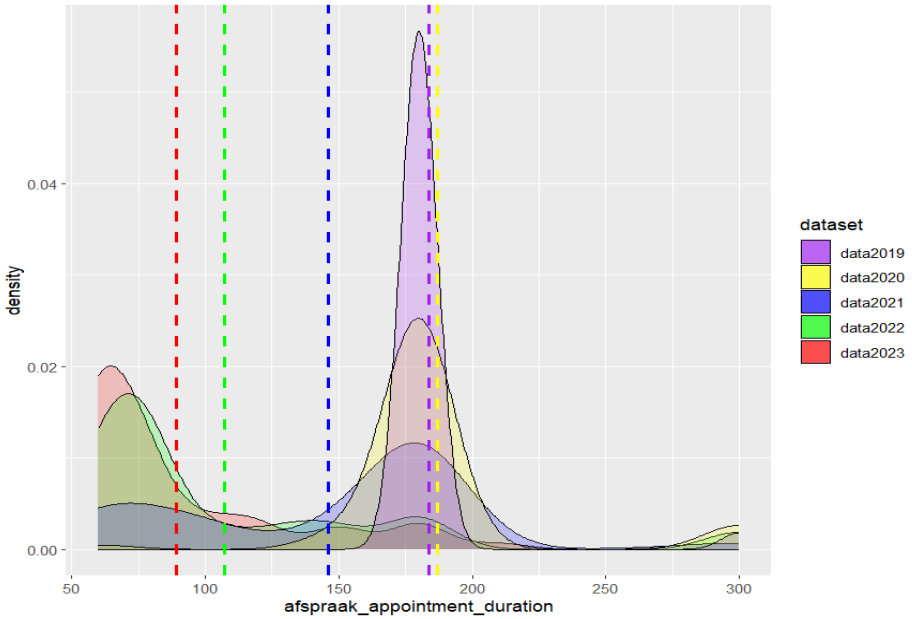


Figure 68: Density plot of the appointment duration (Abatacept)

Table 126: Median, Mean, 95% CI of appointment duration (Abatacept)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	180	183.7	180.5	187.0
2020	180	187.0	180.0	193.9
2021	180	146.2	136.6	155.8
2022	75	107.0	100.2	113.9
2023	75	89.2	83.2	95.2

Table 127: SD, 95% CI of appointment duration (Abatacept)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	20.9	18.8	23.4
2020	38.9	34.6	44.4
2021	56.3	50.3	64.0
2022	62.3	57.8	67.6
2023	40.1	36.2	44.8

14.1.1 Location of administration

Table 128:Median appointment duration per location (Abatacept)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	180	180	NA	NA	NA
2020	180	180	NA	NA	NA
2021	180	75	NA	NA	NA
2022	75	75	NA	NA	NA
2023	75	75	NA	NA	NA

Table 129: Mean and 95% CI appointment duration per location (Abatacept)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	181.8	179.3	184.3	193.8	178.1	209.6	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	186.9	180.6	193.1	187.5	150.8	224.2	NA	NA	NA	NA	NA	NA	NA	NA	NA
2021	159.6	150.3	168.9	92.8	71.8	113.8	NA	NA	NA	NA	NA	NA	NA	NA	NA
2022	110.4	102.1	118.7	102.7	91.1	114.3	NA	NA	NA	NA	NA	NA	NA	NA	NA
2023	98.2	89.6	106.9	72.8	68.6	76.9	NA	NA	NA	NA	NA	NA	NA	NA	NA

14.1.2 First three appointments

Table 130: Median appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Abatacept)

	Appointment			
Year	First	Second	Third	Others
2019	180	180	180	180
2020	300	300	300	180
2021	270	NA	60	180
2022	135	75	75	75
2023	210	210	210	75

Table 131: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Abatacept)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	194.1	173.6	214.6	194.1	173.6	214.6	187.5	171.5	203.5	180	180	180
2020	300	300	300	300	300	300	300	300	300	181.3	175.8	186.7
2021	270	NA	NA	NA	NA	NA	60	NA	NA	145.9	136.5	155.4
2022	189.8	155.6	224.1	121.6	87.6	155.6	102.1	71.7	132.5	95.6	90.2	101.1
2023	210	NA	NA	210	NA	NA	210	NA	NA	87.1	81.5	92.7

15. Immunoglobulins

15.1 Appointment duration

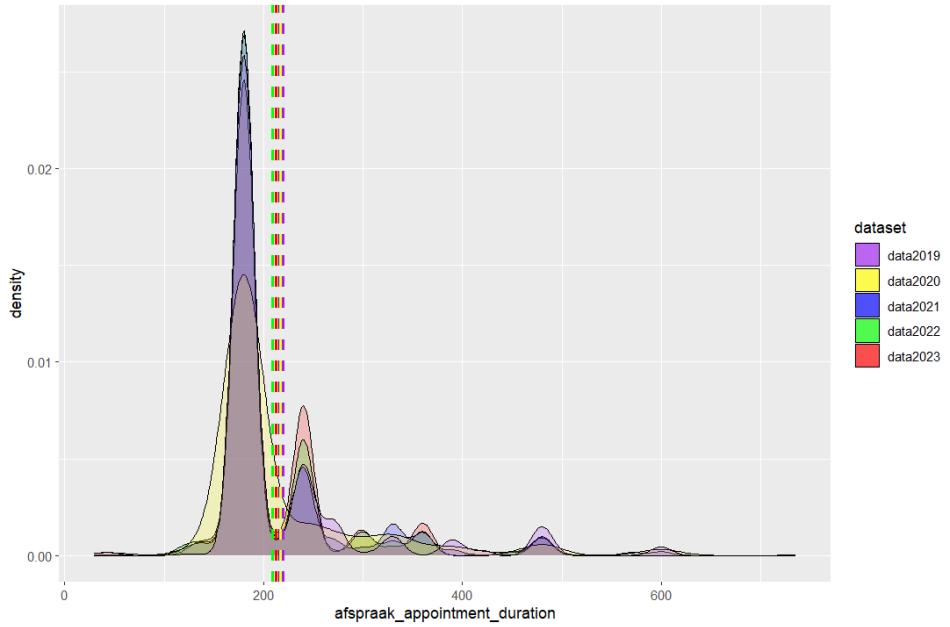


Figure 69: Density plot of the appointment duration (Immunoglobulins)

Table 132: Median, Mean, 95% CI of appointment duration (Immunoglobulins)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	180	218.9	212.9	224.9
2020	180	217.2	211.6	222.9
2021	180	215.8	210.8	220.7
2022	180	208.7	204.8	212.7
2023	180	212.8	208.7	216.9

Table 133 SD, 95% CI of appointment duration (Immunoglobulins)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	84.4	80.4	88.8
2020	87.0	83.2	91.3
2021	78.1	74.8	81.7
2022	64.4	61.7	67.3
2023	63.9	61.1	66.9

15.1.1 Location of administration

Table 134: Median appointment duration per location (Immunoglobulins)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	180	180	NA	NA	NA
2020	180	180	NA	NA	NA
2021	180	180	NA	NA	NA
2022	180	180	NA	NA	NA
2023	180	180	NA	NA	NA

Table 135: Mean and 95% CI appointment duration per location (Immunoglobulins)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	232.1	224.4	239.8	179.9	179.8	180.1	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	232.9	225.1	240.7	180.7	179.4	182	NA	NA	NA	NA	NA	NA	NA	NA	NA
2021	224.6	218.1	231	194.7	189.1	200.3	NA	NA	NA	NA	NA	NA	NA	NA	NA
2022	216.9	211.6	222.3	192.9	188.2	197.5	NA	NA	NA	NA	NA	NA	NA	NA	NA
2023	216.2	210.5	222	207.9	202.2	213.5	NA	NA	NA	NA	NA	NA	NA	NA	NA

15.1.2 First three appointments

Table 136: Median appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Immunoglobulins)

	Appointment			
Year	First	Second	Third	Others
2019	120	165	120	300
2020	NA	240	120	NA
2021	NA	180	120	60
2022	180	NA	45	90
2023	NA	NA	45	90

Table 137: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Immunoglobulins)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	144.8	135.1	238.8	141.1	132.4	149.8	403.3	137.5	155.6	60	60	96.8
2020	NA	NA	NA	NA	NA	NA	267.5	170.7	NA	62.2	NA	NA
2021	NA	NA	76.8	170	158.6	181.4	139.5	NA	295.6	NA	105.2	60
2022	180	NA	NA	NA	NA	NA	79.3	NA	107.2	60	60	60
2023	NA	53	67.3	NA	NA	NA	58.6	NA	73.2	NA	NA	90

16. Infliximab

16.1 Appointment duration

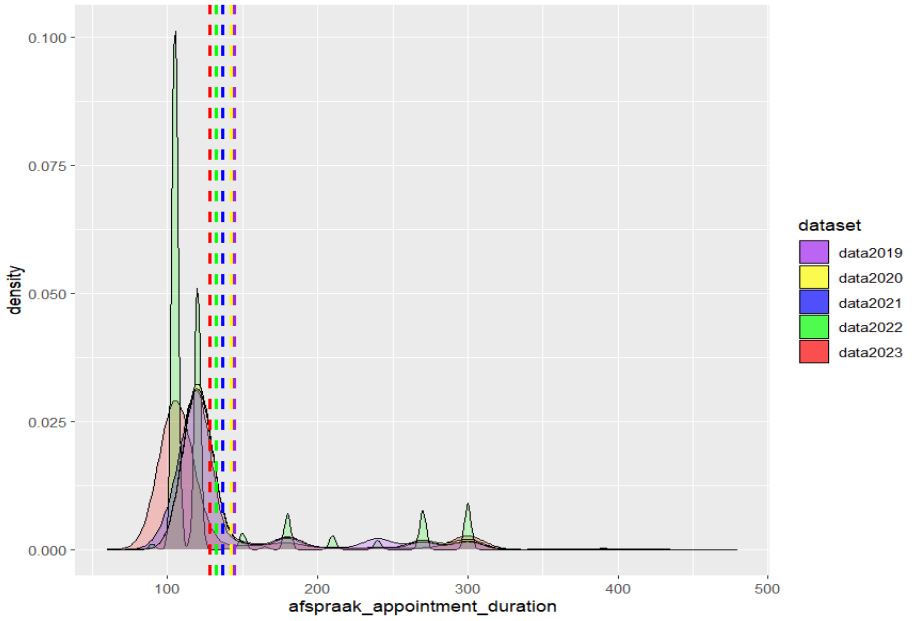


Figure 70: Density plot of the appointment duration (Infliximab)

Table 138: Median, Mean, 95% CI of appointment duration (Infliximab)

			95% CI	
Year	Median	Mean	Lower CI	Upper CI
2019	120	144.3	142.2	146.4
2020	120	142.3	140.2	144.4
2021	120	136.4	134.5	138.3
2022	105	132.4	130.3	134.5
2023	105	128.1	125.7	130.5

Table 139: SD, 95% CI of appointment duration (Infliximab)

		95% CI	
Year	Standard deviation	Lower CI	Upper CI
2019	51.6	20.2	53.1
2020	51.9	50.5	53.4
2021	48.6	47.3	50.0
2022	55.1	53.7	56.6
2023	56.8	55.2	58.6

16.1.1 Location of administration

Table 140: Median appointment duration per location (Infliximab)

	Median				
Year	Zwolle	Meppel	Thuis	Kampen	Heerde
2019	120	120	NA	NA	NA
2020	120	120	NA	NA	NA
2021	120	120	NA	NA	NA
2022	105	105	NA	NA	NA
2023	105	105	NA	NA	NA

Table 141: Mean and 95% CI appointment duration per location (Infliximab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**Zwolle**			**Meppel**			**Thuis**			**Kampen**			**Heerde**		
2019	126.4	125.5	127.3	120	120	120	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	120	120	120	120	120	120	NA	NA	NA	NA	NA	NA	NA	NA	NA
2021	120	120	120	112.7	112	113.4	NA	NA	NA	NA	NA	NA	NA	NA	NA
2022	110.7	110.3	111.1	106.8	106.3	107.2	NA	NA	NA	NA	NA	NA	NA	NA	NA
2023	105	105	105	105	105	105	NA	NA	NA	NA	NA	NA	NA	NA	NA

16.1.2 First three appointments

Table 142: Median appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Infliximab)

	Appointment			
Year	First	Second	Third	Others
2019	120	120	120	120
2020	300	300	270	120
2021	300	300	270	120
2022	300	300	270	105
2023	300	300	300	105

Table 143: Mean and 95% CI appointment duration for the first, second, third and all other appointments at Zwolle and Meppel (Infliximab)

	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI
Year	**First appointment**			**Second appointment**			**Third appointment**			**Other appointments**		
2019	160.1	153.2	167.1	156.5	149.8	163.3	149.4	143.5	155.3	135.2	133.1	137.3
2020	274.6	259.4	289.8	274.7	258.7	290.8	252.8	238.9	266.6	132.4	130.9	133.9
2021	266.2	245.5	287	261.1	239.9	282.4	234.5	215.6	253.3	129.1	127.6	130.5
2022	266.4	249.6	283.2	262.2	245	279.4	238.1	222.5	253.6	121.6	120.1	123
2023	290.2	278	302.3	262	241.1	282.9	221.7	192	251.4	116.8	115.2	118.4

Appendix H: Results experiments per KPI

Table 144: CO2 emissions per experiment in kg

Experiment	Median	Mean	Lower CI	Upper CI	SD
1	266.5	266.8	265.6	268	6
2	271.4	272	270.9	273	5.4
3	270.1	270	268.9	271	5.3
4	273.1	272.6	271.6	273.6	5
5	272.5	272.7	271.6	273.8	5.5
6	271.4	271.3	270.2	272.5	5.7
7	265.1	265.4	264.2	266.6	6
8	266	265.8	264.6	266.9	5.6
9	263.4	262.6	261.5	263.7	5.3
10	216.8	216.5	215.4	217.6	5.4
11	268.8	269.4	268	270.7	6.7
12	270.7	269.9	268.4	271.5	7.3
13	272	271.8	270.6	273	6
14	277.1	277.2	276	278.4	5.5
15	265.9	266.5	265.4	267.6	5.3
16	274.9	274.3	273.2	275.4	5
17	270.9	272	270.8	273.2	6.1
18	267.3	266.7	263.5	269.9	3.8
19	265.1	265.5	264.3	266.7	6.1
20	277.2	277.2	276	278.5	6.4
21	266.6	266.8	265.7	267.8	5.3
22	273.9	274	272.8	275.3	6.3
23	271.7	272.3	271.2	273.4	5.4
24	341.9	341.4	340.1	342.7	6.4
25	288.7	289.1	287.9	290.4	6
26	303.8	304.1	302.5	305.8	7.5
27	328.6	328.7	327.4	330	5
28	351.3	352.5	349.2	355.9	6.5
29	268.9	269	267.7	270.3	6.6
30	269	269.4	268	270.7	6.8
31	272	272	270.9	273.2	5.9

Table 145: Total costs per experiment in euros

Experiment	Mean
1	3643.1
2	3720.5
3	3724.1
4	3724.1
5	3722.1
6	3723.7
7	3801.4
8	3643.1
9	3643.1
10	3643.1
11	3562.2
12	3483.8
13	3402.8
14	2865.2
15	3133.2
16	2955.6
17	3042.9
18	2888.5
19	3630.3
20	3619.9

21	3887.9
22	3710.2
23	3797.6
24	3643.1
25	3643.1
26	3643.1
27	3643.1
28	3643.1
29	4316.8
30	4238.4
31	4157.5

Table 146: Travel distance per experiment in km

Experiment	Median	Mean	Lower CI	Upper CI	SD
1	32	32.5	32.3	32.7	0.9
2	32	32.2	32.1	32.3	0.6
3	32	32	31.9	32.1	0.5
4	32	32.3	32.2	32.4	0.7
5	32	32.4	32.2	32.5	0.8
6	32	32.2	32.1	32.3	0.6
7	32	32.5	32.3	32.6	0.8
8	32	32	31.9	32.1	0.5
9	32	32.1	32	32.2	0.5
10	32	31.5	31.3	31.7	0.9
11	34	33.1	32.9	33.3	1
12	34	33.4	33.2	33.6	1
13	34	34	33.9	34	0.4
14	38	38	38	38.1	0.4
15	36	36	35.9	36.1	0.4
16	38	37.2	37	37.4	1
17	36	36.9	36.7	37.1	1
18	32	32.2	31.7	32.8	0.7
19	32	32.5	32.3	32.7	0.9
20	38	38	37.8	38.1	0.8
21	36	36	36	36.1	0.4
22	38	37.2	37	37.4	1
23	38	37.1	36.9	37.3	1
24	42	42.9	42.7	43.1	1
25	32	32.9	32.7	33.2	1
26	34	33.3	33	33.5	1
27	34	33.9	33.8	34	0.4
28	34	34	34	34	0
29	34	33.2	33	33.4	1
30	34	33.5	33.3	33.6	0.9
31	34	34	33.9	34.1	0.5

Table 147: Travel times per experiment in minutes

Experiment	Median	Mean	Lower CI	Upper CI	SD
1	36	35.6	35.5	35.8	0.8
2	36	35.6	35.4	35.8	0.8
3	36	35.5	35.3	35.7	0.9
4	36	35.8	35.7	35.9	0.6
5	36	35.7	35.6	35.9	0.7
6	36	35.6	35.4	35.7	0.8
7	36	35.6	35.5	35.8	0.8
8	34	34.7	34.5	34.9	1
9	36	35.5	35.3	35.7	0.9
10	34	34.1	34	34.2	0.4
11	36	36	35.9	36.1	0.4

12	36	36	35.9	36.1	0.4
13	36	36.1	36	36.1	0.3
14	40	40.6	40.4	40.8	0.9
15	40	39.8	39.7	39.9	0.6
16	40	40.1	40	40.2	0.5
17	40	40.1	40	40.2	0.5
18	36	35.5	34.7	36.3	0.9
19	36	35.6	35.5	35.8	0.8
20	40	40.6	40.4	40.8	0.9
21	40	39.9	39.8	40	0.5
22	40	40.2	40.1	40.3	0.6
23	40	40.1	40	40.2	0.4
24	48	47.6	47.4	47.7	0.8
25	36	35.9	35.8	36	0.5
26	36	36	35.9	36	0.2
27	36	36	36	36.1	0.3
28	36	36.1	35.9	36.4	0.5
29	36	35.9	35.9	36	0.3
30	36	35.9	35.8	36	0.4
31	36	36.1	36	36.2	0.4

Appendix I: Confidential Information

[Restricted]