L. C. H. Maton

Stimulating the interdisciplinary collaboration between pharmacists and pharmacometricians using a model-informed precision dosing platform.

TU Delft

Stimulating the interdisciplinary collaboration between pharmacists and pharmacometricians using a model informed precision dosing platform.

How the interdisciplinary collaboration between pharmacists and pharmacometricians using a MIPD platform could contribute to their shared vision of implementing personalised medicine.

By

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This thesis is confidential and cannot be made public until June 30, 2022.

TU Delft

Preface

Learning together and connection, two terms that are repeatedly present over the last years of my life; not only in the study described in this thesis, but they were also key elements of the Master of Communication Design for Innovation. During this master's degree, the focus was emphatically on collaborating and communicating with and to each other, respectively, which is something I feel is a unique quality for a Technical University. This focus is something that I really admired during my double degree, the realisation it is sometimes more important to connect with others, talk about our thoughts and inspirations, and collaborate towards the ultimate goal, instead of only focussing on your own experiences and achievements. Collaboration and communication are not something obvious and often taken for granted; in my Bio-Pharmaceutical Sciences master's degree, I did not like to collaborate with others, and I rather worked for myself as I knew it would be finished successfully. However, during the SEC master's degree, I learned how important it is to involve others in your work and that together you can work to something way better than you ever expected. Furthermore, the collaboration on and talking about all these projects together brought us closer together, which brings a lot of positive energy and joy. We, together, worked on moving forward and successfully finish our projects and courses to eventually finalise our master's degree.

These thoughts were leading for this research thesis, written for my SEC graduation. All these healthcare practitioners are such clever people, who are really good at what they do. However, they often do not realise they could even be better and grow when they collaborate and make use of the knowledge of other professionals. In this thesis, the emphasis was on the collaboration between pharmacists and pharmacometricians, who are known to prefer working on their own, while they realise it is important to make sure their decisions are the best since it regards the healthcare of other human beings. This study focused on the collaboration and connection between two different kinds of professionals, the more technical one and the more social one. As they share the same vision of treating each patient with care and dedication, they need to adapt themselves in order to come closer and build that connection necessary to work towards this shared vision together. Furthermore, to work towards this shared vision, each patient needs to be treated differently as every human being differs significantly. The focus of current research is often focused on treating an individual patient, instead of treating as the second one in the row, which is a concept that is called personalised medicine. The use of personalised medicine focuses on improving patient treatment by treating them as an individual, which could increase the efficacy and decrease the toxicity. To make this ideal way of treatment applicable to all different patients, there is a long way to go and a lot more research to be performed. Nevertheless, as I am dedicated to helping others and I strive to improve their care, this research addressed a really small piece of establishing the application of personalised medicine. By exploring and creating a connection and a collaborative learning environment for healthcare professionals, I wanted to motivate and experience the advantages of collaborating by using a MIPD platform, which incorporates personalised medicine. Showing pharmacists and pharmacometricians how the other discipline works and decides on dosing regimen, I wanted to inspire them to work towards the future of personalised medicine through the use of a MIPD platform.

This study reflects the importance of being motivated to collaborate, the connection with other professionals, and how learning together can improve your achievements and makes you move forward as a person as well, which is something I learned and experienced a lot during my master's degrees. I'm proud to say that I successfully brought together the aspects that drove my life decisions in regard to my studies: medicine's use to improve patient care, the communication between different kinds of professionals, and of course the communication regarding these medicines. I'm looking forward to learning more about these aspects and to move towards a future where patient care continuously improves, while connecting and collaborating with others.

L.C.H. Maton
Den Haag, May 2022

Acknowledgements

Before the thesis will really start with the next chapter, I would like to use this moment to thank a lot of people that went with me through all the struggles and joys of performing and writing this thesis. I would like to start with thanking my graduation supervisors, Maarten van der Sanden, Jeannine McCune, and Steven Flipse. Maarten, thank you so much for all your creativity you brought during our meetings. You made me look different at each and every thought I had, which gave me a wide range of ideas and inspirations guiding me towards the next step. You really took me out of my comfort zone, which taught me a lot over the past months. Jeannine, thank you so much for everything in the past year (almost), you were my guidance through all the struggles on the scientific part and were always available to discuss and brainstorm on both the complex matters of the scientific parts and the social aspects within the healthcare system. Your efforts and warmth were very much appreciated. Steven, thank very much you for your help on finding the right focus, putting everything into perspective, and giving me feedback on the theoretical and written parts of the thesis.

Besides my supervisors, I would like to thank my housemates, friends, and family, who all kept up with me during my best and worst times of the last months. It wasn't always easy, but you were always there to let me complain or to keep me calm. You also stimulated me to move forward and go on, even if I didn't see how to anymore. Thanks for always listening, challenging me, bringing me creativity by just asking questions, and of course by also taken me out to have fun and do relaxing activities. Thank you all for always being there. I can't imagine having better people close to me.

Furthermore, I would also like to thank all the participants of this study. Without your motivation on either the topic or on your own expertise and willingness to help me with performing the research, I wouldn't have made it. I hope I gave you some insights in possibilities in the future and that I inspired you just as much as you inspired me.

Contents

Abstract

Personalised medicine represents an increasingly used practice using a patient's biology to guide their treatment. The implementation of personalised medicine possibly increases the quality of health care and life of the patient by minimising side effects and increasing effectiveness. Personalising medicine can be implemented through a platform which facilitates model-informed precision dosing (MIPD), including various models describing the pharmacokinetics of a specific drug. To make MIPD become clinical practice, wider interdisciplinary collaborations, for example, between pharmacometricians and pharmacists should be studied to learn about their communication and collaboration when using a MIPD platform, and to generate data evaluating the cost–benefit of MIPD in healthcare to motivate professionals to use a MIPD platform. Barriers to implementing these MIPD platforms into clinical practice are not thoroughly studied. However, the functionalities of the MIPD platform should align with the needs of the practitioners as they have to base their dosing regimen on that MIPD platform. As an exemplar for identifying barriers and facilitators of MIPD and corresponding MIPD platforms, this study focuses on the alkylating agent busulfan. Busulfan was chosen because it has a narrow therapeutic index, which often necessitates dosing to a target plasma exposure, while the use of MIPD is beneficial compared to the current clinical practice. Thus, busulfan dosing highlights the importance of using MIPD to improve patient outcomes. Identifying the barriers and facilitators of the MIPD platform, and the interdisciplinary collaboration between pharmacists and pharmacometricians will hopefully give insight on how to stimulate their collaboration and the use of MIPD.

This research, therefore, aimed to explore and describe 1) the obstacles in the interdisciplinary collaboration between pharmacists and pharmacometricians, 2) why MIPD platforms are not widely used in clinical practice and what practitioners would need to implement these platforms, and 3) what pharmacists and pharmacometricians need to establish an effective interdisciplinary collaboration using a MIPD platform and thereby create a learning environment. Through conducting a literature research and interviews, collaboration and technology acceptance aspects were studied more in-depth to define the problem and subsequently explore ideas to address this problem. Both disciplines perceived building a connection and keeping their own expertise as important in their collaboration. They also needed their roles in the collaboration and the MIPD platform to be clear in terms of knowing what to expect from the other and how handle the MIPD platform. Because of these perceptions and needs, we proposed two ways to improve the collaboration and the MIPD platform to subsequently contribute to establishing a learning environment through the MIPD platform. Those two implementations are: 1) the implementation of an introductory course where the disciplines collaborate through the introduction, and 2) tailoring the MIPD platform into two discipline-specific portals, which are based on their skills and tasks. The implementations were tested in interaction through conducting a focus group where pharmacists and pharmacometricians were asked to rank codes retrieved from the interviews on their relevance based on hypothetical scenarios, representing real-world cases. Pharmacists and pharmacometricians perceived connection and trust as important aspects of their collaboration and did expect these to be sufficiently stimulated through the implementation of the introductory course. Regarding the MIPD platform, they perceived the efficiency, in terms of easiness and time-effectiveness in use, as its most important aspect. Thus, efficiency should be ensured in the development of the MIPD platform. To adopt the MIPD platform, it should cover a lot of different patients highlighting the extensive research necessary when building the models within the MIPD platform. To stimulate the implementation of MIPD platforms and the collaboration between pharmacists and pharmacometricians using the MIPD platform, further research should focus on introductory MIPD courses, the MIPD platform design, and including other disciplines in the collaborations around MIPD and MIPD platforms.

Key words: Interdisciplinary collaboration, personalised medicine, model-informed precision dosing, MIPD platform, connection, collaborative learning environment, decision support systems

1 Introduction

This introduction is divided into four sections. The first section explains the background information on the topic of interest. That topic is personalised drug dosing through the use of a model-informed precision dosing platform, which is termed MIPD platform hereafter. A MIPD platform is a ready-to-use tool incorporating the pharmacokinetics, meaning what the body does to the drug during its movement in the body, of a specific drug described in a model. This section also describes how such MIPD platforms should be used and how the disciplines could collaborate and communicate through the MIPD platforms. The meaning of personalised medicine through a MIPD platform and the technical aspect of the MIPD platform are discussed. The second section describes the aim of this study. The third section describes the research questions that need to be answered in order to achieve the aim of the study. The fourth and last section describes the outline of the study, which steps are taken and followed by other steps.

1.1. Model-informed precision dosing platforms

Personalised medicine addresses the issues regarding the possibility of lower efficacy of certain drugs caused by treating large numbers of patients with the one size fits all approach, combined with the increasing healthcare costs due to more prevalent chronic diseases[1]. That one size fits all approach, known as Evidence Based Practice (EBP) is not unknown in the healthcare system, as it is perceived as common practice by practitioners aiming to base drug treatment on the best current, available, and relevant evidence[2–5]. However, the individual patient response differs widely from the average responses accounted for in using EBP, highlighting the need to individualise treatment for each patient[5]. Therefore, the use of personalised medicine is desired as personalised medicine represents the emerging practice of people being separated into different groups, creating the possibility of using an individual's genome to guide their treatment[6]. Implementation of personalised medicine has the possibility to increase the quality of health care and life of the patient by ensuring minimisation of side effects and increasing the potential for a beneficial outcome, and would also possibly reduce the costs of healthcare by decreasing the amount of treatments[1]. Personalising medicine can be implemented through a platform which facilitates model-informed precision dosing (MIPD). The use of MIPD may improve treatment outcomes by achieving the optimal dosing regimen for an individual patient, which ultimately also results in decreased healthcare cost per patient[7,8]. MIPD includes various modelling approaches, e.g., pharmacometrics using mathematical models of biology, pharmacology, and physiology. However, MIPD's use in determining the personalised dosing regimen is incessantly low[7,9]. For MIPD to become "widespread clinical practice", wider interdisciplinary collaborations, specifically between pharmacometricians and pharmacists, are necessary to generate data showing the evidence-based efficacy and cost–benefit analysis of MIPD in healthcare[7]. In agreement, the obstacles within interdisciplinary collaborations between pharmacists and pharmacometrician were also observed during the internship of my previous thesis, which regarded the building of a population pharmacokinetic model for busulfan to eventually personalise busulfan dosing regimen (Supplementary A). The issues were recognised since I worked closely together with pharmacists and pharmacometricians, giving me the opportunity to gain insight and understanding in their collaboration. During the internship, I observed the current way of collaboration between the two disciplines, which revealed their communication either lacked at all or was perceived as inefficient since both pharmacists and pharmacometricians did complain about their collaboration. Both tried to address this interdisciplinary collaboration but were not able to satisfy both disciplines within their collaboration, thus, no significant improvements were made. Whenever the interdisciplinary collaboration between pharmacists and pharmacometricians would be improved to their satisfaction, evidence for the effectivity and cost-benefit analysis for the use of MIPD can be generated, which will stimulate the implementation of MIPD.

MIPD is already implemented in several different software programs that are available for pharmacists to use in clinical practice to facilitate MIPD. Initial dosing regimen predictions can be estimated based on a population model making use of this approach. After quantitating the concentrations and their modelling, subsequent doses can be further personalised[9,10]. Software programs in which MIPD is implemented include but not limit to InsightRX and NextDose[11–14]. The MIPD platforms are ready-to-use tools

incorporating the pharmacokinetics of a specific drug described in a model, which means that the MIPD platform predicts what the body does to the drug. Using these tools, an personalised dosing regimen can be estimated based on population parameters and patient characteristics[11,15,16]. Both tools are accessible as applications on the web, where they rely on electronical medical record integration or the manual input of the pharmacokinetic data and patient characteristics[11,12,15]. The following patient characteristics are required in both MIPD platforms to be able to determine the personalised dose: body weight, sex, age, height. InsightRX also requires the knowledge of whether the treatment is meant for a malignant or non-malignant condition[12]. A value for the target exposure of the drug of interest needs to be entered in both tools; NextDose made use of either steady-state average concentrations or the target exposure over a specific dosing interval, while InsightRX made use of the individual target cumulative exposure[12]. An example for the MIPD platform InsightRX is shown in Figure 2; The characteristics of a specific patient can be entered, and different dosing regimen can be tested to see whether the combination of patient characteristics and the regimes fits the threshold for the drug reaching a positive ratio between efficacy and toxicity. Regardless of the fact that no prior experience or knowledge in modelling is necessary and that the use of MIPD implemented in these tools provide significant advantage in achieving target exposures, these tools have still not been generally integrated into clinical practice[9,11,12,15].

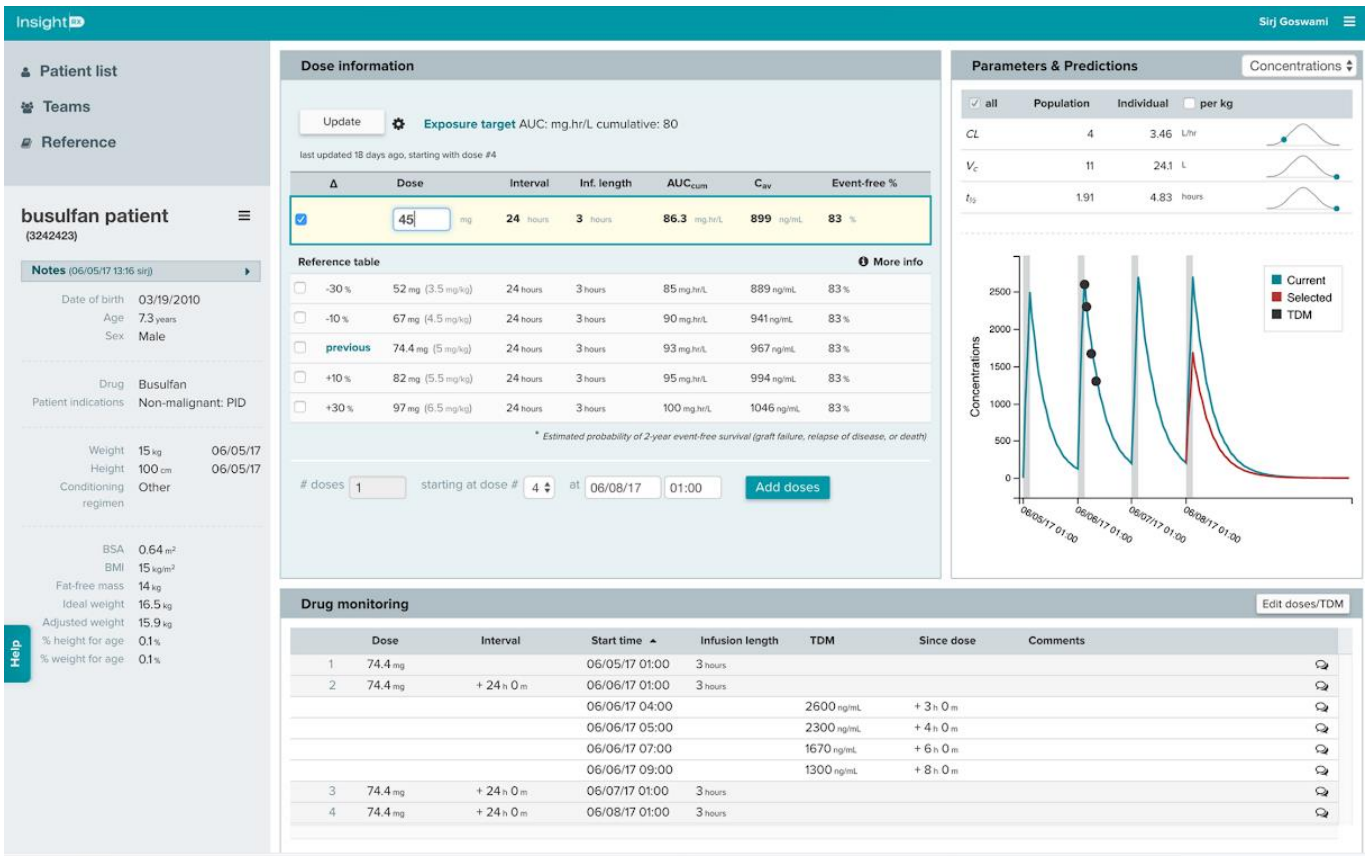


Figure 1. Dashboard of MIPD platform InsightRX[14]. This MIPD platform provides the possibility to note the characteristics of a patient and test different doses to see whether the concentration fits threshold values for efficacy.

Despite the advantages of these software programs, the application of MIPD through such platforms is not widely implemented[9,16]. Barriers keeping these software programs from being generally integrated into clinical practice could include the lack of more user-friendly features, lack of technical- and high-level pharmacokinetic knowledge from clinical practitioners, and lack of validity in licensed programs in clinical settings[7,9,16]. The user-friendliness of the MIPD platform is from major importance if pharmacists will be willing to use such new technology without having extensive prior technological knowledge. Thus, the design, implementation and the operation perspectives of the software needs to be analysed[9]. The functionalities of the MIPD platform should align the needs of the pharmacist who eventually needs to base the dosing regimen on it. As an exemplar for identifying barriers and facilitators of MIPD, we have chosen the alkylating agent busulfan. The population model for busulfan is studied and developed in the previous written thesis and is described in detail in Supplementary A. Busulfan is often dosed to a target plasma area

under the plasma concentration-time curve (AUC) when used as part of the conditioning regimen (Figure 2) for patients undergoing allogeneic hematopoietic cell transplantation (HCT). To achieve the target AUC, busulfan's dose is often personalized to a target exposure in a process using pharmacokinetic-directed dosing. This approach involves the following processes in the following order: 1. Dosing busulfan based on body weight; 2. Obtaining numerous blood samples after its first dose; 3. Quickly quantitating their busulfan concentrations; 4. Use a pharmacokinetic modelling program to fit the individual patient's concentrations obtained at the different times (called concentration-time points) to estimate that patient's busulfan exposure; 5. Estimate how fast that individual patient clears busulfan; 6. Personalise their busulfan dose to achieve the target exposure and their individual clearance. This process has remained unchanged over the past 30 years, despite the availability of MIPD for busulfan implemented in for example InsightRX or NextDose, which could further improve the efficacy of the treatment by more precise estimation of the first busulfan dose.

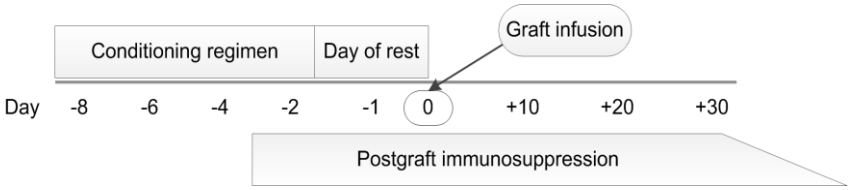


Figure 2. Hematopoietic Cell Transplant (HCT) regimen. All regimen implemented in the HCT procedure are presented over time.

To be able to employ MIPD implemented in a platform, a clear communication and collaboration between the pharmacometrician and pharmacist is necessary[7]. Pharmacists usually dose patients based on long-existing protocols, which they know by heart, and which are very easy to use. Because of unidentified reasons, most pharmacists do not use such available MIPD platforms and stick to the old protocol, risking a decrease in efficacy of busulfan treatment and increasing the risk of toxicity in a patient.

1.2. Research aim

To explore the reasons for the lack of or the obstacles in their collaboration and what elements should be addressed to improve the dosing regimen using such software platforms, we aim to compare their communication and collaboration behaviour to the theoretical background related to collaborative and interdisciplinary learning, motivational behavior, individual adaptability and technology adoption.

Consequently, this project aims to explore and describe the difficulties in the communication and collaboration between pharmacometricians and pharmacists, specifically why drugs, such as busulfan, are still dosed based on the standard, earlier developed procedures regardless of the availability of MIPD implemented in such software programs. Furthermore, the project aims to describe what pharmacists and pharmacometricians need in their collaboration through such software programs, meaning what elements are needed in the MIPD platform or in their communication to improve the pharmacists' practice and to create a learning environment for both disciplines. These needs will be described and elaborated to improve the MIPD platform are meant to make their practice in dosing more accessible, applicable, less time-consuming, and more attractive to be used and improved constantly. Creating a learning environment from MIPD implemented in these software programs enables the possibility to increase the efficacy and reduce the toxicity of drugs in each individual patient.

1.3. Research questions

To be able to achieve the described aims project, the following research question is defined as a guidance for the project:

To what extent could using a MIPD platform contribute to the interdisciplinary collaboration between pharmacists and pharmacometricians on model-informed precision dosing of busulfan?

Based on the previously mentioned themes and obstacles leading to and to be able to answer the main question, the following sub-questions were formulated:

1. What are the specific tasks of 1) pharmacometrician and 2) pharmacists?
2. How is the decision-making for dosing regimen set up currently?
3. What are the (dis)advantages of model informed precision dosing compared to clinical based for 1) pharmacists and 2) patients?
4. Why is clinical-based dosing merely used over model-based dosing?
5. How can a MIPD platform serve as the foundation of the pharmacist-pharmacometrician collaborative learning environment?
6. What would a MIPD platform need to make both pharmacists and pharmacometricians enthusiastic to use and learn from it?
7. How can the collaboration between pharmacists and pharmacometricians be improved to subsequently increase the use of the MIPD platform and thereby create a learning environment?

1.3. Research outline

The research consists of six parts, including background, methodology, research, design, discussion, and conclusion. In the current chapter, the scientific background and its correlation to communication are discussed, and subsequently research aims, and questions are formulated. Chapter two describes the methodology, meaning how the study is approached in terms of methods to answer the research sub-questions. The methods conducted results in chapter three, where the results are described into two stages: research and design. In the research stage, problem exploration and description are studied and formulated. In the design phase, the implementations to address the problem are described followed by testing the propositions in a focus group. The results sections provide noteworthy insights in the answers to the sub-questions and in the recommendations to stimulate collaboration and learning through the use of the MIPD platform. In chapter 4, the research aim, methodology, results, limitations, and future perspective and recommendations will be discussed both based on experience and explored literature. Using all previously written chapters, answers to the sub-questions will be presented followed by answering the main research question in chapter 5. In this conclusion section, the research questions and corresponding conclusions are summarised. An overview of the structure, as described here, of the research is depicted in Figure 3.

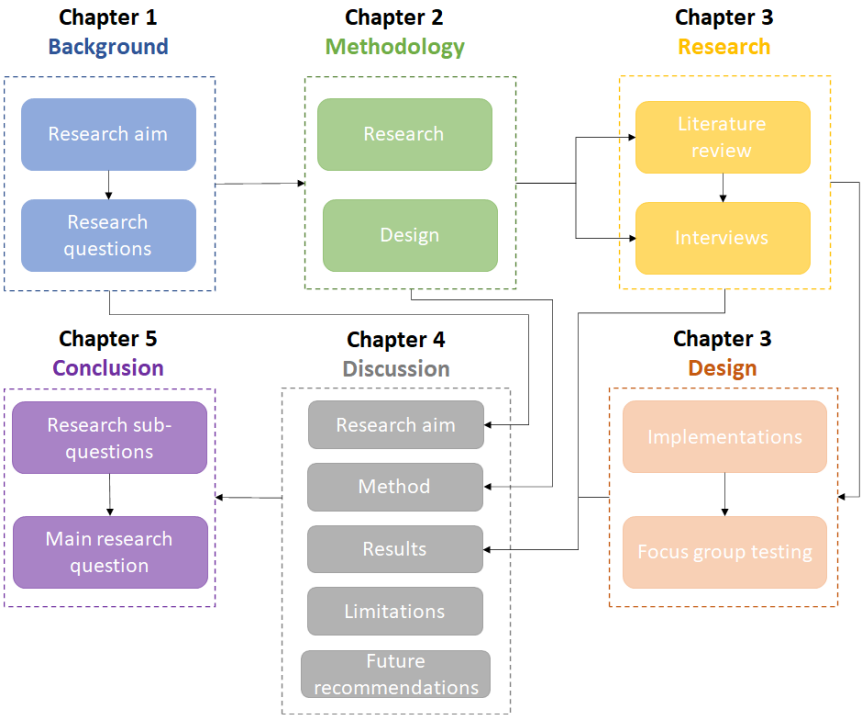


Figure 3. Outline of the research. This study consists of six stages: background, methodology, research, design, discussion, and conclusion. These stages are expressed into five chapters, where research and design are combined into the results section. Arrows indicate the input of each section to the subsequent section. The solid boxes indicate different subchapters and key topics of the stage, whereas the dotted lines indicate the overarching stages of the combined key topics.

2. Methods

The methods employed in the current study were exploratory and descriptive, to fit the aim of finding obstacles in collaboration and communication between pharmacists and pharmacometricians and of describing how to improve their collaboration and the use of MIPD platforms. This chapter will describe the methodological steps taken in the design process of the study. The study conducted used design-based elements and was based on the double diamond model (Figure 4), describing the iterating process between problem awareness, definition, and solution designing and subsequent delivering[17–19]. The problem was first identified during the internship for writing of my previous thesis, where was revealed that their communication and collaboration on dosing decision-making lacked or was perceived as inefficient. They tried to improve their collaboration, but without satisfactorily success, therefore, no significant improvements were made. The further discovery and exploration of the problem was done through an extensive literature research and the conduction of interviews, where as much information as possible was obtained to understand the wide context within the problem. Narrowing down the scope and thereby defining the problem was done through the deepening of our knowledge using the literature study and the conduction of qualitative, semi-structured interviews with both pharmacists and pharmacometricians, mainly to assess their experiences in collaborating and using MIPD through a platform. By conducting semi-structured interviews, it was possible to address concrete aspects of collaboration and learning through such MIPD platform, while still giving the interviewees time to express and explain their experiences and feelings regarding these aspects without being biased or limited by a strict interview protocol. The different interviewees' experiences were then categorised through coding and the differences between them were analysed to specify the focus of the study. Based on the results of this analysis and the knowledge obtained previously, recommendations and suggestions for their interdisciplinary collaboration and for the development of a learning environment through a MIPD platform were written in the development phase of the second diamond[17–19]. These proposed implementations regarding the prototype for establishing an interdisciplinary collaboration between pharmacists and pharmacometricians through a MIPD platform were then tested in the last phase of the design process, the delivery phase. In a focus group with pharmacists and pharmacometricians, their thoughts on the recommendations and suggestions for the implementations were tested. The methodological steps employed to guide this research are described in the rest of this Methods section. The iteration aspect of this double diamond was present based on continuously adjusting the formation and descriptions belonging to each phase of the diamond based on newly obtained insights in every step of the research, leading to each phase of the double diamond influencing other phases.

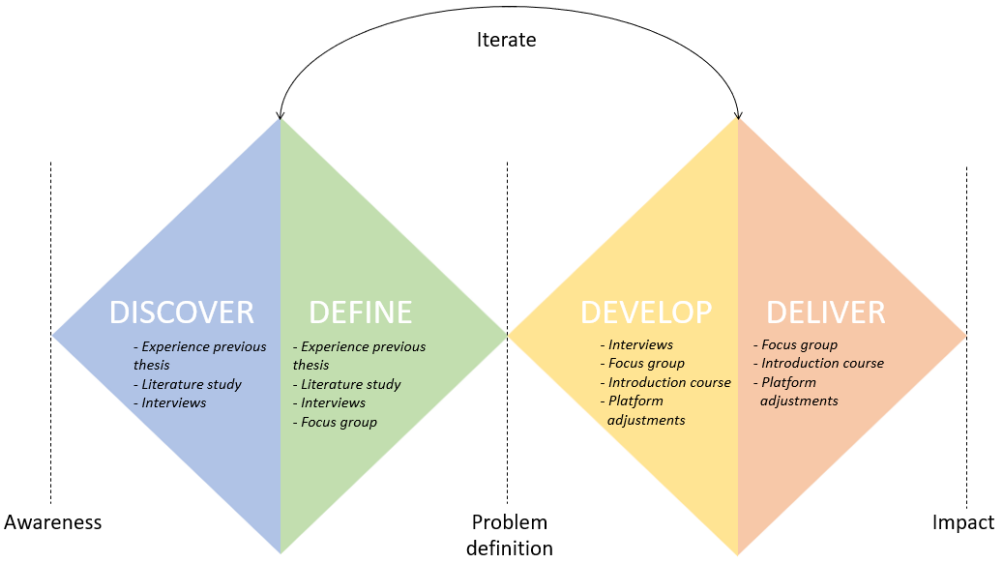


Figure 4. Double diamond design process. Design thinking process of the study described in the adapted double diamond scheme[17,19].

2.1. Literature review

An extensive literature review was performed to discover the obstacles in the collaboration and communication between pharmacists and pharmacometrician in treating patients. The literature review was focused on collaborating and communicating factors and social theories, such as collaborative and interdisciplinary learning, motivational behavior, individual adaptability, technology adoption, interdisciplinary collaboration, and transdisciplinary learning. The goal of the literature research was to give an overview of theories and methods, which can be used to describe, specify, and find solutions to the communication and/or collaboration issues between the two disciplines. Since these research themes have been studied for many years and their meaning have evolved enormously, a specific selection of all found literature based on the different configurations was conducted; the literature of the theories that were focussed on professionals within the healthcare system were selected.
The literature review started with the formulation of characteristics of both pharmacists and pharmacometricians, and of characteristics necessary to establish an effective interdisciplinary collaboration. These characteristics were used to select the obtained literature based on the theories; all literature found on each theory was narrowed down to only focus both on disciplines within healthcare and on one of the characteristics formulated. The most important literature was collected and summarised on their relevance in Appendix B. The combination of all these theories and the characteristics were used as a base to develop the theoretical framework of this study, where all theories were related to specific characteristics necessary to establish an effective interdisciplinary collaboration.

Literature was searched using search engine Scopus, Google Scholar, and PubMed. The six major theories were sought for in different configurations in relation to healthcare, corresponding practitioners (specifically pharmacists and pharmacometricians), and the formulated characteristics. All literature sources found were directly saved to a separate desktop used for referencing, Mendeley[20,21]. After the first selection of literature based on their content, the literature was selected based on the number of citations, where more citations where preferred as it indicates relevance and reliability, and on the year of publication, where newer literature was preferred over older literature as it could indicate the literature to be outdated.

2.2. Subject selection

Both pharmacists and pharmacometricians needed to be selected as study participants, in order to obtain experiences to analyse from both collaborating parties. As this study was conducted during a global pandemic, the subjects approached consisted mainly of professional and personal networks of the researchers. All participants were selected based on convenience and stratified sampling. For each discipline, three participants were selected for semi-structured interviews. To achieve a more diverse sample and obtain more diverse experiences, the final three participants per category were selected to reflect different genders, age, and study background. To test the results from the analysis, 5 subjects were selected for the focus group, of which three were pharmacists and two were pharmacometricians. For the focus group, participants were selected based on their prior experience and knowledge on MIPD, since they are the practitioners that ultimately needs to benefit from this research. The differences between each participant were considered as a possible influence on the results. Participant characteristics were summarised in table 1. All participants agreed upon the potential risks of the study and signed the informed consent form, which is shown in Supplementary C.

Table 1. Participant characteristics selected for the study.

Participant	Discipline	Participation[a]	Age[b]	Educational background	Experience[b]	Technology-use[c]
P1	Pharmacometrician	Interview	25	Pharmacy/ Drug innovation	2.5	4
P2	Pharmacometrician	Interview	27	Pharmacy	3	3
P3	Pharmacometrician	Interview	31	Pharmacy	7	4
P4	Pharmacist	Interview	35	Medicine	6.5	3
P5	Pharmacist	Interview	58	Medicine	30	2
P6	Pharmacist	Interview	36	Bio-Pharmaceutical Sciences	9	3
P7	Pharmacometrician	Focus group	25	Clinical technology	2	NR
P8	Pharmacometrician	Focus group	26	Bio-Pharmaceutical Sciences	4	NR
P9	Pharmacist	Focus group	27	Medicine	4	NR
P10	Pharmacist	Focus group	26	Medicine	3	NR
P11	Pharmacist	Focus group	25	Medicine	2	NR

[a]interview/ focus group; [b]year; [c]scale 1 (minimal use) to 5 (high use); NR: not requested

2.3. Data collection

Data was collected through conducting individual interviews with six interviewees and through conducting a focus group with five participants.

2.3.1. Interviews

For the discover and define part of the study, qualitative, semi-structured interviews were conducted with three pharmacists and three pharmacometricians. The questions included in the protocol were ensured to be open and unbiased, to make sure people felt free to express their own feeling and did not feel like the interviewer gave direction to the conversation. Both pharmacists and pharmacometricians got the same introduction for the study, however, both were asked different questions through different interview protocols. The first questions are merely related to how both disciplines work at this point in their career. To get a general idea how the two are collaborating right now, both parties were asked how and when they collaborate, how they feel about this collaboration, and what like or do not like about their collaboration. Furthermore, to explore the thoughts and motivation on collaborating through a MIPD platform to improve dosing regimen, the parties were asked whether they were familiar with MIPD platforms, whether they used them or would be interested to, and what the optimal MIPD platform would look like to them. The interview protocols composed for both pharmacists and pharmacometricians is shown Supplementary D. The interviews were recorded and subsequently transcribed. After transcription, the recordings were deleted.

2.3.2. Focus groups

The results of the data analysis of the conducted interview transcriptions were used to define adjustments and recommendations in the development phase, regarding the MIPD platform and the collaboration and learning through that platform by pharmacists and pharmacometricians. In the delivery phase of the study, a focus group was performed, where two aspects were discussed in detail. One aspect of the MIPD platform and one of the collaborations were tested: 1) two portals separated for pharmacists and pharmacometricians; and 2) learning together during an introductory course. For the focus group, three pharmacists and two pharmacometricians were selected. The pattern for the focus group was as followed: 1) Introduction to the topic; 2) Setting the rules for the discussion; 3) Ranking scenarios based on codes from interview; 4) Asking the questions; and 5) Closing focus group by everyone commenting upon the discussion. The detailed protocol for the focus group is found in Supplementary F.

During the ranking, the two disciplines were allowed to discuss within their disciplines what five codes, out of all codes obtained from the interviews regarding both collaboration and MIPD platform, were perceived as being most relevant and/or important in that specific case. After selecting the five codes, the participants ranked these codes per theme from one to five, where one is perceived as least relevant and five as most relevant. The code ranked at position five received five points for data analysis, whereas the code ranked at position one received one point. Codes not selected as most important or relevant did not receive any points. During the stage of asking the questions, questions relevant to the collaboration between pharmacists and pharmacometricians through the use of a MIPD platform were asked and discussed within the focus group. All participants were allowed to give their opinions and to respond to other participant's opinions in return. While closing the focus group, the participants were asked whether they had something to share which was not yet discussed.

The rules for the focus group included listening to each other and the moderator, only one person is talking at the same time, respect other participants in the conversation. Furthermore, it was made clear that no answer is wrong or right, and people are allowed to discuss different views upon a matter. The discussion was recorded and subsequently transcribed. After transcription, the recordings were deleted.

2.4. Data analysis

The collected data obtained from the transcription of the interviews were analysed using the analysis technique called coding, which involves identifying categories, concepts of interest, or even phrases and

labelling these based on their meaning. The first cycle coding will be descriptive coding, whereby the topic of a specific smaller unit of the data, usually a sentence, is summarised through a descriptive word or noun[22,23]. All these descriptive codes together lead to a categorised inventory of the data in all interviews. The descriptive codes are then after coded using pattern coding, whereby the different codes are clustered together to generate or to be assigned to major themes which were either identified during the interview analysis or were predefined beforehand. This coding method creates the opportunity to discover emerging patterns or themes in the dataset, facilitating the possibility to find connections between data and theory. In this study, coding was used to draw out the following predefined or identified themes related to the research questions: 1) daily jobs; 2) feeling towards healthcare technology; 3) collaboration; 4) MIPD platform; and 5) future perspectives.
The coding was done manually. After identifying these codes and corresponding themes within the interview transcriptions, the themes were linked to elements within theories of the theoretical framework, which will be discussed in the results section. The terms were linked to these codes and corresponding themes can be found in Supplementary E.

The first set of results from the focus group are described in a ranking, creating insight in what participants perceive as important regarding the specific case. The two rankings and the one ranking regarding the MIPD platform and the collaboration, respectively, are used to define crucial elements for improvement of the future MIPD platform and collaboration between pharmacists and pharmacometricians. Furthermore, the recorded data is analysed through framework analysis, which is an analytical process with separate but still highly interconnected phases. In this study, a combined approach for framework analysis is used[24]. The four key phases of this analyses after data collection are as followed: 1) Familiarization, meaning getting sense of the interview by transcribing and carefully reading through the interview; 2) Developing thematic framework, where sentences are coupled to themes already defined or newly emerged themes; 3) Managing the data, regarding sorting out the data by reducing and re-arranging and put data in context; and 4) Mapping and interpretation, where correlations between data is studied and find ideas encapsulating the themes.
The second set of results from the group were collected through asking questions regarding the collaborative introductory course and the (adjusted) MIPD platform. The interaction on these questions was also recorded and subsequently transcribed, creating the possibility to recognise quotes and relate the answers to elements of the theoretical framework and research (sub)questions.
The coding was done manually. Afterwards, the ideas and correlations were linked to elements within the theoretical framework and to the research (sub)questions. The correlation between ideas and/or quotes and the collaboration and/or MIPD platform are depicted in Supplementary G.

3. Results

This section describes all the results obtained in this study in detail. First, the discovery phase of the design process is presented through an overview of the literature research. This review leads to literature-based interpretations of the issues in communication and collaboration as described in chapter 1 introduction, which subsequently were used as a guidance to develop the theoretical framework. Secondly, the results of the conducted interviews in the define phase are presented, describing the actual problem statement. Thirdly, in the development phase the results of the coding analysis are used to develop adjustments and recommendation towards the improvement of collaboration, communication, and MIPD platform. Lastly, the testing results of the adjustments and recommendations in a focus group are reported in the delivery phase.

3.1. Literature review

Literature research was performed to dig deep into social theories regarding the communication and collaboration between pharmacists and pharmacometricians and to address factors involving the stimulation or hindering of these disciplines working together, either through classical communication or through the use of a MIPD platform. To find a starting point for the literature search, both disciplines were drawn next to one another noting the characteristics necessary to work towards the goal of this study being effective interdisciplinary collaborations (Figure 5). The characteristics described for each discipline in Figure 5 were

thought up during a brainstorm session, based on both experience, and discussions with professionals and observations of previous internship. The literature research was focused on finding theories that involve and influence all characteristics as described in Figure 5. In addition, the definition of effective interdisciplinary collaboration was based on the ten principles of effective interdisciplinary collaboration as reported by Nancarrow et al. (2013), including the following principles: clear and shared vision, flexibility of the team and participating professionals, communication strategies, respecting and understanding roles of collaborating disciplines, supportive and trustful team climate, quality in outcome (patient-centered focus), appropriate team procedure and structure, appropriate skill mix between practitioners that support interdisciplinary team work, opportunities for personal career development in terms of training and learning, and positive leadership and management[25]. The selected theories that are addressed in the literature review include collaborative and interdisciplinary learning, motivational behavior, individual adaptability, and technology adoption. For all theories, their specific meaning in and their application to this study are summarised in different sub-chapters. Moreover, the resulting theoretical framework is discussed in the last sub-chapter and describes the connection between the theories, the different disciplines, and their corresponding characteristics.

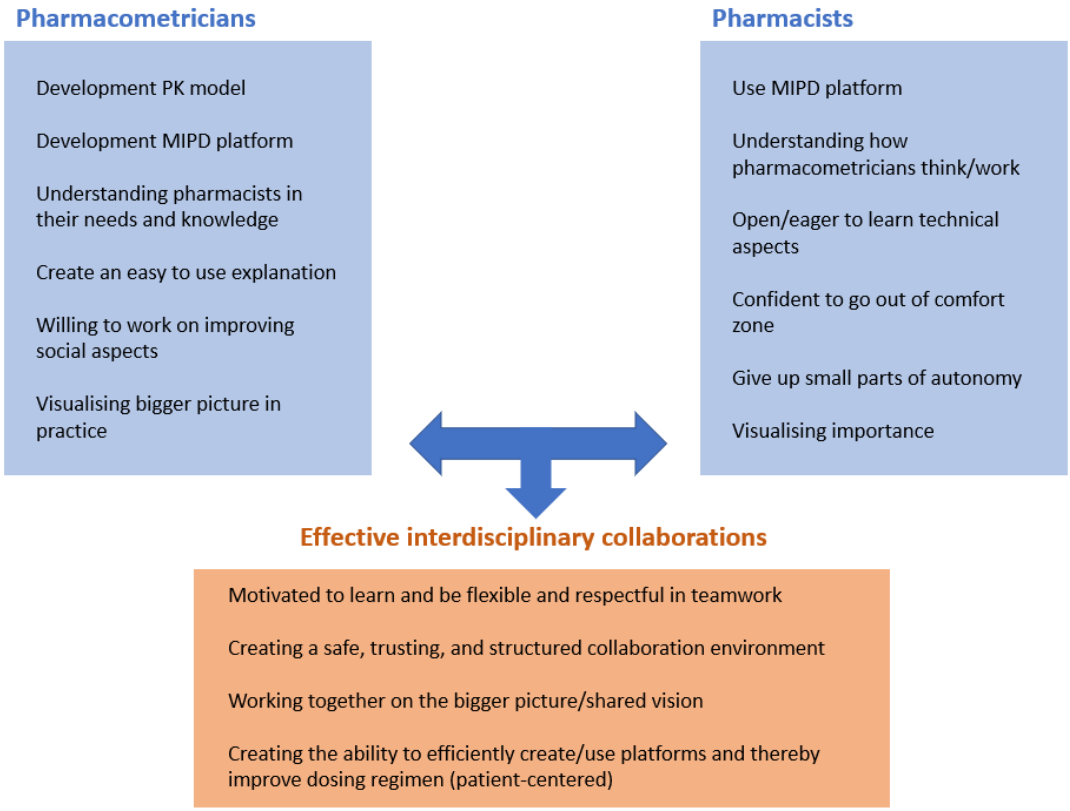


Figure 5. Characteristics of pharmacometrics and pharmacists, perceived to be needed to create effective interdisciplinary collaboration. For both disciplines the characteristics important to create an effective collaboration through a MIPD platform are described in the blue boxed. The orange box depicts benefits of an effective interdisciplinary collaboration, as defined by Nancarrow et al. (2013) and adapted to fit this research context[25].

3.1.1. Interdisciplinary and collaborative learning

Both interdisciplinary learning and collaborative learning include the need for different individuals or whole disciplines to work together to solve a specific problem[26,27]. Interdisciplinary and collaborative learning describe a method which is used to bring together different disciplines around shared issues, meaning the combination of two or more disciplines into common problems[28]. Both approaches enhance the learning process through collaborating with different disciplines towards a shared goal[29]. Possible advantages in using interdisciplinary learning include awareness of interconnectedness between disciplines, higher-level thinking and decision-making, increased control of personal learning processes, and increases motivation since the real-world application of the knowledge is visible[30]. The need for interdisciplinary learning is also recognised in healthcare systems: different disciplines in the healthcare system need to adopt new knowledge and skills in their collaboration and patient treatment in order to improve patient care[26,31].

Furthermore, collaborations in the health care systems are defined as professionals in different expertise cooperatively working together and sharing responsibility for the problem solving and decision-making processes in patient care. These professionals working together raises the awareness of the other member's knowledge and skills, subsequently leading to improved decision-making[32].

Effective interdisciplinary and collaborative learning will reduce morbidity through safer use of drugs, and thereby decrease the high healthcare costs. Effectiveness of interdisciplinary learning and collaboration is characterized by a level of trust and acceptance of all disciplines, meaning how willing they are to partly hand in their autonomy to the other party, by a high level of energy focused on accomplishment of the shared goal, which is improved healthcare for patients[26,31]. All practitioners have their own strength in a specialism with corresponding knowledge and skills. When bringing these disciplines together, all specific assets can supplement the lacking strengths of collaborating disciplines[26,32]. The theories of interdisciplinary and collaborative learning are rooted in the social development theory and zone of proximal development, where the necessity of communication and interaction in learning is describes. These theories explain how disciplines rely on collaborating disciplines to complete their tasks successfully, meaning the combination of two or more disciplines working together as a group creates the ability to retain more knowledge[33].

Using these theories in practice in this study, the most important part is directing and stimulating pharmacists and pharmacometricians towards this interdisciplinary and collaborative learning. Taking the aspects of the literature review on these theories into consideration, pharmacists and pharmacometricians need to use their own expertise to teach the other discipline their knowledge and skills, but also adopt their knowledge and skills, to move together to an effective interdisciplinary and collaborative learning environment (Figure 6). In order to get to the shared goal of improving the dosing regimen of patients, both disciplines need to learn together and share their knowledge for the other to move in their direction. If both parties understand the knowledge of the other and is able to reproduce, they can look critically at each other's work, which will even improve decision-making through such MIPD platform. By creating an actual learning environment in the MIPD platform, that platform will continually be improved as well. Both will gain in-depth knowledge on the day-to-day jobs of the others and can thereby trust and respect one another, which will subsequently stimulate an effective collaboration. By sitting down together and talk through all the topics involved, they can together get to bigger improvements than each separately. Therefore, in this study it's important to find out what the one disciplines desires from the other: how they would like to collaborate and communicate, and what they know from the other discipline in order to improve their daily jobs.

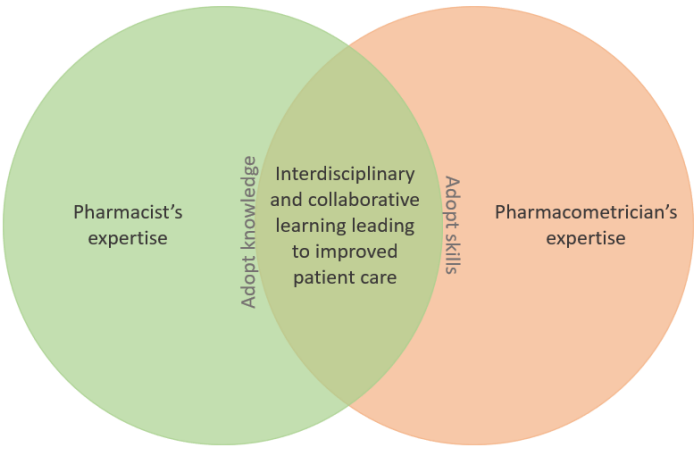


Figure 6. Schematic depiction of interdisciplinary and collaborative learning between pharmacists and pharmacometricians. The green colour shows the expertise of the pharmacists, whereas the orange colour depicts the pharmacometrician's expertise. Both parties adopting knowledge and skills leads to effective interdisciplinary and collaborative learning.

3.1.2. Motivational behaviour

The theory of motivation is used to understand the urge of an individual to work towards a specific goal. Motivation theory consists of two factors: extrinsic motivation and intrinsic motivation[34,35]. Extrinsic motivation is driven by extrinsic factors, such as receiving a reward for hard work or receiving a punishment

for neglecting work. Intrinsic motivation is driven by the desire to please another individual's needs, such as the desire to satisfy their boss and/or achieve specific personal or professional goals[34,35].

Regarding the motivational factors as described above, the collaboration between pharmacists and pharmacometricians through for example such a MIPD platform merely depends on intrinsic factors. Both disciplines need to be motivated through the desire to satisfy the needs of others and the desire to achieve their professional goal to provide the best care for a patient possible. The use of a MIPD platform would be beneficial for the patient by reaching the efficacy with a decreased risk of toxicity. The patient wellbeing and beneficial outcome using MIPD should be an intrinsic motivation for both disciplines to collaborate towards the most successful learning environment, using an improved MIPD platform, as possible.

Achievement motivation, which often causes intrinsic motivation, is a well-researched field that is highly relevant to learning[36,37]. Achievement motivation is driven by the desire for success, the expectancy for success, and the incentives provided[38]. Several studies show that individuals rather have tasks of intermediate difficulty, because they are more likely to achieve the results they would desire to see. Regarding achievement motivation, the attributions of ability, effort, task difficult, and luck all influence future achievement motivation[38–40]. For example, when an individual successfully fulfils a task and attributes their success to ability, they are more likely to be motivated to approach new comparable situations in the future. Similarly, if their success is attributed to intense effort, it is less likely that they approach the new achievement situation. Future achievement behaviour then depends upon the willingness to put such effort in a specific task[40]. Furthermore, the difficulty of a task is judged based on social norms; if most individuals are unsuccessful, the task is judged as being difficult, while if most individuals succeed, the task is judged as being easy. The attribution of success to task difficulty will most likely modify future achievement behaviour[38–40].

Also, achievement motivation is likely be an important influence in willingness and finding motivation to contribute to the development and use of a MIPD platform. For pharmacists, the use of such MIPD platform seems difficult since they do not have the technical knowledge and need to dig deep to obtain such knowledge. Since it is expected to be difficult, their willingness to put effort in the task is probably not too high. This creates an environment where they do not find the motivation to learn from the MIPD platform in order to use it and subsequently make its use easier. Furthermore, for a pharmacometrician is can be quite difficult to estimate how in-depth the knowledge of a pharmacist is regarding dosing based on MIPD. Therefore, they might consider the task to develop a MIPD platform, which is understandable and thereby usable for pharmacists, as difficult. Taken the attribution achievement motivation theory into consideration, there would be expected that whenever both parties feel like learning from such a MIPD platform is manageable, they are more likely to be motivated to make use of the MIPD platform.

3.1.3. Individual adaptability

One model describing individual adaptability, is I-ADAPT[41,42]. The model defines individual adaptability as the characteristics of an individual, including knowledge, abilities, and skills, that have a major influence on their adaptability. Not only these characteristics are included in the model, but the model also describes adaptability as the willingness and/or motivation of an individual to change or fit different tasks, socially and professionally[41,42]. Furthermore, other research on individual adaptability was focused on the adaptability in the work space, and described it as behaviour demonstrating the individual's ability to cope with change and to be able to transfer learning from one task to another[43]. Adaptability can be seen as individual differences, whereby the skills, abilities, willingness and motivation differ between individuals[42]. Lots of models and theories describe individual differences, such as the Cattel-Horn-Carrol model of intelligence. This model approaches individual differences in intelligence as a three-level structure, using one general over-arching third-order factor, some broad abilities in the second-order factor and a lot of narrow abilities at the first-order factor[43]. Individual differences in adaptability can also be approached using such triarchic structure and would ideally be combined with the individual's characteristics affecting adaptability as proposed in I-ADAPT. Combining these approaches would explain individual adaptability as the proposed characteristics being involved in all situations requiring adaptability, but it depends on the situation and the individual to what extend these characteristics are expressed[43].

Another approach adaptability is the interaction adaption theory, which attempted to explain individual's behavioural adjustments in communicating with others[44,45]. Adaptation patterns in communication depend on the individual's requirements, expectations, and desires[46,47]. These factors influence how the individual is projected during any communication or collaboration. The theory describes how certain circumstances require more of one factor, while in other situations the other factor should be express to a higher level. Individuals need to be able to adapt to situations requiring another ratio between requirements, expectations, and desires.

To improve collaboration between both disciplines requires the ability to adapt to one another. Thus, the theory of individual adaptability considering the ability to adapt being related to be able to cope with change and to transfer knowledge, is crucial for different disciplines to move towards an effective collaboration. Furthermore, it is important to alter your behaviour to meet the demands of others. Pharmacists need to adapt their view and actions to meet the needs of the pharmacometricians, and the other way around. Pharmacometricians need to adjust their working models implemented in a MIPD platform to make pharmacists understand how to approach the tool. On the other hand, the interaction adaptation theory can be related to the collaboration of pharmacometricians and pharmacists by the fact that two different groups have their different requirements, expectations and desires. However, they need to coordinate and adapt these three factors to one another in order to realize or improve the communication. Moreover, people reciprocate behaviour of others automatically, which can be useful in improving such a communication. For example, when a pharmacist is willing to adapt to a pharmacometrician by listening and giving input, it is likely that a pharmacometrician will return this behaviour.

3.1.4. Technology acceptance

Technology acceptance in healthcare, but also in other specialism, describes the psychological state of an individual regarding a specific technology and its use[48]. Revelation of factors that influence the use of these healthcare technologies is of major importance in order to understand how to approach healthcare technology to improve its use effectiveness. Enhanced effectiveness will improve the quality of healthcare and the satisfaction level of patients, stimulating their technology acceptance[48]. Developers of these technologies need to focus on the intention of the user to increase the level of acceptance. One of the most influential theories regarding technology acceptance, is the technology acceptance model (TAM), which was used to study the social mechanism of technology adoption. The model describes two core factors that influence the patient's intention to use a specific technology, namely perceived ease of use and perceived usefulness[48–50]. TAM would also be applicable to healthcare professionals, as Kalayou (2020) described the cruciality of the healthcare professional's experience of the healthcare IT and of the technical infrastructure, reflecting the availability of systems enhancing the healthcare IT's use[50]. Confirming the applicability of TAM to healthcare professionals, Holden and Karsh (2010) and Melas et al. (2011) reported the impact of the perceived usefulness of a health IT on the level of acceptance of healthcare professionals and whether they would be motivated to use that health IT[51,52]. Holden and Karsh (2010) did not confirm the easiness in use to impact the level of acceptance, however, as the easiness in use if correlated to the perceived usefulness, it is likely that healthcare IT perceived as difficult in use cannot be perceived as useful[51–53]. Furthermore, both core factors of TAM show it is mandatory to make new technologies user friendly and to deliver a convenient information provision[54]. Design, training, and information session are crucial to guarantee the specific healthcare IT improves patient outcomes and the healthcare IT is not difficult to use, meaning that an individual who is familiar with other technologies and perceives this healthcare IT as easy to learn and use, is more likely to be motivated to adopt this healthcare IT[51,54]. The other model that is most prevailing in describing what affects the level of acceptance of specific healthcare technologies is called the unified theory of acceptance and use of technology (UTAUT)[48]. This model also includes factors perceived ease of use and perceived usefulness, but approaches these factors merely as effort expectancy and performance expectancy, respectively[54]. However, UTUAT also recognises contextual factors that enhance or inhibit the adoption of new technologies, including facilitating conditions and social influences. In accordance, Ifinedo (2012) reported the influence of UTUAT's elements, effort expectancy, social influence, and facilitating conditions, on usage behaviour of healthcare professionals[55]. However, they did not yield significant influence of performance expectancy[55]. Combining the factors described in both TAM and UTAUT that ultimately influence the acceptance of technology are described in Figure 7.

Measuring the level of acceptance in different disciplines will support successful implementation of a technological healthcare system[56]. Obtaining knowledge before implementing the technology creates the opportunity to influence the acceptance level of its users and thereby prevent rejection of the technology. Therefore, before implementing the system, it is important to identify all factors influencing the acceptance and to remove all potential barriers in adoption[56]. Understanding members of the medical team, like pharmacists and pharmacometricians, gives a prediction if they would accept or reject. Thereby, this information can be used to anticipate and subsequently increase the level of acceptance and adoption. Factors that should be considered include the ease of use, usefulness, and social impact, which is also shown in the TAM and UTAUT models[50,56].

The technology acceptance model (TAM) is mainly related to the psychological state of the pharmacists, whether they feel acceptance towards the technology of dosing through a MIPD platform designed by pharmacometricians. In accepting such MIPD platform, the perceived usefulness, and subsequently the easiness in use, play an important role. Pharmacists need to be able to use such MIPD platform easily and must see its importance for improving patient outcomes in order for them to accept it. To guarantee that the pharmacists realise the importance and do not perceive the MIPD platform as difficult in use, training and the design of the MIPD platform are crucial. Therefore, pharmacometricians need to communicate clearly on the importance of implementing precision medicine, but also need to adapt their view and adjust the MIPD platform to the needs of the pharmacists as well to make them understand how it should be used. They need to accept the adjustments suitable for pharmacists as well. Both parties need to learn in order to learn; both need to learn about the other's expertise in order to learn how to approach the use of the MIPD platform and learn from using that platform.

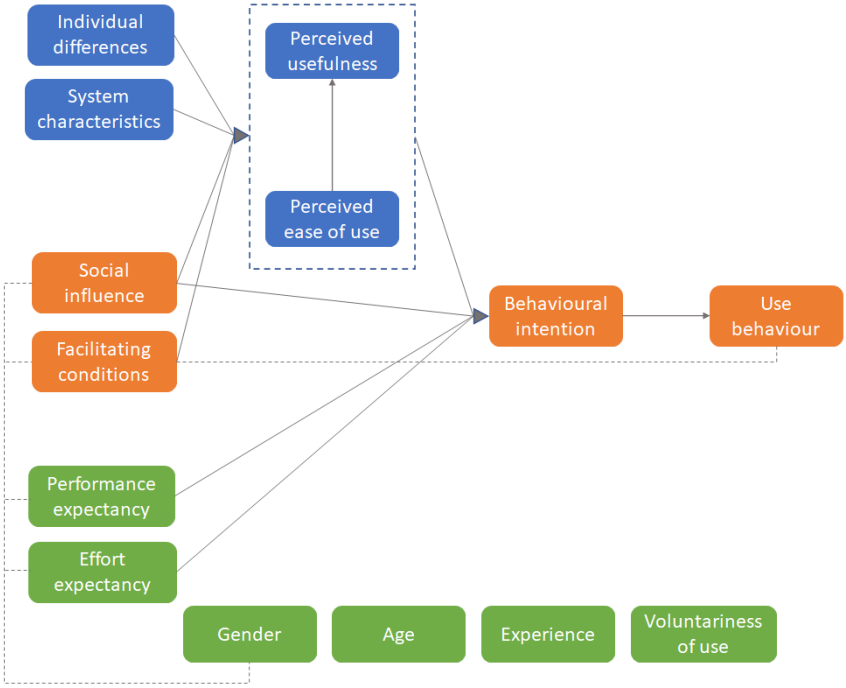


Figure 7. Technology acceptance model based on earlier developed TAM and UTAUT models. The blue boxes describe the Technology Acceptance Model[49], whereas the green boxes describe the Unified Theory of Acceptance and Use of Technology[48]. The orange colour depicts the overlapping factors and the positive influence of all depicted factors.

3.1.5. Interdisciplinary collaboration

In healthcare, interdisciplinary collaboration is something that exists for a very long time. The World Health Organisation already stated in 1978 that such collaboration is essential for the success of health care[57]. Interdisciplinary collaboration decreases medication errors, which might cause toxicity in a patient, and thereby has a positive influence on health care[58]. However, even though it decreases the medication errors, there still are errors causing such toxicity, meaning that strategies encouraging the collaboration improvements can still be improved[58]. The most important facet of interdisciplinary collaboration in health care would be professionals of different disciplines in the hospital share knowledge, make decisions

together, and share responsibility in improving the care of a patient[57,58]. The Model of Interdisciplinary Collaboration of Bronstein is the most extensively used model for interdisciplinary collaboration. The theory describes five core components: interdependence, newly created professional activities, flexibility, collective ownership of goals, and reflection on the process. The intention of this theory is to find a depiction of the important components in optimal collaboration between professionals[25,59]. Interdisciplinary collaboration in healthcare can be described as an interpersonal process whereby healthcare professionals from several discipline show all these components in solve problems regarding patient care. Understanding how this collaboration can be improved by gaining a better understanding of the level of experience, manner of work, and management of patient care. Therefore, further research in interdisciplinary collaboration in healthcare has the potential to improve healthcare[58].

As Manias (2018) describes that healthcare professionals share same objective and work together to solve patient care problems, depicts how it should be between the pharmacists and the pharmacometricians. They should collaboration on finding the best way to approach such collaboration, through such MIPD platform, to both be able to use and adjust it, in order to improve dosing regimen for specific patients. When there is a positive interdisciplinary collaboration, less medication errors will occur. Therefore, it is of major importance to address the gaps in this collaboration and explore the issues. The focus should be on the differences in experience level in this collaboration and in the use of technology in dosing, what different disciplines are important in the collaboration, and what all disciplines would want from the other party in that collaboration. Identifying how these disciplines work separately may be used to describe how they should work together, which has great potential in developing strategies to improve patient care.

3.1.7. Theoretical Framework

Bringing together the characteristics of the disciplines described in Figure 5, all these theories and their relation to this study, the theoretical framework was developed as depicted in Figure 8. The theories interdisciplinary and collaborative learning both stimulate pharmacists and pharmacometricians to share knowledge and parts of their expertise with the other discipline, without losing autonomy. The correct amount of learning together would create a MIPD platform which is understandable and usable for both disciplines. To be able to create an environment with interdisciplinary and collaborative learning, both disciplines need to be motivated to share and subsequently obtain knowledge and skills. Furthermore, they need to adapt to the other discipline to improve the collaboration, which also relies on the level of motivation. This improved collaboration and both the levels of adaption and motivation should lead to the acceptance of adoption of the MIPD platform and thereby create an interdisciplinary collaboration through the MIPD platform. By both going out of their standard expertise and find a way to collaborate efficiently, they work together towards the overarching goal of increased patient wellbeing, expressed in a positive level of transdisciplinary learning. This improved level of interdisciplinary learning contributes to the exploration and solvation of the over- and underdosing problem in healthcare, creating an interdisciplinary learning and collaborative environment where EBP and/or personalised medicine can be correctly applied. Furthermore, improved interdisciplinary collaboration will show positive feedback on the motivation and adaption of pharmacometricians to adjust the MIPD platform based on the needs of the pharmacist. This improvement will also show positive feedback on the motivation and adaptation of pharmacists to obtain the technological knowledge and to therefore adopt the MIPD platform.

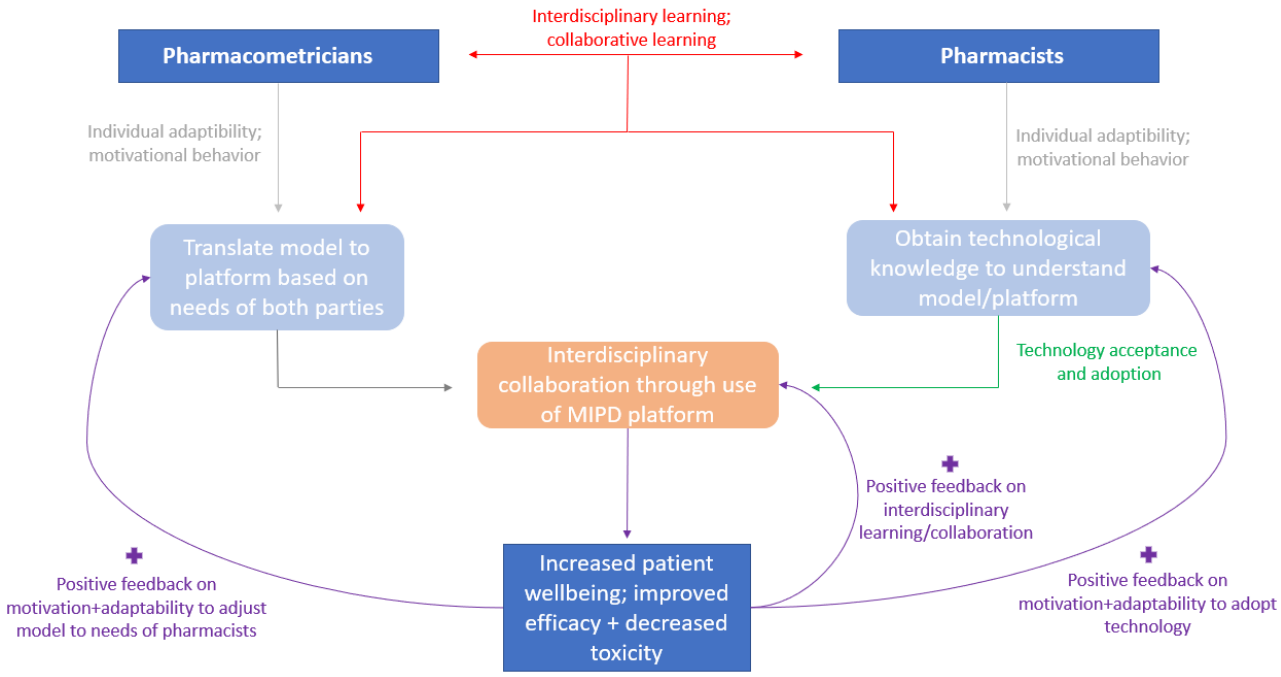


Figure 8. Theoretical framework. The framework is developed based on social theories, aspects of pharmacometricians and pharmacists, and the ultimate goal.

3.2. Interview derived insights

The theoretical framework led to topics that could be researched to better understand the obstacles in the collaboration and communication between pharmacists and pharmacometricians, both in terms of interdisciplinary collaboration through a MIPD platform and day-to-day communication about patients. Interviews were held to obtain more information regarding how both professionals work, collaborate right now on a daily basis, their attitudes towards technology expressed in a MIPD platform in healthcare, their thoughts on the lay-out of such MIPD platform, and their overall thoughts on the future regarding dosing protocols. The interviews can serve for problem definition and help in developing adjustments and improvements in their interdisciplinary collaboration through a MIPD platform. A total of six interviews were held with three pharmacometricians and three pharmacists to obtain different point of views of both disciplines. The participant characteristics are found in table 1. The transcripts of the interviews were analysed through coding; the full coding table where the quotes of participants are summarized into specific codes is presented in appendix D. The specific codes were then assigned to the either a predefined or an emerging theme of the five main themes studied in this research: 1) daily jobs; 2) feelings towards technology; 3) collaboration; 4) MIPD platform; and 5) future perspectives. The assignment of the codes to these themes is also presented in the coding table in appendix D. Furthermore, all assigned codes and how often they are mentioned by the two groups participants is summarised in Table 2. The ratio of how often one code is mentioned compared to the times all code is mentioned is also given. The result of each theme is discussed below in chapter 3.2.1 to chapter 3.2.5., where a coding tree is added to summarise the results of that theme and to link these results to elements of the theoretical framework.

Table 2. Code frequencies obtained from interviews with pharmacometricians and pharmacists. All codes mentioned are included and the number of times mentioned for each discipline and in total are given. The percentage of the ratio of one code mentioned compared all codes is given.

Code	Pharmacometrician (nr. mentions)	Pharmacists (nr. mentions)	Total (nr. mentions (% ratio))
Daily jobs			
Answer clinical questions	0	1	1 (0.7%)
Autonomy	1	1	2 (1.3%)
Clinical trials	1	0	1 (0.7%)
Diagnostics	0	2	2 (1.3%)
Discussions close colleagues	1	0	1 (0.7%)

3.2. Interview derived insights

Doctor (specialist)	0	2	2 (1.3%)
Dosing based on experience	0	2	2 (1.3%)
Dosing based on MWPharm modelling system	2	0	2 (1.3%)
Dosing based on literature	0	3	3 (1.9%)
Dosing based on prescribing system	0	3	3 (1.9%)
Modelling	3	0	3 (1.9%)
Modelling in clinical practice	1	0	1 (0.7%)
Feelings towards healthcare technology			
Beneficial for patients	0	1	1 (0.7%)
Big changes	1	0	1 (0.7%)
Clear	1	0	1 (0.7%)
Efficient	0	1	1 (0.7%)
Expensive	1	0	1 (0.7%)
Faster	1	0	1 (0.7%)
Handy	1	0	1 (0.7%)
Important	1	1	2 (1.3%)
Interesting	0	1	1 (0.7%)
Less prone to fraud	0	1	1 (0.7%)
More accessible	1	0	1 (0.7%)
Necessary focus	1	1	2 (1.3%)
Predominance in future	1	1	2 (1.3%)
Fear of resistance	1	0	1 (0.7%)
Specialistic use	0	1	1 (0.7%)
Time-consuming	1	2	3 (1.9%)
Tricky	0	1	1 (0.7%)
Collaboration			
Clarity improvement	0	1	1 (0.7%)
Compromising	1	0	1 (0.7%)
Connecting	1	0	1 (0.7%)
Correct ratio giving/taking	1	2	3 (1.9%)
Decision-making	1	2	3 (1.9%)
Discussions	2	1	3 (1.9%)
Efficiency	1	0	1 (0.7%)
Expectation management	0	1	1 (0.7%)
Giving/taking advice	2	2	4 (2.6%)
Inefficient	0	1	1 (0.7%)
Interdisciplinarity	2	2	4 (2.6%)
Keep expertise	1	1	2 (1.3%)
Learning together	4	3	7 (4.5%)
Making aware/controlling	5	3	8 (5.2%)
Multidisciplinary	3	1	4 (2.6%)
Trust	0	3	3 (1.9%)
MIPD platform			
Autonomy	1	1	2 (1.3%)
Clear	1	0	1 (0.7%)
Clinical awareness	1	0	1 (0.7%)
Covers easy cases	1	0	1 (0.7%)
Efficiency	1	5	6 (3.9%)
Fast in use	1	2	3(1.9%)
Flexible	1	0	1 (0.7%)
Implementation	1	0	1 (0.7%)
Interdisciplinarity	2	1	3 (1.9%)
Intuitive	2	0	2 (1.3%)
Lots of models needed	1	0	1 (0.7%)
Model overview	1	0	1 (0.7%)
Scientific proof	0	2	2 (1.3%)

Practical in use	2	1	3 (1.9%)
Precision dosing	3	1	4 (2.6%)
Serving clinical purpose	2	1	3 (1.9%)
Simulating different situations	1	0	1 (0.7%)
Time-consuming	2	0	2 (1.3%)
Training needed	1	1	2 (1.3%)
Understandable/easy to use	2	2	4 (2.6%)
Up to date	2	3	5 (3.2%)
Future perspectives			
Affordable care	0	1	1 (0.7%)
Autonomy	1	0	1 (0.7%)
Extended scope patient groups	2	0	2 (1.3%)
International	1	0	1 (0.7%)
Limiting toxicity	1	0	1 (0.7%)
Lots of models needed	2	0	2 (1.3%)
Precise dosing	0	3	3 (1.9%)
Safety	0	1	1 (0.7%)
Up to date	0	1	1 (0.7%)

3.2.1. Daily job

The theme regarding the daily job of the pharmacists and pharmacometricians was focused to gain more understanding of their day-to-day jobs. This improved understanding, in turn, allows us to understand their current collaborations and where improvements can be made. In figure 8, the coding tree details the tasks mentioned by each discipline. As this theme is merely related to the context of this study, no linking to the theoretical framework was included. As can be seen in Figure 9, pharmacometricians focus on modelling, using their models in choosing the dosing regimen, and discuss these recommendations with other pharmacometricians. Their jobs are mainly focused on implementing MIPD in clinical practice, meaning that their model needs to answer clinical questions (P1, P2, P3). To ensure the implementation is as useful for the practitioner as desired, there is also discussion between these disciplines to ask for help or clarification. Furthermore, as described in appendix C, two pharmacometricians were familiar with a MIPD platform called MWPharm (P2, P3). Both used the MIPD platform to serve clinical practice of pharmacists. One described the MWPharm as being old-fashioned and not user-friendly, since it was not clear or easy to use. That participant exactly stated:

'The computer mouse does not work in MWPharm, you have to use the arrows on the keyboard, making its handling very 90's or even earlier. (Een muis werkt niet want in MWPharm moet je met pijltjes werken en dus hartstikke jaren 90 of zelfs daarvoor.)' (P2)

The other pharmacometrician, who seemed to have more experience in MIPD, described the MWPharm as handy and a great step forward to personalized medicine, since MWPharm already included models and is already in use (P3). However, they expressed some criticism that MWPharm is not consistently updated with the newest modelling information or patient data

On the right side of the coding tree, the pharmacist's daily jobs are described as being a doctor or specifically a specialist where all pharmacists were busy working on diagnostics or working in clinical trials. All pharmacists were involved in prescribing doses of drugs to patients (P4, P5, P6). Decision-making in dosing regimen differed significantly each pharmacist, both in the decision-making protocols and in the amount of use of a protocol. However, all were familiar with dosing systems even though all used different systems. Furthermore, all pharmacists used 'Farmacotherapeutisch Kompas' when feeling uncertain on their thoughts or when an unknown patient came across for the first time (P4, P5, P6). Furthermore, all pharmacists based their dosing decisions based on their previous job experience. However, the two more experienced pharmacists stated they usually base their dosing only on experience, where one explained they either know by heart or they search through the existing protocols (P6). In contrast, that same

participant later stated it was always advised to use other sources to decide on the dosing regimen of a specific patient besides experience (P6).

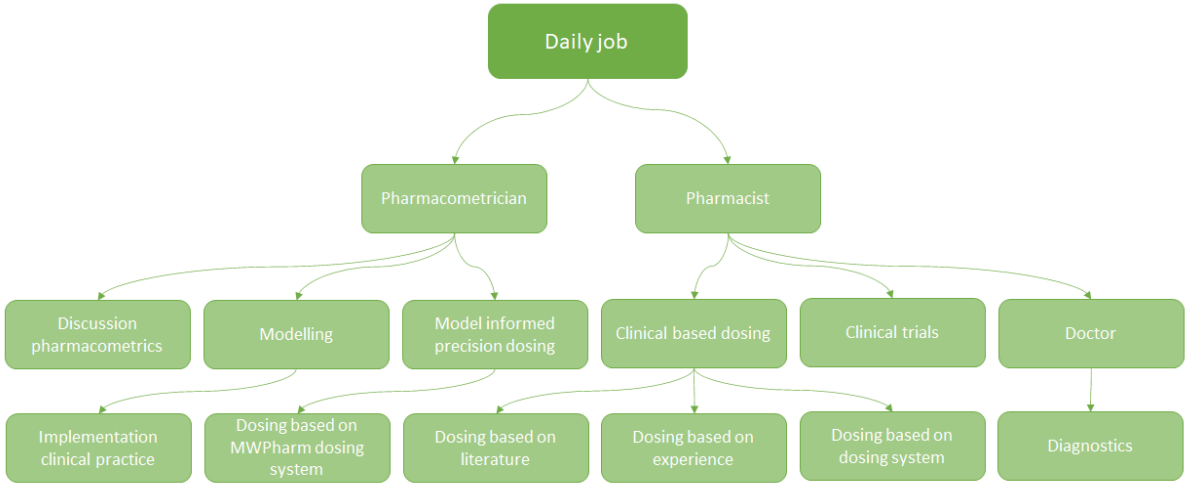


Figure 9. Coding tree describing the daily jobs of pharmacometricians and pharmacists. The codes were obtained from quotes out of the conducted interviews. Related quotes were linked based on their meaning or the quote itself.

3.2.2. Feelings towards healthcare technology

The participants were interviewed to better understand their feelings towards technology, both in their personal life and in healthcare. Their feelings of technology in their personal life may affect their attitude towards healthcare technology. For example, those are not familiar or comfortable in technology in their personal life may reject healthcare technology as well, because their motivation to use and trust in technology is low. Alternatively, when they are technology-users, they are more likely to accept and possibly even encourage greater use of healthcare technology.

The codes obtained from the conducted interviews were divided in positive and negative feelings, creating the ability to address these feelings in the further improvement of the 'technology', i.e., the MIPD platform in this study. All codes regarding participants' feelings are depicted in Figure 10. In general, the participant's attitudes had positive attitudes towards technology, both in their personal life and in healthcare. even though none of them were extensive technology users in their personal life. Positive feelings included the increased accessibility and efficiency of healthcare due to technology, handy, and clarity in what they were doing (P1, P2, P6). One of the participants even emphasised the important of healthcare technology which presence would ultimately be beneficial for the patient's wellbeing as they stated:

'I absolutely see models as one of the aspects to focus on in our expertise and definitely something that we need to implement in clinic. Ik zie de modellen ook als absoluut één van de focussen binnen ons vakgebied en ook iets wat wij moeten uitdragen naar de kliniek'. (P3)

On the other side, the negative feeling codes revealed possible concerns. One concern is resistance because of concerns of losing responsibility or jobs. An additional concern is that implementation of new technology would be expensive and time-consuming, which has been ongoing in healthcare. Furthermore, one of the participants was a little reticent as they stated healthcare would be changed partly, which could be too substantive of a change for specific professionals (P2). The growth of healthcare technology is also seen as something tricky that decreased motivation, since it changes not only the healthcare system as a whole but also the specific jobs of professionals (P5). Finally, the increased implementation of technology would be very expensive (P3); it might cost more money than hospital or other healthcare organisation have available to invest. Therefore, the benefits and expected cost-savings of the new MIPD platform need to be explained to the professionals and hospitals.

In general, all participants had positive feelings towards healthcare technology. Some had doubts about how it would work in the current system, with time and money being the most crucial aspects in need to implement healthcare technology correctly (P3, P4, P6). All participants see healthcare technology as an important development in the future, which will be described in chapter 3.2.5.

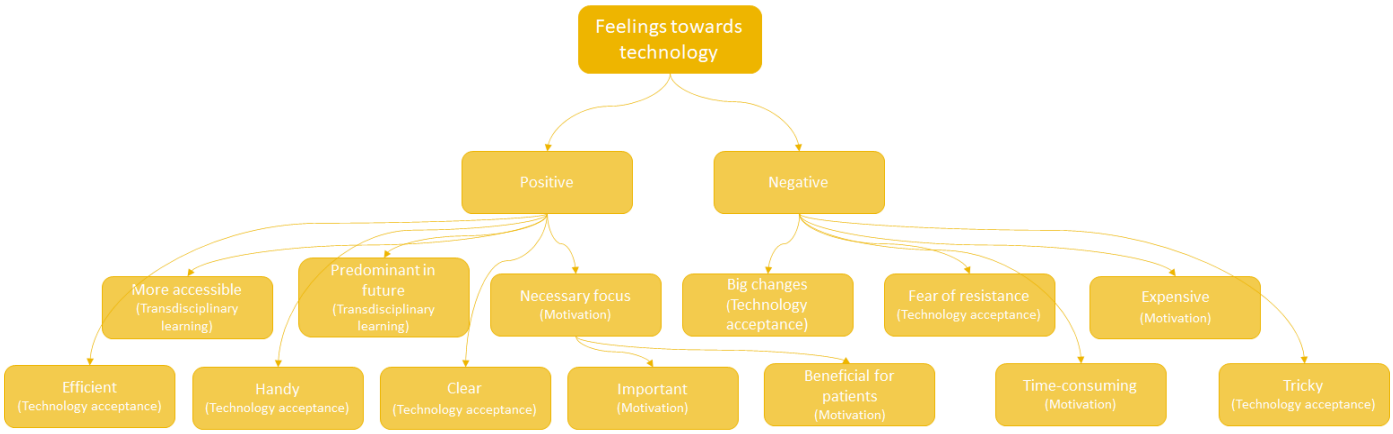


Figure 10. Coding tree describing the feeling of pharmacometricians and pharmacists towards healthcare technology. The codes were obtained from quotes out of the conducted interviews. Related quotes were linked based on their meaning or the quote itself. In between the brackets, the link of that specific code to the theoretical framework is added.

3.2.3. Collaboration

One of the subjects that was most prevalent during the interviews, is the collaboration between pharmacists and pharmacometrician. This collaboration is crucial in studying the use of a MIPD platform, since both disciplines are necessary in the correct development and implementation of the MIPD platform. The discussion mainly identified improvements and elements to be maintained in their collaboration. The coding tree of the collaboration between the two disciplines is shown in Figure 11. The elements that need improvement are learning together, correct ratio between giving and taking, trusting one another, expectation management, inefficiency, and the clarity of the collaboration (P2, P3, P4, P5, P6).

Learning together could be divided between compromising and connecting, where connecting refers to getting to know the professional from another discipline, who you are going to collaborate with, both on a personal and professional level (P3). Both pharmacists and pharmacometricians mentioned they do not know the other professionals and their expertise well enough to be willing to adapt and be able to adapt correctly to the other expert. One example in which the collaboration between pharmacists and pharmacometricians went satisfactorily, the participant explained

'You lobby and try to win over clinicians. I try to find enthusiastic clinicians who see the added value and I try to keep in touch with them, but I also try to find researchers who already collected a lot of data of which I think we can use that data too. I'll tell them about myself, what I did and why I think it is important. I explain how we decide dosing and what could be improved using these techniques what we need to start this collaboration. (Dan ga je eigenlijk lobbyen, dus eigenlijk ga je proberen zieltjes te winnen. Ik heb daarin nu echt wel geprobeerd enthousiaste clinici te zoeken die daar het nut van inzien en dat warm te houden, maar ook bij mensen die veel onderzoek doen en die dus al veel data verzamelen waarvan ik denk van: god, dan kunnen wij ook van die data gebruik maken. Dan zeg ik van ik wil iets over mijzelf vertellen en wat ik gedaan heb en waarom ik het belangrijk vind en uitgelegd hoe we nu tot dosering komen en waarom ik denk dat we dat beter kunnen doen met technieken en wat ik daarvoor nodig heb en hoe we dan een samenwerking kunnen opstarten.)' (P3).

That participant delineated how a connection between disciplines can arise or be strengthened through open communication with professionals from the other discipline. During that interview, the importance of connecting with each other is a key element of an adequate collaboration. The other element of learning together which was perceived as important in a collaboration would be compromising, described as 'meeting in the middle', where you meet others to be met in return (P3). This element is correlated to

another major aspect of collaborating: a correct ratio between giving and taking (P1, P3, P5). The correct ratio between giving and taking gives each professional the idea that they do get something in return for the hard work they put into other professionals in the collaboration. Thus, a professional should give as much as they take from the other expert, which they collaborate with in order to create an environment where both disciplines feel comfortable in sharing.

Furthermore, expectation management, inefficiency and clarity could be improved to establish collaborations between pharmacists and pharmacometricians. Some participants perceived their collaboration as being inefficient, because of multiple phone calls and checking up (P6). Clarity was lacking during these phone calls and also in written prescriptions (P2). Regarding expectations management, it was not always clear what the one discipline expected from the other discipline to satisfy their needs. Lastly, trust is perceived as a crucial factor in collaboration (P1). The interview outcomes have raised the thoughts of trust lacking in the collaboration between both disciplines. For example, pharmacometricians feel the need to check the dosing recommendations of the pharmacists all the time, while the pharmacist does not fully trust MIPD; pharmacists constantly need proof for the MIPD decisions that pharmacometricians made (P4, P6). However, there was variability in the perceived trust; One pharmacist explained they trust the expertise of the pharmacometrician. The participant stated:

'We trust the work of the pharmacy; that they understand how the system works and how I decide dosing. I trust their expertise, because you have to as I do not have that knowledge. I even think I would not be able to understand. (Wij vertrouwen ook op het kunnen van de apotheek. Dat zij snappen hoe het werkt en waar ik het op baseer. Ik vertrouw op hun expertise, want je zult wel moeten, want die kennis heb ik niet. Ik denk ook niet dat ik dat kan begrijpen.)' (P6)

They reflected on how pharmacometricians in a pharmacy decided dosing regimen based on pharmacokinetic models, which would be something that wouldn't be understandable for a pharmacist (P6).

On the other hand, elements that were already perceived as being sufficient included their decision-making in different tasks, keeping their own expertise separate from the other discipline, and being efficient in collaborating (P2, P3, P4, P5, P6). One pharmacometrician explained how the collaboration with pharmacists is efficient; they explained at their job they add the data standard into such a MIPD platform, since the communication with a colleague the next day is made easier as they can just read what happened the other instead of needing to call to check (P3). However, it is important to note that this pharmacometrician already uses a MIPD platform, called MWPharm, in collaboration with their colleagues in the same discipline. Generally, pharmacists did not have the authority to use MWPharm, however, the collaboration between both disciplines is simplified and quickened through the fact all pharmacometricians share the same knowledge and no further discussion is needed before understanding at which state the case of interest is by the use of a MIPD platform. Another collaboration element which is perceived as being sufficient is the multi- and interdisciplinarity, which is expressed in giving and taking advice, making the others aware and controlling them, and having discissions with other disciplines (P1, P2, P3, P4, P5, P6). One pharmacometrician explained how they wanted suggestions from the pharmacist involved in the study. 'I ask them about their suggestions. Or I say something like oh, I see something in the data, but I'm not completely sure about what this means, and I want to discuss with them because they are really much more closer to this', was said by this participant, indicating both disciplines support the job of the other (P1). Supporting professionals specialized in other disciplines is a key factor in correct collaboration and is thereby crucial to be maintained.

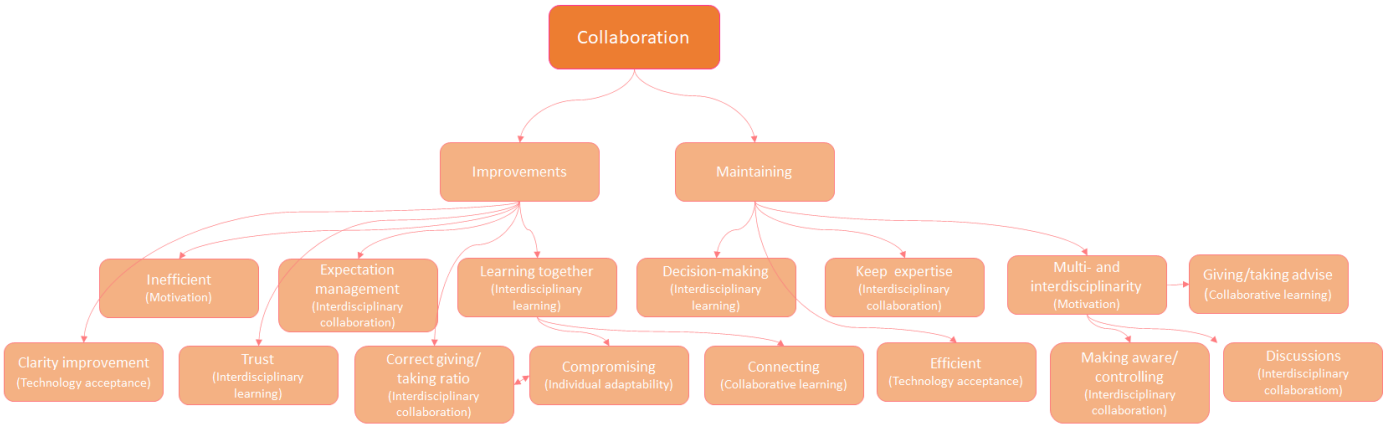


Figure 11. Coding tree describing the collaboration between pharmacometricians and pharmacists. The codes were obtained from quotes out of the conducted interviews. Related quotes were linked based on their meaning or the quote itself. In between the brackets, the link of that specific code to the theoretical framework is added.

3.2.4. MIPD platform

The fourth theme was regarding the MIPD platform, one of the two most prevalent subjects of the interview results (Figure 12). During the interviews, the participant's desires and attitudes with regards to a MIPD platform were studied combined with testing their ideas upon an existing dosing platform. One of the subjects that came across were the necessities (i.e., essential features) of the MIPD platform to attract its use. Necessities included creating flexibility in use, being up to date with all the newest models for MIPD, and it should serve a clinical purpose (P1, P2, P3, P4, P5, P6). All pharmacists emphasized the importance of using the MIPD platform should serve a clinical purpose, since that would be the main goal of its use (P4, P5, P6). One of the pharmacometricians agreed and explained it is necessary the MIPD platform is practical in use and answers clinical questions, instead of just being something they find interesting (P3). Pharmacists mentioned they were in need of proof that such a MIPD platform would improve dosing regimen for them to be motivated to use it (P4, P5). Furthermore, interdisciplinarity was mentioned in regard to the MIPD platform for creating an environment where both disciplines work towards the most convenient dosing regimen for a patient. Two participants outlined a situation where the characteristics of a specific patient and all their corresponding data are synchronized with the MIPD platform, creating the possibility for all experts to use the information (P4, P6). Even though interdisciplinarity was seen a key component, all participants valued their autonomy and considered keeping their autonomy in collaborating through such a MIPD platform necessary. To be able to make use of a MIPD platform, both disciplines need to be trained; they need to understand and see how the MIPD platform works, what to click and enter and how to interpret the outcomes (P2, P5). Before they would be able to implement a MIPD platform in their protocols, they need to be introduced and need to be able to decide dose based on the MIPD platform autonomously.

Another theme regarding the MIPD platform discussed was the use of such a platform. Participants perceived the MIPD platform's easiness, practicality, and fast use as fundamental aspects (P1, P2, P3, P5, P6). If the MIPD platform is easy and practical to use, working with the MIPD platform would probably fast as well, which all will ultimately be beneficial for patient care. Furthermore, the MIPD platform should be intuitive in its use for pharmacists and pharmacometricians to make the MIPD platform their own and thereby embrace its use (P2). It should be clear how to use the MIPD platform; by making the discussed aspects key components of the MIPD platform, the clarity of the MIPD platform will be improved. Development of a clear use for the MIPD platform, pharmacists and pharmacometricians are more likely to adopt the platform in their dosing protocols.

Possible risks of the development and use of a MIPD platform could be related to the perception that several models are needed for the MIPD platform to be beneficial (P1). A lot of models equal a lot of research and time to develop these models. This is related to another risk, the time-consuming factor (P1, P2, P3, P4, P6). If a professional is not trained to dose based on a MIPD platform, it might take too long for them to be motivated to decide the dose using such a MIPD platform. As one of the participants was hesitant on whether they would really be using it in the future as they did not feel like they would have the

time or would want to take the time to invest in learning such a technology (P6). Eventually, dosing based on the MIPD platform will most likely go faster whenever professionals are used to it and all the models are implements, but it might take some time before the benefits can be confirmed, making it easier to stick to their known protocols. The last possible risk discussed during the interviews regards the fact that in the beginning of the MIPD platform implementation, the MIPD platform would mainly be applicable in easy cases, since not all special occasion models are yet developed (P1).

The last topic discussed during the interviews was focused on the features of the desired MIPD platform, so what the participants would need to use and learn from the MIPD platform. One of the most mentioned aspects involved the MIPD platform providing the best dose based on the characteristics of the patient. One participant explained:

'I get to decide the medication and that the platform calculates the dosing based on the patient characteristics. I want to keep thinking myself or a specialist want to keep thinking themselves on what to prescribe. Stil it would be desired that the platform ultimately states: in this case of miss Janssen, it would be wise to dose a little lower. (Dat ik het medicijn kies, en de computer dan de dosering op basis van de karakteristieken van de patient. Ik wil zelf nadenken of een specialist die wil altijd zelf nadenken over wat ie voorschrijft zeker. Maar wat dan wel ideaal zijn is dat de computer uiteindelijk zegt: nou ja, bij deze mevrouw Jansen is toch wel verstandig om iets lager te gaan doseren.)' (P6)

They made clear that professionals desire to keep their expertise in thinking on possible drugs to prescribe. Nevertheless, all participants did see that the precise dosing decided by the MIPD platform, would be the most convenient for the patient's health and therefore demand the MIPD platform to provide the best possible dose, however, two pharmacists approached it merely as future perspective (P4, P5). Other features mentioned included clinical awareness and implementation, mainly focusing on the implementation of several models and providing an overview of these models and what they add (P1, P3, P4). An overview could include all the influences of a specific drug based on the characteristics of a patients, as one participant explained they would be very curious to know what the influences are and what characteristic is leading in what drug and why; it is perceived as interesting to see all possible consequences on drug effectivity influenced by the characteristics of an individual patient (P4).

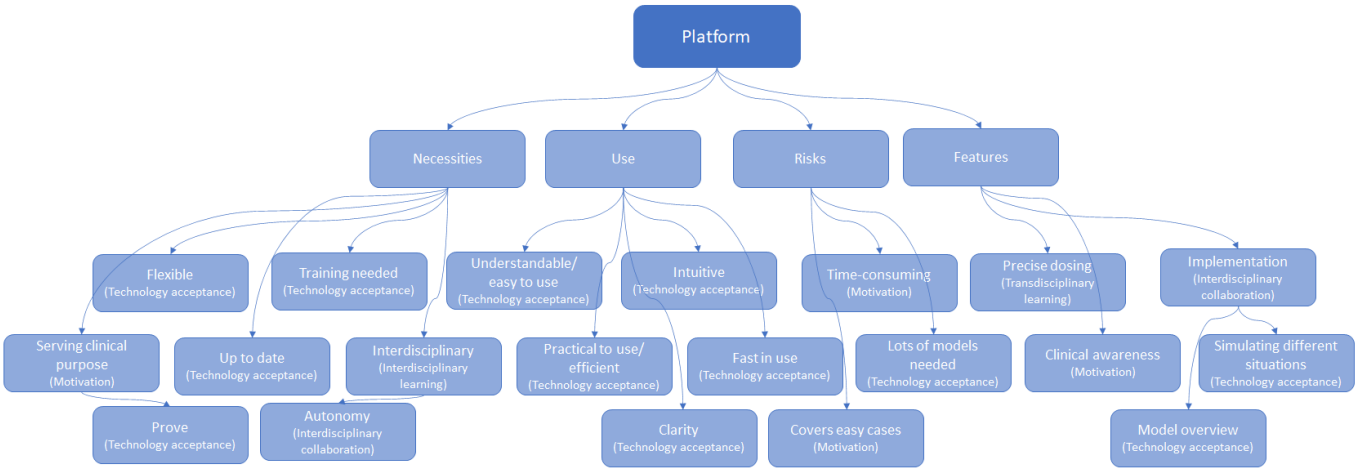


Figure 12. Coding tree describing the elements the model informed precision dosing platform needs. The codes were obtained from quotes out of the conducted interviews. Related quotes were linked based on their meaning or the quote itself. In between the brackets, the link of that specific code to the theoretical framework is added.

3.2.5. Future perspectives

The last theme identified from the interviews comprised future perspectives. Participants dreamed how the future would look like whenever such MIPD platform is implemented in all healthcare systems involved in drug dosing. The participants fantasised about both the care of patients and the healthcare system as a whole. All participants were optimistic on the future regarding patient care and healthcare systems. Positive aspects that were discussed involved the improved patient care through the limitation of toxicity and the fact

that such MIPD platforms enable specialised care for all individual patients (P2, P3, P4, P5, P6). All patients are able to get their personalised dose based on their individual characteristics. Furthermore, the whole healthcare system would be improved by international implementation, creating an environment where all healthcare professionals share data and thereby keep the MIPD platforms up to date (P1, P6). Improved patient care would also lead to reduced costs since patients are less likely to return to the doctor or hospital when their care is more efficient (P4). Taking these factors into consideration, one of the participants discussed the international implementation of these MIPD platforms and stated:

'There are a lot of countries, for example in Asia, where the pharmacokinetic modelling, which we showed, is minimally developed. But they still want to use this kind of information to improve their clinical practice.' (P1)

That participant fantasised that even though healthcare systems in countries that are not as developed in modelling would still be able to make use of these MIPD platforms and thereby improve their healthcare. However, to improve the healthcare system and make sure the precision dosing is applicable for every patient and the MIPD platform keeps being up to date, a lot of models are needed (P2). Thus, the development of models should continue, and the considerable emphasis should be on proper implementation of the MIPD platform. Combining precision dosing and the extended scope for patient groups, which means healthcare can become more specialised to different groups and the individual patient, could positively affect individual patient care and the entire healthcare system, which is something all participants would be motivated to work towards. The overview of results regarding the future perspectives of the interviewees is shown in Figure 13.

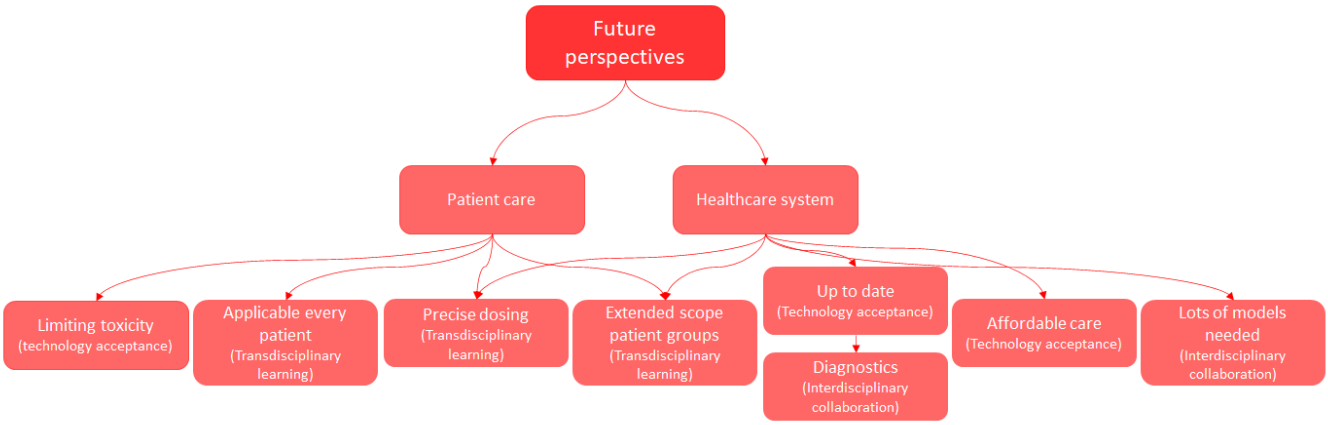


Figure 13. Coding tree describing the future perspectives of pharmacometricians and pharmacists towards patient care and healthcare systems. The codes were obtained from quotes out of the conducted interviews. Related quotes were linked based on their meaning or the quote itself. In between the brackets, the link of that specific code to the theoretical framework is added.

3.2.6. Conclusions interviews results

The themes predefined and ultimately identified for the interviews included daily jobs, feelings towards technology, collaboration, MIPD platform, and future perspectives. The interviews provided insight in the daily jobs of both disciplines and provided an idea of how the professional roles are divided between their disciplines in healthcare. Furthermore, no difference in feelings towards technology in daily life and in healthcare was found between the two studied disciplines: both pharmacists and pharmacometricians perceived technology as an important tool in healthcare. In addition, both disciplines perceived technology expressed in a MIPD platform as an important aspect for the future of healthcare. For the pharmacists and one pharmacometrician, the concept of MIPD and specifically MIPD implemented in a platform was still a hypothetical concept, as they were not aware of its existence. Nevertheless, they did perceive the concept of a MIPD platform as a key focus for future dosing decision-making improvements. Even though there is a long way to go, ultimately, such MIPD platform would be expected to be internationally implemented, covering for all patient groups or the individualized patient and could lead to improved and affordable care.

Overall, the most discussed topics in the interview included the collaboration and the MIPD platform itself. These topics are expected since the interview protocol focused on these topics. Regarding the collaboration, learning together was perceived as something that needed to be improved as now most professionals work around each other instead of together towards a shared goal. Specifically, within learning together, the connection between pharmacists and pharmacometrician could be improved, which is related to getting to know and trust the expertise of the other discipline to compromise on certain tasks. This trust in the other discipline's expertise was perceived as a crucial factor that needs improvement since it takes both professionals a lot of time to check upon each other to make sure their tasks are successfully conducted; thus, the participants highlighted to importance to connect and thereby build a trusting environment. However, an element that was perceived as being important but was already recognised as sufficient, is keeping their own expertise in this collaboration, which meant making use of the other professional's expertise without handing in their own. Their inter- and multidisciplinary collaboration is experienced as adequate, since the interviewed professionals explained how several different disciplines are involved in their collaboration while working their individual expertise, and thus needs to be retained in future collaborations.

The other most discussed topic, the MIPD platform, mainly focused on what each discipline would experience as crucial to use such a MIPD platform. The MIPD platform is meant to serve a clinical purpose, and therefore, the participants experienced this as one of the MIPD platform's greatest necessities and should be made clear to its users from the start of implementation. To focus on serving a clinical purpose, the MIPD platform needed to be easy and fast in use, making its use practical. Since pharmacists do not have a lot of time per patient, the MIPD platform needs to handled fast and accurate, and therefore its easiness, fastness and practicality in use are a priority. To pharmacists, proof of the effectiveness of using a MIPD platform is important for them to be motivated to learn how to use it; they are not aware of the existence of MIPD implemented in a platform that is available to use in dosing decision-making and therefore they need evidence for its effectivity. Another key aspect would be the learning and/or teaching aspect; both disciplines need to be introduced to the MIPD platform and need to learn how to make use of the MIPD platform in dosing decision-making efficiently to make them motivated to include its use in their protocols. On the other hand, some feared it would be too time-consuming to learn or to use and therefore are sceptical about the implementation of the MIPD platform. To successfully develop a MIPD platform, it should contain a substantive number of models to personalise dosing for each patient, which is a very time-consuming process. Another feature perceived as necessary to make the MIPD platform attractive is an overview of these models to make the MIPD platform understandable and thereby increase trust in dosing based on a MIPD platform.

3.3. Insights and proposed implementations testing

The results of conducted interviews were used to propose future collaborations and education focused on the MIPD platform. As explained in chapter 3.2.6, key aspects to address in improving the interdisciplinary collaboration and learning between pharmacists and pharmacometricians included: strengthening collaboration, improving the MIPD platform, and how the MIPD platform should be used. Since the results of the interviews focused on the collaboration and the MIPD platform, the scope of this study is narrowed to those two topics (i.e., collaboration and the MIPD platform). In this section, implementations were proposed to improve the collaboration and MIPD platform and the connection between both. These implementations may be used together to ultimately improve patient care. First, the adjustments and the implementation for the MIPD platform were described since the proposed collaboration between pharmacists and pharmacometricians will be based on the improved MIPD platform. After describing the implementations for the MIPD platform, the collaborating aspects between pharmacists and pharmacometricians were addressed in regard to the new MIPD platform. A focus group was conducted to test the appropriateness of the implementations according to the two stakeholder groups. In the focus group, the interview results regarding these adjustments and how it would work in practice were tested by ranking the codes obtained from the interviews. Lastly, the attitudes and opinions of the focus group's participants were researched by asking questions regarding the collaboration and learning through the MIPD platform. This chapter of the thesis focused on their attitudes in interaction with other professionals, to confirm whether their opinions in interaction matched opinions from the individual interviews.

3.3.1. MIPD platform implementations

Suggestions for the MIPD platform were made based on its current use, which is limited, specific and possibly not user-friendly. To make the MIPD platform's use more widespread, the first amendment is creating an easy- and fast-to-use MIPD platform which most dosing experts, who either advise on drug dosing or prescribe drugs, can comfortably use. Creating understandable features for practitioners who are not specialized in the field of modelling is crucial to make them motivated to base dosing on models implemented in such a MIPD platform. However, both pharmacists and pharmacometricians want to keep the autonomy of their own expertise and do not necessarily desire to fully understand or be able to perform other's expertise, which raised thought of the need for a distinction in the MIPD platform. Pharmacometricians desire to keep their expertise in building models and assuring they are implemented and combined to decide the optimal dosing regimen. Pharmacists desire to keep their expertise in dosing based on their knowledge, and capability of reproduce and searching the literature. Pharmacists agree upon the contribution of MIPD to personalized medicine but do not wish to use several different systems to choose one dosing regimen. Therefore, combining their prescribing system into the MIPD platform would benefit the ease and speed of dosing decisions which would benefit the pharmacist's motivation.

To meet all requirements from both disciplines, different implementations for the MIPD platform are proposed. These implementations are proposed based on the different opinions and ideas shared in the interviews, to stay as close as possible to the desires of the professionals. As a starter for these implementations, the InsightRX platform will be used as an example. The first and foremost operationalisation comprises the split-up of the one dashboard into two: one portal for the pharmacists, and on portal for the pharmacometricians. The pharmacist's portal allows to view and adjust patient characteristics, similar to their previously used prescribing systems. The patient dossiers of these prescribing systems are implemented into the MIPD platform. Browsing the number of the patient of interest leads the pharmacists to the dashboard of that specific patient, depicting an overview of his/her characteristics and medication history. These characteristics and medication history provide assistance in deciding on what drug to prescribe for the condition the patient visits the hospital, since the MIPD platform will show a pop-up whenever there is an interaction and therefore advises not to prescribe this drug. The pharmacist is allowed to keep autonomy of decision-making regarding drug prescription; they decide on the drug to prescribe, and the MIPD platform provides the optimal dose. For this dose, a concentration-time profile is shown on the dashboard, of which the pharmacist can read whether the suggested dose reaches the therapeutic window, and thereby is effective without being toxic. This first portal of the MIPD platform preserves the autonomy of the pharmacists, while stimulating the communication with the pharmacometricians and creating a fast, easy, and more secure way of making dose decisions. Stimulation of this communication creating an improved collaboration environment for both the pharmacists and pharmacometricians.

The second portal is meant for the pharmacometricians. In this second portal, newly developed population pharmacokinetic models are implemented to make the MIPD platform as comprehensive as possible; the more models implemented, the more accurate specific patients can be treated. Thus, pharmacometricians are able to implement their new or improved models to the MIPD platform and combine them with previously implemented models. Pharmacometricians are able to use their portal to check upon prescriptions sent to them; whenever they receive a prescription for a specific patient, they can search for that patient and subsequently select the model showing the most optimal fit for the characteristics and genomic information of the patient. By selecting the most accurate model, the pharmacometrician can check if the prescribed dosing regimen is sufficient. If not, they can reject the prescribed regimen and decide how to adjust the dose based on the optimal model. In the unfortunate case no model has yet been developed for that special patient, the pharmacometrician is able to contact the pharmacists to discuss how to approach this case. After decision-making and administration of the regimen to the patient, the pharmacometrician can use the collected data from that 'new' special patient in a later stage to implement data for the new defined special patient group, which can be used as guidance for dosing this group in the future. However, when the prescribed regimen is anticipated to have a positive outcome, the pharmacometrician accepts the prescribed dose, which is then ready to be produced.

3.3.2. Collaboration establishment

To still improve their collaboration and trust in the other disciplines within the boundaries of two separate portals, both pharmacists and pharmacometricians need to get acquainted with the portal and thereby understand the other's expertise. By incorporating an introductory course into the MIPD platform, both disciplines are obligated to get into all the materials provided by the MIPD platform; first into the pharmacist's materials and their methods of operating, and then after, into the pharmacometricians materials and their way of operating. In this course, users will be guided through how to use the MIPD platform and will be explained what each step and feature adds. For this introductory course, busulfan, a drug often dosed to a target AUC, as explained in the chapter 1.1, is used as an example to guide pharmacists and pharmacometricians through all features of the newly developed MIPD platform. As both disciplines explained in the conducted interviews they desire to collaborate more closely and want to get to the know the other professionals both on personal and professional level, their collaboration and connection should be stimulated through this introductory course. Therefore, the introductory course needs to be completed through the collaboration of both a pharmacist and pharmacometrician, creating an environment where both learn from the other party and where they collaborate towards a solution. Both disciplines would like to better understand the work ethics and approaches of the other discipline, in order to improve trust and motivate to collaborate. Creating a shared introductory course would stimulate an interdisciplinary collaboration atmosphere, which could ultimately lead to a faster and more precise way of decision-making regarding the dosing regimen per patient.

The idea of the course is to ascertain pharmacists and pharmacometricians are afterwards able to use the MIPD platform separate from each other, making their collaboration more efficient but still maintaining the control aspect as desired. Since the MIPD platform is split into two portals, both disciplines would get an introduction to each of the portal together. The course starts with an explanation video of MIPD and busulfan, to make sure all participating professionals are aware of the existence and meaning of MIPD, and of what busulfan is used for and how it works in the body. Then, the course continues opening the portal for pharmacists, showing both the pharmacists and pharmacometricians its features including explanations. The course exposes an overview of all patient numbers corresponding to one specific patient. Clicking on patient number 0, corresponding to the introductory patient, the portal is brought to the dashboard of that hypothetical patient. On the dashboard, there is displayed how the characteristics and genomic information of the patient were entered and can be renewed based on the latest data. Furthermore, an overview of which medication patient 0 is currently using is shown combined with a list of medication previously used. A prescription for busulfan can then be added to that by clicking on the plus-button, where every drug that the pharmacists would like to prescribe can be added. To stimulate the interaction and collaboration, the pharmacist is asked to explain to the pharmacometrician on what they base decisions for a drug and corresponding dosing regimen for that patient, showing each step of their decision making such as literature research or browsing through Farmaceutisch Kompas. Explaining the pharmacist's way of making dosing decisions provides pharmacometricians insight into their expertise and approximation of clinical questions. The decided busulfan dosing regimen based on the common approach of pharmacists can then be filled in to be tested or the optimal regimen can be calculated by the MIPD platform based on the characteristics and genome information of patient 0. Looking at the concentration-time graph showing the target concentration and the concentration induced by the specific dose, the pharmacometrician is asked to explain how to interpret such a graph and how to know whether the concentration is sufficient or needs to be adjusted by changing the dose. If the dosing regimen is sufficient, the drug can be dispensed as prescribed, which subsequently will be sent to the portal of the pharmacometrician.

The hypothetical prescription is forwarded to the pharmacometrician's portal, which leads the course to the portal of the pharmacometrician, where an overview of the dosing regimen as prescribed in the previous phase of the course is shown. The pharmacometrician explores what the prescribed dosing is based on, what characteristics are important, and whether the information on the patient is up to date. Then after, to check the dosing regimen, all implemented models for this drug are shown on the dashboard. The pharmacometrician needs to check whether the model necessary to base patient 0's dose on is correctly developed and implemented. This feature of different models being implemented causes a pop-up in the course where a short explanation in lay language is given on how a model is developed and what should be included to validate. The pharmacists and pharmacometrician need to discuss these different models,

where the pharmacometrician will answer questions asked by the pharmacist and explains how they approach these models and base their dosing on such a model. After deciding the dosing regimen of busulfan is sufficient since the correct model is found and shows the right concentration-time profile for adequate efficacy, the regimen needs to be accepted by clicking on the accept button, causing the recipe for the regimen to be sent to the pharmacy. Whenever the models are not up to date, which raises the suspicion that the dosing will be insufficient, the pharmacometrician does research on the dose, while contacting the pharmacist to discuss. When the discussed dose is entered and accepted, the MIPD platform sends the prescription to the pharmacy.

3.3.3. Focus group testing

These implementations regarding the MIPD platform and the collaboration between pharmacists and pharmacometricians were tested through a focus group (protocol is found in Appendix F). The focus group was split into two stages: 1) case studies ranking and 2) questioning. In the first stage, the group was asked to rank the codes acquired from the interview from least important or relevant to most important or relevant based on a hypothetical case study. In a discipline-specific discussion, out of all codes regarding both collaboration and MIPD platform, the five most relevant codes are selected per theme. The code ranked most relevant out of the selected five, is ranked position five and receives five points. The code ranked least relevant out of the selected five, is ranked position one and receives one point. In the second stage, the group was asked to answer and discuss questions related to the implementations. The different sub-stages of stage 1 are depicted in Figure 14, where the scenario is written down, leading to the discipline-specific discussions where all codes acquired from the interviews per theme were depicted. Then lastly, the Miro board led to the ranking of the five selected codes from each discipline.

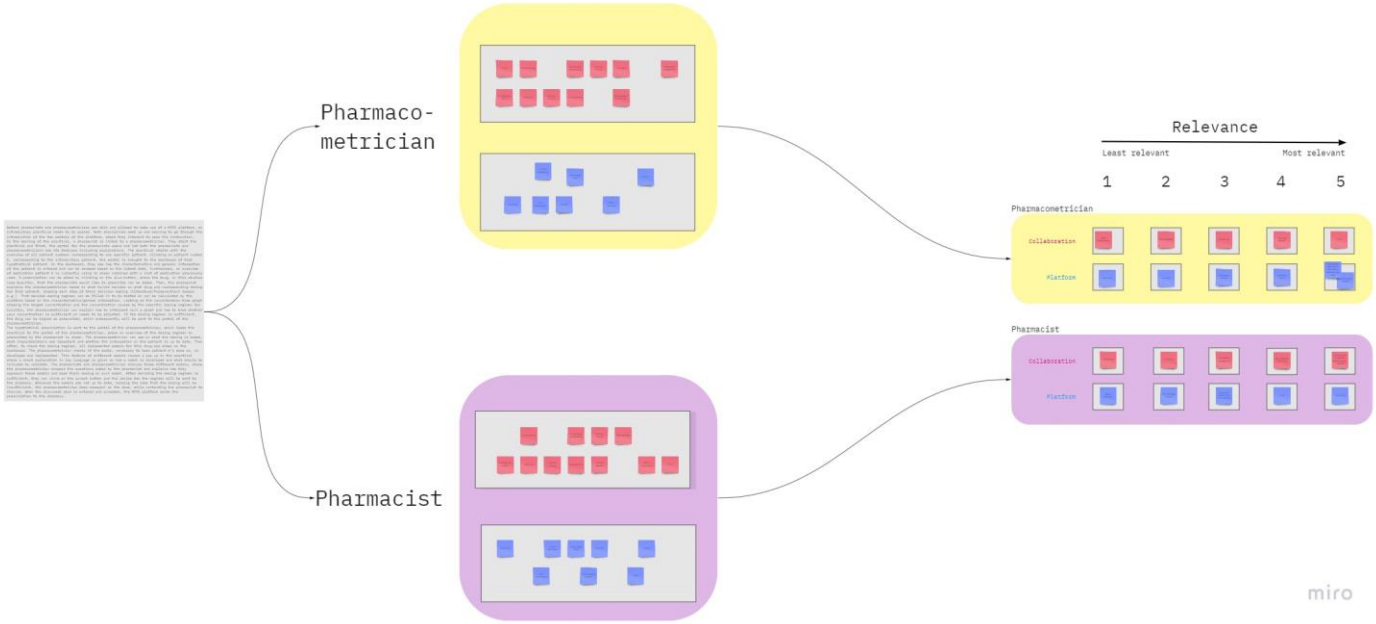


Figure 14. Miro board describing the sub-stages of stage 1 of the focus group. On the left, the scenario description is depicted, also read to the participants. In the middle, the board is divided into the two disciplines: pharmacometricians (upper) and pharmacists (lower). On the right, the ranking board is shown from 1 (least relevant) tot 5 (most relevant) to rank the five selected codes from the middle part.

In stage 1, one scenario regarding the introductory course for the MIPD platform, one hypothetical busulfan scenario using the MIPD platform, and the overarching terms of collaboration and the MIPD platform were tested. The results of the rankings from both the pharmacometricians and the pharmacists are shown in Figure 15. Scenario 1 of the ranking focused on the introductory course to the MIPD platform. Where pharmacometricians identified the trust in the other discipline as being most important in the collaboration in the introductory course, the pharmacists agreed to find the clarity regarding what to expect from the course most important. The pharmacometricians agreed upon trust since both disciplines needed to introduce the other discipline to their field and way of working by explaining and showing how, which necessitates trust in each other. One pharmacometrician stated:

3.3. Insights and proposed implementations testing

'When you explain what such a model means, they need to be able to trust you. (Ook op het moment dat jij toelicht wat zo'n model precies inhoudt, moeten zij jou wel kunnen vertrouwen.)' (P8)

The pharmacist needs to trust the expertise of the pharmacometrician as they explain how such models work and how they use them (P8). One pharmacist explained they agreed with the pharmacometricians upon trust but that their discipline felt trust was included in the clarity, meaning clarity is in need of scientific substantiation, which is accompanied by trust (P10). Both disciplines had connection in their selected five since both perceived the connection between the two disciplines as being crucial in an efficient collaboration. During such an introductory course, the connection can be built or improved, since they get to know each other and their discipline. Both pharmacists and pharmacometricians agreed knowing the person behind the other portal of the MIPD platform would be beneficial in establishing a comfortable collaboration between them. For the pharmacists, getting to know the expertise of the other discipline goes hand in hand with making aware, as they explained how important it is for the pharmacometricians to be aware of the clinical aspects and to take the patient into consideration (P9, P10, P11). The pharmacometricians ranked learning together as 4th, as they explained that learning from the other discipline and how their portals should be used would contribute to the understanding of the other discipline (P7).

Regarding the use of the MIPD platform in the introductory course, the pharmacists rated the fastness of use of that MIPD platform as the most important. As they felt that the MIPD platform should be handled fast in order to make it attractive for them to use (P10, P11). This fast-in-use aspect is related to intuition, which was also selected by the pharmacists, as they explained the MIPD platform should be logically in its use (P11). The pharmacometricians agreed upon the necessity of the MIPD platform being fast in use since they also realised the importance of the MIPD platform not being time-consuming. Both also identified the clarity of the MIPD platform as a major aspect of the introduction to the MIPD platform, as they feel like the MIPD platform should immediately provide a clear view of what it holds. Pharmacists included a model overview in this clarity of the MIPD platform, which creates the opportunity to immediately get a clear view of what the MIPD platform has to offer. Moreover, both disciplines also perceived the implementation of the MIPD platform into practice as an important aspect since it is important that the MIPD platform is usable for both disciplines before it can be implemented into the healthcare system.

The second scenario of the focus group was focused on an actual hypothetical busulfan scenario. In the collaboration through a MIPD platform, as described in this scenario, pharmacometricians perceived keeping the discipline's expertise as most important, as they perceive developing your individual knowledge and combine them interdisciplinary into shared knowledge as a critical aspect in collaborating. Keeping their expertise separately facilitates the next important defined aspects; these pharmacometricians identified compromising, expectation management, and taking/giving advice as key element of the collaboration through a MIPD platform. Taking and giving/advice was also by the pharmacists identified as an important element of their collaboration. Furthermore, pharmacists expanded the thought of the pharmacometricians from interdisciplinary to multidisciplinary, where they mentioned patient involvement and need in decision-making. One pharmacist explained this concept where they mentioned:

'Also, disciplinary I suppose, definitely in an oncology case. This treatment brings so much disadvantages and side effects that it's so important to look at the case more holistic to what the patient could still handle. Based on his weight he should be, but he would suffer so much of the side effect, do we want to accept that? (Ook multidisciplinair denk ik, zeker in zo'n oncologie geval. De behandeling voor die mensen is niet niks. Aan dit soorten behandelingen zit zo veel nadelen en bijwerkingen dat het ook wel belangrijk is om naast gewoon uberhaupt het doseren in de behandeling, dat je er ook iets meer holistisch kijkt naar wat kan die patiënt überhaupt nog aan kan. Bijvoorbeeld op zijn gewicht gebaseerd kan het allemaal wel, maar hij heeft zo ontzettend veel bijwerkingen van, accepteren we dit dan nog?)' (P9).

Nevertheless, again clarity was perceived as the most crucial aspect of the collaboration according to the pharmacists. However, clarity in this scenario was explained as the clarity regarding the usefulness of the MIPD platform for the clinic. Pharmacists also identified discussion and decision-making as important elements of the collaboration, whereas they did not agree on the idea of the pharmacometrician to include compromising on their top five. They thought decision-making together and discussing all the options were

important, while compromising is out of the question since all needs to agree upon a dosing regimen before that regimen is accepted.

In the discussion between the two pharmacometricians on the MIPD platform's use in scenario two, they agreed that the most crucial part of a working MIPD platform would be the implementation of a lot of models. If only a few were implemented, the MIPD platform would not work properly and would just waste the time of its users. Another aspect they perceived as a key element included clinical awareness, where they explained the MIPD platform should most definitely serve a clinical purpose, and the professionals involved in this clinical purpose should be aware of the strict rules there are for such a study needed for the MIPD platform to be up to date. To make the use of such a MIPD platform attractive to all disciplines involved, the MIPD platform should be able to be handled fast, otherwise, people will skip using it in a rush even though it would be useful. The pharmacists did not fully agree with the fast-to-use aspect desired by the pharmacometricians. They would like to use it as fast as possible but would not mind when it would take a little time to do it more precise. One pharmacist explained:

'If it is complicated, it does not matter it takes some time. If the effort I take benefits the patient, I think it is more important that the input/output ratio is in balance than it should only work fast. (Als het ingewikkeld is, dan geeft het niets als het een beetje tijd kost. Als de moeite die ik doe iets nuttigs oplevert, dan vind ik het belangrijker dat de input output in balans is dan dat het per se alleen maar snel moet zijn.)' (P10)

Another pharmacist added they integrated this aspect more into efficiency (P9). The aspect the pharmacists identified as most important would be the clarity of the MIPD platform, that at one glance, it would be clear what to do with it and that its use would be intuitive. As the pharmacometricians thought proof should be included in the introductory course, pharmacists rather saw the proof in the actual scenario. One explained they often do not see the urgency through e-learning, whereas in a real-life scenario, they would recognise it, which would motivate them to use the MIPD platform. Another major aspect for the pharmacists included the flexibility of the MIPD platform, where they considered the MIPD platform too rigid as they had the idea that special patients would be too different for the MIPD platform to be applicable for all patients (P10). When the pharmacists explained the need for a lot of models to cover special patients as flexible, they meant the same as the pharmacometricians in the need for a lot of models. The two disciplines agreed efficiency should a key element in the use of such a MIPD platform to make it attractive to use.

Scenario 3 includes the concepts of collaboration and the MIPD platform as a whole without any context. Regarding the collaboration concept, the focus of the pharmacometrician was kept at keeping the expertise of your discipline and trust in each other to establish the most effective and comfortable collaboration. Nevertheless, they also still perceived expectation management as being important, as they mentioned expectation management to be influenced by keeping the expertise and to related to trust (P9). All three factors were thought to influence the other factors either positively or negatively proportionally. For example, if they understand what the other discipline wants from them and the other way around, both disciplines should be able to keep and trust their expertise, whereas if they do not trust the expertise of the other and thereby do not keep within their own expertise, the expectation management between both cannot be proportional. The other elements the pharmacometricians perceived as key elements in the collaboration included the connection between the two disciplines and learning together towards a shared goal. Again, to establish a learning environment between the disciplines, the connection between them should be experienced as positive to make them motivated to collaborate. The pharmacists got their most important aspect of the concept of collaborating with pharmacometricians based on their answers on both the introductory course and the hypothetical busulfan scenario, where they perceived the clarity within their collaboration as most important. One pharmacist explained:

'The collaboration depends on how clear the tasks are divided, so who does what, and how they work together towards this. (De samenwerking hangt af van hoe duidelijk het is wie wat doet en hoe ze samen te werk gaan.)' (P9)

They agreed it should be very clear how they would collaborate and how each task within the collaboration would be divided (P9). In agreement with the pharmacometrician, the pharmacists perceived connection as one key element of a successful collaboration. A positive connection would lead to a more comfortable

environment, where others would be more confident to share. This positive connection could be related to the multidisciplinary element, where not only the pharmacist and the pharmacometrician collaborate towards a unified goal, but also the patient's perspectives and quality of life would be taken into consideration.

Regarding the concept of the MIPD platform, pharmacometricians identified the need for a lot of models as the most crucial aspect of the MIPD platform. They realised a lot of models and work is needed to prove the improved healthcare for patients using such an MIPD platform. Therefore, before the MIPD platform can be correctly implemented, it should be ensured enough models are developed for that specific drug. Even though the pharmacists choose another word, they gave the same explanation to the code flexible, which they perceived as one of their key elements of the MIPD platform. These pharmacists thought it would be majorly important to realise all the differences between the patients and were sceptical in imaging a couple of models would cover for all these differences (P10, P11). Therefore, another aspect perceived as valuable included the model overview, where they could see with their own eyes that the technology worked. However, the pharmacists again identified the clarity of the models to be the most important aspect since they would the user aspects need to be clear for them to be able to make use of this MIPD platform. Both disciplines recognised efficiency as a key element of the MIPD platform.

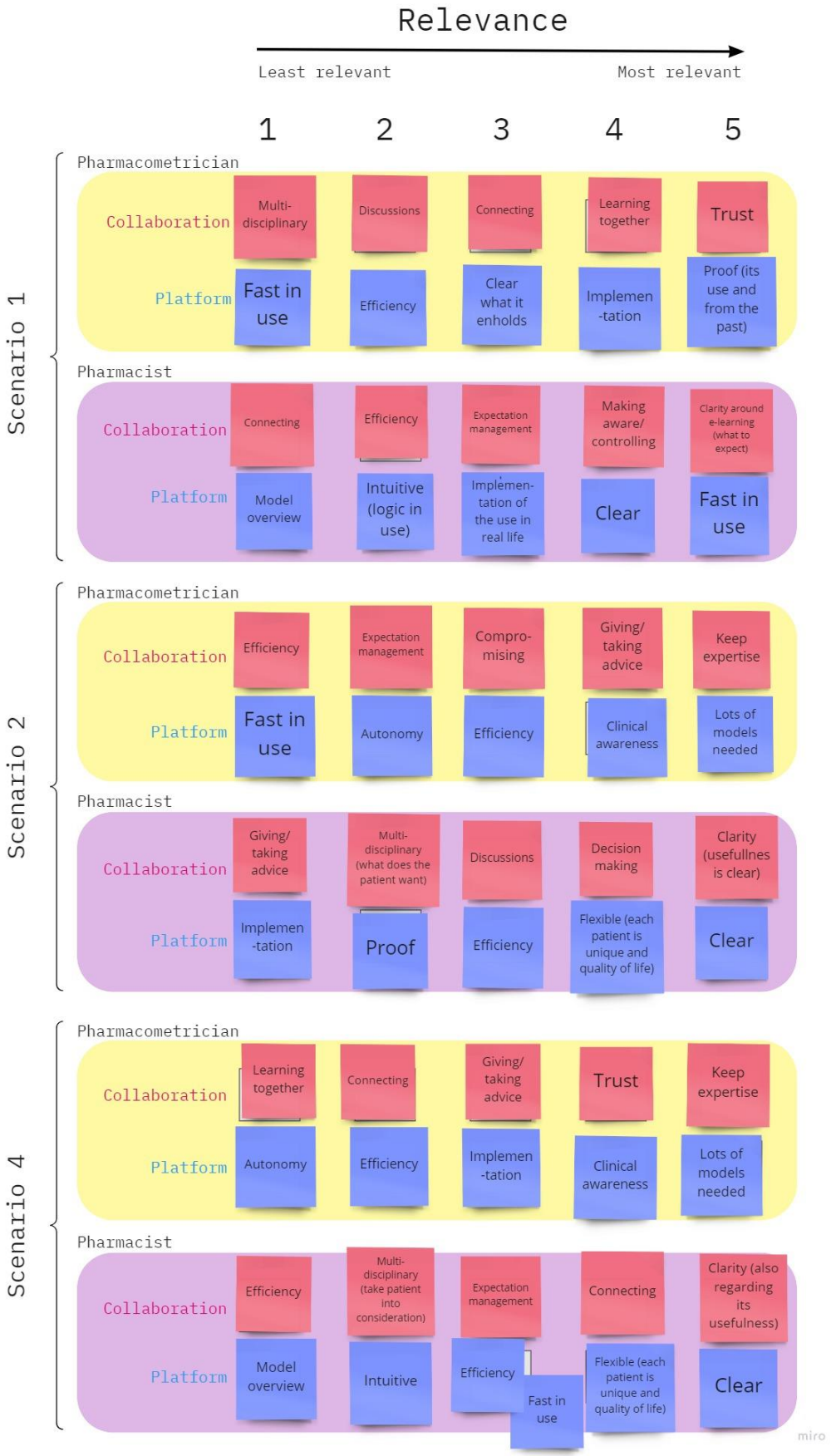


Figure 15. Results of the ranking of each scenario tested. Scenario 1 regarded the introductory course for the MIPD platform. Scenario 2 regarded an actual Busulfan scenario where the MIPD platform was used. Scenario 4 focused on the concepts of collaboration and MIPD platforms. The codes acquired from the interviews were ranked from 1 being least relevant to 5 being most relevant in each scenario by pharmacists and pharmacometricians.

3.3. Insights and proposed implementations testing

The 5 codes selected and ranked by both pharmacometricians and pharmacists were assigned points based on their ranking for each scenario: rank 5 (most relevant) receiving 5 points to rank 1 (least relevant) receiving 1 point. Table 3 summarises the results of the focus group regarding the collaboration between the disciplines and links these results to elements of the theoretical framework. Only the codes selected for the ranking were assigned points. Clarity was perceived as the most important aspect of the collaboration between pharmacometricians and pharmacists as it was assigned a total of 15 points. Nevertheless, it should be noted that only the pharmacists assigned clarity points, making clear how important the clarity in collaboration is for that discipline. The pharmacists described the clarity as providing a clear view of the usefulness of the collaboration and what to expect, both from the e-learning and the collaboration. Also, connecting and keeping expertise were rated highly in regard to the collaboration. Connecting was perceived as a key element by both the disciplines, as they assigned 5 points each. Connecting was merely approached as getting to know the other professional on a more personal levels but mostly on their expertise. Keeping expertise was only ranked by the pharmacometricians as they thought it would be crucial separate their expertise from the other's expertise to maintain the controlling aspects of dosing decision making. Another highly rated element by pharmacometricians includes trust. While pharmacists explained that if there is a collaboration through, for example, a MIPD platform, there is already trust between the disciplines; they perceive trust as something that already exists and if not, there would not be a collaboration in the first place (P10). Giving and taking advice and expectation management were also assigned a notable number of points, indicating their importance in the collaboration. However, it is good to note that the codes regarding collaboration are subjective and leave room for interpretation. As pharmacists had put clarity on rank 5 in all three scenarios, the meaning of clarity was related to their meaning of expectation management as well, as both were (partly) explained to create clarity on what to expect from the other discipline in their collaboration. The same was noticed for multidisciplinary, as it was also explained as keeping your discipline's expertise by both pharmacometricians and pharmacists, which increases the importance for multidisciplinary collaboration in the means of keeping their expertise.

Table 3. Ranking interview obtained codes with regard to the collaboration between pharmacometricians and pharmacists.

Collaboration codes	Pharmaco-metricians	Pharmacists	Total (% ratio)	Relation to theoretical framework
Clarity	0	15	15 (16.7%)	Technology acceptance; Collaborative learning
Connecting	5	5	10 (11.1%)	Technology acceptance; Motivation; Collaborative learning
Keep expertise	10	0	10 (11.1%)	Multi- or interdisciplinary collaboration
Trust	9	0	9 (10.0%)	Interdisciplinary learning and collaboration
Giving taking advice	7	1	8 (8.9%)	Interdisciplinary or collaborative learning; Motivation
Expectation management	2	6	8 (8.9%)	Interdisciplinary collaboration; Individual adaptability
Discussion	2	3	5 (5.6%)	Interdisciplinary collaboration; Individual adaptability
Multidisciplinary	1	4	5 (5.6%)	Motivation; Collaborative learning
Learning together	5	0	5 (5.6%)	Interdisciplinary learning; Technology acceptance
Efficiency	1	3	4 (4.4%)	Technology acceptance; Interdisciplinary learning
Making aware/controlling	0	4	4 (4.4%)	Interdisciplinary collaboration
Decision making	0	4	4 (4.4%)	Interdisciplinary learning and collaboration
Compromising	3	0	3 (3.3%)	Individual adaptability; Interdisciplinary learning

The results of the ranking regarding the MIPD platform and their connection to the theoretical framework are shown in Table 4. Pharmacists again rated clarity the highest, where they explained the clarity of the use and usefulness of the MIPD platform was the most crucial element for them. Both disciplines perceived efficiency as a key aspect of the usability of the MIPD platform; if the MIPD platform works efficiently, both disciplines agreed to be motivated to use the MIPD platform to collaborate and learn. Another element identified as relevant was the way the MIPD platform would be implemented, both how it would be implemented into their daily protocols and if the MIPD platform is designed properly. Pharmacometricians rated the need for a lot of models as relevant; to make the MIPD platform usable and effective, a lot of models are needed to cover for all special cases. The development of all these models is time-consuming and is thereby relevant for the development of the MIPD platform. Pharmacists also stated a lot of models is necessary due to the diversity of patients, however they included this aspect in the code proof, as they stated that to provide proof a lot of models are needed. Interestingly, the pharmacometricians perceived clinical awareness as a key element for the MIPD platform; it should always serve a clinical purpose and that purpose needs to be understanded and visible for both disciplines. They explained the clinical awareness is also important for nurses e.g., as they are involved in data collection for data enrichment of

the MIPD platform. Pharmacists did agree with this but did not perceive the clinical awareness as a major element. For them to be motivated to collaborate through the MIPD platform, they need the MIPD platform to be fast in use and flexible in terms of usable for all unique patients, which is also related to the codes lots of models needed and proof.

Table 4. Ranking interview obtained codes with regard to the MIPD platform between pharmacometricians and pharmacists.

MIPD platform codes	Pharmaco-metricians	Pharmacists	Total (% ratio)	Relation to theoretical framework
Clear	3	14	17 (18.9%)	Technology acceptance; Interdisciplinary collaboration
Efficiency	7	6	13 (14.4%)	Technology acceptance; Interdisciplinary collaboration
Implementation	7	4	11 (12.2%)	Interdisciplinary collaboration; Motivation; Transdisciplinary learning
Lots of models needed	10	0	10 (11.1%)	Technology acceptance
Clinical awareness	8	0	8 (8.9%)	Motivation; Interdisciplinary collaboration
Flexible	0	8	8 (8.9%)	Technology acceptance; Motivation
Proof	5	2	7 (7.8%)	Technology acceptance; Motivation
Fast in use	2	5	7 (7.8%)	Technology acceptance
Intuitive	0	4	4 (4.4%)	Technology acceptance
Autonomy	3	0	3 (3.3%)	Interdisciplinary collaboration
Model overview	0	2	2 (2.2%)	Technology acceptance; Motivation

In stage 2 of the focus group, the questions of the protocol (Appendix E) were discussed within the focus group discussion with both disciplines. However, due to the lack of time, this discussion was not as extensive as stage 1. As most information is already obtained through conducting stage 1 and the corresponding discussions, the questions were discussed shortly to prevent repeating answers. The first question asked regarded their positive or negative thoughts on the proposed implementations. Overall, the collaboration through the implementation of an introductory course was perceived as a positive aspect. Both disciplines thought it would be a successful way of getting to know professionals from the other discipline who you are going to collaborate with, on both a personal and a professional level (P7, P8, P9, P10). However, one pharmacist did doubt the effectiveness of such an introductory course in ways of understanding the expertise of the other discipline (P11). They feared the possibility of not fully understanding the MIPD platform as that professional explains their job themselves, which can negatively influence their communication as a pharmacometrician is not trained to explain difficult matters in lay language (P10, P11). This possible risk could be solved by creating an introductory video where their skills are explained in lay language and then after discussion between the two disciplines, but that would also decrease the collaboration and communication level between the two.

The second and third questions regarded the general feelings of both pharmacists and pharmacometricians on both the MIPD platform and the collaboration between them using such a MIPD platform, which regarded the general feelings towards such a MIPD platform, their responses again different somewhat. Pharmacometricians were overall quite positive about the presented MIPD platform, as most of them are already familiar with some sort of MIPD platform. Their familiarity makes it easier for them to see what such a situation would look like (P8). Nevertheless, the pharmacists again expressed some doubts, as they had a hard time imaging what the future would look like when such a MIPD platform is implemented in their protocols (P10, P11). They wondered if they would have enough time to get familiar with the use of the MIPD platform more than they doubted the effectiveness (P9). One pharmacometrician did agree with this concern of that pharmacist, however, they mentioned it would bring efficiency and eventually take less time, but only if time is invested at the beginning (P7). That participant stated:

I think its use will eventually bring efficiency, but only if time is actually invested. (Ik denk dat het uiteindelijk ook efficiency oplevert. Maar wel als er daadwerkelijk tijd in geïnvesteerd wordt.) (P7)

Regarding the collaboration, both perceived their collaboration as a crucial element in making dosing decisions and the correct treatment of patients. The use of a MIPD platform in their collaboration was expected to make their collaboration more straight forward and efficient for both disciplines (P7, P8, P9, P11). However, both had also doubts about this way of collaborating. Pharmacometricians expressed their doubts in how many aspects should be implemented to make it easier and efficient to make this collaboration useful for both, as two portals need to be developed; one specialised n pharmacist's use and

one specialised in pharmacometrician's use (P7, P8). Nevertheless, they realised the importance of the development of an improved collaboration environment and did see the added value of the collaboration through such a MIPD platform (P7). Pharmacists merely doubted the effectivity of the collaboration and communication; they could not imagine yet how this would make their collaboration more efficient, since the personal communication aspects would be decreased (P10, P11). However, they did see how easy cases would be discussed and handled faster as no actual discussions would be necessary. For the special patient populations, they would still like to implement a discussion aspect to come to the best solution together (P9, P10, P11).

The discussion moved forward to the discussion on what both disciplines would like from the other in their collaboration and what they would like to give in return. Both agreed upon the fact that they would expect the other not to rush their task in their collaboration; each disciplines needs to take the time to make sure they make the most convenient decision before forwarding and accepting (P7, P8, P9, P10, P11). Moreover, the pharmacists would want the pharmacometricians to first do the research into the dosing regimen decided by the pharmacists, before rushing to contact them to discuss, as more than once the contact was unnecessary after all and just consumes a lot of time (P10, P11). Pharmacometricians agreed upon this but suggested adding a comments box within the receipt to create the ability for the pharmacists to add a short explanation in a special case; this way, it would not take the pharmacometricians too much time to research the odd decision of the pharmacist (P7). Both pharmacists and pharmacometricians agreed to give the other professional to collaborate with as much effort to decide the best dosing regimen and to get to know each other on a somewhat more personal level in order to understand better the communication behaviour of the other. Furthermore, they agreed to do plan a meeting or a call whenever a complicated case is identified to make sure they together get a comfortable feeling in this dosing decision-making.

Question five, regarding the thoughts on the effect of the collaboration and use of the MIPD platform when implementing such an introductory course led mostly to the repetition of the insights of stage 1 of the focus group. Again, the pharmacists emphasised the clarity of the collaboration, making clear what is expected in the collaboration during this course and the foreseeable future, and their thought of this course not being time-consuming and just mostly straight forwards and discussing the different aspects of the MIPD platform as fast as possible without being incomplete (P9, P10, P11).

The most important aspect is that you understand one another. You have someone working in coding. That is a whole different view than someone working in the clinical. Therefore, clarity is crucial in communicating on what you want, what they have to offer and what you have to offer. (Het belangrijkste is dat je elkaar goed begrijpt. Want je hebt natuurlijk iemand die heel erg in de code zit. Dan is dat een heel ander leven dan als je iemand hebt die vanuit de kliniek kijkt. Ja, je moet heel duidelijk zijn over wat je wil ook, wat bied jij en wat bied ik.) (P9)

On the other hand, the pharmacometricians again emphasised the building of trust during such an introductory course; they would see building a connection between the two disciplines and thereby an increase in trusting the other and the MIPD platform (P8). Regarding the MIPD platform, the pharmacometricians repeated the importance of providing proof of the effectivity of the MIPD platform, which would subsequently increase the trust between the disciplines (P7, P8).

The future of the use of such a MIPD platform, as discussed in question 6, was not quite clear for the pharmacists, as they still had some doubts regarding time and effectiveness. However, they did see the necessity of such a MIPD platform and were motivated to learn the use of the MIPD platform and to collaborate through this (P9, P10, P11). They did identify such technologies as something they were going to use in the future but could not imagine how and when yet (P9, P10). The pharmacometricians did see the use of such a MIPD platform in the foreseeable future, as they felt it was an easy way to store all different models regarding one specific drug (P7, P8). Furthermore, they perceived such a MIPD platform as an easy tool to collaborate and store all data regarding one individual patient, which would make the use for both the pharmacists and the pharmacometricians easy (P7).

No additive concepts or aspects had been addressed besides the topics discussed in the focus group.

3.3.4. Implementations conclusion

Two designed implementations, based on the results of the interviews and explained within Chapters 3.3.1 and 3.3.2., are tested through a focus group discussion with professionals in the fields of pharmacometrics and pharmacy. The implementations include the addition and development of an introductory course, where a pharmacometrician and a pharmacist together go through all the aspects of the newly improved MIPD platform. The proposed platform adjustments of the existing MIPD platform included the addition of a second portal. The first portal of the platform is developed to be used by pharmacists, where they can see the specific patient characteristics, their currently and previously used medication, and are able to check the proposed dosing regimen based on literature. The second portal of the adjusted MIPD platform is used by the pharmacometricians, who can check the prescription of the pharmacists, and who can work on the implementation of models regarding a specific drug and on updating all data collected to strengthen the creditability of the MIPD platform. During the introductory course of the proposed MIPD platform, the pharmacometrician and pharmacists collaborate through the course and learn the expertise of the other by discussing and explaining to each other step by step. First, a short introductory video on MIPD and busulfan will be played, followed by opening of the pharmacist's portal where all features are explained and previewed. The pharmacists explain their protocols and how they handle their daily tasks regarding dosing decision-making, based on the pharmacist's features of the MIPD platform. After successfully prescribing an example dosing regimen for busulfan based on the hypothetical case of the introductory course and the pharmacist's common protocols implemented in the MIPD platform, the platform is moved to the portal of the pharmacometricians, where all features related to the tasks of the pharmacometricians are shown and explained. An overview of the tasks performed by pharmacometricians using the MIPD platform are completed within the introductory course, creating an indication of how pharmacometricians check upon the busulfan prescription of the pharmacists based on models implemented in the platform, and how they update the models implemented for busulfan. For pharmacists, there is the possibility to ask questions regarding the daily tasks of the pharmacometricians and to discuss the decision-making on busulfan dosing regimen based on MIPD.

Testing these implementations regarding the introductory course in the focus group, based on the codes that were obtained from the interviews, brought to light that during an interaction, pharmacists do perceive clarity and connecting as being more relevant than in the interviews where clarity was only mentioned once. Ranking clarity and connecting higher in interaction upon the introductory course could be related to the addition of a new aspect in their collaboration, which is the course itself. As one participant explained that both the course itself and the usefulness of their collaboration should be very clear from the start of the course already for them to be motivated to learn from that course and to collaborate through the MIPD platform in real-life cases. Whenever the course is unclear, no correct view of the future can be recognised, which makes them less motivated and eager to learn. Thus, clarity is an important aspect to take into consideration in introducing the topic and the course and then after also the actual development of the introductory course. Moreover, through the collaboration within the course, the connection between the pharmacists and pharmacometricians is stimulated, which might explain why both disciplines perceived connecting as relevant in the successful implementation of a collaborative introductory course. Another interesting aspect included the fact that while during the interviews the pharmacists perceived trust as an important element, during the focus group, pharmacists did not rank trust as relevant as they felt like trust is already present in a collaboration between two different disciplines. They explained how trusting someone in their expertise should already be present, but can be stimulated through such an introductory course, because you actually see the skills with your own eyes. Trust is related to connecting by positively influencing this, and both are thereby crucial aspects in the development of an introductory course. During stage 2 of the focus group, all agreed that a collaborative introductory course would contribute to them getting to know each other, thereby connecting and hopefully building trust. They did express some doubts in understanding the expertise of the other by only them explaining them. Therefore, the connecting and collaborative aspects of the course are crucial to be preserved, without making the course and its goal vague. The aspects regarding giving/taking advice, having discussions, multidisciplinary, and learning together were perceived as key elements both in the interviews and in the interaction during the focus group. During the focus group discussion, these elements were perceived as connected; giving and taking advice related to discussion through the fact they discuss the advice given, which creates a multidisciplinary environment where they learn from each other and together. This multidisciplinary environment can only

exist by keeping your expertise within your discipline, which was identified as an important aspect by the pharmacometricians. However, creating a connection between the two disciplines without losing the discipline's expertise can be challenging as both aspects are contrasted in some ways, highlighting the need to find the correct ratio between the connection and the individuality between pharmacists and pharmacometricians. Therefore, these aspects are also key elements to take into consideration in the implementation of an introductory course. These aspects are considered in the proposed introductory course as the pharmacists and pharmacometricians are together collaborating through the introduction while explaining each other on their own disciplines, and thus building a connection in this interaction; whereas after the introductory course is finished, they are individually working on dosing decisions through their own discipline's portal, but are obligated to collaborate and discuss on the best treatment when a complex case appears.

The implementations in the adapted MIPD platform were also discussed using the codes derived from the interviews. Interestingly, pharmacists again perceived clarity as the most important aspect of the MIPD platform during the focus group, whereas during the interviews, clarity was not mentioned by any pharmacist. During the focus group discussion, they identified the clarity of the MIPD platform as crucial as they needed to understand and be able to use the MIPD platform easily. In the discussion, the pharmacists mentioned in regard to the clarity that the MIPD platform's use should be efficient, intuitive and understandable. The easiness and understandability of use were during the interviews also perceived as key elements, but these were integrated into the codes, efficiency, and clarity to prevent the focus group participants from feeling overwhelmed. Moreover, the efficiency of the MIPD platform was identified as one of the most critical elements of the MIPD platform by both the pharmacists and pharmacometricians during interaction in the focus group, which was in accordance with the results of the interviews. Therefore, the efficiency and easiness in the use of the MIPD platform should be a major focus in the recommendation regarding the development and implementation of the MIPD platform. During stage 2 of the discussion, both disciplines agreed the use of a MIPD platform in their collaboration was expected to make their collaboration more straightforward and efficient by both disciplines, which thereby highlighted the importance of the MIPD platform in their collaboration as well. Furthermore, the implementation of many models was a major element for the pharmacometricians during an interaction, while during the interviews, it was only mentioned once. During the course and the overview of the MIPD platform dashboard, the pharmacometricians noted how important it is to implement as many models as possible to increase efficacy, which could possibly be explained by an enlargement of the imagination of how complicated it would actually be. Pharmacists agreed with the implementation of a lot of models to be important, however, they did perceive flexibility of the MIPD platform as providing applicability to a lot of different patients, equivalent to a lot of models. Thus, it is important to make sure enough models are implemented before using the corresponding dashboard. Clinical awareness, which was also a combined code from serving clinical purpose and clinical awareness, was perceived as an important factor by all participants in the focus group discussion; interestingly, that aspect was only ranked by pharmacometricians, as the pharmacists explained all their work involves clinical awareness and they felt other aspects would be more important to focus on in such a MIPD platform. Scientific proof and fast-in-use were both aspects that were perceived as important both during interaction and during individual interviews, where the discussion was focused on a correct ration between the time-effectiveness and knowing for sure the use of the MIPD platform was beneficial for the individual patient. Ultimately the patients' needs and treatment should be central, and thus the MIPD platform should serve the best care as possible.

4. Discussion

In this section, all the different phases of the double diamond as explained in chapter 2 Methods are debated separately using literature e.g. The methods used, and results obtained in this study are critically discussed, wherein the quality of the research is reviewed. These points of discussion will eventually be used to provide advice on how to approach future use of the MIPD platform through interdisciplinary collaboration towards a learning environment. This chapter is used to shed light on new insights regarding the applicability of the MIPD platform and regarding interdisciplinary collaboration and learning between the

two disciplines. Ultimately, these insights will be related to the advice on how to approach future inter- and transdisciplinary collaboration and learning through a MIPD platform.

4.1. Research aim

The obstacles in the collaboration between pharmacists and pharmacometricians were explored and defined in order to describe what implementations are needed for them to collaborate through a MIPD platform. Most pharmacists and pharmacometricians consistently use their standard procedures in making dosing decisions, despite the availability of MIPD platforms enabling the possibility to increase drug efficacy and decrease drug toxicity. The drug used as an example to discuss the collaboration through a MIPD platform is called busulfan, a drug often dosed to a target AUC. Since busulfan has a narrow therapeutical window which increases the chance of toxicity during treatment, the use of a MIPD platform in busulfan dosing decisions would be beneficial for the individual patient's care. The use MIPD platform enables the possibility to decide on dosing based on the characteristics and genomic information of an individual patient. However, these MIPD platforms are not widespread in clinical practice due to still unidentified reasons. This study focused on defining implementations necessary for the collaboration and the MIPD platform simulating collaboration through the MIPD platform and thereby create a collaborative learning environment. The data obtained from the interviews suggested professionals from the two disciplines perceive the connection and a learning environment between these professionals as most important, without handing in the controlling aspects of their collaboration while keeping the multi- and interdisciplinary bond between them. Regarding the MIPD platform, the interview data suggested that both disciplines perceive the efficiency, understandability, or easiness of use, and precision dosing as the key elements of the MIPD platform. Furthermore, keeping the MIPD platform up to date was also a crucial aspect of being motivated to use that MIPD platform. In interaction during the focus group on the collaboration between both, the ranking suggested that the clarity was the most important aspect for the pharmacists, whereas pharmacometricians identified the remaining of their expertise while improving trust between the disciplines as most important. The disciplines agreed the connection between them was a crucial aspect of the collaboration through an introductory course. In regard to the MIPD platform, the pharmacists again perceived the clarity of the MIPD platform as most important, explaining MIPD platform's use should be clear and intuitive. Pharmacometricians did agree the clarity of the MIPD platform should be an important element of the implementations, while they perceived the implementation of a lot of models as the most important aspect. Pharmacists also emphasised the need for a lot of models, as the MIPD platform should be flexible in use to dose all special patients. In agreement with the interview data, the pharmacists and pharmacometricians suggested the efficiency of the MIPD platform as another crucial aspect that needed to be taken into consideration to motivate them to use the MIPD platform in making dosing decisions together. These suggestions obtained in this study were used to address improvements of the MIPD platform and their collaboration through the use of the MIPD platform. The creation of a learning environment through collaboration using the MIPD platform might enable improved patient care through improved efficacy of drug dosing.

4.2. Methods

The discussion regarding the methods used in this study is mainly focused on the structure of the research, the literature review, subject selection, semi-structured interviews, testing proposed implementations through the focus group, and data analysis. Each of these concepts are argued in different subchapters. Within these concepts the validity, reliability and ethics of the research is reflected based on how the research is conducted and on relevant literature.

In the introduction of the methods section, there was explained how this study method was structured by the design-based process of the double diamond. Even though, this research was indeed based on design-based elements, this study was not performed fully design-based, as the structure turned out to be quite clear. Each step of the research followed was followed by the next: the researched started with experiences obtained from the previous internship followed by further exploring the concept through the literature research and the interviews, which were subsequently used to narrow down the scope to formulate the obstacles. These specific obstacles were addressed using the information of the interviews and, after testing these implementations in the focus group, from the focus group as well. By implementing an introductory course and addressing all the adjustments that were suggested in the interviews and focus

group, the delivery of the collaboration through the MIPD platform was proposed. However, this study only provided proposed implementations, instead of full developed adjustments or additions, decreasing the appearance of the development and the delivery phase. Missing actual developed interventions to the obstacles in collaboration between pharmacists and pharmacometricians and in the MIPD platform indicated that the double diamond does only fit certain aspects of this study, which was therefore perceived to not be a full-grown design-based study[60,61]. Nevertheless, some of the elements of the study were used to iterate back to earlier steps to improve the proposed implementations, which belongs to design-based research aspects[60,61]; For example, the results of the focus group were again used to narrow down the scope of the problem statement to help developing the best implementation and the results of first the interviews and thereafter of the focus group were used to develop the proposed implementations. There can be concluded that this research was guided by elements of the design-based process of the double diamond that led to the proposed introductory course, however, did not fully fit the whole process but just used elements to structure the research.

4.2.1 Literature review

Literature used in the literature review section was found using three search engines: Scopus, Google Scholar, and PubMed. Google scholar is a search engine indexing scholarly literature such as peer-reviewed conference papers, journals, and academic books, and thus not only literature published the traditional way like PubMed and Scopus. Therefore, the use of this search engine could decrease the validity of the literature research. However, this search engine was merely used to search literature that was locked using the other two engines. The literature search was mainly focused on the six major theories: collaborative and interdisciplinary learning, motivational behavior, individual adaptability, technology adoption, interdisciplinary collaboration, and transdisciplinary learning. The theories were searched in different configurations to collect as much literature as possible. However, more literature could have been yielded by using a broader scope of configurations and a larger extend of search engines. Due to time limitations, the scope for the search was kept quite broad. This made sense, since the concept is not extensively studied in the past, even though it is not new. Therefore, the extensiveness of literature, related to the collaboration between healthcare practitioners focused on the use of such a technology, was restricted. Nevertheless, sufficient literature was found regarding related theories to gain enough insights to touch the key elements of the collaboration between pharmacists and pharmacometricians through a MIPD platform.

To save time in searching literature while still collecting a more extensive amount of literature, a clearer structure could have been defined beforehand. A structure, like the structure written by Rowley and Slack (2004)[62] combined with the structure written by Cooper (1984)[63] and adjusted by Randolph (2009)[64], could have been used, which describe five different stages: problem formation, data collection, data and information sources evaluation, analysis and interpretation by developing conceptual frameworks, and writing the literature review. By defining such a structure, a better focus on the problem could have been maintained and better track of all the articles already found but not meeting the requirements for the literature could have been kept. However, my strategy worked out for me since we first defined the characteristic building blocks for adequate collaboration through the MIPD platform. Then after, we would study different theories that were related to such characteristics and then analyse them and develop frameworks using all the different analysed theories. Even though, it did not fully fit a well-structured literature review, the steps described in the literate review framework, as defined by Rowley and Slack (2004)[62] and Randolph (2009)[64], did match the steps we took in this literature review. Besides, we might have lost time in browsing through the same literature. However, since the scope of theories was already narrowed to only six major theories, the search was fastened. Theories that were discussed within the literature found, that did not fully meet requirements for the theoretical framework or lost relevance to the research subject were left out, which kept a clear structure to the literature review section. Furthermore, by defining the characteristics of pharmacists and pharmacometrics needed to create effective interdisciplinary collaboration before searching the literature, the search was already focused on the narrowed scope of the study and could thereby accelerate the search for literature.

4.2.2. Subject selection

Participants chosen in this study were mostly selected within my personal network. Two out of eleven participants were approached through the networks of other participants. This sampling method could have biased and decreased the reliability of the results since most participants are connected through their jobs, and I could not ensure they did not discuss their interview beforehand, or they did not get influenced by the others during the focus group. To increase reliability, a practiced interviewer will conduct the interviews. Using a practiced interviewer will reduce overdirecting the interview and thereby decrease the chance of the interviewer's bias influencing the interviewee.

The participants were recruited based on their experience in collaborating with other disciplines and prior knowledge of a MIPD platform. This kind of sampling is known as purposive sampling and is often explained to ensure richness in gathered data[65]. I tried to recruit participants that were already a bit longer in the field to make sure they were very familiar with the old protocols and were very experienced in that discipline, but also younger participants that were more familiar with using technology in healthcare. This way I wanted to ensure data enrichment in the interviews, but also wanted to create a discussion in the focus group with participants sharing different points-of-view.

Ethical justification of the study was ensured by taking these ethical basic principles into account: beneficence, justice, and respect for persons[66]. These base principles were ensured by letting the participants of both the interviews and the focus group sign an informed consent form (Appendix B) and by being careful in participant selection. Al participants are treated equally, and all hospital parties are equally represented. All statements of the participants will be included anonymously, ensuring no answers could be leading back to a specific participant.

4.2.3. Interviews

The interviews were designed and performed in a semi-structured style, enabling an interactive interview where the questions are asked based on the answers of and the discussion with the specific participant. A semi-structured style enables 1) the possibility to create a natural conversation making the interviewee feel comfortable to share, and 2) the possibility to dig deep into the thoughts of the interviewee, leading to a better understanding of the answers and getting unprompted new ideas or insights of that specific interviewee. The structure allows asking additional questions to make sure the answer is clear and correctly interpreted. However, the semi-structured style also creates the risk of not creating a comparable environment for all interviewees, as the interview is adjusted to the needs of the interviewee. Such interactive interviews create the risk of not asking the exact same questions, which might lead to a divergent covering of the research topics. To prevent the appearance of skewed data, the same probing questions were asked during the interview and the initiating questions were selected based on the answers after all interviews.

The questions formulated for the interviews were split into the two disciplines, where both were asked similar questions but more specific for their expertise. The interviews were first focused on the interviewee as a person: their daily jobs, personal preferences, and prior knowledge of the research topic. Validity of the interviews was ensured by correct preparation of the interviews in terms of asking correct and understandable questions to reduce bias. To ensure validity, the questions were formulated in an open—ended and non-suggestive matter, creating a comfortable and honest environment for the interviewees. Furthermore, the interview protocol was critically evaluated by several researchers (two of my supervisors and one colleague student), the questions in the protocol were iterated and discussed multiples times, and the interviewees will be asked whether they fully understood the questions asked. Multiple evaluation iterations decrease the chance of bias while increasing the validity and relevance of the questions asked. The validity of the interview is thought to depend on the expectations of the researcher, meaning that while conducting the interview session, the researcher needs to ensure that interviewees understand the questions while still managing to data for the research questions[67]. These aspects were taken into consideration in the development of the interview protocol and during interview conduction, increasing the validity of the research. However, the validity and reliability of the interviews could have been improved by conducting a pilot study as it would be helpful first to test the questions and adjust the protocol before starting the study; Conduction a pilot study is seen as a preparation trial for the actual study and is

conducted to pre-test the interview questions[67,68]. Due to time-dependent boundaries, the pilot study was not conducted, and the multiple evaluations of the questions were perceived as sufficient.

In the end, three pharmacists and three pharmacometricians were interviewed in this study, which is seen as a rather small sample size. It was important to ensure that this study also met appropriate reliability, which depends on whether a repetition of the study would provide similar results and was thereby identified as consistent[69,70]. However, in interviews with a small participant group, it is difficult will provide the exact same answers. Nevertheless, it is important to note that analysis of the data relies mainly on the interpretations of the researchers and might thereby decrease the reliability. Besides, due to the exploratory focus of the study, this number of interviewees was perceived sufficient as the opinions of the six interviewees could give an indication of the problem and possible solutions.
The interviewees were either conducted in English or Dutch, depending on the preference of the interviewee, to create a comfortable environment causing a more elaborate discussion. Most participants were bound to a limited timeframe as their jobs are usually very busy. In some interviews, this caused a limited time to collect data. However, all questions were discussed in sufficient elaboration to identify themes and obtain quotes describing their thoughts. Thus, no time-dependent diminishing of information was identified in the interviews.

4.2.4. Insights and proposed implementations testing through a focus group

The proposed implementations described would be based on the results of the interview. However, due to the small number of participants in the interviews, the implementations could only be based upon a small number of opinions. However, the implementations were not fully newly developed, decreasing the insecurity of adopting the technology. As these implementations regarding the MIPD platform were mainly focused on adapting an already existing MIPD platform, named InsightRX, the foundation did not have to be built saving time. However, barriers keeping of this MIPD platform from being generally integrated into clinical practice might include the lack of more user-friendly features and the lack of technical- and high-level pharmacokinetic knowledge from clinical practitioners, as explained in Chapter 1. Introducion[7,9,16]. Therefore, besides building the implementations based on only the interviews, also these aspects were taken into consideration to provide the best adjustments. The lack of this technical- and pharmacokinetic knowledge of the pharmacists was addressed in the introductory course, where they would become superficially acquainted with skills regarding the technological- and pharmacokinetic aspects of the MIPD platform. However, regardless of the fact that no prior experience or knowledge in modelling is needed to use the MIPD platform as a pharmacist, they need to be introduced in how the MIPD platform should be handled[9,11,12,15]. Pharmacometricians generally do know how to approach dosing based on models but are not widely familiar with MIPD through the use of such a MIPD platform and would therefore also need to be introduced on how to work with the MIPD platform. Insights on the formulation and development of the implementations regarding both the MIPD platform and the collaboration through that MIPD platform were based on ideas directly obtained from the interviews; More than one participant thought up the same or similar implementations, increasing the reliability of the ideas.

To test, validate, and subsequently make last adjustments of the implementations, a focus group with both pharmacists and pharmacometricians was conducted. The methodology of conducting a focus group was chosen to clarify, qualify, and extend collected data from earlier methods, as was described as a criteria to use of a focus group[71,72]. The focus group was meant to test the results of the interviews and the proposed implementations in interaction within the disciplines and between the two disciplines. The reason for performing the focus group was in accordance with the literature, as was explained that a focus group generates three units of data to analyse: individual, the group, and the interaction[73]. Within the individual unit, the data obtained was used to triangulate the conduction of interviews, increasing the validity of this research[71]. The group unit was merely used to evaluate the validity of the measurements. The interaction unit is used for exploration, since the interaction in the focus group allows for deliberation among participants and for generating a rich understanding of participants' experiences, beliefs, and attitudes towards the implementations[72,73].

The protocol developed for the focus group included an introduction to the research topic, a setting rules section, a ranking of codes derived from the interview results based on hypothetical cases, an asking-

questions part, and was wrapped up by the closing part and asking for comments. First an extensive introduction was given to give all participants inside on the topic, with and without technological- or pharmacokinetic prior knowledge. The aim of this research was also explained to give them an idea of the questions that would be asked. The last step of the introduction was explaining how the focus group was build-up, in which was made sure that the order of scenario ranking and asking questions was focused on going from general to more specific. This order of going from general to more specific questions was identified as one of the base principles of formulating a focus group protocol[72]. A setting rules section was developed to make moderating a focus group for the first time easier, as being a good focus group moderator requires a quite extensive set of skills, which we do not necessarily have since I have never moderated a focus group before. Prior to actual conducting the focus group, I read about how to moderate such a focus group and watched a focus group that was posted on YouTube. The ranking of interview derived codes and asking questions regarding the concepts followed; in the hypothetical scenarios, the proposed implementations were introduced to test their beliefs and attitudes towards these implementations. The participants were asked to rank the codes first within their own discipline, creating an environment where all participants were able to express themselves in a language and attitude with which they were comfortable. The two separate disciplines got one working laptop during their discussion to rank the codes in a Miro board, which was chosen as it was the most efficient for saving the rankings and creating figures during the focus group ranking stage. On the Miro board, the scenario could also be read again to have clear in mind what the exact scenario was. The scenario led to a board depicting all codes derived from the interview, of which the participants had to select the five most relevant and transfer to the last board, where the codes could be ranked from least relevant (1) to most relevant (5) per theme, being collaborative introductory course and the MIPD platform. All participants perceived the Miro board as a useful tool to save their answers, even though they had to get used to how to use Miro. Then, after ranking within the disciplines, the ranking was discussed within the group also to check the interaction between both disciplines and examine how their attitudes changed in this changed environment. Checking both within and between the disciplines, individual and interactive units could be tested. The scenarios described in the protocol included one collaborative introductory course, two hypothetical scenario depicting the collaboration through a MIPD platform in ‘real-life’ setting, and the overall concepts of the collaborative introductory course and the MIPD platform. I chose to start with the introductory course, to also introduce the participants to the hypothetical MIPD platform before ‘using’ the MIPD platform in the following two scenarios. Due to time limitations, the third scenario in stage 1 regarding the dosing of Tamoxifen was left out.

After closing the discussion on stage 1 ranking of the interview derived codes, the questions were asked in stage 2 to deepen the understanding of the ranking. Unfortunately, due to time-related issues, the questions were not discussed extensively. However, looking at the data obtained, it did not affect the quality of the data as most of the answers were a repetition of discussions in stage 1. None of the participants had additions to the discussion topics when I asked for additional information during the closing of the focus group, confirming all beliefs and attitudes were shared on the research topic.

Six participants were recruited for the focus group: three pharmacists and three pharmacometricians. As the optimum of the group size for a focus group ranges from 6 to 8 participants, the number of participants that were selected for this study’s focus group was optimal[72]. However, unfortunately one of the participants had to cancel last minute, leaving us with 5 participants attending the focus group: three pharmacists and two pharmacometricians. A smaller group size risks less in-depth or extensive discussion occurring, but can still be successful[71,72]. As an inexperienced moderator, the smaller focus group was to my satisfaction because I could better handle the discussion. I could have recruited more participant to cope with non-attenders; however, as I recruited participants from my personal network, I did not calculate a non-attender. Even though the participants were selected within my network, they did not work together and did only know the others by name. As all participants knew me, I assumed that they would feel comfortable sharing, which was subsequently enhanced by not knowing the other participants. Stranger focus groups, where the participants do not know each other, stimulates them to share their attitudes more freely without repercussion[72]. As interaction is key to a focus group, I did select participants based not only on their prior knowledge but also on their interest in the topic since being interested in a topic increases motivation to share thoughts. This selection was perceived to be the optimal selection of participants for an interactive group discussion on these specific topics.

The focus group was conducted in Dutch, as Dutch was the native language for all participants, which was decided to create a comfortable environment causing a more elaborate discussion.

4.2.4. Data analysis

Both the interviews and the focus group were fully transcribed, allowing for the extraction of relevant quotes to support the results, which contributed to the credibility of the study. Nevertheless, it is important to note that analysis of the data and selecting the quotes rely mainly on the interpretations of the researchers and might thereby decrease the reliability. The validity of the study will be assessed by making sure that the collected and analysed data reflects the properties that are targeted, so whether the data represents what the study desires to research[70,74]. To preserve validity of the study analysis, only quotes directly related to the research topic were select to include in the data analysis and relation the theoretical framework.

The first cycle of coding the interview transcription was descriptive coding. This first cycle was chosen due to get all the data organised. However, unlike usual descriptive coding, in some cases a short description was used instead of only one descriptive word[22,23]. This change was decided as the long quotes could not be carefully and accurately described into just one code and since the descriptive coding cycle was merely used an easy way to summarise the extensive data, it was not identified as a risk for the study[75]. By using a short description, the quotes were summarised more accurately and were therefore easier to code in the second cycle. Furthermore, these somewhat longer descriptive codes were easier to combine into general topics that could be used in the focus group ranking, preventing the participants in the focus group to lose sight in the number of codes. However, a risk regarding this kind of coding includes creating codes that are not directly related to the research topic. To ensure reliability of the coding analysis, the transcriptions were read several times to verify the coding and the combination of similar codes. After repeating descriptive coding a few times, another coding cycle, pattern coding, was used to pull together the descriptive codes into more meaningful smaller units of data[75]. In pattern coding, the different codes are clustered to emerging themes in the dataset. Codes that were not directly related to any of the predefined or clearly emerging themes were left out of the analysis. The pattern coding led to the recognition of five themes that could be related to the research (sub)questions: 1) daily jobs; 2) feelings towards healthcare technology; 3) collaboration; 4) MIPD platform, and 5) future perspectives. The descriptive codes related to the emerging patterns were discussed within in Chapter 3.2. Descriptive codes were also linked whenever either the interviews or literature indicated they influence the other code, which could also be somewhat biased by my personal interpretation of the codes.

Regarding the data analysis of the focus group, in stage 1, the Miro board ranking was used to state what each discipline found important. The discussions were transcribed to formulate meaning on these selected codes and why they had chosen these codes. The combined approach for framework analysis was used, where the transcription of the discussions was already part of the first phase of the framework[24]. As the phases were interconnected, by making the participants rank the codes derived from the interviews, phase 2 was already finalised by linking quotes of the transcription to the codes selected by the participants. By assigning points to the codes selected, the focus of the results of the focus group was narrowed to these codes. By describing the discussion and quoting the participants regarding this narrowed scope of the results, the data was put into context in phase 3. Phase 4 included the interpretation of the data, where it was examined whether the proposed implementations were perceived as useful and sufficient, if adjustments needed to be defined, or if the idea would not work out in an interactive collaboration between pharmacists and pharmacometricians. In this study, the framework analysis approach was closely followed and thereby increased the validity of the data analysis of the focus group.
In stage 2 of the focus group, the questions asked and discussed with the two disciplines were transcribed. Relevant quotes were selected and linked to elements of the theoretical framework that would eventually contribute to the answering of the (sub)questions. Only one cycle of descriptive coding was conducted in this analysis. Only descriptive coding was conducted multiple times, as the quotes and codes only needed to be related to the theoretical framework. Thus, no pattern coding was conducted in this stage of the data analysis. By including a pattern coding cycle, the data could be made more concise and would make it easier to link to the theoretical framework. However, we, on purpose, decided to just use descriptive coding to not miss any possible relevant aspects of this stage of the focus group.

As most of the interviews and the focus group were conducted in Dutch, the quotes used in this research had to be translated into English to make it fit in this thesis, which might have decreased the credibility of the research as some approaches can be interpreted differently in a translation or disappear altogether. To prevent this decrease in credibility, also the exact quote in Dutch was presented.

4.3. Results

The results section within the discussion mainly focused on reflecting on the literature review used to develop the theoretical framework, the collaboration between pharmacists and pharmacometricians, and the MIPD platform. As the scope of the study was narrowed down after analysing the results of the interviews to the collaboration and the technology, being the MIPD platform, the discussion focused mainly on these topics. However, the daily jobs, feelings towards technology, and future perspective as extracted from the interview data were discussed and linked to these main themes within their subchapters. Within the subchapters regarding the results of the collaboration and the MIPD platform, the connection to literature related to the theoretical framework was discussed as well.

4.3.1 Literature review

In the literature study performed for this research, a deeper understanding of the collaboration and communication between pharmacists and pharmacometricians, and of factors stimulating or hindering them to collaborate either through old-used protocol or through the adoption of a MIPD platform, were studied by connecting social theories to the context of the research. By formulating characteristics or tasks related to the specific disciplines, a clear vision of what kind of social aspects would be interesting to study. As the final goal of this research would be to describe implementations to improve the collaboration on dosing busulfan between pharmacists and pharmacometricians through the use of MIPD platform, the literature review mainly focused on interdisciplinary and collaborative learning, motivational behaviour, individual adaptability, and the adoption of technology.

As interdisciplinary and collaborative learning is defined as two or more disciplines with different expertise being brought together to work towards a shared goal, where they share a responsibility to solve the problem and improve decision-making processes regarding in this case, patient care[26–28,31,32]. Where in this study, the shared vision of both the pharmacists and pharmacometricians was stated to be the improvement of their collaboration to improve dosing decisions for patients, which would ultimately lead to better patient treatment, the interdisciplinary and collaborative learning levels between these disciplines are crucial to reach their shared goal. An effective interdisciplinary and collaborative learning environment is characterised by both disciplines being able to hand in part of their autonomy by developing high levels of trust and acceptance towards the other professionals without losing control over their own expertise[26,31]. Anderson-Cook (2019) adds respect, commitment, and execution to the fundamentals of effective interdisciplinary collaboration between a technical professional and a more social professional[76]. Since respect is meant to be a starting point where collaborating professionals acknowledge their differences, strengths, and weaknesses to work towards reaching a consensus on dosing decisions in this study. These starting points would build a safe environment where open discussions to seek the best solution are common practice[76]. Regarding the collaboration between pharmacists and pharmacometricians, both disciplines acknowledged the importance of getting to know the other professional on a personal and professional level, which could be related to acknowledging their differences and strengths and weaknesses which creates an environment where both disciplines respect the expertise of the other and thereby are able to openly discuss dosing issues and come to the best solution through collaboration. Furthermore, the commitment of both collaborating disciplines ensures that team members work both towards the desired results by following the plan-of-action formulated together, in which holding the other professionals accountable for their performance is not something new. Commitment to a specific result is closely linked to trust, since disciplines that trust one another feel more comfortable in challenging the other discipline to stick to the plan and adapt their views by acquiring new knowledge[76]. In accordance with defining commitment as a fundamental aspect for effective collaborative and interdisciplinary learning to retain and create more knowledge, McLeod (2014) described how a professional of one discipline relies on a professional of another discipline to complete their tasks successful in order to retain more knowledge[33]. The results of this study also showed that the pharmacists and pharmacometricians perceived the trust and connection to the professionals of the other discipline as a crucial aspect in establishing a positive

interdisciplinary collaboration and learning environment. Therefore, besides only adopting skills and knowledge from the other expertise as described within the literature research, it is also important to build respect, commitment trust between the two disciplines to establish an effective interdisciplinary and collaborative learning environment.

Another factor influencing the interdisciplinary collaboration of pharmacists and pharmacometricians through the use of a MIPD platform includes motivational behaviour, especially the intrinsic motivational factors describing how an individual desires to please the needs of another, e.g., the desire to satisfy their colleagues or to achieve professional goals[34,35]. The improved patient well-being by the use of such a MIPD platform should be perceived as an intrinsic motivation for both the pharmacists and pharmacometricians, which was in accordance with the results explaining both disciplines work towards the shared goal of improved patient care and thereby stating the intrinsic motivation is a key element in the correct collaboration through such a MIPD platform. Furthermore, related to collaborative learning, achievement motivation is driven by the desire for success and is influenced aby ability, effort, task difficulty and luck[36–40]. Achievement motivation in regard to the collaboration between pharmacists and pharmacometricians is merely related to the task difficulty as described in the literature review; whenever both parties feel like learning from such a MIPD platform is manageable, they are more likely to be motivated to make use of the MIPD platform. However, it is not a necessary achievement that stimulates the motivation to achieve the shared goal, according to Tran (2019), where it is reported that collaborative learning enhances the connection between the two disciplines involved[77]. This positive connection between the pharmacists in pharmacometrician in this case would increase the motivation and persistence to achieve the shared vision of improving patient dosing regimen through the use of a MIPD platform, which is in agreement with statements of the two researched disciplines explaining a connection between both is crucial to establish an effective collaboration and to adopt the new technology in their collaboration. Reading more extensively into the motivational factors of healthcare practitioners and into motivational factors related to collaborative learning and adoption of technology might have led to more in-depth insights on the motivation of the pharmacists and the pharmacometricians before conducting the research. Nevertheless, using their statements and attitudes towards motivation in collaborating through a MIPD platform and subsequently reflect to newly discovered literature, the motivational factors of the disciplines could be taken into consideration in the proposed implementations to our satisfaction.

The individual adaptability, described by I-ADAPT, of the disciplines researched relates to the motivation or willingness of an individual to accept different tasks professionally and to transfer learning from one task to another, which is thereby connected to the motivational and learning behaviour of pharmacists and pharmacometricians[41–43]. To improve collaboration between both disciplines requires the ability and motivation to adapt their behaviour to the other professional and their demands. Thus, the theory of individual adaptability considering the ability to adapt being related to be able to cope with change and to transfer knowledge, is crucial for different disciplines to move towards effective collaboration. However, this research did not focus thoroughly on their adaptability or their willingness to adapt as these factors were barely or not mentioned during the interviews and interaction. Nevertheless, there was stated that they were not familiar enough with other professionals personally and professionally to be willing to adapt and be able to adapt correctly to the other professional, showing the importance of the connection between both for them to be motivated to adapt to the other professionals.

In regard to the adoption of the MIPD platform in their daily jobs, the study focused on what was needed for the pharmacists and pharmacometricians to adopt this new technology and use it in their collaboration. Technology acceptance as a social theory in healthcare describes the psychological state of an individual regarding a specific technology and its use, describing the two core factors influencing the intention to use a specific technology; in this study's case the intention of implementing the MIPD platform[48]. The core factors include perceived ease of use and the perceived usefulness, which were also identified as key elements by the participants in this study[48,49,54]. Other aspects influencing the acceptance levels of the future users are described in Figure 7 where the theories of TAM and UTAUT are combined into one to influence user behaviour. However, in this study, the aspects described by TAM were most prominent causing the implementations for the collaboration through the MIPD platform to focus on the easiness of use of the MIPD platform and communicating the usefulness of such a MIPD platform correctly. To facilitate the collaboration through the MIPD platform, the perceived ease of use is crucial and needs to be proven to the

users since the participants of study did perceive the use of a MIPD platform in precision dosing as beneficial for patient care. To prove the perceived usefulness, a convenient information provision should be delivered that guarantees beneficial patient outcomes[54], which should be implemented in the introductory course as that would the first time the disciplines get the learn the MIPD platform. Furthermore, this introduction would also contribute to their easiness in use in terms of the pharmacists and pharmacometricians getting to know the MIPD platform and how to handle basing dosing regimen on that MIPD platform. In accordance, Kurahashi (2018) tested the perceived ease of use and usefulness of a web-based tool used in complex healthcare collaborations and showed the importance of introducing future users to such MIPD platforms at the early stages of implementation to ensure the system is both usable and useful, thereby increasing technology adoption in a real-life setting[78]. They highlight the need to consider how to minimize the impact on the workflow and still optimize the usefulness of a system before it can be implemented[78]. In regard to this research, the participants also perceived the minimal impact on their workflow as important but still wanted to see collaborative decision-making on the dosing regimen optimized, which agreed with the study of Kurahashia (2018) highlighting the importance of the easiness in use and the usefulness.
Establishment of interdisciplinary collaboration decreases medication errors, which might cause toxicity in a patient, and thereby has a positive influence on health care, as Manias (2018) showed in her research[58]. In agreement, Palanisamy (2017) reported higher-quality care is given when healthcare professionals collaborate as a team in their practice[79]. The most important facet of interdisciplinary collaboration in health care would be professionals of different disciplines in the hospital share knowledge, make decisions together, and share responsibility in improving the care of a patient[57,58]. This study depicted how the two disciplines currently collaborate, however, do not perceive this collaboration as sufficient. Manias (2018) also explained how further research into this interdisciplinary collaboration has the potential to improve healthcare. Since the professionals do not perceive their interdisciplinary collaboration as optimal, this study aimed to study further, and possible improve the collaboration. To address and simplify this collaboration, the MIPD platform design was evaluated into two different portals to be handled by the two collaborating disciplines. They would be able to collaborate by just using the MIPD platform, which also saves all patient and medication data, which would contribute to improved patient care as well. Palanisamy (2017) and Byrd (1992) reported that the integration of technology lowers transactions costs and increased decision quality, highlighting the importance of introducing new technology into the collaboration and decision-making between pharmacists and pharmacometricians[79,80]. Furthermore, the integration of technology-enabled collaboration between disciplines[79], which strengthens the idea of implementing a MIPD platform in the collaboration between pharmacists and pharmacometricians.

Another social theory on a collaborative and learning environment between disciplines within, for example, the healthcare system would include transdisciplinary learning, which is a theory that was not fully present in this study or the theoretical framework. However, transdisciplinary learning is an upcoming theory that would be something interesting in regard to this study whenever the research is extended. Transdisciplinary learning is strongly linked and complementary to interdisciplinary collaboration as it focuses on the exploration of a specific problem that integrates perspectives of all different disciplines involved in order to collect and create new knowledge to understand and ultimately solve that problem[81,82]. The theory describes how transdisciplinary learning creates the possibility to build skills in a specific topic, integrating and transforming knowledge from different perspectives and different disciplines to understand and solve problems in de present world together, for example the field of health care[82,83]. The effectiveness of transdisciplinary collaboration can be studied through four domains, in which the kind and scope of collaborations between disciplines differs majorly from each other. Research discussing the differences in these types of collaboration can be used to develop a typology of circumstances where this transdisciplinary collaboration is improved[84]. Factors influencing the effectiveness of transdisciplinary collaboration regarding science initiatives included inter- and intrapersonal, organisational, technologic, societal, political, and physical environmental factors. These factors may ultimately be used to derive guidelines to evaluate and manage successful team collaborations[84].

Also in healthcare systems, the term transdisciplinary collaboration is increasingly prevalent as it is seen as important in increasing the efficiency and effectiveness of patient care[83]. Several factors for these transdisciplinary collaborations in healthcare include transcendence of disciplinary boundaries, sharing knowledge and skills, and make decisions together[83,85]. These aspects are already discussed within this

study, however, this study only focused on two disciplines within healthcare and thereby only presents a small scope and could not fully cover the concept of transdisciplinary collaboration. Furthermore, integrating these factors into healthcare allows the different disciplines to share the same goal towards improved patient care by inclusion of multiple disciplines, besides the discussed disciplines within this study, like the patient themselves, and thereby provide a framework to complete or solve clinical tasks and issues[83,85]. The combination and correct ratio between these three factors of transdisciplinary learning, being decision-making in practice being conscientiously based on the evidence, clinical expertise, and patient preferences, lead to the right use of EBP, and to the correct approach of personalised medicine (Figure 16)[2,3,86]. Transdisciplinary collaboration within EBP and/or personalised medicine can be identified as translation of integrated knowledge, meaning shared decision-making among for example researchers, practitioners, patients, and community, which subsequently will create a high-quality patient care environment[2]. However, some professionals will perceive transdisciplinary collaboration as a treat to their daily job and to the autonomy within that job, which may lead to distrust of the other disciplines when sharing personal knowledge and skills. Furthermore, sharing knowledge and skills to other disciplines and thereby handing in parts of their autonomy might also be seen as a risk for patients, which makes clinicians decide to not hand in these parts of autonomy[85]. On the other hand, some professionals may find it very interesting to move away from the boundaries of their discipline. They might appreciate to share knowledge and skills in order to grow by increasing their own knowledge and skills. These professionals also see the potential of patient benefiting from these transdisciplinary collaborations, by increased knowledge and skills for all disciplines creating the possibility to increase efficiency in treatment[85]. As one participant highlighted during the interviews, professionals within these disciplines who are willing and motivated to go out of their comfort zone to work towards the transdisciplinary collaboration, should be included to establish the foundation of a transdisciplinary collaboration environment. Finding a more in-depth definition of transdisciplinary in collaboration may provide guidance for these professionals to move together towards the ultimate shared goal of improving patient care through implementation of personalised medicine[83].

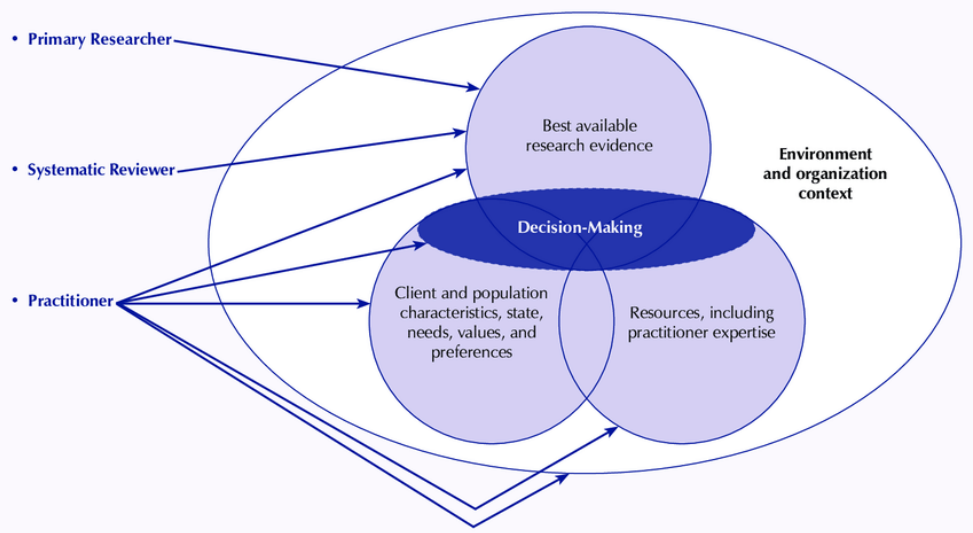


Figure 16. Transdisciplinary Model of Evidence-Based Practice and Health Professionals' Roles in Evidence-Based Practice. The environment inside an organisation is shown by research evidence, clients/population, and practitioners' expertise. Combining these factors to tasks of researchers and practitioners into decision-making creates a transdisciplinary collaboration between the disciplines. Figure retrieved from Schreiber (2013)[2] and Newhouse (2010)[3].

In the end, the literature review related to the characteristics described for pharmacists and pharmacometricians to establish an effective collaboration through the use of a MIPD platform was used to develop the theoretical framework. Efficient interdisciplinary and collaborative learning is still perceived to positively influence the translation of models into a MIPD platform split into two portals, where one is developed for and used by pharmacists and the other is developed and used by pharmacometricians, and to positively influence the obtain new knowledge to understand the expertise of the collaborating professional by obtaining new knowledge, which positively influences the understanding of the MIPD platform. The effectiveness of interdisciplinary and collaborative learning depends on the level of trust between the collaborating disciplines. Furthermore, intrinsic motivation, which is related to the connection between pharmacists and pharmacometricians, also influences the translation of models into the MIPD

portals and the understanding of the MIPD platform by gaining new knowledge. Adaptability of the pharmacists and pharmacometricians, which also depends on their motivational behaviour, also influences the model translation into the MIPD platform and the gaining of new knowledge to understanding the MIPD platform. These factors lead to interdisciplinary collaboration between the two disciplines by making use the MIPD platform as pharmacists adopt the technology that is developed to their needs by the pharmacometricians. The effective interdisciplinary collaboration through the use of the MIPD platform would create a transdisciplinary learning environment by integrating the perspectives of all disciplines in dosing decisions, like the pharmacists, pharmacometricians, and the patient, into new knowledge to understand and solve the emerging issue, which improves EBP and personalised medicine implementation. The establishment of an efficient transdisciplinary collaboration making use of technology in the form of a MIPD platform should be the breakthrough for healthcare practitioners to improve their dosing decision-making, as these protocols have not evolved over the past years. Therefore, it would be expected that the efficient transdisciplinary collaboration would have positive feedback on the model translation into the MIPD platform, the gaining of new knowledge to understanding the expertise of the other professional and the platform, and stimulation to adoption of the MIPD platform the interdisciplinary collaboration through the MIPD platform will be improved again as well. As professionals experience the positive effects of implementing the collaboration through the MIPD platform, they would be motivated to learn and collaborate more and to adapt their individual behaviour to the other professionals and could be motivated to adopt more technologies into their jobs. This positive feedback on the factors in the theoretical framework form a positive feedback loop. However, this learning on dosing decisions will eventually reach an equilibrium in learning, as the practice will slow down the learning path, as the way of administration will not change within this loop. The learning environment will mainly be stimulated by improving the dosing of patients. Thus, the collaborative learning loop will eventually reach an equilibrium, which can be related to the cognitive development theory from Piaget as it covers one out of four of the critical constructs describing cognitive development, namely the cognitive equilibrium[87]. The cognitive equilibrium is a mental state of balance between assimilation and accommodation, occurring when expectations meet the newly obtained knowledge, and it is perceived as being normal. People usually seek the assimilation towards an equilibrium because a disequilibrium mismatches their way of thinking or working. Implementation of the MIPD platform will first lead to a disequilibrium, which is uncomfortable, making them seek to restore the equilibrium by verbal exploration through collaboration, since collaboration is emphasized as the mechanism through which cognitive development takes place[88]. Therefore, the pharmacists and pharmacometricians will seek for the learning equilibrium by collaborating and ultimately will reach this equilibrium where they feel comfortable in using the MIPD platform for making dosing-decisions.

4.3.2. Collaboration

The exploration of the collaboration between the pharmacists and pharmacometricians was initiated by studying how they currently work and collaborate. However, their collaborating behaviour differed between different organisation, which did not indicate an overarching behaviour or clarity in their collaboration techniques. The lack of having a clear structure in how to collaborate does not have to be an issue, as long as within the organisation the structure should be clear to the professionals collaborating. However, the participants of study often addressed how their collaboration did not go as efficient regarding dosing decision-making as they would like, consuming them a lot of extra time and work. They mentioned the urgency to improve this for them to create a more comfortable and relaxed way of working and to ultimately also provide better patient care. These professionals addressed their desire to improve patient care, since several patients not limited to subpopulations are susceptible to suboptimal treatment due to treating them the average way instead of implementing Model Informed Precision Dosing (MIPD), which may improve the individual treatment of patients by achieving the optimal dose[7]. More certainly in the dosing of busulfan, which is known to have a narrow therapeutic window, the use of MIPD would be beneficial for the patient as their efficacy would improve combined with the decrease of side effects. Since MIPD platforms that incorporate MIPD might be beneficial for these professionals to base dosing regimens on are not widely used for unidentified reasons, this research addressed the obstacles in the use of the MIPD platform, the collaboration between pharmacists and pharmacometricians, and how to improve the collaboration of the disciplines through the use the MIPD platform[12]. Since the collaboration between pharmacists and pharmacometricians is crucial in studying the use of the MIPD platform, the collaboration between the two disciplines was one of the key themes studied in this research.

The obstacles in the collaboration between pharmacists and pharmacometricians were researched through the conduction of interviews, where they were asked how they currently collaborate, how they would like to collaborate, and how they would approach these collaboration improvements. The results of these interviews led to two main topics within the overarching collaboration theme: improvements and aspects to maintain. Elements that were perceived as being sufficient and that needed to be maintained included their inter- and multidisciplinary collaboration, where they checked the decisions made by the other discipline, had discussions on these decisions and did give and took advice in regard to the decisions. Thus, the decision-making aspects of their collaboration were also perceived as sufficient, even though there was explained the decision-making process was not as efficient as they desired. All participants also perceived the keeping of their own expertise as an element that should be maintained, as it enables the possibility for them to have that interdisciplinary environment. However, elements that need to be improved in their collaboration include learning together, the clarity of their collaboration, trusting the other professionals, the correct ratio between giving and taking, and the expectations management. Both disciplines, but mainly the pharmacists, did find the clarity in their collaboration very important; what is expected from the other discipline and what is expected in return? This definition is closely related to expectation management, which the professionals would like to improve as well. To establish an effective collaborative patient management and team performance, expectation management for performance outside their disciplines should be perceived as clear and sufficient by collaborating disciplines[89,90]. Thus, both literature and this study highlight the importance of expectation management and clarity in their collaboration to be effective. Another key element of establishing sufficient collaboration identified in this study includes learning together, which is defined as learning from the other discipline in terms of how they make dosing decisions. Within learning together, compromising is perceived as being important, as they need to make decisions together which sometimes means they need to compromise. Besides, learning together needs a connection between the two collaborative disciplines in order to effectively build a learning environment[77]. A positive connection between the pharmacists and pharmacometricians would increase the motivation and persistence to achieve the shared vision of improving patient dosing regimen through the use of a MIPD platform[77]. As shown in this study, both disciplines perceive their connection as insufficient to be able to learn from the other; both would desire to get to know the other professional on a personal but also professional level to collaborate, learn, and make decisions effectively. In agreement, earlier research showed that an effective interdisciplinary collaborative learning environment is characterised by high levels of trust and acceptance[26,31], comprising the connection between the two disciplines and was thereby perceived as a key component in improving the collaboration between pharmacists and pharmacometricians.

To tackle the collaboration between these disciplines and stimulate the use of MIPD based dosing, this study proposed to build a connection through developing an introductory course to the proposed MIPD platform. Despite no prior experience or knowledge in modelling is needed to use the MIPD platform as a pharmacist, the pharmacists perceived getting to know the tasks of pharmacometricians as crucial to connect and feel motivated to use such a MIPD platform in their dosing decision making. The recommendations for MIPD platform adjustments will be further discussed in Chapter 4.3.3. The proposing of such an introductory course was meant to introduce both the disciplines to the expertise of the other discipline to connect both on a personal and professional level, while collaborating through getting to know the MIPD platform and how to use it in making dosing decisions. Building a connection and collaborating to become familiar with the MIPD platform stimulates learning together aspects in the collaboration between pharmacists and pharmacomertricians. By going step-by-step through each portal of the platform, where each discipline is meant to explain their procedures of making dosing decisions within each step of the MIPD platform introductory course, both disciplines will gain knowledge and experience in the expertise of the other. Pharmacists will guide the pharmacometricians through their daily tasks by explaining each step of their portal, starting with searching for a specific patient (in case of the introductory course: patient 0), check for the medication that patient is using, and base their recommended dosing regimen on either experience or literature. After the pharmacists add the recommended prescription, the pharmacometricians will guide the pharmacists through their portal, where they check the recommended dosing regimen of a specific drug (in case of the introductory course: busulfan) based on models implemented in the MIPD platform. Furthermore, they explain the pharmacists how the models are developed and implemented in the MIPD platform, giving them an impression of the effectivity of the MIPD platform in order to build trust. By

introducing the other discipline to your expertise and skills set, they are able to build a connection while still preserving their individual expertise. Kurahashi (2018) also reported how the implementation of an introduction to a new technology in the early stages would improve the adoption of the new technology[78], which compares to this study's case where the implementation of a new technology needs to be introduced. The adoption of technology integration in learning together necessitates the establishment of e-learning allowing the collaborating practice to assist and share their best practice through the technology[91]. The study of Ndebele (2022) reports the importance of implementing an e-learning component to stimulate efficient collaboration in terms of learning together[91], which agrees with the proposed implementation of an introductory course to the MIPD platform for both collaborating disciplines. The concept of the introductory course is explained in Chapter 3.3.2. and was tested in a focus group with professionals of both disciplines. During the focus group interaction, the connection and clarity in the collaboration between pharmacists and pharmacometricians were again perceived as the most important elements of an efficient collaborative environment through a MIPD platform. The connecting element through the implementation of an introductory course was recognised by the participants, which is crucial in motivating disciplines to establish a collaborative learning environment as described by Tran (2019)[77]. However, they did add how important the clarity of this collaboration element was from the start of the course. Whenever the introduction does not make clear how to use the MIPD platform or the usefulness of the MIPD platform, the MIPD platform will not be adopted, which is in accordance with TAM[48,49,54]. The introductory course was expected to introduce how interdisciplinary collaboration would work within the implementation of a MIPD platform, which motivated both pharmacists and pharmacometricians to adopt the MIPD platform whenever the giving and taking advice, and discission elements in difficult cases would be preserved. Furthermore, as both pharmacists and pharmacometricians seek for the cognitive equilibrium, both disciplines will be motivated to take part in the introductory course to adopt the MIPD platform and reach the equilibrium fast. The hypothetical introductory course was experienced as an added value to the implementation and the adoption of the collaboration through a MIPD platform, however, within the introductory course, it was perceived as important to take into consideration the understanding of how the MIPD platform works while collaborating through the introductory course, the preservation of giving and taking advice related to compromising in complicated cases, and the usefulness and easiness in use of the MIPD platform. The current proposed introductory course requires further elaboration before it can be developed and implemented, however, it is perceived to provide a clear and convincing explanation on the usefulness and easiness in use of the MIPD platform, and to create a collaborative learning environment by building connection and trust between pharmacometricians and pharmacists while remaining their individual expertise but stimulating the interdisciplinary collaboration on making dosing decisions.

4.3.3. MIPD platform

The existing MIPD platforms, such as the InsightRX platform, which has a specific busulfan dashboard where its existing models are implemented, are not widely implemented due to unidentified issues. These issues could include user-friendliness but also the lack of technical knowledge needed to understand and handle the MIPD platform[7,9,16]. In this study, we tried to address and improve the user-friendliness and solve the technological knowledge gap in order to stimulate the collaboration and use of the MIPD platform in making dosing decision for busulfan and possibly other drugs as well. However, even if the pharmacometricians were able to handle the MIPD platform correctly, it would not solve for the collaboration issue between the pharmacometricians and the pharmacists as the unnecessary phone calls and checking up that were mentioned by the participants would not be reduced. Through conducting interviews with both disciplines, we wanted to gain a deeper understanding of the issues regarding the MIPD platform as it exists and how it should be adjusted to make its users more motivated to learn and use it. The interviews led to extensive insight into the necessities, use, risks and desired features of the MIPD platform by pharmacists and pharmacometricians. In regard to the necessities of the MIPD platform, all professionals agreed the use of the MIPD platform should serve a clinical purpose, to which it was perceived as necessary to provide proof on the effectivity and how it serves that clinical purpose. Furthermore, the MIPD platform should be up to date in order to provide the best dosing regimen possible at that time. Another aspect that the participants identified as a key element in implementing the MIPD platform was the addition of a training to learn how to use the MIPD platform, which was an aspect that we already addressed in Chapter 4.3.2., where we explained the implementation of an introductory course to the MIPD platform. Moreover, participants found it crucial to have clear interdisciplinary aspects of the MIPD platform, where

both focused on keeping their autonomy while collaborating, which is a concept that sounds counter-intuitive as collaboration is a process involving interaction with others, whereas autonomy regards working independently and self-determined[92,93]. Nevertheless, both aspects can be complementary since autonomy may stimulate collaboration by enhancing the relationships between professionals[93–95]. The concept of empowering autonomy of the professionals of the two disciplines, to subsequently enhance interdisciplinary collaboration is something that we address by involving the pharmacists in the use of the MIPD platform is a later stadium of this study, enhancing their autonomy in model informed precision dosing through a MIPD platform while still decide dosing collaborative with the pharmacometricians[95].

During the interviews, the participants also highlighted the importance of the use of the MIPD platform, where they discussed the importance of the MIPD platform being easy to use, efficient and practical, clear in how to handle the MIPD platform, and that it should be fast in use. The last element was perceived as least important as they rather invested a little more time when providing improved care. All these elements do relate to the MIPD platform, but also to how it is communicated: whenever the introductory course discussed in Chapter 4.3.2. is clear and explains all the aspects in detail, the MIPD platform will be perceived as easy to use, efficient and clear how to use the MIPD platform. However, the pharmacists that were interviewed emphasized on their aversion towards using several different programs in their daily jobs. Using patient's dossiers describing the patient list of medication and medical history and subsequently also needing to use the MIPD platform to base their dosing prescription on, would demotivate them to invest time in learning how to use the MIPD platform. Besides the use of the MIPD platform, the interviews also highlighted the features they perceived as crucial for them to be motivated to use the MIPD platform. All pharmacometricians were focused on making sure precision dosing is the main concept of the MIPD platform, which only one pharmacist mentioned showing their lack of awareness of the concept of personalised dosing of drugs. Therefore, the clinical awareness was also perceived as a crucial element in the MIPD platform implementation which included the overview of several models describing different clinical cases.

On the other hand, the interviews also brought possible risks of the development of the MIPD platform to light. Earlier studies described that implementation of MIPD is a complex task since it requires sophisticated modelling or pharmacokinetic knowledge, that needs to be widely improved to make the use of MIPD beneficial[96]. The transfer of such complex knowledge is time-consuming, which is an aspect that the participants also perceived as a possible risk in the implementation of MIPD platform[7,96]. Furthermore, the building of fruitful collaborations and turning the sceptical attitudes of some pharmacists towards MIPD based dosing into positive and enthusiastic behaviour, is a very time-consuming task. Pharmacometricians did recognise the need for a lot of models covering different cases to make the use of a MIPD platform beneficial for the health care system, which again takes a lot of time and effort for the field. Investing this amount of time in a concept that has insufficient prove yet is perceived as a risk and decreases the motivation of professional to work on the implementation.

To address both the issues regarding the user-friendliness and the pharmacokinetic knowledge gap, we decided to propose implementations to improve the MIPD platform which still focuses on the MIPD platform serving a clinical purpose and on creating autonomy in a collaborative environment. To enable the possibility of solving both the emerging issues, the MIPD platform would be split into two portals, creating the opportunity for the pharmacists also use MIPD in their own discipline's portal, stimulating their autonomy in using MIPD. That portal would include the patient dossiers they already work with creating an easy dashboard for them where they only need to use just on MIPD platform for all tasks related to prescribing doses of a drug for one specific patient. The prescribed drug recipes were automatically sent to the pharmacometrician through that MIPD platform. This would simplify their collaboration by using the same program to base and decide dosing regimen. The implementations as proposed in this study are presented in detail in Chapter 3.3.3., describing all components of the adjusted MIPD platform for both the pharmacists and pharmacometricians.

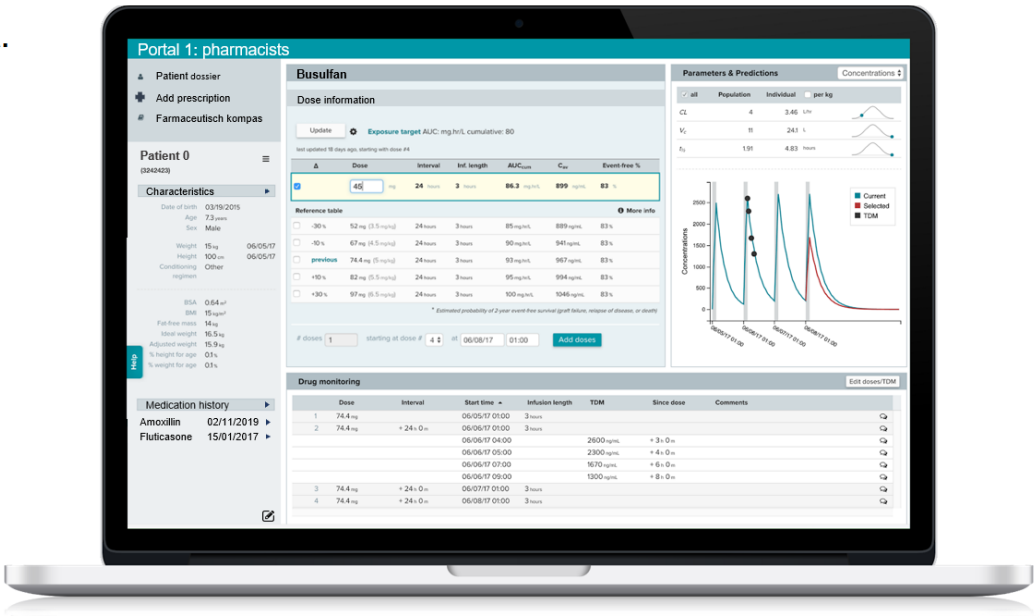
The implementations for the MIPD platform were tested through the conduction of a focus group, where the participants had to rank the terms that were perceived as important in the interviews for different hypothetical cases that comprised the proposed implementation. After this ranking, the MIPD platform and its proposed implementations were further evaluated through the discussing of some MIPD platform related

questions. As Ryan (2000) and Radel (2016) reported, the motivation of professionals would be improved by the desire to achieve professional goals, which could include the improving of patient care in means of drug dosing[34,35]. In regard of our study, pharmacists and pharmacometricians would be motivated intrinsically by actual showing them the use of MIPD is beneficial for the patient's wellbeing through providing an overview of the models developed and their concentration-time profile compared to the target. The overview of the concentration-time profiles of the model in the MIPD platform was perceived as important by the pharmacists to better show them what the use of such a model has to offer. In agreement, while interacting, pharmacometricians ranked the number of models as being most crucial in the implementation of the MIPD platform as they realise the importance of having several models explaining the data and the drug. Pharmacists did also realise the relevance of implementing several models but approached the aspect merely as the flexibility of the MIPD platform; All patients are unique and need to be taken into consideration, leading to the necessity of implementation multiple models to cover for all these different patients. Repeatedly, as the pharmacists ranked the clarity as the most important aspect in their collaboration, they also perceived the clarity of the implementations and the actual MIPD platform as being most relevant in the development of this MIPD platform. This need of clarity was mainly focused on convincing the professional of the usefulness of the MIPD platform is making dosing decisions. Kurahashi (2018) reported earlier, as mentioned in Chapter 4.3.2., how the usefulness of a MIPD platform would be best delivered when introducing users of the MIPD platform in early stages of the development, which was something we addressed by the proposed implementation of the introductory course[78]. Subsequently, this proof and experience of usefulness would improve the technology adoption of both the disciplines. Another element, which was perceived as important in the development of the proposed MIPD platform included the efficiency of the MIPD platform, being ranked second most relevant aspect in the MIPD platform as ranked by both pharmacists and pharmacometricians. The efficiency aspect also influences the adoption of technology, as it is described as the ability to maximise the possible output given the quantities of input and technology, highlighting the urgence of improving the technology absorption[97]. During the interaction of the focus group, all participants highlighted the relevance of scientific proof of the effectivity of MIPD through a platform to convince professionals in these disciplines to use that MIPD platform. Thus, to improve the user-friendliness and the pharmacokinetic knowledge to motivate its users to adopt the MIPD platform, the implementations should focus on making the MIPD platform clear in use, while implementing a lot of models and also depict these models to show and prove the effectivity of MIPD for that specific drug.

Taken the results of the interviews and the focus group together and combine them with the studied literature discussed in this chapter, a general and abstract idea on the two portals of the MIPD platform is shown in Figure 17. In Figure 17, panels A and B show the portals for pharmacists and pharmacometricians, respectively. As both pharmacists and pharmacometricians explained in the interviews and focus group that they would be stimulated to use the MIPD platform when its benefits are proven by depicting concentration-time profiles, both portals include concentration-time profiles for the specific patient based on the chosen dosing regimen and the selected pharmacokinetic model. The concentration-time profiles of the different implemented models can be used to check the effectivity of the prescribed busulfan dosing regimen based on the target concentration, convincing the effectivity of the use of the MIPD platform. Furthermore, pharmacists emphasised the importance of the MIPD platform being easy to use and not having to switch between different electronical systems; therefore, the patient dossiers are implemented in the MIPD platform. Pharmacists can easily look up patients with their characteristics and medical history, helping them making busulfan dosing decisions. These elements are also implemented in the portal for pharmacometricians to strengthen their understanding of the prescribed dosing regimen of the pharmacist. In addition, a hyperlink to Farmaceutisch Kompas is implemented for pharmacists to make their literature-based dosing decision making easier. The suggested busulfan dose can be tested in the dose information- and the parameter and predictions box, where the target AUC and concentration are depicted together with the suggested dose and corresponding values. For the pharmacometricians, the prescribed, and thus suggested by the pharmacists, busulfan dosing regimen can be compared to several dose adjustments and corresponding values based on different model. The pharmacometricians can select different (population) pharmacokinetic (PK), pharmacodynamic (PD), and PK/PD models to find the best fit for that specific patient. Panel C depicts a setting for Panel B showing the options for different developed models and to what patient group they belong, out of which the pharmacometricians can select the optimal model. Whenever Panel C is introduced during the introductory course, the great number of models implemented is shown, which provides prove of the effectivity of the MIPD platform for busulfan as desired by both

pharmacists and pharmacometricians. After the pharmacometricians checked the prescribed busulfan dose, they can either accept the dosing regimen or reject and adjust the regimen.

A.



B.

C.

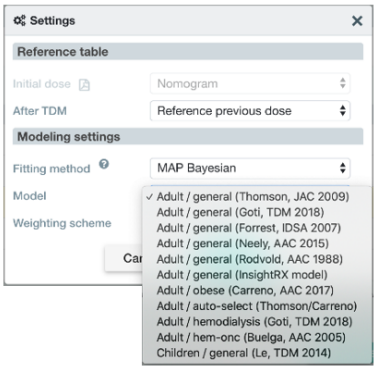


Figure 17. Proposed implementations of the MIPD platform. The MIPD platform InsightRX is used as a base for the proposed implementations and that dashboard was adjusted based on this studies' results[14]. Panel A shows the portal for pharmacists, showing the possibility to see the standard patient dossier, add prescriptions, and make use of Farmaceutisch Kompas to research dosing regimen. Furthermore, the patient characteristics and medication history are shown, helping the pharmacist to decide the optimal dose. Deciding the dose of busulfan is done using the dose information, busulfan monitoring, and parameters and predictions. The busulfan dosing regimen is added to the MIPD platform. Panel B shows the portal for the pharmacometricians, depicting the possibility to check the prescribed dosing regimen for busulfan of the pharmacists, see the patient dossiers and contact the treating pharmacist. The prescription, patient characteristics, and medication history are shown to be used in the check. Furthermore, a model section is added, showing the different kind of models available for busulfan. The population PK model for busulfan and metabolites, as researched in my previous thesis (Appendix A) is shown with corresponding pcVPC and Goodness-of-Fit. The model is used to predict the fit of the prescribed dosing regimen. The prescription can either be accepted or rejected and adjusted. Panel C shows the settings option that can be used the choice of different models. For example, several models for general adults are developed, but also models for obese and children. The setting gives the opportunity to search for the optimal model for the specific patient.

4.4. Limitations

One and most likely the biggest limitation of this study is the narrow scope which was researched. This study is only focused on the collaboration and communication between pharmacists and

pharmacometricians, which are only two of the disciplines within the whole health care system involved in treating patients by making dosing decisions. Healthcare is already a very complex system, therefore, we decided to keep it small and focused on this small scope due to time limitations but also due to my prior knowledge and previous thesis, which was merely focused on pharmacokinetic modelling of busulfan[98–100]. As pharmacists and pharmacometricians are both (partially) involved in drug dosing based on patient characteristics or genomics, these two disciplines were selected for this study. For these two disciplines, only a small number of participants for each discipline were selected due to time limitations, and therefore only cover a small part of all the information out there, limiting the reliability of the research. Besides the collaboration between pharmacists and pharmacometricians, this research was also focused on communicating MIPD to pharmacists in terms of drug dosing through a MIPD platform. However, again focusing on only one discipline within a whole healthcare system limits this study. Even if both pharmacists and pharmacometricians are able to successfully use the MIPD platform to decide dosing regimen for patients, other disciplines (e.g., physicians, physician assistants, and nurse practitioners) are not familiar with this dosing system, which creates a collaboration gap between these disciplines. Moreover, the implementations as proposed in this study could be quite overwhelming to those having no prior knowledge on MIPD, which could demotivate them to use and collaborate through a MIPD platform. Due to these narrowed scopes, the study is only focused on a small part of the health care system and could not explain how to address the collaboration and communication obstacles for the whole system.

Furthermore, this study is focused only on Dutch pharmacists and pharmacometricians (except for one foreign pharmacometrician during the interviews), which means it is not internationally applicable and thereby limited to the Dutch healthcare system. The Dutch healthcare system has extra discipline, clinical pharmacometricians who are both specialised in modelling and are involved with patients, that increasingly emerges in their system and thereby differs from other nation's healthcare systems where the specialty of clinical pharmacology is declining[101,102]. This third discipline has the technical pharmacokinetic modelling knowledge necessary to use the MIPD platform while treating patients, and thereby have all characteristics described in this study. However, the number of professionals within this third discipline is limited and is even declining[101], which highlights the importance of this study as other nation's healthcare systems will have more barriers in communication MIPD.

Another limitation in this study is regarded the proposed implementations. This study sought to explore the user-friendliness of the existing MIPD platforms and address this in the proposed implementations, however, as far as we know and could find in literature, there are minimal publications regarding the user experience of MIPD platforms. The only literature found regarding the experience of MIPD platform suggested the user-friendliness or technical knowledge of the users could influence its widespread use, but did not report any significant prove[7,9,16]. Because of this limited number of publications, we assumed the user-friendliness was perceived as insufficient due to the lack of widespread applications of MIPD platforms, however, we were unsure in the beginning of this research. Nevertheless, this study showed that the participants indeed did perceive, for example, the InsightRX platform as not sufficient user-friendly. Another proposed implementation perceived part of our study limitations, regards the fact that the implementations do not address how to educate pharmacometricians (and/or pharmacists) about revisions to the models used for MIPD. We only reported to update the model by adding obtained data, however, revisions were not included in neither of the interview and focus group protocols.

A final limitation of this study includes that we did not address how the results of this study and the proposed implementations of the MIPD platform would be communicated to patients, creating the lack of multidisciplinary in this research. In our daily world, there are a lot of complex mathematical equations used for graphical user interfaces (e.g., video screens like Zoom or apps on smartphones), of which the public is not aware or does not know anything about. This lack of awareness and understanding of the mathematics in terms of, including but not limited to, numeracy is also seen in health care, negatively influencing health outcomes for patients[103,104]. Therefore, a discussion within professionals related to dosing patients based on MIPD is needed regarding how much detail about these mathematical models is relevant to the patient and how this should be communicated in a more simple way[105]. However, this is a very complex and extensive topic in science and was thereby unrealistic to address in this study.

4.5. Future perspectives and recommendations

Following up on the insights obtained in this study, by first obtaining problem-solving implementations through the conduction of interviews and then after testing these implementations through the conduction of a focus group, we would like to propose to further study the implementations regarding the introductory course and the MIPD platform before these can be implemented into the healthcare system since the healthcare system is a complex and crucial system that needs to be approached carefully. This study suggests that the implementation of an introductory course to let pharmacists and pharmacometricians get to know one another to build a trustful collaboration and to learn how to dose based on MIPD. As they perceive getting to know the expertise of the other discipline crucial in building an effective collaboration, the focus of the introductory course should be on getting to know the other discipline on a professional and personal level. Furthermore, the introductory course should highlight how to handle the platform and how the MIPD platform simplifies their collaboration without changing their expertise. Regarding the MIPD platform, this study highlights the importance of keeping the expertise of its users as it is, but only focus on simplifying their tasks. Splitting the MIPD platform into two portals, one specified to each discipline, was perceived as useful since the disciplines were able to implement aspects that they need to perform their tasks successfully, e.g., the implementation of the patient dossiers preventing the pharmacists from using several platforms in their jobs and the implementation of an overview of all models implemented in the platform providing a clear view of how developed the MIPD platform is for that specific drug. Pharmacists and pharmacometrician emphasised on clarity, efficiency, and flexibility to be crucial aspects of the MIPD platform for them to learn and use the MIPD platform. This flexibility was related to ascertaining the MIPD platform to serve a clinical purpose, meaning a lot of models are needed to make the MIPD platform applicable for large numbers of individual patients. Even though, the recommended implementation was perceived as beneficial for their collaboration through the use of a MIPD platform and as beneficial for the implementation of MIPD to improve patient care, this study focused mainly on the exploration of the collaboration obstacles and the proposing of implementations to improve this collaboration in dosing decision-making, since the obstacles in the collaboration between pharmacists and pharmacometricians were not studied thoroughly before. Therefore, future research is needed to confirm or negate these recommendations by studying a larger scope of professionals and different disciplines involved in dosing decision-making.

As this study covered only a small scope of the collaboration and adoption of a MIPD technology in the healthcare system, more research is needed to address other disciplines within the whole healthcare system. Therefore, future research is crucial to further explore the obstacles regarding the collaboration between pharmacists and pharmacometricians to confirm or negate the results of this study. Moreover, future studies should address how other disciplines in the healthcare system are involved in dosing decision-making, how these disciplines collaborate, and identify the obstacles in their collaboration, in order to extend the scope of the results obtained in this study, and to address the transdisciplinary collaboration between all these disciplines. Extending the research scope would subsequently allow the recommendations formulated in this current study to be extended. Regarding the collaboration between pharmacists and pharmacometricians through the use a MIPD platform, the participants of this study confirmed that the implementation of an introductory course would create a connection and build trust between them, stimulating their collaboration. However, this study only focussed on the implementation of an introduction to build a connection and an improved collaborative environment between pharmacists and pharmacometrician, thus, future research should explore how such an introductory course could be implemented for a larger group of disciplines and whether it would still be beneficial for their inter- and transdisciplinary collaboration.

Furthermore, future research should focus on broadening the scope towards an international description of the collaboration between disciplines within healthcare since they most definitely differ enormously and both show advantages and disadvantages; thus, these different interpretations of jobs within healthcare could be used to try to harmonise their job description. The establishment of an effective interdisciplinary and multidisciplinary environment between all different disciplines within the healthcare system would improve patient care and thereby increase effectivity, decrease toxicity, and ultimately decrease healthcare costs. However, before an effective interdisciplinary and multidisciplinary environment can be build, more research

should be conducted in the different disciplines, their current collaborations, and their desires and motivations in collaborating with other disciplines.

Future studies should not only explore the collaboration between these disciplines, but also on their prior knowledge on MIPD and dosing based on a MIPD platform, before being able to rewrite the implementations addressing the obstacles and then finalise the learning environment expressed in the MIPD platform. Since MIPD platforms are not widely implemented, it should be as user-friendly for all disciplines relevant to dosing decision-making as possible. As this study showed that the addition of another portal specifically for pharmacists to improve their understanding of the modelling concept, without losing their expertise, was perceived as a positive transition and would motivate them to swap from clinical-based dosing to MIPD, this implementation should be studied further within the extended scope of adding more disciplines. If more disciplines are going to be involved in dosing based on the MIPD platform, they would probably want their own portal as well, which is not feasible. To address their desires for their own discipline's platform, the MIPD platform could be adapted to have the capability to personalize the views, e.g., pharmacometricians can see more about the implemented models, pharmacist can see more about the patient characteristics. Therefore, future studies should address what the MIPD platform would look like and be handled whenever more disciplines were added to the collaboration through the MIPD platform and would be using the MIPD platform to make dosing decisions.
To stimulate the implementation of MIPD platforms, further research should also focus on providing evidence-based efficacy and benefit-cost analysis of MIPD platforms in healthcare. Since pharmacists, who commonly do have some pharmacokinetic understanding, were sceptical, it is expected that disciplines who are completely unaware of the existence of MIPD need proof for its effectivity and improvements in patient care, before they will be motivated to learn how to decide dosing through a MIPD platform.

The interdisciplinary nature of MIPD and the use of MIPD platforms further highlights the necessity of the establishment of effective collaboration between disciplines both inside hospitals (e.g., physicians, physician assistants, and nurse practitioners) and outside hospitals (e.g., patient groups, pharmaceutical companies, and regulatory institutions). The establishment of the collaboration through the MIPD platform would provide a (part of the) solution in the collaboration obstacles between pharmacists and pharmacometricians, but only cover for a small part of the collaborations between all disciplines within the hospitals. Building effective collaborations between all these disciplines, both in and outside the hospital, through the use of a MIPD platform is a very time-consuming process that needs to be studied extensively and requires patience. However, increased levels of awareness, knowledge transfer, and increased funding will accelerate the building of effective and sought after MIPD platforms and thereby contribute to improved patient care.

5. Conclusion

This chapter summarises the noteworthy findings of this study; it addressed the formulated research (sub)questions, reflects on the research performed, and reiterates the key implementations and recommendations for pharmacists and pharmacometricians. The research aim, and corresponding research questions will be discussed and answered.

5.1. Research questions

This thesis was meant to address the collaboration between two disciplines within the Dutch healthcare system, namely pharmacists and pharmacometricians. Their current work and collaboration were discussed in regard to decision-making on busulfan dosing regimen for HCT patients through the use of a MIPD platform, which would lead to improved patient care due to increased efficacy and decreased toxicity. To stimulate the use of a MIPD platform in dosing decisions, implementations regarding the (interdisciplinary) collaboration and the MIPD platform were proposed in this study. To guide the research to the main research question, several sub-questions were formulated. A total of seven sub-questions are presented to detail the answer to the main research question.

5.1. Research questions

To answer this main research questions, first the sub-questions are discussed and answered. These answers will lead to the explanation and answering of the main question. The first sub-question regarded the daily jobs of the pharmacometricians and pharmacists and was formulated as followed:

1. What are the specific tasks of 1) pharmacometricians and 2) pharmacists in the hospital?

The tasks of the pharmacometricians and pharmacists differ between hospitals in the Netherlands, and thus this study only reflects on their general daily jobs inside the hospital where the participants of the interviews work. To answer the question regarding their daily jobs, during the interviews, the participants were asked on how they work on a daily basis, what their schedule looks like, and with whom they collaborate during the day. The interview results showed that both disciplines are involved in decision making on dosing regimen for patients, however, the way the disciplines decided dosing regimen differed from another. While pharmacometricians guided their dosing decisions on MIPD implementing the models they built, the pharmacists merely based their dosing on their experience, on literature, and on their standard dosing system. Pharmacometrician's daily jobs also regarded the building of models guiding MIPD that are based on clinical practice data and discussed their modelling obstacles within their discipline of pharmacometrics. In contrast, pharmacist's daily jobs regarded the diagnostics belonging to their specialism and working on clinical trials. Despite both disciplines have different jobs, they are involved in making dosing decisions, and thus collaborate on deciding dosing regimen for each patient. How this dosing decisions are made and how they collaborate to this decision was asked and discussed in the second sub-question:

2. How is the (collaborative) decision-making for dosing regimen set up currently?

As explained in sub-question one, pharmacists and pharmacometricians both have different ways of making dosing decisions. Nevertheless, both disciplines do collaborate in making these dosing decisions as the interviews gave insight in how they discuss and check their decisions back and forth. The pharmacists see the patient the most, and thus prescribes a dosing regimen for a specific patient based on their standard dosing protocols (described in sub-question one); this prescription is sent to the pharmacometricians, which checks if the dose of the prescribed drug is sufficient and has the correct efficacy-toxicity ratio. For example, in the case of a busulfan prescription, this checking by the pharmacometricians is crucial since the drug is known to have narrow therapeutic window, meaning that the concentration for efficacy and the concentration for toxicity are close. However, in more complex cases (e.g., the case of busulfan), which often occurs in hospitals, the pharmacometrician does not fully agree with the decision made by the pharmacists, causing a back-and-forth discussion on the optimal regimen. More than often, the pharmacometricians calls the pharmacist, who is already into another patient and topic and thereby needs to invest time to get back into the topic of discussion. Ultimately, both give and take advice on the dosing regimen, and they decide together on the best dose. Their interdisciplinary decision-making is perceived as being successful, nevertheless, the collaborative decision-making procedure is perceived as inefficient and should be improved. This interdisciplinary collaboration in dosing decisions is discussed further from sub-question 5.

This study also focussed on the way dosing regimen are decided, which differs between the two disciplines. Pharmacists decide based on the old, well-known procedure called clinical-based dosing, whereas pharmacometricians base their dosing on a newer concept of model informed precisions dosing, which is focused on personalised treatment of patients. In the following two sub-questions, the advantages and disadvantages of MIPD compared to clinical-based dosing are discussed and the reasons why clinical-based dosing is still used more often than MIPD. These two sub-questions are taken together since both answers are related to each other and are thereby more easily discussed in combination. The following sub-questions address this comparison:

3. What are the (dis)advantages of model informed precision dosing compared to clinical based for 1) pharmacists and 2) patients?

4. Why is clinical-based dosing merely used over model-based dosing?

Sub-question three was partly already addressed in the introduction of this thesis, where it was explained how the use of MIPD does improve dosing regimen since MIPD comprises treating patients on a personalised level. Personalised medicine has the potential to improve healthcare outcomes as the patient is treated as an individual and thereby receives the dose specifically for them, showing a great advantage over clinical-based dosing, which treats patients the one-size-fits-all way[1,6]. Despite these advantages for the patient, the use of MIPD is not widely implemented in dosing decision-making by pharmacists. Moreover, the implementation of MIPD in specific dosing platforms, meant to simplify the use of MIPD in dosing decisions, did not significantly stimulate the use of MIPD. Both the interviews and focus group did gave insight on one of the problems regarding the lack of MIPD use; all pharmacists in this study had never heard of either MIPD or MIPD platform or they were not familiar with actual clinical practice of MIPD. Therefore, the awareness of pharmacists regarding MIPD's advantage over their old, standard protocols partially explains the choice of clinical-based dosing. Furthermore, the pharmacists were sceptical on the effectiveness of MIPD over clinical-based dosing and highlighted the importance of evidence-based efficacy. As there is only minor proof of the effectivity of MIPD, pharmacists do not feel motivated to learn and adopt this new dosing technology and stick to their old protocols.

Regarding the (dis)advantages of MIPD through a platform for the pharmacists separate from the pharmacometricians was mentioned in the interviews and subsequently discussed in the focus group. Pharmacists emphasised during the interviews on the importance of personalised dosing for each patient, and thereby recognised the relevance of adopting MIPD in their daily routines. However, they did feel like the MIPD platform should be adapted to make it more approachable for them in use. In the literature study conducted in this research, the approachability of a technology influences the technology acceptance, which highlights the importance of creating a MIPD platform that is usable for both disciplines. During the focus group, the implementations of the MIPD platform, regarding the addition of a pharmacist's specific portal to make its use easier and provide clarity, were tested to check if they felt like this version of the MIPD platform would be sufficiently approachable for them to be motivated to use this platform. This focus group resulted in pharmacists being more open towards the implementation of MIPD through a platform but were still sceptical on how to use it. During the interaction of the focus group, they did perceive it as important that eventually MIPD would be standardised since they recognised the advantages but would still need to be convinced of the easy, practical, efficient, and fast use of the MIPD platform to be motivated to adopt it. According to our literature study, these aspects are crucial to motivate users to adopt the MIPD as a new technology in their protocols. Nevertheless, they expected the introductory course to contribute to the conviction of these aspects, but they still need to experience the use of the MIPD platform before either accept or reject it.

To stimulate the use of MIPD through a platform, this study addressed to combine the collaboration between pharmacists and pharmacometricians with the use of the MIPD platform. Therefore, the following sub-question was researched:

5. How can a MIPD platform serve as the foundation of the pharmacist-pharmacometrician collaborative learning environment?

In this study, we explored and addressed the collaboration between pharmacists and pharmacometricians to stimulate their use of MIPD in making dosing decisions, as it would be beneficial for the patient and eventually for healthcare costs as well. Since MIPD platforms are developed to simplify dosing decision-making, but are not widely implemented, we sought to stimulate its use by motivating pharmacists and pharmacometricians to collaborate through the MIPD platform. The interviews and focus group showed the importance of building a connection between pharmacists and pharmacometricians by getting to know them on a more personal level and to get to know the expertise of the other in order to build an environment where trust and acceptance are central to be able to learn from the other disciplines. As their collaboration to decide on dosing regimen is perceived as inefficient, we wanted to address that inefficiency combined with addressing the building of a collaborative environment. The MIPD platform is used as the foundation of their collaborative learning environment, since their collaboration is initiated by the introductory course which they have to succeed together while learning from the other discipline about their expertise. Furthermore, by using the MIPD platform as a foundation of their collaboration in deciding on dosing regimen, both disciplines work within the MIPD platform and all their steps and decisions are traced and are

communicated to the other discipline, preventing the numerous of calls and discussions. Nevertheless, necessary discussions and phone calls are unavoidable in complex cases, however, the MIPD platform portals provide the ability to search the patient and corresponding drug fast and find the bottleneck in the dosing decision that need discussion, which thereby fastens their collaboration. Using the MIPD platform as the foundation for the pharmacist-pharmacometrician collaborative learning environment would simplify their collaboration, while making their collaboration more accurate and while implementing precision medicine which is beneficial for the patient.

To motivate pharmacists and pharmacometricians to adopt the MIPD platform in dosing decisions, this study addressed the necessary elements of the MIPD platform in sub-question six:

6. What would a MIPD platform need to make both pharmacists and pharmacometricians enthusiastic to use and learn from it?

As our literature study regarding the technology acceptance theory showed, the easiness in use and usefulness of the MIPD platform need to be clear to motivate users to adopt the MIPD platform. To realise the technology acceptance, we sought to address the easiness in use and usefulness by exploring the attitudes of this study's participants towards the MIPD platform. The interviews showed that, in agreement with the technology acceptance theory, the MIPD platform needed to efficient, easy, fast, and clear in use for the pharmacists and pharmacometricians to be motivated to adopt the MIPD platform. Also, flexibility of the MIPD platform was perceived as important in terms of the MIPD platform being applicable to a wide range of patients to prescribe personalised dosing regimen, highlighting the necessity of implementation of a lot of models for each drug. The MIPD platform should be fast and easy to handle, as the pharmacists do not have a lot of time per patient to decide dosing regimen. The use of the MIPD platform should therefore make their dosing decisions more efficient instead of more time-consuming. Furthermore, the participants perceived the clinical awareness and/or serving a clinical purpose as another key element to motivate their use of the MIPD platform since the MIPD platform should be ultimately beneficial for the patient. However, as the MIPD platform is driven by precision medicine, its use would be serving a clinical purpose of individualised treatment of patients, which improves their care. Other necessities of the MIPD platform to motivate pharmacists and pharmacometricians to use it include the establishment of an interdisciplinary collaboration, where both collaborated while keeping their autonomy, and the providing of proof of effectivity of the MIPD platform as they need to know for sure the MIPD platform is beneficial before adopting the technology.

In the last sub-question, the collaboration between the two disciplines was addressed in detail. The improved collaboration should stimulate the use of and learning from the MIPD platform and is thereby crucial to be addressed. The seventh sub-question was formulated as followed:

7. How can the collaboration between pharmacists and pharmacometricians be improved to subsequently increase the use of the MIPD platform and thereby create a learning environment?

The answer to sub-question seven is merely discussed throughout the other sub-questions already, however, addressing the stand-alone collaboration between pharmacists and pharmacometricians and its influence on the use of the MIPD platform in order to create a learning environment was not discussed yet. During the interviews, the participants were asked about their collaborations and about the elements that need improvement. They explained how the trust between them and the clarity on their collaboration could be improved. As explained earlier, their trust would be improved to let them build a positive connection by working through the introductory course together, which also contributes to the build of a collaborative learning environment. The lack of clarity within their collaboration was mostly related to them not knowing what to expect from the other in terms of giving and taking, and the amount of phone calls about not understanding the decision-making process of the other discipline. The clarity would be addressed to provide them with clear steps in their collaboration by the implementation of the introductory course, showing them what each step of the decision-making of each discipline holds, which subsequently also contributes to the building of a collaborative learning environment and to the motivation of the professionals to use the MIPD platform. Therefore, it is not necessarily the collaboration only that influences the use of the MIPD platform, creating a feedback loop where both concepts influence each other in order to improve

and stimulate the other concept; this means that whenever the disciplines collaborate, the use of the MIPD platform will be increased, while whenever the MIPD platform is used, the collaboration between pharmacists and pharmacometricians is established through the introductory course. The improved collaboration and the increased use of the MIPD platform together will lead to the development of a collaborative learning environment.

Taken the sub-questions and corresponding answers together, they lead to the strategy of improving the collaboration between pharmacists and pharmacometricians through the use of a MIPD platform. Therefore, the answer to the main research question could be formulated. The main question was as followed:

To what extent could using a MIPD platform contribute to the interdisciplinary collaboration between pharmacists and pharmacometricians on model informed precision dosing of busulfan?

The communication and collaboration between pharmacists and pharmacometricians on model informed precision dosing of busulfan through the use of a MIPD platform can be stimulated by motivating the users through highlighting the aspects that make the MIPD platform approachable (e.g., making the efficiency, reliability, easiness in use, usefulness, and serving of clinical purpose clear). By developing an introductory course where the pharmacists and pharmacometricians need to collaborate to successfully finish the course, contributes to the establishment of a collaborative learning environment while using the MIPD platform for making dosing decisions. Since the introductory course is focusing on introducing the pharmacists and pharmacometricians to both their own discipline's portal and to the other discipline's portal, they will already be involved in using the MIPD platform and build a connection with the other discipline, improving their interdisciplinary collaboration, at the same time. By implementing an introductory course and splitting the MIPD platform into two portals specific for the pharmacists and the pharmacometricians each, their collaboration through the MIPD platform will be made more efficient as it makes their collaboration straight forward; both disciplines do know what to expect from the other and they better understand the expertise of the other discipline. Furthermore, these proposed implementations will highlight the importance of MIPD as the MIPD platform will show that the target concentrations of busulfan will be reached more often ultimately leading to improved patient care, and thereby motivate the disciplines to further improve their interdisciplinary collaboration using the MIPD platform. However, even though these proposed implementations regarding the collaboration between the pharmacists and the pharmacometricians are promising, they are only a small part of collaboration between disciplines within the whole healthcare system, therefore, more research should be conducted to either confirm or provide adjustments in the improvement of the interdisciplinary collaboration through the use of a MIPD platform.

Bibliography

1. Mathur S, Sutton J. Personalized medicine could transform healthcare. 2017:3-5. doi:10.3892/br.2017.922
2. Schreiber JA. Beyond Evidence-Based Practice—Achieving Fundamental Changes in Research and Practice. 2014;(May 2013). doi:10.1188/13.ONF.208-210
3. Newhouse RP. Interdisciplinary Evidence-based Practice: Moving from Silos to Synergy. 2011;58(6):309-317. doi:10.1016/j.outlook.2010.09.001.Interdisciplinary
4. Kumar D. The personalised medicine . A paradigm of evidence-based medicine. 2011:31-40. doi:10.4415/ANN
5. Blackstone EH. Precision Medicine Versus Evidence-Based. 2019:1236-1238. doi:10.1161/CIRCULATIONAHA.119.043014
6. Burau V, Nissen N, Terkildsen MD. Personalised medicine and the state: A political discourse analysis. 2020. doi:10.1016/j.healthpol.2020.10.005
7. Darwich AS, Ogungbenro K, Vinks AA, et al. Why has model-informed precision dosing not yet become common clinical reality ? Lessons from the past and a roadmap for the future This article has been accepted for publication and undergone full peer review but has not been through the copyediting , ty.
8. Gonzalez D, Rao GG, Bailey SC, et al. Precision Dosing : Public Health Need , Proposed Framework , and Anticipated Impact. 2017;(August):443-454. doi:10.1111/cts.12490
9. Kumar AA, Coorey C, Burgard M, et al. An evaluation of the user - friendliness of Bayesian forecasting programs in a clinical setting. 2019;(July):2436-2441. doi:10.1111/bcp.14066
10. de Gatta F, Garcia J, Lanao M, Dominguez-gip A. Bayesian Forecasting in Paediatric Populations. 1996;31(5):325-330.
11. Shukla P, Goswami S, Keizer RJ, et al. Assessment of a Model-Informed Precision Dosing Platform Use in Routine Clinical Care for Personalized Busulfan Therapy in the Pediatric Hematopoietic Cell Transplantation (HCT) Population. 2020;11(July):1-8. doi:10.3389/fphar.2020.00888
12. Lawson R, Paterson L, Fraser CJ, Hennig S. Evaluation of two software using Bayesian methods for monitoring exposure and dosing once - daily intravenous busulfan in paediatric patients receiving haematopoietic stem cell transplantation. *Cancer Chemother Pharmacol*. 2021;(0123456789). doi:10.1007/s00280-021-04288-0
13. Holford NHG, Holford S. NextDose—a web based dosing tool. 2017. https://www.paganz.org/abstracts/nextdose-a-web-based-dosing-tool-development-version-2017/.
14. Goswami S, Keizer R, Mangat R. The InsightRX Platform - A cloud-based clinical decision support tool for use at the point-of-care. 2015. https://www.insight-rx.com/product/platform.
15. Zwart TC, Vries APJ De, Engbers AGJ, et al. Model - Based Estimation of Iohexol Plasma Clearance for Pragmatic Renal Function Determination in the Renal Transplantation Setting. *Clin Pharmacokinet*. 2021;60(9):1201-1215. doi:10.1007/s40262-021-00998-z
16. Kantasiripitak W, Daele R Van, Gijsen M, Ferrante M, Spriet I, Dreesen E. Software Tools for Model-Informed Precision Dosing : How Well Do They Satisfy the Needs ? Search Strategy and Selection Criteria. 2020;11(May). doi:10.3389/fphar.2020.00620
17. Pereira A, Santos C. Design Thinking as a methodology for solving problems : contributions from academia to society . 2017;(January). doi:10.18687/LACCEI2017.1.1.256
18. Design Council. Design methods for developing services. 2015.
19. Banbury A, Byrne L, Pedell S, Parkinson L. Using the Double Diamond model to co-design a dementia caregivers telehealth peer support program. 2021. doi:10.1177/1357633X211048980
20. Lorenzetti DL, Ghali WA. Reference management software for systematic reviews and meta-analyses : an exploration of usage and usability. 2013.
21. Gilmour R, Cobus-kuo L. Reference Management Software : a Comparative Analysis of Four Products. 2011. doi:10.5062/F4Z60KZF
22. Onwuegbuzie AJ, Frels RK. Mapping Saldaña's Coding Methods onto the Literature Review Process. 2016;2(1):130-150. doi:10.5296/jei.v2i1.8931
23. Linneberg MS, Korsgaard S. Coding qualitative data : a synthesis guiding the novice. 2019;(February 2020). doi:10.1108/QRJ-12-2018-0012
24. Rabiee F. Focus-group interview and data analysis. 2004;(2004):655-660. doi:10.1079/PNS2004399
25. Nancarrow SA, Booth A, Ariss S, Smith T, Enderby P, Roots A. Ten principles of good interdisciplinary team work. *Hum Resour Health*. 2013;11(1):1. doi:10.1186/1478-4491-11-19
26. Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. National Academies Press; 2001. doi:10.17226/10027
27. Laal M, Laal M. Social and Collaborative learning : what is it ? 2012;31(2011):491-495. doi:10.1016/j.sbspro.2011.12.092
28. Klein JT. A Platform for a Shared Discourse of Interdisciplinary Education Interdisciplinary Education i. 2006.
29. Gokhale AA. Collaborative Learning Enhances Critical Thinking. 1995;7(1):22-30.
30. Alberta Education. Interdisciplinary Learning. 2005:1-3.
31. Given B, Simmons S. Interdisciplinary health-care team: fact or fiction?
32. Daniel MO, Rosenstein AH. Professional Communication and Team Collaboration. :271-284.
33. McLeod SA. Lev Vygotsky Theories. 2014.
34. Ryan R, Deci E. Self-Determination Theory and the Facilitation of Intrinsic Motivation, Social Development, and Well-Being. 2000;55(1):68-78.
35. Radel R, Pjevac D, Davranche K, Colson SS, Lapole T, Gruet M. Does intrinsic motivation enhance motor cortex excitability ? 2016;00. doi:10.1111/psyp.12732
36. Sorrentino RM, Roney CJR. Uncertainty orientation, achievement-related motivation, and task diagnosticity as determinants of task performance. *Soc Cogn*. 1986;4:420-436.
37. Weiner B. History of motivational research in education. *J Educ Psychol*. 1990;82:616-622.
38. Weiner B. Attribution Theory, Achievement Motivation, and the Educational Process. *Rev Educ Res*. 1972;42(2):203-215. doi:10.3102/00346543042002203
39. Anderman EM. Achievement motivation theory : Balancing precision and utility. *Contemp Educ Psychol*. 2020;61(April):101864. doi:10.1016/j.cedpsych.2020.101864
40. Weiner B. An Attributional Theory of Achievement Motivation and Emotion. 2017;(November 1985):293-304. doi:10.1037/0033-295X.92.4.548
41. Zorzie M. Individual adaptability: testing a model of its development and outcomes. 2012.
42. Murphy SL. Individual adaptability as a predictor of job performance. 2015.
43. Trundt KM. Toward a New Model of Adaptability. 2010.

44. Hubbard ASE. Interaction Adaptation Theory. 2016:1-5. doi:10.1002/9781118540190.wbeic0136
45. Burgoon J, Dillman L. Interpersonal Adaptation : Dyadic Interaction Patterns. 2015;(August). doi:10.1017/CBO9780511720314
46. Burgoon JK. Interaction Adaptation Theory. 2008. doi:10.1002/9781405186407.wbieci041
47. Floyd K, Burgoon JK. Reacting to Nonverbal Expressions of Liking: A Test of Interaction Adaptation Theory. 2001;(October 2014):37-41. doi:10.1080/03637759909376475
48. Alqudah AA, Al-emran M. Technology Acceptance in Healthcare : A Systematic Review. 2021.
49. Davis FD, Davis F. Perceived Usefulness , Perceived Ease of Use , and User Acceptance of Information Technology. 1989;(January 2015). doi:10.2307/249008
50. Kalayou MH, Endehabtu BF, Tilahun B. The applicability of the modified technology acceptance model (Tam) on the sustainable adoption of ehealth systems in resource-limited settings. *J Multidiscip Healthc*. 2020;13:1827-1837. doi:10.2147/JMDH.S284973
51. Holden RJ, Karsh B. The Technology Acceptance Model : Its past and its future in health care. *J Biomed Inform*. 2010;43(1):159-172. doi:10.1016/j.jbi.2009.07.002
52. Melas CD, Zampetakis LA, Dimopoulou A, Moustakis V. Modeling the acceptance of clinical information systems among hospital medical staff: An extended TAM model. *J Biomed Inform*. 2011;44(4):553-564. doi:10.1016/j.jbi.2011.01.009
53. Davis FD, Bagozzi RP, Warshaw PR. User Acceptance of Computer Technology: A Comparison of Two Theoretical Models. *Manage Sci*. 1989;35(8):982-1003. http://www.jstor.org/stable/2632151.
54. Charness N, Boot WR. *Technology, Gaming, and Social Networking*. Elsevier Inc.; 2016. doi:10.1016/B978-0-12-411469-2.00020-0
55. Ifinedo P. Technology acceptance by health professionals in Canada: An analysis with a modified UTAUT model. *Proc Annu Hawaii Int Conf Syst Sci*. 2012:2937-2946. doi:10.1109/HICSS.2012.556
56. Garavand A, Mohseni M, Asadi H, et al. Factors influencing the adoption of health information technologies: a systematic review. 2016;(August):2713-2718.
57. Petri L. Concept Analysis of Interdisciplinary Collaboration. 2010:73-82.
58. Manias E. Effects of interdisciplinary collaboration in hospitals on medication errors: an integrative review. *Expert Opin Drug Saf*. 2018;0(0). doi:10.1080/14740338.2018.1424830
59. Bronstein LR. A Model for Interdisciplinary Collaboration. *Soc Work*. 2003;48(3):297-306. doi:10.1093/sw/48.3.297
60. Joseph D. The practice of design-based research: Uncovering the interplay between design, research, and the real-world context. *Educ Psychol*. 2004;39(4):235-242. doi:10.1207/s15326985ep3904_5
61. Wang F, Wannafin M. Design-Based Research and Technology-Enhanced Learning Environments. *Educ Technol Res Dev*. 2005.
62. Rowley J, Slack F. Conducting a Literature Review. 2004.
63. Cooper HM. Scientific Guidelines for Conducting Integrative Research Reviews. 1984;52(2):291-302.
64. Randolph JJ. A Guide to Writing the Dissertation Literature Review A Guide to Writing the Dissertation Literature Review. 2009;14.
65. Ryan F, Coughlan M, Cronin P. Step-by-step guide to critiquing research. Part 2: quailitative research. 2007;20(12):738-745.
66. Research T national commission for the protection of human subjects of biomedical and behavioral research. Ethical Principles and Guidelines for the Protection of Human. 1979.
67. Dikko M. Establishing Construct Validity and Reliability : Pilot Testing of a Qualitative Interview for Research in Takaful (Islamic Insurance) Establishing Construct Validity and Reliability : Pilot Testing of a Qualitative. 2016;21(3):521-528.
68. Razak RA. Establishing Validity And Reliability of Semi-Structured Interview Questionnaire in Developing Risk Communication Module : A Pilot Study Establishing Validity And Reliability of Semi-Structured Interview Questionnaire in Developing Risk Communication Modu. 2021;(June). doi:10.51276/edu.v2i3.177
69. Noble H, Smith J. Issues of validity and reliability in qualitative research. 2015.
70. Hammersley M. Some Notes on the Terms “Validity” and “Reliability.” 1987;13(1):73-81.
71. Morgan DL. Focus Groups : A New Tool for Qualitative Research Focus Groups : A New Tool for Qualitative Research. 2014;(April). doi:10.1007/BF00987314
72. Gill P, Stewart K, Treasure E, Chadwick B. Methods of data collection in qualitative research : interviews and focus groups. :291-295. doi:10.1038/bdj.2008.192
73. Cyr J. The Pitfalls and Promise of Focus Groups as a Data Collection Method. 2016. doi:10.1177/0049124115570065
74. Leung L. Validity , reliability , and generalizability in qualitative research. 2015;4(3):324-327. doi:10.4103/2249-4863.161306
75. Elliott V. Thinking about the Coding Process in Qualitative Data Analysis. 2018;23(11):2850-2861.
76. Anderson-cook CM, Lu L, Parker PA, Lu L, Effective PAP. Effective interdisciplinary collaboration between statisticians and other subject matter experts. 2019;2112. doi:10.1080/08982112.2018.1530357
77. Tran VD. Does Cooperative Learning Increase Students ’ Motivation in Learning ? 2019;8(5). doi:10.5430/ijhe.v8n5p12
78. Kurahashi AM, Stinson JN, van Wyk M, et al. The Perceived Ease of Use and Usefulness of Loop: Evaluation and Content Analysis of a Web-Based Clinical Collaboration System. *JMIR Hum Factors*. 2018;5(1):e2. doi:10.2196/humanfactors.7882
79. Palanisamy R, Taskin N, Verville J. Impact of Trust and Technology on Interprofessional Collaboration in Healthcare Settings : An Empirical Analysis. 2017;13(2). doi:10.4018/IJeC.2017040102
80. Byrd TA. Implementation and Use of Expert Systems in Organizations: Perceptions of Knowledge Engineers. *J Manag Inf Syst*. 1992;8(4):97-116. doi:10.1080/07421222.1992.11517941
81. Collin A. Multidisciplinary, interdisciplinary, and transdisciplinary collaboration: implications for vocational psychology. 2009:101-110. doi:10.1007/s10775-009-9155-2
82. Nicolescu B. The transdisciplinary evolution of learning. :1-11.
83. Bewer V Van. Transdisciplinarity in Health Care: A Concept Analysis. 2017;00(0):1-9. doi:10.1111/nuf.12200
84. Stokols D, Misra S, Moser RP, Hall KL, Taylor BK. The Ecology of Team Science: Understanding Contextual Influences on Transdisciplinary Collaboration. 2008;35. doi:10.1016/j.amepre.2008.05.003
85. Martin A, Green T, Sowa M. Allied health transdisciplinary models of care in hospital settings : a scoping review protocol Abstract Protocol information. (January 2021):1-22.
86. Lehane E, Leahy-warren P, Riordan CO, et al. Evidence-based practice education for healthcare professions : an expert view. 2019;24(3):103-108.
87. Bormanaki HB. The Role of Equilibration in Piaget ’ s Theory of Cognitive Development and Its Implication for Receptive Skills : A Theoretical Study. 2017;8(5):996-1005.
88. Sills J, Rowes G, Emerson L-M. The role of collaboration in the cognitive development of young children: a systematic review. 2016. doi:10.1111/cch.12330
89. Page A. Keeping patients safe: Transforming the work environment of nurses. 2004.
90. Schaefer HG, Helmreich RL, Scheidegger D. Human factors and safety in emergency medicine. *Resuscitation*. 1994;28(3):221-225. doi:10.1016/0300-9572(94)90067-1
91. Ndebele C, Mbodila M. Examining Technology Acceptance in Learning and Teaching at a Historically Disadvantaged University in South Africa through the Technology Acceptance Model. 2022.
92. Henneman EA, Lee JL, Cohen JI. Collaboration: a concept analysis. *J Adv Nurs*. 1995;21(1):103-109. doi:10.1046/j.1365-

2648.1995.21010103.x
93. Cameron A. Impermeable boundaries? Developments in professional and inter-professional practice. *J Interprof Care*. 2011;25(1):53-58. doi:10.3109/13561820.2010.488766
94. Rafferty AM, Ball J, Aiken LH. Are teamwork and professional autonomy compatible, and do they result in improved hospital care? *Qual Health Care*. 2001;10 Suppl 2(Suppl 2):ii32-7. doi:10.1136/qhc.0100032..
95. MacNaughton K, Chreim S, Bourgeault IL. Role construction and boundaries in interprofessional primary health care teams: a qualitative study. *BMC Health Serv Res*. 2013;13:486. doi:10.1186/1472-6963-13-486
96. Polasek TM, Rostami-hodjegan A, Yim D, et al. What Does it Take to Make Model-Informed Precision Dosing Common Practice ? Report from the 1st Asian Symposium on Precision Dosing. 2019:1-9. doi:10.1208/s12248-018-0286-6
97. Kalirajan KP. The Importance of Efficient Use in the Adoption of Technology : A Micro Panel Data Analysis *. 1991;126:113-126.
98. Lipsitz LA. Understanding health care as a complex system: the foundation for unintended consequences. *JAMA*. 2012;308(3):243-244. doi:10.1001/jama.2012.7551
99. Kannampallil TG, Schauer GF, Cohen T, Patel VL. Considering complexity in healthcare systems. *J Biomed Inform*. 2011;44(6):943-947. doi:10.1016/j.jbi.2011.06.006
100. Best A, Greenhalgh T, Lewis S, Saul JE, Carroll S, Bitz J. Large-system transformation in health care: a realist review. *Milbank Q*. 2012;90(3):421-456. doi:10.1111/j.1468-0009.2012.00670.x
101. Schellens JHM, Grouls R, Guchelaar HJ, et al. The Dutch model for clinical pharmacology : collaboration between physician- and pharmacist-clinical pharmacologists. 2008. doi:10.1111/j.1365-2125.2008.03156.x
102. Maxwell SRJ, Webb DJ. Clinical pharmacology--too young to die? *Lancet (London, England)*. 2006;367(9513):799-800. doi:10.1016/S0140-6736(06)68316-5
103. Apter AJ, Paasche-orlow MK, Remillard JT, et al. Numeracy and Communication with Patients : They Are Counting on Us. 2008:2117-2124. doi:10.1007/s11606-008-0803-x
104. Reyna VF, Brainerd CJ. The importance of mathematics in health and human judgment : Numeracy , risk communication , and medical decision making. 2007;17:147-159. doi:10.1016/j.lindif.2007.03.010
105. Rothman RL, Montori VM, Cherrington A, Pignone MP. Perspective: the role of numeracy in health care. *J Health Commun*. 2008;13(6):583-595. doi:10.1080/10810730802281791
106. Negrin RS. Patient education: Hematopoietic cell transplantation (bone marrow transplantation) - beyond the Basics. 2021:1-15.
107. Lin YS, Kerr SJ, Randolph T, Shireman LM, Senn T, Mccune JS. Prediction of intravenous busulfan clearance by endogenous plasma biomarkers using global pharmacometabolomics. *Metabolomics*. 2016;12(10):1-12. doi:10.1007/s11306-016-1106-6
108. Mccune JS, Bemer MJ. Pharmacokinetics , Pharmacodynamics and Pharmacogenomics of Immunosuppressants in Allogeneic Haematopoietic Cell Transplantation : Part I. *Clin Pharmacokinet*. 2016;55(5):525-550. doi:10.1007/s40262-015-0339-2
109. Mckiernan S, Maarseveen E Van, Huitema ADR, et al. Prediction of Acute Graft versus Host Disease and Relapse by Endogenous Metabolomic Compounds in Patients Receiving Personalized Busulfan-Based Conditioning˘. 2020. doi:10.1021/acs.jproteome.0c00599
110. Blazar, BR; Murphy, WJ; Abedi M. Advances in graft-versus-host disease biology and therapy. 2013;12(6):443-458. doi:10.1038/nri3212.Advances
111. Mccarthy PL, Bredeson C, Hospital TO, Hale GA, Children A, Loberiza FR. Significant Improvement in Survival After Allogeneic Hematopoietic Cell Transplantation During a Period of Significantly Increased Use , Older Recipient Age , and Use of Unrelated Do ... Significant Improvement in Survival After Allogeneic Hematopoietic C. 2016;(January). doi:10.1200/JCO.2012.46.6193
112. Palmer J, Mccune JS, Perales M, et al. Personalizing Busulfan-Based Conditioning : Considerations from the American Society for Blood and Marrow Transplantation Practice Guidelines Committee. *Biol Blood Marrow Transplant*. 2016;22(11):1915-1925. doi:10.1016/j.bbmt.2016.07.013
113. Mccune JS, Quinones CM, Ritchie J, et al. Harmonization of Busulfan Plasma Exposure Unit (BPEU): A Community-Initiated Consensus Statement. *Biol Blood Marrow Transplant*. 2019;25(9):1890-1897. doi:10.1016/j.bbmt.2019.05.021
114. Williamson T, Russell JA, Kangarloo SB, et al. Establishing a Target Exposure for Once-Daily Intravenous Busulfan Given with Fludarabine and Thymoglobulin before Allogeneic Transplantation Establishing a Target Exposure for Once-Daily Intravenous Busulfan Given with Fludarabine and Thymoglobulin befor. *Biol Blood Marrow Transplant*. 2013;19(9):1381-1386. doi:10.1016/j.bbmt.2013.07.002
115. Bartelink IH, Kesteren C Van, Boelens JJ, et al. Predictive Performance of a Busulfan Pharmacokinetic Model in Children and Young Adults. 2012:574-583.
116. Andersson BS, Thall PF, Valdez BC, et al. Fludarabine with pharmacokinetically-guided IV busulfan is superior to fixed-dose delivery in pretransplant conditioning of AML/MDS patients. 2017;52(4):580-587. doi:10.1038/bmt.2016.322.Fludarabine
117. Langenhorst JB, Boss J, Kesteren C Van, et al. A semi-mechanistic model based on glutathione depletion to describe intra-individual reduction in busulfan clearance. 2020;(September 2019):1499-1509. doi:10.1111/bcp.14256
118. Nguyen L, Fuller D, Lennon S, Leger F, Puozzo C. Conditioning regimens I.V. busulfan in pediatrics : a novel dosing to improve safety / efficacy for hematopoietic progenitor cell transplantation recipients. 2004:979-987. doi:10.1038/sj.bmt.1704446
119. Veal GJ, Nguyen L, Paci A, Riggi M, Amiel M, Valteau-couanet D. Busulfan pharmacokinetics following intravenous and oral dosing regimens in children receiving high-dose myeloablative chemotherapy for high-risk neuroblastoma as part of the HR-NBL-1 / SIOPEN trial. *Eur J Cancer*. 2012;48(16):3063-3072. doi:10.1016/j.ejca.2012.05.020
120. Zwaveling J, Press RR, Bredius RGM, et al. Glutathione S-transferase Polymorphisms Are Not Associated With Population Pharmacokinetic Parameters of Busulfan in Pediatric Patients. 2008:504-510.
121. Trame MN, Bergstrand M, Karlsson MO, Boos J, Hempel G. Population Pharmacokinetics of Busulfan in Children : Increased Evidence for Body Surface Area and Allometric Body Weight Dosing of Busulfan in Children Population Pharmacokinetics of Busulfan in Children : Increased Evidence for Body Surface Area and All. 2011;(October 2015). doi:10.1158/1078-0432.CCR-11-0074
122. Mccune JS, Batchelder A, Guthrie KA, et al. Personalized Dosing of Cyclophosphamide in the Total Body Irradiation – Cyclophosphamide Conditioning Regimen : A Phase II Trial in Patients With Hematologic Malignancy. *Nature*. 2009;85(6):615-622. doi:10.1038/clpt.2009.27
123. Booth BP, Rahman A, Dagher R, Griebel D. Population Pharmacokinetic – Based Dosing of Intravenous Busulfan in Pediatric Patients. 2007:101-111. doi:10.1177/0091270006295789
124. Savic RM, Cowan MJ, Dvorak CC, et al. Effect of Weight and Maturation on Busulfan Clearance in Transplantation. *Biol Blood Marrow Transplant*. 2013;19(11):1608-1614. doi:10.1016/j.bbmt.2013.08.014
125. Mccune JS, Bemer MJ, Barrett JS, Baker KS, Gamis AS, Holford NHG. Busulfan in Infant to Adult Hematopoietic Cell Transplant Recipients : A Population Pharmacokinetic Model for Initial and Bayesian Dose Personalization. 2014;20(3):754-764. doi:10.1158/1078-0432.CCR-13-1960
126. Myers AL, Kawedia JD, Champlin RE, Kramer MA, Ghose R, Andersson BS. *Clarifying Busulfan Metabolism and Drug Interactions to Support New Therapeutic Drug Monitoring Strategies: A Comprehensive Review*. Vol 0. Taylor & Francis; 2017. doi:10.1080/17425255.2017.1360277
127. BUSULFEX is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic 2 DOSAGE AND ADMINISTRATION 2 . 1 Initial Dosing Information Administer BUSULFEX in combination with cyclophosphamide as a conditioning regi. 1999.

128. Czerwinski, M, Gibbs P, Slattery T. Busulfan conjugation by glutathione s-transferase alpha, beta and pi. 1996.
129. Gibbs, JP; Liacouras, CA; Baldassano, RN; Slattery J. Up-regulation of Glutathione S-Transferase Activity in Enterocytes of Young Children. *Drug Metab Dispos*.
130. El-serafi I, Terelius Y, Abedi-valugerdi M, et al. Flavin-containing monooxygenase 3 (FMO3) role in busulphan metabolic pathway. 2017;3:1-17.
131. Younis IR, Elliott M, Peer CJ, et al. Dehydroalanine analog of glutathione: An electrophilic busulfan metabolite that binds to human glutathione S-transferase A1-1. 2009;327(3):770-776. doi:10.1124/jpet.108.142208.Dehydroalanine
132. Fred Hutchinson Cancer Research Center. Blood Samples to Identify Biomarkers of Busulfan. https://clinicaltrials.gov/ct2/show/NCT02291965?term=busulfan&cntry=US&state=US%3AWA&city=Seattle&draw=2&rank=4. Published 2014.
133. Sheiner LB, Rosenberg B, Marathe V V. Estimation of Population Characteristics of Pharmacokinetic Parameters from Routine Clinical Data. 1977;5(5).
134. Lindbom L, Pihlgren P, Jonsson N. PsN-Toolkit —– A collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. 2005. doi:10.1016/j.cmpb.2005.04.005
135. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing. 2017. https://www.r-project.org/.
136. Schellens JHM, Huitema ADR. Pirana and PCluster: A modeling environment and cluster Pira na infrastructure for NONMEM ®. *Comput Methods Programs Biomed*. 2011;101(1):72-79. doi:10.1016/j.cmpb.2010.04.018
137. Anderson BJ, Holford NHG. Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics. 2008. doi:10.1146/annurev.pharmtox.48.113006.094708
138. Hooker AC, Staatz CE, Karlsson MO. Conditional Weighted Residuals (CWRES): A Model Diagnostic for the FOCE Method True Model. 2007;24(12). doi:10.1007/s11095-007-9361-x
139. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-Corrected Visual Predictive Checks for Diagnosing Nonlinear Mixed-Effects Models. 2011;13(2). doi:10.1208/s12248-011-9255-z
140. Bergstrand M, Karlsson MO. An automated sampling importance resampling procedure for estimating parameter uncertainty. 2017:509-520. doi:10.1007/s10928-017-9542-0
141. Bartelink IH, Boelens JJ, Bredius RGM, et al. Body Weight-Dependent Pharmacokinetics of Busulfan in Paediatric Haematopoietic Stem Cell Transplantation Patients Towards Individualized Dosing. 2012;51(5):331-345.
142. Slattery JT RL. Therapeutic monitoring of busulfan in hematopoietic stem cell transplantation. 1998. doi:10.1097/00007691-199810000-00017
143. Russell JA, Kangarloo SB. Therapeutic Drug Monitoring of Busulfan in Transplantation. 2008:1936-1949.
144. M Hassan, G Oberg, A N Bekassy, J Aschan, H Ehrsson, P Ljungman, G Lönnerholm, B Smedmyr, A Taube IW. Pharmacokinetics of high-dose busulphan in relation to age and chronopharmacology. 1991. doi:10.1007/BF00689702
145. Nadkarni MV, Trams EG SP. Preliminary Studies on the Distribution and Fate of TEM, TEPA, and Myeleran in the Human. 1959.
146. Vodopick H, Hamilton HE, Jackson HL, Peng CT SR. Metabolic fate of tritiated busulfan in man. 1969.
147. Navarro SL, Randolph TW, Shireman LM, Raftery D, Mccune JS. Pharmacometabonomic prediction of busulfan clearance in hematopoetic cell transplant recipients. 2016. doi:10.1021/acs.jproteome.6b00370
148. Ritter CA, Bohnenstengel F, Hofmann U, Kroemer HK SB. Determination of tetrahydrothiophene formation as a probe of in vitro busulfan metabolism by human glutathione S-transferase A1-1: use of a highly sensitive gas chromatographic-mass spectrometric method. 1999.
149. Cooper AJ, Younis IR, Niatsetskaya ZV et al. Metabolism of the cysteine S-conjugate of busulfan involves a beta-lyase reaction. 2008.
150. Peer CJ, Younis IR, Leonard SS, et al. Glutathione conjugation of busulfan produces a hydroxyl radical-trapping dehydroalanine metabolite. 2012;42(April):1170-1177. doi:10.3109/00498254.2012.696740
151. Gibbs JP, Murray G, Risler L, Chien JY, Dev R, Slattery JT. Age-dependent Tetrahydrothiophenium Adults Receiving High-Dose Busulfan1 Ion Formation in Young Children and. 1997.
152. El-Serafi I, Terelius Y, Twelkmeyer B, Hagbjork AL, Hassan Z HM. Gas chromatographic-mass spectrometry method for the detection of busulphan and its metabolites in plasma and urine. 2013.
153. Bleyzac N, Souillet G, Magron P, et al. Improved clinical outcome of paediatric bone marrow recipients using a test and Bayesian pharmacokinetic individualization of busulfan dosage regimens Improved clinical outcome of paediatric bone marrow recipients using a test dose and Bayesian pharmacoki. 2001;(June 2014). doi:10.1038/sj.bmt.1703207
154. Evans ND, Godfrey KR, Chapman MJ, Chappell MJ, Aarons L DS. An identifiability analysis of a parent-metabolite pharmacokinetic model for ivabradine. 2001. doi:10.1023/a:1011521819898
155. Shivva V, Korell J, Tucker IG, Duffull SB. An Approach for Identifiability of Population Pharmacokinetic – Pharmacodynamic Models. 2013;(June). doi:10.1038/psp.2013.25
156. SUMO user guide. 2018:1-7.
157. Montgomery DC, Peck EA VG. *Introduction to Linear Regression Analysis*.; 2012. doi:978-0-470-54281-1

Supplementary

In this last chapter, all supplementary materials will be shown.

Supplementary A. Thesis regarding the development of busulfan's population model

The body of the thesis written in the graduation project of Bio-Pharmaceutical Sciences is shown below. The supplementary of this thesis is left out, however, can be shared upon request. The thesis is written to

describe the development of the population model of busulfan and its metabolites, which explains how busulfan is processed in the body.

RESEARCH REPORT

ABSTRACT

Patients undergoing allogeneic hematopoietic cell transplant (HCT) conditioning often receive high dose of the bifunctional alkylating agent busulfan (busulfan). Busulfan has a narrow therapeutic window. Pharmacokinetic (PK)-directed dosing is often conducted to estimate the patient's busulfan clearance and then personalize their busulfan dose to achieve the target busulfan exposure, expressed in area under the plasma concentration-time curve (AUC). Because of this narrow therapeutic window and recent in vitro data suggesting busulfan's metabolites are pharmacologically active, we hypothesize that the exposures of busulfan's metabolites are associated with clinical outcomes in HCT patients. We developed a population pharmacokinetic (popPK) model for busulfan and four of its sequential metabolites: tetrahydrothiophenium (THT+), THT-1-oxide, sulfolane, and 3-OH-sulfolane. Plasma AUCs could be estimated based on this model and the patient's concentration-time data. The popPK model was constructed in this study using nonlinear mixed-effect modeling and data from 138 HCT patients conditioned with busulfan, with varying dosing frequencies of 6, 12 or 24 hours. The final model, consisting of a two-compartmental model for busulfan and a one-compartmental model for the sequential metabolites including time-associated clearance on THT-1-oxide and 3-OH-sulfolane, described the data adequately. The inter-individual- and residual variability were captured satisfactorily. This popPK model enables the ability to estimate the AUC (0-192h) of busulfan and the four sequential metabolites, which can ultimately be used to analyse their relevance in clinical outcomes.

INTRODUCTION

Allogeneic hematopoietic cell transplant (HCT) is a potential curative treatment for several non-malignant and malignant diseases, particularly disorders related to the blood[106]. The aim of allogeneic HCT is to cure the patient, as well termed as recipient or host, of their underlying disease by using hematopoietic cells from a healthy donor to replace their own cells[107]. In allogeneic HCT, transplanting cells from one individual (i.e., the donor) to another (i.e,. the host) provokes various immunologic reactions such as engraftment of the donor cells, graft-versus-host disease (GVHD), and control of a malignancy (termed graft versus tumor, GVT)[108,109]. These immunologic reactions reduce the curative power of this treatment[110]. Treatment mortality of HCT has progressively decreased and currently ranges from 10% to 40%, indicating a crucial need for the improvement of the HCT procedure[111].

One potential opportunity to improve HCT is to increase the efficacy and decrease the toxicity of the bifunctional alkylating agent busulfan. Most HCT patients receive high doses, defined as a daily dose >3.2 mg/kg intravenous (IV), of busulfan (abbreviated as busulfan hereafter) as part of the conditioning regimen as shown in figure 1[112].

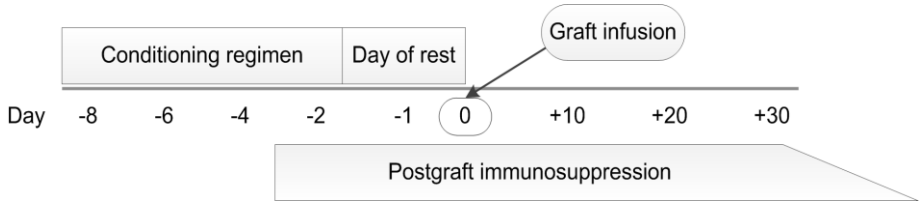


Figure 1. Hematopoietic Cell Transplant (HCT) regimen. All regimen implemented in the HCT procedure are presented over time.

Busulfan is a drug known to have a narrow therapeutic window, whereby its exposure, reflected in the area under the plasma-concentration curve (AUC), is associated to efficacy and toxicity of the conditioning regimen[112–114]. Lower busulfan plasma exposure is often associated to graft rejection or disease relapse, while higher plasma exposure is often associated with liver toxicity, specifically sinusoidal obstruction syndrome, and non-relapse mortality[115]. For the majority of patients receiving busulfan, the initial dose is based on weight or body surface area (BSA), whereafter sequential doses are personalized to a target AUC using therapeutic drug monitoring (TDM) after their first dose. Compared to weight- or BSA-based dosing, the use of busulfan TDM improves attainment of busulfan's narrow therapeutic window and thereby increases the overall patient survival rate by 20%[112,116]. TDM means that the administered dose is based on patient-specific busulfan clearance[112,116]. Ideally, the target AUC of busulfan is achieved after administration of the first dose. However, even with busulfan TDM, improvements are needed regarding the efficacy and toxicity of busulfan-based conditioning regimens.

A potential approach to improve busulfan-based conditioning regimens is to improve the accuracy of TDM. Several researchers developed population pharmacokinetic (popPK) models of busulfan to guide the initial (i.e., before concentration-time data are available for TDM) dosing and improve TDM for every individual patient. The majority of the models were built from patients with a varying age from 0.1 to 73 years who received IV administration of busulfan. Body weight was often found to be a significant covariate[115,117–125]. The most of these popPK models supported allometric scaling to body weight varying between empirical and theoretical scaling, considering the effect of size and maturation on busulfan volume of distribution and clearance. Early busulfan popPK models based on a small number of patients receiving traditional dosing (every 6 hours, Q6H) used only one compartment[118,120,123,124], whereas more recent popPK models with contemporary dose (Q24H) used a two-compartmental model for busulfan pharmacokinetics[115,117,125]. This change most likely represents a distribution phase that may only occur with higher concentrations with the higher Q24H doses and/or the additional data from larger patient populations. The two-compartmental model developed by Langenhorst et al., explained the inter-individual variability of patients using a semi-mechanistic population PK model, based on glutathione (GSH) depletion of busulfan by addition of a separate GSH compartment[117]. Despite the improvements in clinical outcomes with busulfan TDM because

of these models[125], patients still have adverse outcomes - either disease relapse or aberrant toxicity. We hypothesize that busulfan's metabolites may contribute to these adverse outcomes. Thus, expansion of the popPK model with busulfan's metabolites might enable the ability to quantify their AUC, and thereby, the expansion could contribute to evaluating the association of busulfan metabolites with the narrow therapeutic window and to improve accuracy of busulfan TDM-guided dosing.
Busulfan metabolism in the liver is its primary elimination route; only 2% of busulfan is excreted unchanged in the urine[117]. Busulfan is conjugated with glutathione (GSH), both spontaneously and by glutathione S-transferase (GST)-mediated metabolism[117,126]. GST metabolism forms an unstable S-glutathione sulfonium conjugate (GS+THT), which is further metabolized subsequently into tetrahydrothiophenium ion (THT+) via either β-elimination, or through conversion to an N-acetylated cysteine conjugate[127–130]. Subsequently, THT+ is metabolized to tetrahydrothiophene-1-oxide (THT-1-oxide) via flavin-containing monooxygenase 3 (FMO3) and cytochromes (CYPs)[130]. THT-1-oxide is then converted into sequential sulfolane and 3-hydroxysulfalone (3-OH-sulfolane) via enzymes that have yet to be studied. The metabolic pathway of busulfan is shown in figure 2. Recent data indicate that busulfan's metabolite γ-glutamyldehydroananylglycine (EdAG), formed by the β-elimination of GS+THT, contributes to the narrow therapeutic window of busulfan by altering GSH, interfering with GST function, and redox-related cytotoxicity[131]. These effects increase the suspicion of busulfan's metabolites to contribute to its pharmacologic activity.

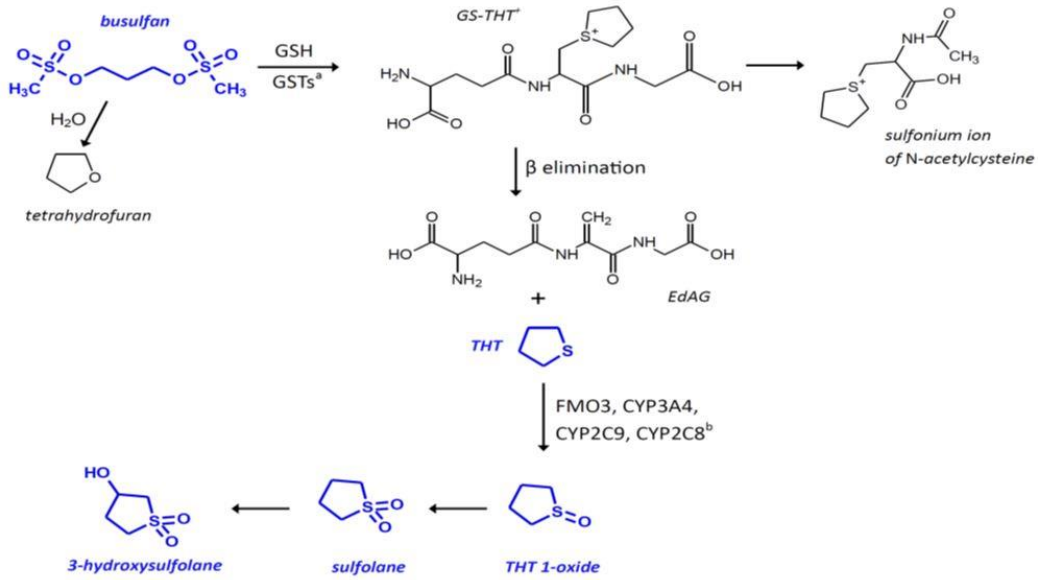


Figure 2. Busulfan metabolism. The metabolic pathway of busulfan is shown in chemical structures of each compound.

There is a paucity of data regarding the pharmacokinetics of busulfan's metabolites. Therefore, we sought to build the first popPK model of busulfan and its four sequential metabolites – specifically THT+, THT-1-oxide, sulfolane, and 3-OH-sulfolane. By creating a popPK model of busulfan and its metabolites, empirical estimates of the AUC for busulfan and each metabolite can be determined. These AUCs can be analysed for their relevance of in clinical adverse outcomes, such as GVHD, relapse and overall survival. Eventually, the popPK model may contribute to improving the prediction of an individual patient's busulfan clearance, and thereby to improving the percentage of patients achieving target busulfan AUC after first dose. Furthermore, characterizing the association of the exposure of busulfan's metabolites to its effectiveness, and toxicity may also identify novel biomarkers for busulfan-based conditioning regimens.

MATERIALS and METHODS

Study population

All population data used in this study is obtained from the Fred Hutchinson (Fred Hutch) Cancer Research Centre. All patients receiving IV busulfan as part of their HCT conditioning were eligible for recruitment in the study. The exclusion criteria of the study included: inability to read English, female patients who are

pregnant or breastfeeding, and severely limited life expectancy caused by other diseases. Prior to the prospective ancillary biomarker study, approved by the Institutional Review Board of the Fred Hutch Centre (FHCRC protocol 91107[132]), all 138 patients provided written informed consent. Antiemetics, antibiotics, and antifungals were given per Institutional Standard Practice Guidelines.

Busulfan dosing and pharmacokinetic sampling
All patients received their busulfan dose over 3 or 4 days, of which most patients (n=116) received daily busulfan (every 24 hours). The other patients received busulfan every 6 hours (n=20) or every 12 hours (n=2).
The first dose of busulfan was either based on the body weight or body surface area of the patient (see FAQ6 of Palmer & McCune et al.[112]). After administering the initial dose, sequential PK samples were drawn, to be able to estimate the busulfan AUC for each patient. The doses administered on the second, third and fourth day of busulfan are adjusted based on the AUC of the individual patient for busulfan, which was calculated from the PK samples. The PK samples were drawn according to the following time schedules: immediately before start of infusion, after end of infusion (for most patients 3h), 4.5h, 6h, 8h, and 24h. For those receiving IV busulfan every 24 hours (Q24H), pharmacokinetic sampling occurred after dose 1, 2, 3, 4 at the following times: end of 3-hour infusion (EOI), EOI + 15 min; 4, 5, 6, 8, 24 h from start of infusion. For those receiving busulfan every 12 hours (Q12H) for 7 doses, pharmacokinetic sampling occurred after every morning dose (i.e., dose 1, 3, 5) at the following times: end of 2-hour EOI, EOI + 15 min; 4, 5, 6, 8 h from start of infusion. For those receiving IV busulfan every 6 hours (Q6H), the pharmacokinetic sampling occurred after every morning dose (i.e., dose 1, 5, 9, 13) at the following time: end of 2-hour EOI, EOI + 15 min, EOI + 30 min; 4, 5, 6 h from start of infusion.

Quantitation of busulfan and its metabolites
Three different assays were used to quantitate the plasma concentrations of busulfan and its metabolites. The assays were divided as followed: 1) busulfan; 2) THT+; 3) THT-1-oxide, sulfolane, and 3-OH-sulfolane. The samples were analysed using either gas chromatography mass spectrometry (GC-MS) or reverse-phase high-performance liquid chromatography with spectrometry detection (LC-MS). A detailed description of each assay is located in the supplementary methods S1. No reliable analytical method could be developed to quantitate the busulfan metabolites GS+THT and EdAG. The metabolites (i.e., THT+, THT 1-oxide, sulfolane, 3OH sulfolane) were not used for personalizing busulfan doses.

Population pharmacokinetic model design, evaluation, and optimization
The busulfan, THT+, THT-1-oxide, sulfolane, and 3-OH-sulfolane concentration-time data were analysed using nonlinear mixed effects modeling using NONMEM® (version 7.5.0 Icon Development Solutions, LLC, Ellicott City, MD, USA)[133], in conjunction with Pearl Speaks NONMEM (version 5.0)[134]. Pirana (version 2.9.9) and R (version 1.4.1717) were used for workflow management, and data handling and visualization, respectively[135,136].

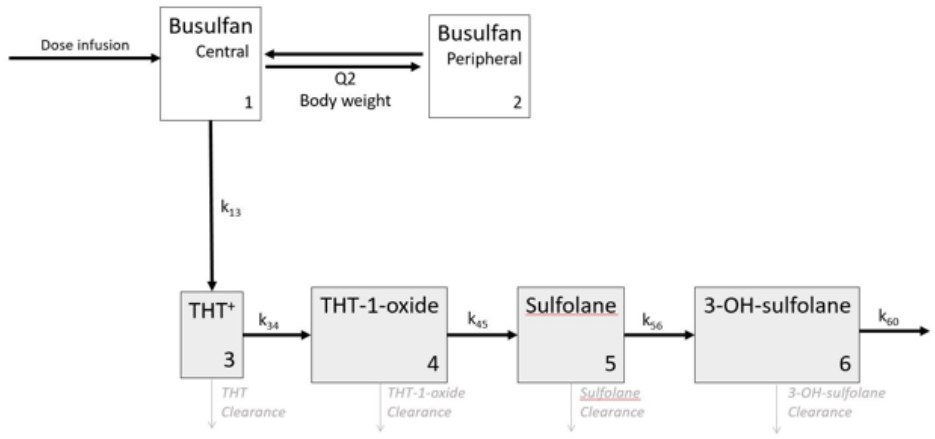
The first-order conditional estimation (FOCE) method, as implemented in NONMEM, was used for model exploration, model validation, and to determine the final model. The predictions for population pharmacokinetics pre-written model, as implemented in NONMEM, was set to ADVAN13, TRANS1, and TOL=6, in combination with SIGL=6 and NSIG=2. Clearances (CL) and volumes of distribution (V) were allometrically scaled to body weight, using theoretical allometric exponents fixed to 0.75 for clearance parameters and to 1 for volumes of distribution[137]. Body weight was normalized to 70 kg and linearly incorporated into all clearances and volumes of distribution.

Model building was performed in 3 different steps: (1) selection of the structural model for busulfan (1-, or 2-compartment model); (2) choice of the error model for that compartment; (3) for each subsequent compartment (metabolite), selection of the structural model and its error model. This was first done with sequential estimation, in which the previous compartments' pharmacokinetic parameters were fixed.

Simultaneous estimation was then used; And (3) model evaluation. Distinctions were made between different models for both the structural and the statistical model by comparing the objective function (−2 log likelihood) value (OFV) for each model. A statistically significant P-value, which was considered to be $P<0.05$, corresponds to a decrease of 3.84 points in the objective function for 1 degree of freedom or 9.49 points for 4 degrees of freedom ($\chi 2$, or chi-square, distribution).
The error model evaluated for busulfan and its four sequential metabolites was first based on a proportional error, meaning the residual variability is proportional to the value of the concentration. Subsequently, the combined proportional and additive error was evaluated; this combined error uses a proportional residual variability for higher predicted concentrations, and a constant residual variability for lower predicted concentrations. The error model with the best fit (considering the OFV value and visual predictive checks through GoF and pcVPC) for each compartment separately was used.
Visual inspection of model performance was done through goodness-of-fit (GoF) plots, such as observed concentrations versus individual- and population predicted concentrations, and conditional weighted residuals (CWRES) versus time (both time from first dose and time from last dose) or predicted concentrations[138], with particular focus on observed versus population-predicted concentrations. The prediction-correct visual predictive checks (pcVPC) were used to assess simulation properties. pcVPCs allow for variability in the dosing regimen[139]. In the pcVPCs, the observed concentrations, the median concentration and 95% confidence interval (CI) were compared to the predicted mean, 5th and 95th percentiles, derived from 200 dataset simulations. A sampling importance resampling (SIR) evaluation (500 samples, 500 resamples) was performed to examine parameter precision and determine the 95% confidence interval (CI)[140].
Model performance was evaluated by visual inspection of the individual plots, analysis of the determined CI of the parameter estimates and the correlation matrix. For the inter-individual variability, CV% was calculated using the formula $SQRT(EXP(\omega 2) - 1)$ Å~ 100%. The formula $SQRT(\sigma 2)$ Å~ 100% was used for the residual error.

The previously published PK model was used as the basis for the structural model[141], which means a two-compartmental model for busulfan was used, describing a central and one peripheral compartment. Full conversion to the subsequent metabolite was assumed for each metabolite. Due to the unknown bioavailability of all metabolites, apparent clearances (clearance/fraction metabolized or CL/F) and apparent volumes of distribution (V/F) were estimated for each metabolite. All metabolites were assumed to be one-compartmental. The final structural model of busulfan and its metabolites, and corresponding equations are depicted in figure 3A and figure 3B, respectively.

A.



B.

Compartment		Equation (Eq)	Eq. number
1	BU central	$\frac{dA_1}{dt} = K_{21} \times A_2(t) - (K_{12} + K_{13}) \times A_1(t)$	1
2	BU peripheral	$\frac{dA_2}{dt} = K_{12} \times A_1(t) - K_{21} \times A_2(t)$	2
3	THT+	$\frac{dA_3}{dt} = K_{13} \times A_1(t) - K_{34} \times A_3(t)$	3
4	THT-1-oxide	$\frac{dA_4}{dt} = K_{34} \times A_3(t) - K_{45} \times A_4(t)$	4
5	Sulfolane	$\frac{dA_5}{dt} = K_{45} \times A_4(t) - K_{56} \times A_5(t)$	5
6	3-OH-sulfolane	$\frac{dA_6}{dt} = K_{56} \times A_5(t) - K_{60} \times A_6(t)$	6

Figure 3. **Final structural model of busulfan and its metabolites with corresponding equations.**
A. Structural model of the two compartments for busulfan and of the one compartment for each metabolite, including the elimination rates. B. Differential equations used for busulfan and metabolites population pharmacokinetic model. A_x represents the amount of each compartment. K_y represents the elimination constant from each compartment.

To find the best predictive performance for a final model, all GoF plots, pcVPCs, and OFV values of different model candidates were compared. The individual etas, reflecting inter-individual variability (IIV), for each parameter were estimated using an exponential error model. Residual variability was analysed using different error models, such as the proportional-, additive-, and combined error models, for each compartment. The residual error was assumed to be normally distributed around a mean of 0. Different combinations of inter-occasion variability (IOV) and/or IIV were explored for the best model fit. All model adjustment that showed a statistically significant improvement of the OFV were included in the final model.

RESULTS

Patient characteristics

The pre-transplant characteristics of the 138 participants included in the study are presented in table 1. The median age was 51.9 years (range: 1.7-70.6), and of all participants a small majority was male (n=88, 64%). The median total body weight was 78.2 kg (range: 10.8-177), and the median body mass index was 26.6 kg/m^2 (range: 15-56.5). The majority of participants were undergoing HCT to treat a variety of hematologic malignancies.

Most of the patients (n=129) received targeted busulfan (^{T}BU) over 4 days; the majority of the participants received one dose busulfan every 24 hours (n=116,84%), whereas the other participants received doses either every 12 hours (n=2, 1.5%) or doses every 6 hours (n=11, 8%). For patients receiving ^{T}BU, the first dose of busulfan, which was administered on the first day of the treatment, was based on body weight or body surface area (see FAQ6 of Palmer & McCune et al.[112]). Sequential pharmacokinetic samples (PK samples) were drawn to estimate the patient's busulfan AUC to be able to personalize the following busulfan doses for

each individual patient, as previously described[142,143]. PK sampling occurred before the subsequent dose was administered, and over an acceptable period of time accounting for the half-life of busulfan (2-3 hours), the dosing frequency, and the necessity to acquire samples quickly enough to be able to estimate the personalized doses in time. PK sampling was typically completed within 4 hours for a 2-hour busulfan infusion corresponding to Q6H dosing, and within 8 hours for a 3-hour busulfan infusion corresponding to Q24H dosing. The doses of busulfan administered on the second, third, and fourth days of ^{T}BU treatment were adjusted based on the patient's busulfan AUC. The clearance of busulfan was estimated from the administered dose and the resulting AUC. The target busulfan AUC for each individual patient was selected by their treating physician. Due to the day-by-day variability of busulfan PK[144], all busulfan PK samples were drawn in the morning.

Table 1. Patient characteristics. For all characteristics, a subject count n, combined with the corresponding percentage from the whole study population, or a median, expressed in a range, is given.

Characteristics	**N(%) or median (range)**
N	138
Age (years)	51.9 (1.9 – 70.6)
< 18 years old	15 (11%)
Male sex	88 (64%)
Actual body weight (kg)	78.2 (10.8 – 177)
Body mass index (kg/m^2)	26.6 (15-56.5)
Diagnosis	
Myelodysplastic syndrome	71 (84%)
Acute myeloid leukemia	33 (24%)
Chronic myeloid leukemia	11 (8%)
Non-Hodgkin's lymphoma	8 (6%)
Other	15 (11%)
Busulfan conditioning without fludarabine	25 (18%)
Busulfan regimen	
PK-guided every 24 hours	116 (84%)
PK-guided every 12 hours for 7 doses	2 (1.5%)
PK-guided every 6 hours for 16 doses	11 (8%)
Weight-based every 6 hours for 12 doses	9 (6.5%)

Busulfan population pharmacokinetic model development

Busulfan was tested in a one- and two-compartmental model, where a structural two-compartmental model with first-order elimination best fitted the data. The pcVPC and GoF plots for observed versus population predictions and individual predictions, and weighted residuals versus population prediction and time of this model for busulfan are shown in figure 4. The final model for busulfan described the observed concentrations adequately combined with a correct predictive performance. The typical values for busulfan volumes of distribution for the central and peripheral compartment, the inter-compartmental clearance, and

apparent clearance to THT+ were estimated to be 39.1 L/70kg, 10.8 L/70kg, 2.17 L/h/70 kg and 10.4 L/h/70 kg, respectively. The proportional error model best fit the busulfan data.

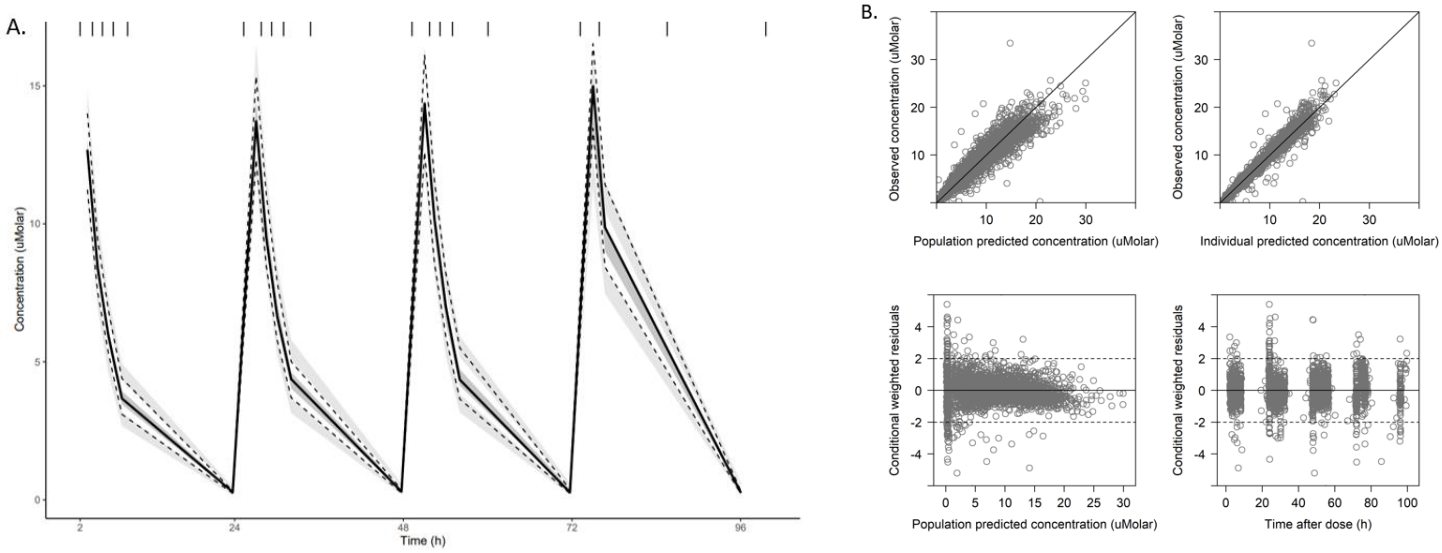


Figure 4. pcVPC and GoF of the final busulfan model. The final busulfan model was based on two compartments and proportional error. Panel A shows the prediction corrected VPC. The black line describes the observed concentration, the black dotted lines describe the 95% confidence interval. The dark shaded area describes the predicted mean and the light shaded area describe the 5th and 95th percentiles of the predictions. Panel B shows the GoF, describing the observed concentrations versus the predicted population- and individual concentrations, and the conditional weighted residuals versus the population predictions and time after dose.

Metabolite model development, optimization and evaluation

All sequential metabolites, THT+, THT-1-oxide, sulfolane, and 3-OH-sulfolane, were each considered to be best described by a one-compartmental model. Initial estimates of THT+ apparent clearance and apparent volume of distribution were relatively high (92.5 L/70kg and 616 L/h/70kg, respectively) compared to other estimates, while pcVPC and GoF indicate the model to describe the data sufficient (supplementary figures S2 and S3, respectively). The pcVPC and GoF of THT-1-oxide, sulfolane and 3-OH-sulfolane indicated misspecification of the model due to a variety in under- and over-prediction of the concentrations (supplementary figures S2 and S3, respectively).

A one-compartmental model with first-order elimination fitted the data for THT+ best. However, the parameter estimates for THT+ apparent volume of distribution and apparent clearance were found to be relatively high, raising the suspicion of a structural issue. Adding a parameter describing busulfan clearance not to THT+ did not improve the model fit and parameter estimates for THT+ (ΔOFV +2524.96). Estimating solely busulfan to THT+ reduced the IIV on busulfan clearance (from 35.9% to 19.1%) and volume of distribution (from 18.2% to 14%), and on THT+ clearance (from 88.5% to 40.4%) and volume of distribution (from 71.7% to 63.6%) compared to the model including the clearance not to THT+. The proportional error model best fit the THT concentration-time data.

The GoF of THT-1-oxide, specifically conditional weighted residuals (CWRES) versus time after first dose, depicted a clear variability in clearance over time, indicating time-associated clearance. Adding time-associated clearance for THT-1-oxide improved the fit substantially (ΔOFV -1184.13). This modification reduced IIV significantly on sulfolane volume of distribution (from 146.6% to 45.5%) and on 3-OH-sulfolane volume of distribution (from 971.1% to 54.1%) but did not show a significant effect on IIV on clearances of the metabolites. Definitive addition of the time-association factor to THT-1-oxide clearance improved the 3-OH-sulfolane fit of the model. However, the GoF of 3-OH-sulfolane still indicated time-associated clearance. Addition of time-associated clearance for 3-OH-sulfolane improved the model fit considerably (ΔOFV -391.33). The addition reduced IIV on 3-OH-sulfolane clearance (from 67.7% to 50.9%). The CWRES versus time after dose plots of THT-1-oxide and 3-OH-sulfolane before and after

addition of time-associated clearance are depicted in figure 5. Addition of this time-associated clearances improved model predictions of the parameter clearance and volume of distribution estimates for THT-1-oxide, sulfolane, and 3-OH-sulfolane.

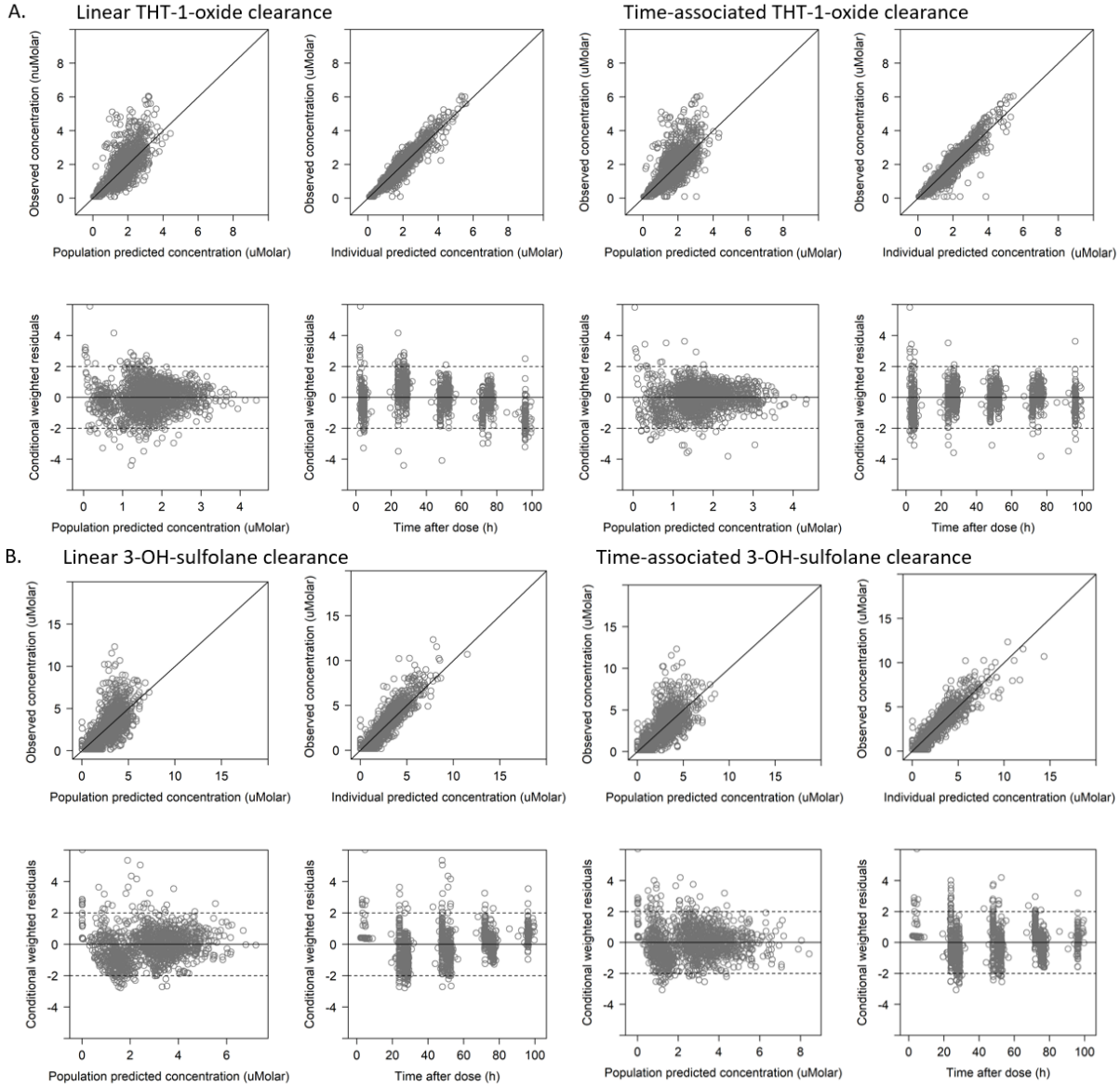


Figure 5. GoF of THT-1-oxide and 3-OH-sulfolane before and after addition of time-associated clearance. Panel A shows the 2-compartmental busulfan model with all 1-compartmental metabolites with on the left side the GoF with linear clearance and on the right side the GoF with time-associated clearance of THT-1-oxide. Panel B shows the 2-compartmental busulfan model with all 1-compartmental metabolites with on the left side the GoF with linear clearance and on the right side the GoF with time-associated clearance of 3-OH-sulfolane. The GoF plots describe the observed concentrations versus the predicted population- and individual concentrations, and the conditional weighted residuals versus the population predictions and time after dose.

Changing linear clearances of THT-1-oxide and 3-OH-sulfolane to being time-associated did not improve the predictions for the lower and higher concentrations of THT-1-oxide, sulfolane and 3-OH-sulfolane to our satisfaction, according to the corresponding pcVPCs shown in supplementary figure S4. The error models used for these metabolites were first based on a proportional error. Analyzing the predictions of the model using a combined error model, suggested the combined error to fit this dataset best. Using the combined error model for THT-1-oxide, sulfolane and 3-OH-sulfolane improved the fit (ΔOFV -361.13).

Due to identifiability issues in combination with overparameterization, the IIV of the apparent volumes of distribution for all metabolites were fixed to 0, causing a decreased model fit (ΔOFV 1948.11), but on the

other hand causing a satisfactory prediction in pcVPC and GoF plots. The pcVPCs and GOF plots including comparisons of individual and population model predictions vs observed values and weighted residuals, shown in figure 6 and figure 7 respectively, confirm satisfactory model precision with negligible bias. For this final model, a sampling importance resampling (SIR) analysis was conducted, and the results are shown in supplementary figure S5. Even though the percentages for relative standard error (RSE) were remarkably low, no correlation between parameter uncertainties was found, suggesting the optimal fit for the data studied. Final parameter estimates for the popPK model of busulfan and all its metabolites are given in supplementary tables S6.

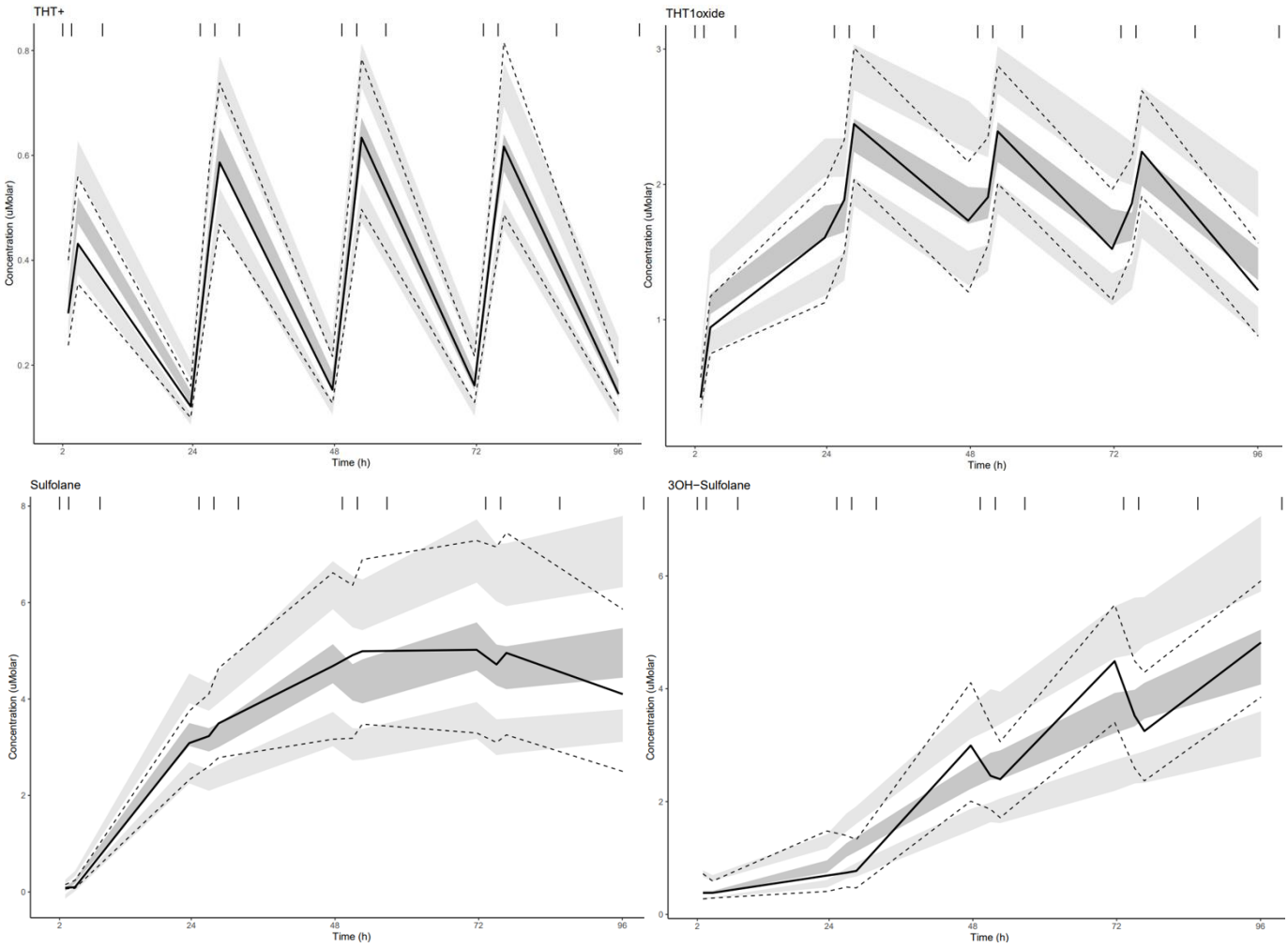


Figure 6. pcVPC of sequential metabolites of the final model. For each metabolite, a one-compartmental model was used to create the prediction corrected VPCs. The black line describes the observed concentration, the black dotted lines describe the 95% confidence interval. The dark shaded area describes the predicted mean and the light shaded area describe the 5th and 95th percentiles of the predictions.

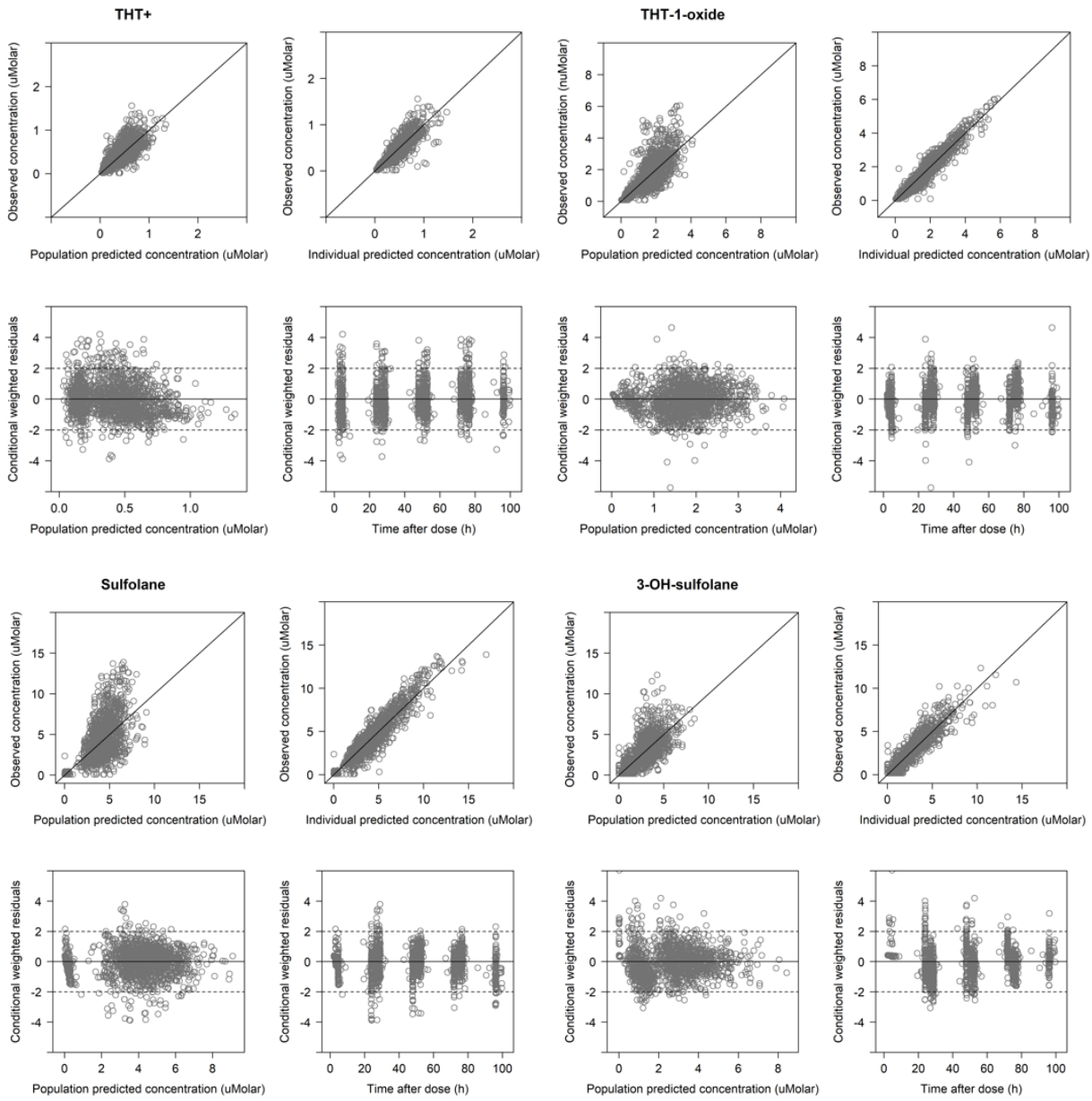


Figure 7. GoF of sequential metabolites of the final model. For each metabolite, a one-compartmental model was used to create the goodness of fit plots. The black line describes the observed concentration, the black dotted lines describe the 95% confidence interval. The observed concentrations versus the predicted population- and individual concentrations, and the conditional weighted residuals versus time and population predictions were described.

DISCUSSION AND CONCLUSIONS

We sought to create a population pharmacokinetic model characterizing the interpatient variability in the pharmacokinetics of busulfan and it four sequential metabolites. In this population of HCT recipients conditioned with busulfan-based regimens, a one-compartment model with first-order elimination adequately described the concentration-time profile of THT+, but difficulty was encountered for THT 1-oxide, sulfolane, and 3OHsulfolane. The inter-individual variability in clearances increased with each sequential metabolite. As shown in the pcVPCs and GoF of the base model (supplementary figures S2 and S3, respectively), there is considerable variability in each sequential metabolite over the duration of busulfan administration. The final popPK model characterized the variability sufficiently.

We decided to focus on busulfan because it is the most common conditioning regimen prior to HCT and because of its narrow therapeutic window. IV BU is a bi-functional alkylating agent with a four-carbon alkyl chain that has two labile methanesulfonates attached to its opposite ends. In aqueous solution, IV BU is hydrolysed and releases its methanesulfonates, resulting in reactive carbonium ions that alkylate DNA. Administration of radiolabelled busulfan IV indicated that less than 50% of the dose was recovered in urine[145,146]. Only 2% of busulfan is excreted in urine unchanged, implying metabolism is the primary route of elimiation[117]. Thus, busulfan is partly urinary excreted and partly metabolized[117,145,146]. In our study, we assumed that all busulfan is converted to THT+ due to the paucity of data regarding the fraction of busulfan metabolized to THT+. Therefore, it is not surprising that the apparent clearance of busulfan to THT+ (which is clearance divided by the fraction metabolized (Fm)) and apparent volume of distribution of THT+ (which is volume of distribution divided by Fm) were relatively high.

The main elimination pathway of busulfan is through conjugation of glutathione, which forms a *S*-glutathione sulfonium conjugate γ-glutamyl-β -(S-tetrahydrothiophenium)-alanyl-glycine (GS^+THT)[131,147]. This conjugation is predominantly catalysed by glutathione transferase (GST) isoenzymes A1-1[128,147,148]. Recent data indicates that GS^+THT undergoes □-elimination to form □-glutamyldehydroalanylglycine (EdAG), which may contribute to busulfan toxicity through various pathways[131,149,150]. Specifically, the weakly cytotoxic EdAG could contribute to the narrow therapeutic index of busulfan by interfering with GST function[131], altering cellular GSH[131], trapping radicals[150], and/or redox-related cytoxicity[131]. Unfortunately, we were not able to quantify EdaG due to its instability and therefore could not include this metabolite to our popPK model. Nevertheless, EdaG could affect GST function and thus, busulfan clearance.

Some popPK models of busulfan suggest time-associated decreases in busulfan clearance. The decreased busulfan clearance has been attributed to various factors, such as glutathione depletion possibly caused by paracetamol administration to mitigate the toxicity of antithymocyte globulin (ATG)[117], the effects of EdaG listed above, or accumulation of the THT+, possibly caused by feedback inhibition (i.e. an enzyme in a biosynthetic pathway may be inhibited by an end product of that pathway)[130]. We did not observe a significant change in IV busulfan clearance from the first dose compared to the observed dose on day 4 of busulfan administration. Thus, our current model does not support these hypotheses, potentially due to a minority of these patients receiving serotherapy and thus paracetamol. Notably, we had similar THT+ plasma concentrations, to previous data after oral busulfan administration[151,152]. These lower THT+ plasma concentrations also do not support the hypotheses of THT+ accumulation.

The pharmacokinetics of THT 1-oxide, sulfolane and 3OHsulfolane were first reported by El-Serafi et al.[152]. In a patient receiving IV busulfan, also low THT, elevated THT 1-oxide, elevated sulfolane, and low 3OHsulfolane plasma concentrations were observed[152]. Our data shows a similar trend. For the urinary concentrations, El-Serafi et al. observed lower concentrations of busulfan, THT, and THT1oxide than sulfolane, which was subsequently lower than 3-OH-sulfolane[152]. One limitation of our dataset is that urinary elimination was not evaluated, due to difficulties with consistent urine collection with cyclophosphamide hyperhydration. Therefore, we weren't able to either confirm or argue this observation.

Although population pharmacokinetic modeling has been applied to optimize HCT conditioning regimens for over 15 years[122,153]. This is the first, to our knowledge, popPK model characterizing the pharmacokinetics of busulfan's metabolites. The model describes the time-concentration profiles of busulfan and its metabolites adequately. However, during model developed we encountered identifiability issues, which led to difficulties in finding the optimal model. Identifiability can be divided into structural- and deterministic identifiability. Since structural identifiability relates to whether the parameters of a postulated population model can be identified and show unique solutions from perfect input-output data[154,155], our dataset focusses on this type of identifiability. Parameters in a model that is unidentifiable show difficulties during the estimation step, which ultimately can lead to for example failure of the model or false conclusions out of the estimates[155]. In this dataset, identifiability was analysed making use of the summary of output from NONMEM, called sumo. Whenever a covariance step has been requested and is successful, sumo reports a condition number, which is the ratio between the largest and smallest eigenvalues, reflecting on the quality of parameter estimates[156]. A failed covariance step combined with a conditioning number exceeding 1000 often implies parameter identifiability issues[157]. We based our identifiability on a successful covariance step and the corresponding conditioning number. The final popPK model for this dataset had a successful covariance step with a conditioning number of 361 and was thereby concluded to be identifiable. The pharmacokinetic sampling schedule, based on what was used clinically for PK-guided busulfan dosing, may also have contributed to difficulties with identifiability. The majority of our patients received busulfan every 24 hours, with no pharmacokinetic samples being drawn between 8 to 24 hours after start of the infusion. This may have contributed to increased IIV for each compartment between these time points. The increased IIV leads to a decreased predictive performance of the final popPK at these time points. To confirm, analyze, and eventually strengthen the busulfan and sequential metabolite model further research should include plasma sampling between 8 to 24 hours after last dose, and urine collection during the entire course of busulfan administration.

In conclusion, an integrated population pharmacokinetic model of busulfan and its metabolites, specifically THT+, THT-1-oxide, sulfolane, and 3-OH-sulfolane, was successfully constructed. The final model precisely described the data and captured the residual- and inter-individual variability sufficiently. However, this model is limited by the paucity of plasma concentration-time points between 8h to 24h after busulfan dosing, and by the lack of urinary excretion data. Further research needs to address this knowledge gap to further improve the popPK model. Characterizing the association of the metabolite's plasma exposure with clinical outcomes and offer new tools to personalize with this additional research, this popPK model may serve as a novel tool to personalize busulfan therapy, and thereby potentially improve HCT conditioning.

REFERENCES

Supplementary B. Detailed literature selection for the literature review

	Link	Author & title	Relevance
MIPD			
	https://pubmed.ncbi.nlm.nih.gov/28182269/	Darwich AS, Ogungbenro K, Vinks AA, et al. Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future	Importance of MIPD implementation and obstacles regarding communication and collaboration
	https://pubmed.ncbi.nlm.nih.gov/28685051/	Mathur S, Sutton J. Personalized medicine could transform healthcare	MIPD's importance in healthcare
	https://pubmed.ncbi.nlm.nih.gov/33158608/	Personalised medicine and the state: A political discourse analysis	MIPD acceptable or not?
	https://pubmed.ncbi.nlm.nih.gov/31313335/	Kumar AA, Coorey C, Burgard M, et al. An evaluation of the user - friendliness of Bayesian forecasting programs in a clinical setting.	MIPD platform
	https://pubmed.ncbi.nlm.nih.gov/28875519/	Gonzalez D, Rao GG, Bailey SC, et al. Precision Dosing : Public Health Need ,	How to approach MIPD implementation

		Proposed Framework , and Anticipated Impact	
	https://pubmed.ncbi.nlm.nih.gov/32714184/	Shukla P, Goswami S, Keizer RJ, et al. Assessment of a Model-Informed Precision Dosing Platform Use in Routine Clinical Care for Personalized Busulfan Therapy in the Pediatric Hematopoietic Cell Transplantation (HCT)	MIPD platform
	https://www.paganz.org/abstracts/nextdose-a-web-based-dosing-tool-development-version-2017/.	Holford NHG, Holford S. NextDose—a web based dosing tool. 2017.	MIPD platform
	https://www.insight-rx.com/product/platform.	Goswami S, Keizer R, Mangat R. The InsightRX Platform - A cloud-based clinical decision support tool for use at the point-of-care	MIPD platform
	https://www.scopus.com/record/display.uri?eid=2-s2.0-85046250055&origin=resultslist&sort=plf-f&src=s&st1=Design+thinking+as+a+methodology+for+solving+problems%3a+Contributions+from+academia+to+society&sid=d3220deb0ddcab35c3ddc7bd5bf2f700&sot=b&sdt=b&sl=108&s=TITLE-ABS-KEY%28Design+thinking+as+a+methodology+for+solving+problems%3a+Contributions+from+academia+to+society%29&relpos=0&citeCnt=4&searchTerm=	Pereira A, Santos C. Design Thinking as a methodology for solving problems : contributions from academia to society .	MIPD platform communication
Inter-disciplinary & collaborative learning			
	https://pubmed.ncbi.nlm.nih.gov/25057539/	Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century	Evolving healthcare systems over the years
	https://pubmed.ncbi.nlm.nih.gov/244357/	Given B, Simmons S. Interdisciplinary health-care team: fact or fiction?	Interdisciplinary collaboration in healthcare disciplines
	https://pubmed.ncbi.nlm.nih.gov/21328739/	Daniel MO, Rosenstein AH. Professional Communication and Team Collaboration	Interdisciplinary collaboration and communication in a team
	https://www.scopus.com/record/display.uri?eid=2-s2.0-85059476011&origin=resultslist&sort=plf-f&src=s&st1=Effective+interdisciplinary+collaboration+between+statisticians+and+other+subject+matter+experts&sid=121c513b6fcce8108040ead4e9bc2b1c&sot=b&sdt=b&sl=111&s=TITLE-ABS-KEY%28Effective+interdisciplinary+collaboration+between+statisticians+and+other+subject+matter+experts%29&relpos=6&citeCnt=4&searchTerm=	Anderson-cook CM, Lu L, Parker PA, Lu L, Effective PAP. Effective interdisciplinary collaboration between statisticians and other subject matter experts. 2019	Respect, commitment, and execution to the fundamentals of interdisciplinary collaboration between a technical and a social professional
Motivation			
	https://pubmed.ncbi.nlm.nih.gov/27479318/	Radel R, Pjevac D, Davranche K, Colson SS, Lapole T, Gruet M. Does intrinsic motivation enhance motor cortex excitability ?	Intrinsic and extrinsic motivation factors
	https://pubmed.ncbi.nlm.nih.gov/11392867/	Ryan R, Deci E. Self-Determination Theory and the Facilitation of Intrinsic Motivation, Social Development, and Well-Being	How intrinsic motivation is stimulated
	https://www.scopus.com/record/display.uri?eid=2-s2.0-85083014335&origin=resultslist&sort=plf-f&src=s&st1=achievement+motivation+theory%e2%80%af%3a+Balancing+precision+and+utility.&sid=ad3a069afd17b691667aaf76a321a193&s	Anderman EM. Achievement motivation theory : Balancing precision and utility.	Motivation to achieve guides professionals

	ot=b&sdt=b&sl=79&s=TITLE-ABS-KEY%28achievement+motivation+theory%e2%80%af%3a+Balancing+precision+and+utility.%29&relpos=0&citeCnt=30&searchTerm=		
	https://www.scopus.com/record/display.uri?eid=2-s2.0-0012631377&origin=resultslist&sort=plf-f&src=s&st1=History+of+motivational+research+in+education&nlo=&nlr=&nls=&sid=9fb4171f5fe8ff919f62446897b99f6e&sot=b&sdt=sisr&sl=60&s=TITLE-ABS-KEY%28History+of+motivational+research+in+education%29&ref=%28Weiner%29&relpos=6&citeCnt=287&searchTerm=	Weiner B. History of motivational research in education	How motivation is used to educate students
	https://www.scopus.com/record/display.uri?eid=2-s2.0-84970331328&origin=resultslist&sort=plf-f&src=s&st1=Attribution+Theory%2c+Achievement+Motivation%2c+and+the+Educational+Process.&nlo=&nlr=&nls=&sid=2d465e11eea8c7a32ccaa6c33a1f1232&sot=b&sdt=sisr&sl=87&s=TITLE-ABS-KEY%28Attribution+Theory%2c+Achievement+Motivation%2c+and+the+Educational+Process.%29&ref=%28Weiner%29&relpos=4&citeCnt=208&searchTerm=	Weiner B. Attribution Theory, Achievement Motivation, and the Educational Process.	Achievement motivation guides students in their learning process
	https://www.scopus.com/record/display.uri?eid=2-s2.0-85070686747&origin=resultslist&sort=plf-f&src=s&st1=Does+Cooperative+Learning+Increase+Students+%e2%80%99+Motivation+in+Learning&nlo=&nlr=&nls=&sid=efe126215251a31afbbdde1488317cda&sot=b&sdt=sisr&sl=83&s=TITLE-ABS-KEY%28Does+Cooperative+Learning+Increase+Students+%e2%80%99+Motivation+in+Learning%29&ref=%28Tran%29&relpos=3&citeCnt=11&searchTerm=	Tran VD. Does Cooperative Learning Increase Students ’ Motivation in Learning ?	Collaborative learning enhances the connection between the two disciplines involved
Individual adaptability			
	https://scholar.google.nl/scholar?hl=nl&as_sdt=0%2C5&as_vis=1&q=Zorzie+M.+Individual+adaptability%3A+testing+a+model+of+its+development+and+outcomes.+2012&btnG=	Zorzie M. Individual adaptability: testing a model of its development and outcomes. 2012	Factors influencing adaptability of an individual
	https://scholar.google.com/scholar?hl=nl&as_sdt=0%2C5&q=urphy+SL.+Individual+adaptability+as+a+predictor+of+job+performance.+2015.&btnG=	Murphy SL. Individual adaptability as a predictor of job performance. 2015.	Individual adaptability influence the performance of professionals
	https://scholar.google.com/scholar?hl=nl&as_sdt=0%2C5&q=Trundt+KM.+Toward+a+New+Model+of+Adaptability.&btnG=	Trundt KM. Toward a New Model of Adaptability. 2010	New approach to adaptability
Technology acceptance			
	https://www.scopus.com/record/display.uri?eid=2-s2.0-85119263164&origin=resultslist&sort=plf-f&src=s&st1=Technology+Acceptance+in+Healthcare%e2%80%af%3a+A+Systematic+Review&nlo=&nlr=&nls=&sid=caf5805b4064c6a76d439fdbbb1309ce&sot=b&sdt=sisr&sl=72&s=TITLE-ABS-KEY%28Technology+Acceptance+in+Healthcare%e2%80%af%3a+A+Systematic+Review%29&ref=%28Alqudah%29&relpos=0&citeCnt=3&searchTerm=	Alqudah AA, Al-emran M. Technology Acceptance in Healthcare : A Systematic Review. 2021.	The acceptance of technology in healthcare systems regarding the UTAUT theory
	https://www.scopus.com/record/display.uri?eid=2-s2.0-84967019924&origin=resultslist&sort=plf-f&src=s&st1=Technology%2c+Gaming%2c+and	Charness N, Boot WR. Technology, Gaming, and Social Networking.	How can technology be communicated to induce acceptance

	+Social+Networking.&nlo=&nlr=&nls=&sid=d8a79744225fa33959fa4d3303a2dd14&sot=b&sdt=sisr&sl=57&s=TITLE-ABS-KEY%28Technology%2c+Gaming%2c+and+Social+Networking.%29&ref=%28charness%29&relpos=2&citeCnt=20&searchTerm=		
	https://www.scopus.com/record/display.uri?eid=2-s2.0-55249087535&origin=resultslist&sort=plf-f&src=s&nlo=&nlr=&nls=&sid=e1f9de3ee63126be78d47518cec6edc3&sot=a&sdt=cl&cluster=scoprefnameauid%2c%22Davis%2c+F.D.%2355817507700%22%2ct&sl=122&s=%28TITLE-ABS-KEY%28Perceived+Usefulness+%2c+Perceived+Ease+of+Use+%2c+and+User+Acceptance+of+Information+Technology.%29%29+AND+%28Davis%29&relpos=4&citeCnt=27250&searchTerm=	Davis FD, Davis F. Perceived Usefulness , Perceived Ease of Use , and User Acceptance of Information Technology. 1989	TAM theory, regarding the easiness of use and usefulness
	https://pubmed.ncbi.nlm.nih.gov/27757179/	Garavand A, Mohseni M, Asadi H, et al. Factors influencing the adoption of health information technologies: a systematic review.	How technology adoption can be stimulated
	https://pubmed.ncbi.nlm.nih.gov/29317386/	Kurahashi AM, Stinson JN, van Wyk M, et al. The Perceived Ease of Use and Usefulness of Loop: Evaluation and Content Analysis of a Web-Based Clinical Collaboration System.	Importance of introducing future users to a technology at the early stages of implementation
	https://www.scopus.com/record/display.uri?eid=2-s2.0-85123777748&origin=resultslist&sort=plf-f&src=s&st1=Examining+Technology+Acceptance+in+Learning+and+Teaching+at+a+Historically+Disadvantaged+University+in+South+Africa+through+the+Technology+Acceptance+Model.&sid=6e8afcc468255cd3129493d587f59218&sot=b&sdt=b&sl=171&s=TITLE-ABS-KEY%28Examining+Technology+Acceptance+in+Learning+and+Teaching+at+a+Historically+Disadvantaged+University+in+South+Africa+through+the+Technology+Acceptance+Model.%29&relpos=0&citeCnt=0&searchTerm=	Ndebele C, Mbodila M. Examining Technology Acceptance in Learning and Teaching at a Historically Disadvantaged University in South Africa through the Technology Acceptance Model.	Technology adoption integration in learning together necessitates the establishment of e-learning → collaborating practice to assist and share their best practice through that technology
Inter-disciplinary collaboration			
	https://pubmed.ncbi.nlm.nih.gov/29303376/	Manias E. Effects of interdisciplinary collaboration in hospitals on medication errors: an integrative review.	Healthcare professionals share same objective and work together to solve patient care problems
	https://pubmed.ncbi.nlm.nih.gov/20536755/	Petri L. Concept Analysis of Interdisciplinary Collaboration.	How interdisciplinary collaboration decreases medication errors
	https://pubmed.ncbi.nlm.nih.gov/12899277/	Bronstein LR. A Model for Interdisciplinary Collaboration.	five core components: interdependence, newly created professional activities, flexibility, collective ownership of goals, and reflection on the process → optimal collaboration between professionals
	https://www.scopus.com/record/display.uri?eid=2-s2.0-85020860573&origin=resultslist&sort=plf-f&src=s&st1=Impact+of+Trust+and+Technology+on+Interprofessional+Collaboration+in+Healthcare+Settings%e2%80%af%3a+An+Empirical+Analysis.&sid=89b33358d5af5453de816c39fb37	Palanisamy R, Taskin N, Verville J. Impact of Trust and Technology on Interprofessional Collaboration in Healthcare Settings : An Empirical Analysis. 2017	Higher-quality care when healthcare professionals collaborate as a team

	4ca1&sot=b&sdt=b&sl=128&s=TITLE-ABS-KEY%28Impact+of+Trust+and+Technology+on+Interprofessional+Collaboration+in+Healthcare+Settings%e2%80%af%3a+An+Empirical+Analysis.%29&relpos=0&citeCnt=8&searchTerm=		
	https://www.scopus.com/record/display.uri?eid=2-s2.0-70449753760&origin=resultslist&sort=plf-f&src=s&st1=Implementation+and+Use+of+Expert+Systems+in+Organizations%3a+Perceptions+of+Knowledge+Engineers&sid=0ce782ff0d7923cb04da943b70598322&sot=b&sdt=b&sl=108&s=TITLE-ABS-KEY%28Implementation+and+Use+of+Expert+Systems+in+Organizations%3a+Perceptions+of+Knowledge+Engineers%29&relpos=3&citeCnt=2&searchTerm=	Byrd TA. Implementation and Use of Expert Systems in Organizations: Perceptions of Knowledge Engineers.	Integration of technology lowers healthcare costs and increased decision quality
	https://pubmed.ncbi.nlm.nih.gov/20795836/	Cameron A. Impermeable boundaries? Developments in professional and inter-professional practice.	Autonomy stimulates collaboration enhancing relationships between professionals.
	https://pubmed.ncbi.nlm.nih.gov/24267663/	MacNaughton K, Chreim S, Bourgeault IL. Role construction and boundaries in interprofessional primary health care teams: a qualitative study.	Empowering autonomy of professionals to enhance interdisciplinary collaboration
	https://pubmed.ncbi.nlm.nih.gov/23663329/	Nancarrow, Susan A. Booth, Andrew et al. Ten principles of good interdisciplinary team work.	Effective interdisciplinary collaboration.
Trans-disciplinary collaboration			
	https://www.scopus.com/record/display.uri?eid=2-s2.0-71349083444&origin=resultslist&sort=plf-f&src=s&st1=Multidisciplinary%2c+interdisciplinary%2c+and+transdisciplinary+collaboration%3a+implications+for+vocational+psychology&sid=368293f87894274909cc8a170ec3e6c1&sot=b&sdt=b&sl=128&s=TITLE-ABS-KEY%28Multidisciplinary%2c+interdisciplinary%2c+and+transdisciplinary+collaboration%3a+implications+for+vocational+psychology%29&relpos=0&citeCnt=43&searchTerm=	Collin A. Multidisciplinary, interdisciplinary, and transdisciplinary collaboration: implications for vocational psychology	Exploration of a specific problem that integrates perspectives of all different disciplines
	https://pubmed.ncbi.nlm.nih.gov/28547926/	Bewer V Van. Transdisciplinarity in Health Care: A Concept Analysis	Integrates and transforms knowledge from different perspectives and different disciplines in solving a shared healthcare problem
	https://pubmed.ncbi.nlm.nih.gov/18619410/	Stokols D, Misra S, Moser RP, Hall KL, Taylor BK. The Ecology of Team Science: Understanding Contextual Influences on Transdisciplinary Collaboration	Effectiveness of transdisciplinary collaboration influences by inter- and intrapersonal, organisational, technologic, societal, political, and physical environmental factors.
	https://pubmed.ncbi.nlm.nih.gov/35341438/	Martin A, Green T, Sowa M. Allied health transdisciplinary models of care in hospital settings : a scoping review protocol	Transcendence of disciplinary boundaries, sharing knowledge and skills, and make decisions together.
	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8162222/	Schreiber JA. Beyond Evidence-Based Practice—Achieving Fundamental Changes in Research and Practice. 2014	Patients are treated based on the best current, available, and relevant evidence.
	https://pubmed.ncbi.nlm.nih.gov/21074648/	Newhouse RP. Interdisciplinary Evidence-based Practice: Moving from Silos to Synergy. 2011	Core element of high-quality patient care
	https://pubmed.ncbi.nlm.nih.gov/30442711/	Lehane E, Leahy-warren P, Riordan CO,	Decision-making based on

		et al. Evidence-based practice education for healthcare professions : an expert view. 2019	the evidence, clinical expertise, and patient preferences
	https://scholar.google.nl/scholar?hl=nl&as_sdt=0%2C5&as_vis=1&q=The+Role+of+Equilibration+in+Piaget+%E2%80%99+s+Theory+of+Cognitive+Development+and+Its+Implication+for+Receptive+Skills%E2%80%AF%3A+A+Theoretical+Study&btnG=	Bormanaki HB. The Role of Equilibration in Piaget ' s Theory of Cognitive Development and Its Implication for Receptive Skills : A Theoretical Study. 2017	Collaborative learning loop will eventually reach an equilibrium, when expectations meet the newly obtained knowledge, and it is perceived as being normal
	https://pubmed.ncbi.nlm.nih.gov/26990809/	Sills J, Rowes G, Emerson L-M. The role of collaboration in the cognitive development of young children: a systematic review	Disequilibrium (uncomfortable), restoring equilibrium through collaborating (comfortable

Supplementary C. Informed consent form

Consent Form "*Communication and collaboration between pharmacists and pharmacometricians through the use of model-based dosing using platform*"

Please tick the appropriate boxes	Yes	No
Taking part in the study		
I have read and understood the study information dated [16/03/2022], or it has been read to me. I have been able to ask questions about the study and my questions have been answered to my satisfaction.	□	□
I consent voluntarily to be a participant in this study and understand that I can refuse to answer questions and I can withdraw from the study at any time, without having to give a reason.	□	□
I understand that the interview will be audio-recorded. The recording will be transcribed as text, and then kept as a primary source document for potential future reference within a research context.	□	□
I understand that the content discussed during the interview will also be documented in real time via handwritten notes.	□	□
Risks associated with participating in the study		
I understand that taking part in the study involves the following risks: - In the case of a data breach, some or all of my identifying information may be compromised/leaked.	□	□
Use of the information in the study		
I understand that information I provide will be used for reports written by the researchers for their university programme.	□	□
I understand that personal information collected about me that can identify me, such as full name or place of residence, will be considered confidential and will not be shared beyond the study team.	□	□
I agree that the information, thoughts, and experiences I discuss during the interview can be quoted anonymously in research outputs.	□	□
Future use and reuse of the information by others		
I give permission for the confidential interview transcript data that I provide to be archived in a repository held by the Delft University of Technology (TU Delft) so it can be used for future research and learning.	□	□
I give permission for the audio recording data that I provide to be archived in a repository held by the Delft University of Technology (TU Delft) so it can be used for future research and learning.	□	□

Signatures

Name of participant	Signature	Date

I have accurately read out the information sheet to the potential participant and, to the best of my ability, ensured that the participant understands what they are freely consenting to.

Researcher name	Date	Signature
Loes Maton	16/03/2022	

Study contact details for further information: Loes Maton, +31 6 39 14 33 13, l.c.h.maton@student.tudelft.nl

Supplementary D. Interview protocol

Introduction interview:
Nowadays, the development of models for model informed precision dosing (dosing based on what the body does with the drug) is very upcoming, since the use of such models would reduce the chance of a patient reaching an exposure leading to toxicity. For a lot of drugs, busulfan in this study's case, a platform is developed to describe the concentration-time and elimination profiles for a specific dose, creating the ability to fully personalize dosing based on patient characteristics. The busulfan dosing process is still mainly based on the patient's body weight, despite the availability of model informed precision dosing platforms. Pharmacists are used to dose patients based on long-existing protocols, which they know by heart, and which are very easy to use. Because of unidentified reasons, pharmacists do not use such the available platform and stick to the old protocol, risking a decrease in efficacy of busulfan treatment and increasing the risk of toxicity in a patient. To be able to make use of population model informed precision dosing implemented in a platform, a clear communication and collaboration between the pharmacometrician and pharmacist is necessary.

This project aims to describe the difficulties in the communication and collaboration between pharmacists and pharmacometricians (for example, what causes pharmacists to stick to the old protocol instead of using the platform) and describe what pharmacists and pharmacometricians need in their collaboration through the platform, meaning what elements are needed in the platform to improve the pharmacists' practice and to create a learning platform for both parties. These adjustments to improve the platform are meant to make it more accessible, applicable, less time-consuming, and more attractive to be used and improved constantly.

In this interview, I would like to explore how both parties feel and think about such a platform and the collaboration between each other. The interview will be used to find answers on the aims of the project and will be tested further in a focus group.

Initiating questions pharmacist:

- Could you tell me a little bit about yourself?
  - What is your exact job in the hospital?
  - What was your background (what did you study)?
  - How long have you been working in the field?
  - With whom do you work most closely together?

    - Are you a technology-user or not on a scale from 1 to 5? What do you use?
    - How do you feel about technology in and outside the hospital?
- How do you decide which dose to use for each patient?
    - Do you feel confident in this way of deciding the dosing regimen? Why or why not?
    - Do you feel like dosing using your standard way is the most beneficial for the patient?
- Are you familiar with model informed precision dosing?
    - If yes, what do you know about it?
    - Do you use population pharmacokinetic-guided dosing? If yes, how often? If not, why not?
    - Would you be motivated to learn this technology used to decide on dosing regimen? And, why or why not? *(Motivation theory, interdisciplinary learning)*
    - What would you like to learn making use of this technology? *(Motivation theory, individual adaptability, technology adoption)*
    - What would you need to be able to adopt the model-based dosing as new protocol? *(Technology adoption, individual adaptability)*
- Do you collaborate with a pharmacometrician, for example in deciding which dose should be administered?
    - How do you collaborate? *(Interdisciplinary collaboration)*
    - How often and in what ways?
    - Are you satisfied with this communication? Why or why not? *(Interdisciplinary collaboration, interaction adaption)*
    - Would you be motivated to collaborate together towards a shared goal? *(Motivation, interdisciplinary communication, collaborative learning)*
    - Are you motivated to learn from the pharmacometricians and make them learn from you in order to create a learning environment together? And, why or why not? *(Motivation, interdisciplinary communication, collaborative learning)*
    - What would you expect from the other party in your collaboration? *(Interdisciplinary learning, Interaction adaption theory, collaborative learning)*
    - What would you expect the other party to want from you in your collaboration? And would you be willing to adapt to this? *(Interdisciplinary learning, Interaction adaption theory, collaborative learning)*
    - How do you think this communication could be improved? *(Interdisciplinary communication, interaction adaption, collaborative learning)*
- Why do you think such a platform is not the usual to use when deciding on a dosing regimen?
    - What do you feel about such a platform?
    - Do you trust the platform? Why or why not? *(Motivation theory, technology adoption)*
    - Would you be willing to learn how to use such a platform? Why or why not? *(Motivation theory, technology adoption)*
    - What do you think the use of such a platform would have for effect on the patient? *(Technology adoption)*
- If you would want to use a population pharmacokinetic-guided dosing platform, what should it contain?
    - What features are necessary? Why? *(Technology adoption)*
    - What would you suggest making it easy in use and to learn? *(Collaborative learning, interdisciplinary learning)*
    - Do you find the ideal platform, as you de scribe, attractive to use and to learn from? If not, what would make you attracted to learn from it? What do you like learn from the platform? *(Motivation theory, inter/transdisciplinary learning)*
- Looking at this existing dosing-platform for Busulfan, what is your first thought?
    - Does it look like it's easy and beneficial to use? Why or why not? *(Transdisciplinary learning, motivation)*
    - How can it be adjusted to make it look easier in use? Think about system characteristics or facilitating conditions. *(Technology acceptance)*
    - Does it encourage you to use and learn from it? *(Motivation theory)*
    - What do you find attractive from this example? And what not? *(Motivation theory, technology adoption)*

    - Giving it a first look, name one strong and one weak point? What do you miss? *(Technology adoption)*
- Could you name the one thing that would help you most in the use of model informed precision dosing? *(Motivation theory, collaborative learning)*
- Given this interview, how do you see the future regarding dosing drugs and the use of model informed precision dosing?
- Do you have any further comments or questions or suggestions?

Initiating questions pharmacometrician:

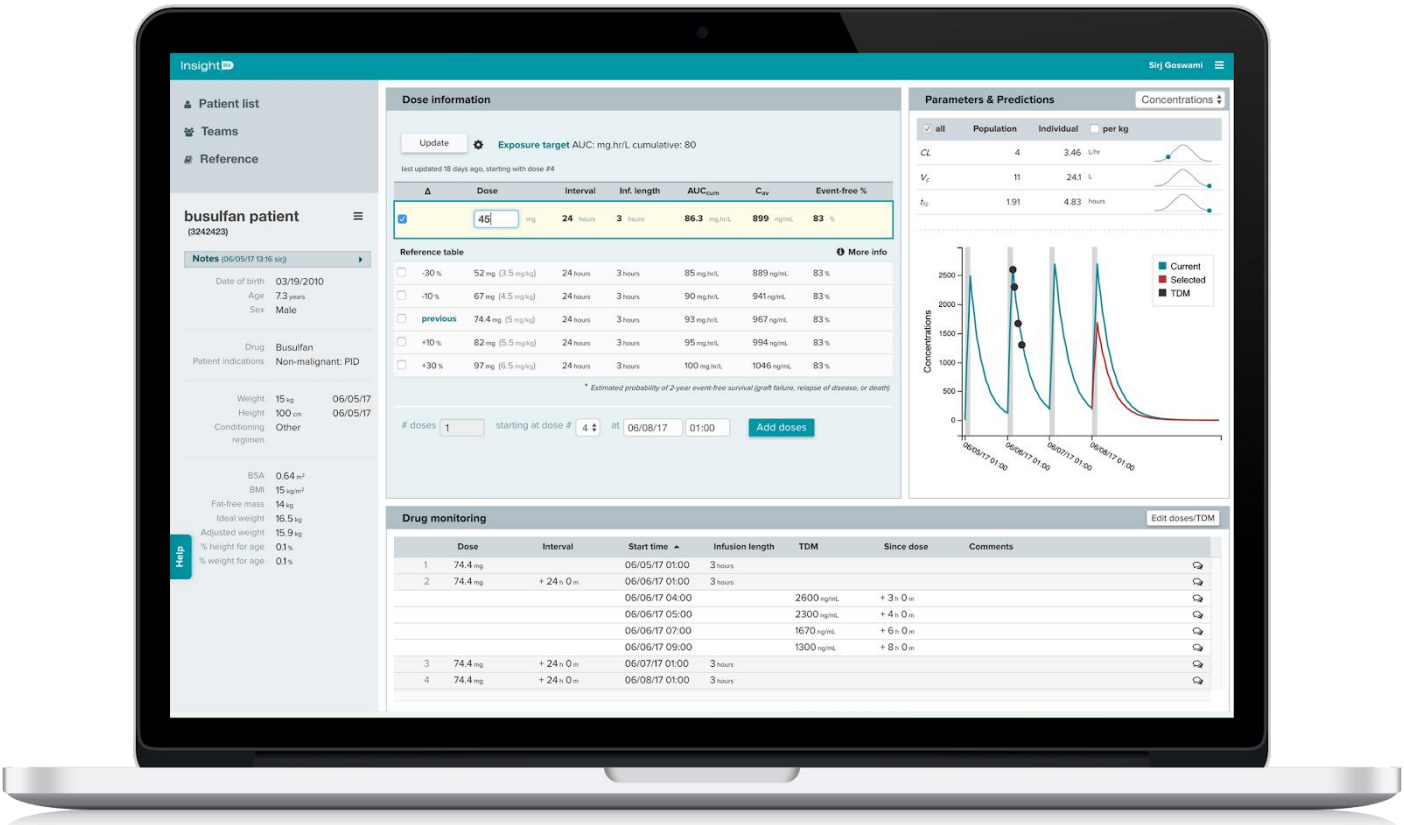
- Could you tell me a little bit about yourself?
    - What is your exact job in the hospital?
    - What was your background (what did you study)?
    - How long have you been working in the field?
    - With whom do you work most closely together? Or what disciplines?
    - Are you a technology-user or not? What do you use?
    - How do you feel about technology?
- Are you currently working on a model which may ultimately be used for drug dosing?
    - If yes, in what stadium is it right now?
    - How do you think it will be used by pharmacists? *(Interpersonal communication, collaborative learning, interdisciplinary learning)*
    - What you think needs to happen to the model in order to make it usable in clinical practice?
- Do you collaborate with a pharmacist in deciding which dose should be administered?
    - How do you collaborate? *(Interdisciplinary collaboration)*
    - How often and in what ways?
    - Are satisfied with this communication? Why or why not? *(Interdisciplinary collaboration, interaction adaption)*
    - Would you be motivated to collaborate together towards a shared goal such as improving drug dosing? *(Motivation, interdisciplinary communication, collaborative learning)*
    - What would you like to learn from the pharmacists and what would you like to make them learn from you in order to create a learning environment together? And, why or why not? *(Motivation, interdisciplinary communication, collaborative learning)*
    - What would you expect from the other party in your collaboration? *(Interdisciplinary learning, Interaction adaption theory, collaborative learning)*
    - What would you think the other party would want from you in your collaboration? And would you be willing to adapt to this? *(Interdisciplinary learning, Interaction adaption theory, collaborative learning)*
    - How do you think this communication could be improved? *(Interdisciplinary communication, interaction adoption, collaborative learning)*
- Are you familiar with a dosing-platform used to base dosing regimen on population pharmacokinetic models?
    - Have you been involved in developing one?
    - Would you have interest in developing one? And, why?
    - What could make you motivated to develop such a platform? *(Motivation theory)*
- Why do you think such a platform is not the usual to use when deciding on a dosing regimen?
    - What do you feel about such a platform?
    - What do you think such platform needs to become common practice?
    - Do you think others trust the platform? Why or why not? *(Motivation theory, interpersonal communication)*
    - Would you be willing to learn how to use such a platform to develop a learning environment for you and pharmacists? Why or why not? *(Individual adaptability, motivation theory, interaction adaption)*
- If you would develop such a platform, what would you include and exclude?
    - What would it look like?
    - What do you think is the bare minimum needed to make it attractive to use and to learn from, if you think of the end-users of such platform? *(Interaction adaption, individual adaptability, collaborative/interdisciplinary learning, interpersonal communication)*

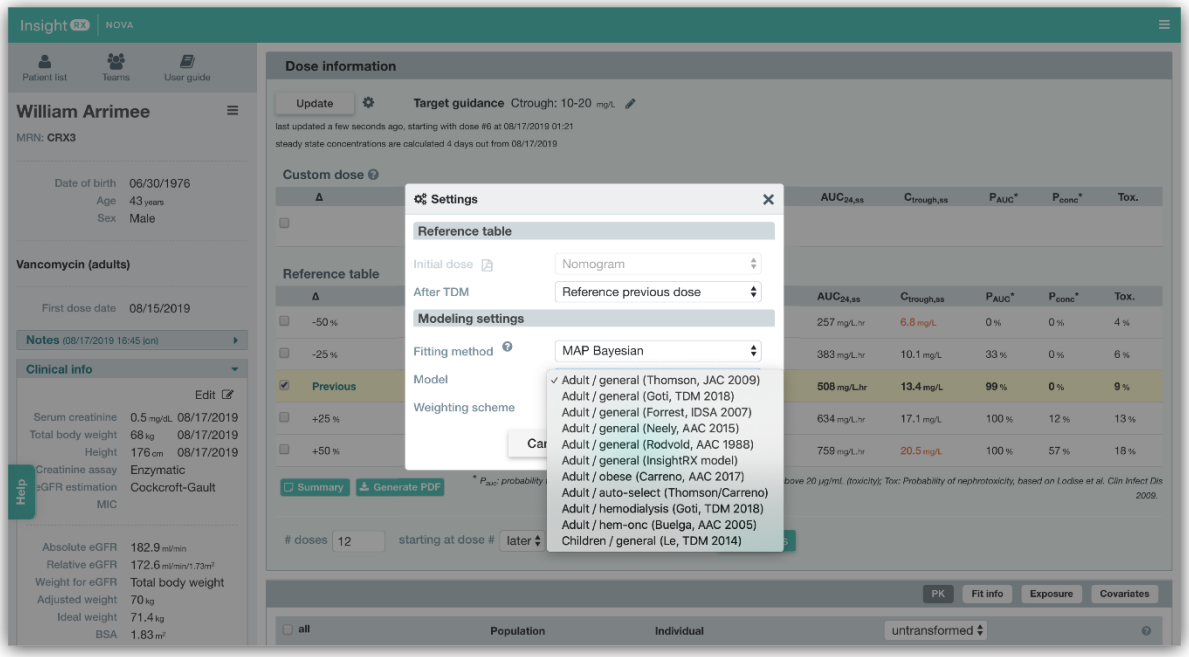
    - What do you think would make it attractive to use and to learn from for pharmacists? *(Interaction adaption, collaborative/interdisciplinary learning, interpersonal communication)*
- Looking at this existing dosing-platform for Busulfan, what is your first thought?
    - Does it look like it's easy and beneficial to use? Why or why not? *(Transdisciplinary learning, motivation)*
    - How can it be adjusted to make it look easier in use? Think about system characteristics or facilitating conditions. *(Technology acceptance)*
    - Do you think it's complete enough to be able to use and learn from it by pharmacists? *(Collaborative/transdisciplinary learning, interdisciplinary collaboration, interpersonal communication)*
    - What do you find attractive from this example? And what not? *(Technology acceptance)*
    - Giving it a first look, name one strong and one weak point? What do you miss?
- Could you name the one thing that would help you most knowing how to approach the development of a dosing-platform? *(Individual adaptability, collaborative/interdisciplinary learning)*
- Given this interview, how do you see the future regarding dosing drugs and the use of model informed precision dosing?
- Do you have any further comments or questions?

To encourage participants to elaborate on their answers, some probing questions were formulated:

- Why do you feel like this?
- What do you think about it?
- How would you do it differently?
- How would like to see it differently?
- What could be worse?
- What could be better?

Example MIPD-platform InsightRX:





Supplementary E. Coding table derived from interviews

Participant	Quote	Code 1	Theme 1	Code 2	Theme 2
P1	I work closely to other people who like to model. And I do have a lot of discussion, a lot, some discussion with people who set up the clinical trials like physicians because my model were well, my models were mainly to answer questions from a clinical trial. So I also have some discussion with them, like what are they expecting to look into and what kind of question they hope that I can initiate from the smallest aspects?	Discussions other modellers/ clinicians	Daily jobs	Answer clinical trial questions	Daily jobs
P1	I'm now mainly working on neglected disease and because neglected disease is often poverty related, which means there's no money for this kind of disease. So, there is really limited study on it. So yeah, I'm building models for this population	Modelling	Daily jobs		
P2	Ik focus op bioanalyse, het opzetten en uitvoeren van klinische studies en een data analyse daarvan. En dan een specifieke subgroep van data-analyse waar ik zelf gespecialiseerd in mijn soort van is dan een populatie farmacokinetic modeling	Clinical trials	Daily jobs	Modelling	Daily jobs
P2	MWPharm is een heel ouderwets dosing platform. Ik heb het zelf nog nooit geïmplementeerd, maar ik werk er wel mee.	Dosing based on MWPharm	Daily jobs		
P3	Mijn promotie bij de kinderIC en deed ik, naast eigenlijk de apotheek taken specifiek voor het Sophia Kinderziekenhuis, dus ook mijn promotieonderzoek waarin ik doseringen ontwikkelde voor geneesmiddelen met behulp van populatie pk-modellen en PBPK modellen voor kinderen en zwangere. En nu binnen mijn opleidingen probeer ik me echt te focussen op hoe krijgen we nu beter en geaccepteerd onderzoek binnen de perinatale en pediatrische farmacologie om ook in deze populatie tot evidence-based de	Modelling	Daily jobs	Implementing modelling in clinical practice	Daily jobs

	beste doseringen te komen				
P3	We kijken wel wat voor spiegels waarvoor we TDM doen. Gebruik dan natuurlijk wel bijvoorbeeld MWPharm, dus een computermodel om maar popPK modellen te implementeren. Daarin zitten vaak ook al ontwikkelde populatiePK modellen die uit de literatuur zijn, dus dat vind ik al wel een goede stap richting personalized medicine. Ehm, voor kinderen doen we dat conform kinderformularium, wat natuurlijk ook deels al echt wel evidence based. En we zijn echt steeds meer binnen het kinderformularion bezig om gebruik te maken van popPK model en PBPK-modellen, maar ook wel echt evidence in plaats van empirisch om doseringen te geven. Als we iets niet kunnen vinden qua dosering, dan kijken we ook wel vaak op pubmet of proberen het daar te baseren. Dus ja, en als het een wat meer rechttoe rechtaan casus is dan kijken we eigenkijk op de KNMP-kennisbank of lokale protocollen	Dosing based on MWPharm	Daily jobs	Dosing based on literature	Daily jobs
P3	Een soort project gestart van goh misschien moeten wij daar wat meer dus bij retrospectieve student laten kijken van hoe waren die spiegels nou? En dan zie je ze bereiken de target niet bijvoorbeeld, waarbij heel veel middelen niet. Bijvoorbeeld bij zwangere patiënten die een transplantatie ondergaan en dat is dan eigenlijk voor een clinici een signaal van goh, dan doen we het dus niet goed	Implementing modelling in clinical practice	Daily jobs		
P4	Specialist ouderengeneeskunde en ik werk dus in het verpleeghuis. Daar ben ik een soort van huisarts voor die patiënten. Daar wonen mensen, vaak met dementie en gedragsproblemen. En daar ben ik dan de dagelijkse arts van. Maar ik, ik werk ook de laatste tijd in ambulant, geriatrisch team en dat betekent dat ik consulten doe voor de huisarts. Ik doe diagnostiek.	Specialist doctor	Daily jobs	Diagnostics	Daily jobs
P4	Ik doseer grotendeels natuurlijk vanuit mijn kennis, gewoon heel gewoon wat ik heb geleerd, wat ik weet uit ervaring. Ja, bijvoorbeeld meeste antibiotica weet ik precies hoeveel zoveel gram nodig is. Maar dat moet zijn er zo nu en en bij ouderen is het wel nog specifiek dat je eigenlijk altijd nog wel eens farmaceutisch kompas moet kijken, want ze zijn voor ouderen echt wel andere doseringen.	Dosing based on experience	Daily jobs	Dosing based on literature	Daily jobs
P4	Ook ons voorschrijfsysteem, Medieval geeft altijd iets aan voor doseringen. Je wordt bijvoorbeeld door het systeem bewust gemaakt van het feit dat er een interactie gaat plaatsvinden en dat je dus moet opletten.	Dosing based on prescribing system	Daily jobs		
P5	Ik geef vooral ook veel supervisie aan een arts in opleiding en dan naar verpleegkundig specialist en de andere helft van mijn tijd. Uhm, bezoek ik er patienten in de eerste lijn, naar mensen die dus thuis wonen, op verzoek van de huisarts. En dan vooral als er vragen zijn rond onmogelijk diagnostiek of gedrag of prognose. Of waar de zorg spaak loopt.	Specialist doctor	Daily jobs	Diagnostics	Daily jobs
P5	Ik gebruik vooral een elektronisch client dossier. Ehm, een elektronisch voorschrijf systeem, vooral het doorgeven van medicatie het precies en vooral het voorschrijven en stoppen en wijzigen van haar medicatie. Soms komt er een pop-up dat ze dat er een contra indicatie is qua diagnose of een waarschuwing bij bijvoorbeeld nierfunctie. Nou	Dosing based on prescribing system	Daily jobs		

	ja, en bij allergie. En verder uhm krijgen we ook wel systeem waarschuwing als de dosering te hoog is. Of er interacties zijn die onwenselijk zijn.				
P6	I run my own doctor's office, so I see the patients over and over and get to know them very well.	Doctor	Daily jobs		
P6	Je kunt zelf gewoon zelf weten wat je doet. Ha, dus jij maakt een voorschrift. We hebben daar richtlijnen voor en dus euh. Je kunt het opzoeken. Je weet het of uit je hoofd of je zoekt het in de richtlijn die we hebben. En je natuurlijk farmaceutisch kompas waar alles in staat. Maar ja, dat wordt geadviseerd altijd te doen. Ook en literatuur in het ziekenhuis. En heb je dus kruising literatuur en en wij hebben wij in huisartsen specialisatie hebben we iets dat NHG richt Lijnen noemen wat staat voor de Nederlanse Huisarts Genootschap en dat die richtlijn die wij hebben.	Dosing based on experience	Daily jobs	Dosing based on literature	Daily jobs
P6	Ook via een dosering systeem, HIS, kun je aanklikken welk medicijn je wilt en in welke dosering. Het systeem geeft waarschuwingen wanneer iets aan de hand is. Via het systeem wordt gedoseerd op basis van gewicht wordt gedoseerd. Ja, eventueel aangepast op basis van je klaring	Dosing based on prescribing system	Daily jobs		
P1	Technology makes the whole healthcare system more and more approachable	More accessible	Feelings towards healthcare technology		
P2	Ik denk dat dat wel een groot deel van de toekomst is. Niet alleen populatie pk, maar ook bijvoorbeeld machine learning. Want ja computers worden steeds sneller en steeds slimmer en die gaan ons werk deels ook overnemen en dat zie je ook met beeldvorming dat alog-ritme beter dingen kan opsporen dan een radioloog of zou bestaan. Dat gaat wel een steeds grote rol spelen.	Predominance in future	Feelings towards healthcare technology	Predominance techonology	Future perspectives
P2	Ik vind doseer platformen altijd wel handig, want je kan het daadwerkelijk zien in een overzicht	Clear	Feelings towards healthcare technology	Clear	Platform
P2	Ik denk dat het ook wel heel handig om te zien is dat je aan verschillende situaties kan simuleren	Handy	Feelings towards healthcare technology	Simulating different situations	Platform
P2	Het zou denk ik wel sneller maken	Faster	Feelings towards healthcare technology		
P2	Maar je verandert wel een deel van de zorg.	Big changes	Feelings towards healthcare technology		
P2	Ik denk dat je dan gewoon weerstand krijgt van de ziekenhuizen apothekers omdat dat hun dingetje is	Resistance pharmacists	Feelings towards healthcare technology		
P3	Ja en ik zie de modellen ook als absoluut één van de focussen binnen onze vakgebied en ook iets wat wij moeten uitdragen naar de kliniek	Necessary focus	Feelings towards healthcare technology	Model implementation clinic	Future perspectives
P3	Ik ben daarin natuurlijk ook extreem gebiast, want ik heb hier promotieonderzoek in gedaan,	Important	Feelings towards		

	dus ik vind het heel belangrijk ja		healthcare technology		
P3	Er hangt natuurlijk ook vaak een ongewild kostenplaatje aan	Expensive	Feelings towards healthcare technology		
P4	Technologie in healthcare, hier sta ik heel open in. Ik denk dat het ons heel veel gaat brengen en overnemen, ook mijn vakgebied. Ja, dat we heel veel meer met die luxe moeten gaan doen om de omslag te maken om uiteindelijk de zorg goedkoper te maken	Predominance in future	Feelings towards healthcare technology	Affordable care	Future perspectives
P4	Ik denk omdat de zorg steeds duurder wordt en nou er steeds meer ouderen komen, dat we het van dat soort technologieën moeten hebben.	Necessary focus	Feelings towards healthcare technology		
P4	Ik denk vooral het klinkt heel specialistisch inzetbaar en iets wat heel erg wat we echt voor bepaalde medicijnen in het ziekenhuis echt zou helpen en natuurlijk al gebruikt zou kunnen worden, bijvoorbeeld in de oncologie	Specialistic use	Feelings towards healthcare technology		
P4	Ik denk wel dat ik dat leuk zou vinden, maar ja, wat je al zei, qua tijd wordt het altijd wat lastig	Time-consuming	Feelings towards healthcare technology	Fast in use	Platform
P4	Interessant om te horen dat die modellen worden gemaakt en hoe dat eruit een beetje ziet. Dat je je bewust gemaakt wordt van de stappen die vooruitgezet worden. En dat ja, dat vind ik interessant.	Interesting	Feelings towards healthcare technology		
P5	Patiënten zouden er dus echt mee opschieten, wat het belangrijkste is.	Beneficial for patients	Feelings towards healthcare technology		
P5	Dat zijn meer de tricky dingen waar wijn mijn motivatie weer zou afnemen	Tricky	Feelings towards healthcare technology		
P6	Het is minder omslachtig, het is zou efficiënter maken wat we doen	Efficient	Feelings towards healthcare technology		
P6	Dat kan digitaal veel beter, want dit papier is fraudegevoelig	Less prone to fraud	Feelings towards healthcare technology		
P6	Wanneer je het veel patient specifieker kunt maken, dan heeft dat zeker meerwaarde. Ja, en als je dat ook nog implementeert in de systemen die er al zijn, dan heb je daar mee een win-win situatie	Important	Feelings towards healthcare technology	Combining existing systems	Platform
P6	De vraag is of ik het echt wil gaan gebruiken. En in zoverre, het is een mooi overzicht, maar het is niet dat ik nou de tijd heb om dat te doen, misschien wel de tijd wil nemen om dat helemaal elke keer weer uit te zoeken	Time-consuming	Feelings towards healthcare technology	Fast in use	Platform
P1	So I also have some discussion with them, like what are they expecting to look into and what kind of question they hope that I can initiate from the smallest aspects?	Discussions	Collaboration	Expectation management	Collaboration
P1	I ask them about their suggestions. Or I say something like oh, I see something in the data, but I'm not completely sure about what this means and I want to discuss with them because they are really much more closer to this	Giving/taking advice	Collaboration		
P1	If not getting the efficacy necessary, you provide them with the correct values of possible	Discussions	Collaboration		

	encouragement of efficacy and debate upon what's best				
P2	Ik wer kvooral met hoofd onderzoek op een van mijn studie. Ja, en en dan werk je vooral ook samen met elke studie krijgt een VS'er toegewezen. Ik weet alleen niet waar VS er eigenlijk voor staat, maar als zeg maar een super verpleegkundige. Die heeft iets meer verantwoordelijkheden dan een gewone verpleegkundige. Die is niet echt met onderzoek bezig, maar begeleid patiënten vooral. Samen beslis je over de patiënt	Decision-making	Collaboration	Interdisciplinarity	Collaboration
P2	Dan mail ik ongeveer een week van tevoren naar die Marjolein in dit geval is de VS door mijn studie van deze patiënt komt dan en dan. En dan heb ik ondertussen wel geleerd dat ik een deadline in moet stellen van kan je voor die dag de midazolam voorschrijven omdat dat de studiemedicatie is. En als zij dat gedaan heeft, dan ga ik Frans mailen. Ook met een tijdlijn kan je voor die tijd de midazolam al coderen, zodat de apotheek weet dat het bereid moet worden. En op de studiedag want zij went planning en moet op de planning anders wordt het zo laat. De patiënt moet tot acht uur na inname blijven. Een duidelijkere communication zou soms fijner zijn.	Making aware/controling	Collaboration	Clarity improvement	Collaboration
P2	Misschien verpleegkundig specialisten moet gaan kijken om dit te gebruiken. Ja, en voor een arts kan het wel, maar dan moet het wel echt wel een stuk simpeler gemaakt worden. Veel meer intuïtief. En eigenlijk moeten ze dan ook wat pk kennis opdoen. Want je ziet natuurlijk wel de curves. Maar wat betekent dat precies? Daarin moet de farmacometrist hen de basis aanleren.	Learning together	Collaboration	Intuitive	Platform
P3	Soms kan je daar jezelf wel eens in verliezen. Maar dan is het altijd weer goed om altijd in je team iemand te hebben die het moet gaan implementeren en die je dan scherp aanhaalt als je afdwaalt.	Making aware/controling	Collaboration		
P3	Voordat ik weer bezig gaan met modellen ontwikkelen, wil ik echt dat het een klinisch doel dient. Ja euh, ja. En dan ga je eigenlijk lobbyen, dus eigenlijk ga je proberen zieltjes te winnen. Ik heb dat heel erg gedaan bij de gynaecologie en dan bij de kindergeneeskunde. En heb daarin nu echt wel geprobeerd een enthousiaste clinici te zoeken die daar het nut van inzien en dat warm te houden. Maar ook ij mensen die veel onderzoek doen en die dus al veel data verzamelen waarvan ik denk van God, dan kunnen wij ook van die data gebruik maken. Dan zeg ik van ik wil iets over mijzelf vertellen en wat ik gedaan heb en waarom ik het belangrijk vind en uitgelegd hoe we nu tot dosering komen en waarom ik denk dat we dat beter kunnen doen met technieken en wat ik daarvoor nodig heb en hoe we dan een samenwerking kunnen opstarten. En ik moet zeggen dat moet je natuurlijk wel onderhouden he.	Connecting	Collaboration	Maintenance	Collaboration
P3	Ik geloof wel dat er zorg en onderzoek en onderwijs hand in hand te gaan. Dus ik geloof niet dat je onderzoek kan doen zonder betrokken te zijn bij de zorg en zonder betrokken te zijn bij het onderwijs. En ik geloof wel dat als je samen een klinisch probleem hebt, dat je die met elkaar kan oplossen en met elkaars expertise, dat dan the way to go is	Interdisciplinarity	Collaboration	Learning together	Collaboration

P3	Hoe kunnen we dat dan met elkaar verbeteren? Nou dat is dus betere studies op te zetten waarin we dus naar meer met meerdere pk monsters kijken naar hoe we dan zo'n model kunnen bouwen en welke variabele er dan van invloed zijn op het feit dat iemand die target niet bereikt. En nou dat je dus met zo'n model en een target concentratie eigenlijk tot evidence based doseringen kan komen die je dan vervolgens kan implementeren. En ik leg dan ook altijd uit hoe dat dat je niet alleen tot evidence based doseringen reikt, maar je ook covarianten kan identificeren, die dus relevant kunnen zijn om te kijken welke populaties er nu anders zijn.	Interdisciplinarity	Collaboration	Learning together	Collaboration
P3	In een wolkje te kijken van welke patiënten underpredicten we nu met die populatiePK modellen. En dat zie je dan heel goed. Dat is dus een hele leuke en waardevolle boodschap voor de kliniek, dus ook dat vinden ze vaak interessant. Dus ik zeg ook vaak het duurt wel even tot we tot die doseer adviezen komen, maar het kan je ook al inzicht geven in welke patiënten er nou anders zijn en waar we extra aandacht aan moeten besteden. Ja nou en zo doen we dat dan eigenlijk. Heel erg multidisciplinair dus met een MDL met gynaecoloog en de apotheek en gaat soms best wel wat tijd overheen	Multidisciplinarity	Collaboration	Making aware/controling	Collaboration
P3	Dan discussieer je zo dan met elkaar en dan uiteindelijk kom je tot een compromis. En dan heb je eigenlijk het beste van beiden, want zij kijken heel erg uit naar die patiënten. Die zien ze ook en wij kijken heel erg naar wat we zien van alle patiënten die wij hier tijdens een dagdienst bijvoorbeeld zien en probeer je dan echt tot elkaar aan te komen. En ja, ik heb wel het idee dat door je zichtbaar op te stellen en maar ook met elkaar ideeen te bedenken die een klinische vraagstelling dienen dus bijvoorbeeld.	Compromising	Collaboration	Making aware/controling	Collaboration
P3	En dat je het vervolgens niet alleen maar dingen bij hen komt halen, maar dat je het echt multidisciplinair doet, want mensen vinden het vaak heel leuk om met elkaar onderzoek te doen.	Multidisciplinarity	Collaboration	Correct ratio giving/taking	Collaboration
P3	Ik denk dat wij heel veel weten van spiegels waarin monsters moet afnemen. Hoe het hoort, wat het beloop is van zo'n spiegel en ik denk dat de arts de patiënt heel goed kent. En je hoeft ook niet over elke patiënt te bellen. Soms kan je ook gewoon prima in het dossier lezen hoe de patiënt eraan toe is en is een spiegel kan je daar heel goed op varen wat je wil, maar voor die paar twijfelgevallen is het wel handig dat het echt een samenspel is. En zij varen daar op de kliniek ook echt op. Dus zij willen ook echt dat wij een spiegel advisering doen en ja gaan dat niet zelf doen	Multidisciplinarity	Collaboration	Giving/taking advice	Collaboration
P3	En ik denk het is wel een complexe handeling, maar als je het elke dag zoals wij hier nu doen, waar we ongeacht of het een goede spiegels of niet is. Wij zetten het er standaard in, want als het over twee dagen geen goede spiegel is, dan hoeft jouw collega van dan niet twee dagen terug te kijken wat er toen allemaal is gebeurd	Efficient	Collaboration	Up-to-date	Platform
P4	Ik zou dat wel een leuk project vinden om samen te werken aan het gebruik van zulke modellen om doses te personaliseren	Learning together	Collaboration	Interdisciplinarity	Collaboration
P4	Maar ik ben dan nog wel echt heel erg benieuwd naar wat kan iemand anders daar toch nog aan toevoegen? Wat zijn de invloeden van elkaar? Is	Learning together	Collaboration	Model overview	Platform

	nou gewicht belangrijker dan leeftijd of van nierfunctie? Op deze antidepressiva ofzo? Want dat zal natuurlijk per medicijn verschillen. Dat zou ik wel willen leren van een expert.				
P4	wat ik denk dat belangrijk is wel om goed aan te geven dat ik denk dat de populatie waaraan ik meewerkt dat dat zo divers is dat ik denk dat dat heel lastig is om in een goed model te stoppen. Of het wordt een zo'n ingewikkeld model dat ik denk dat het ook qua tijd, tijd investering, teveel is want het is echt bizar druk soms. Dat dat gaat elkaar schuren.	Trust	Collaboration	Keep expertise	Collaboration
P4	Flink wat uitleg van hoe gaat het dan? Wat heeft het voor voordelen? Waar zit je verbetering in en niet? Werkt de magie ook echt?	Trust	Collaboration	Proof	Platform
P5	We hebben ook apotheker met wie we samenwerken, dus we hebben sowieso één keer per jaar medicatie review van alle patiënten die daar die in een zorgcentrum wonen. Ja, en we doen zelf ook heel regelmatig voor: twee keer per jaar heb een patiënt bespreking met elkaar en die ook bewoner om hen of familie en dan nemen we de medicatie ook altijd allemaal weer door. Dus er zijn een keer of drie momenten in het jaar dat we vast medicatie allemaal weer evalueren	Giving/taking advice	Collaboration	Discussions	Collaboration
P5	dan gewoon standaard zeg maar om überhaupt nog te kijken of het nog passend is om voorschrijven. En verder is natuurlijk een ja, als je iets tracht dan dan volg je ook of het wat doet. Bij bepaalde medicijnen bijvoorbeeld een Bitinib of zo, dat zijn van die middelen met hier nog met de oudere psychiater overleggen. En ik had pas nog het middel waarbij ik dacht goh, een. Wat is nou precies de bedoeling hiermee? Dan bel ik met apotheker ja.	Decision-making	Collaboration	Giving/taking advice	Collaboration
P5	Kijk, als ik een paar handvatten krijgt, en ik kan het daarmee gebruiken, dan graag. En als ze uitgebreider de kennis nodig heeft, dan vraag ik dat graag aan een ander.	Learning together	Collaboration	Correct ratio giving/taking	Collaboration
P5	Ik zie mijn rol als arts, daarin het toch het meest op de achtergrond, ik hoef de details niet direct te weten, maar mij is het belangrijk dat ik wel weet van het bestaan van en op het juiste moment of kan toepassen of de juiste hulpbronnen kan inschakelen om het toe te kunnen passen.	Correct ratio giving/taking	Collaboration	Keep expertise	Collaboration
P6	Als iemand bij mij op spreekuur komt dan kan ik ook het dossier van de patiënt al eerder inzien, daar staat alles in wat we weten van deze persoon, inclusief alles wat er in ziekenhuizen als teruggestuurd wordt. Daar vullen ze de medicatie die ze gebruiken in enzo. En in sommige komt er indicaties met betrekking op medicatie staan er allemaal in ja vermeld. Dat zat ook weer gekoppeld aan apotheek, dus apotheek koppelt dat ook weer aan ons terug. Dus dat is altijd up to date.	Multidisciplinarity	Collaboration	Up-to-date	Platform
P6	Nierfunctie problematiek bij de apotheek vraagt altijd een relatief recente klaring van nier door te geven, zodat zij iets van medicatie die op aan kunnen passen. Ja, dat is iets wat dan in systeem weer omhoogkomt. Maar dat zijn allemaal dingen die een waarschuwend effect hebben	Making aware/controling	Collaboration		
P6	Het is die bellen vaak binnen 5min. Klopt niet. Of heb je wel over nagedacht? Of waarom doen we dit? Ik heb geen zin in dat telefoontje van de apotheek.	Decision-making	Collaboration	Making aware/controling	Collaboration

P6	En assistent die belt en die assistent belt dan weer met mijn assistent en mijn assistent belt dan weer met mij gaat ze over 4/5 schijven. Terwijl dat niet had gehoeven. Nee dus dat kan veel efficienter.	Inefficient	Collaboration		
P6	Het is noodzakelijk dat de apotheker controleert wat wij doen. Zij weten andere dingen beter.	Making aware/controling	Collaboration	Keep expertise	Collaboration
P6	Klinkt een beetje gek, maar de arts moet moet bedenken wat ie denkt dat goed is. Ja, op de achtergrond moet iemand die verstand heeft van modellen bijvoorbeeld of even zeker wel weten dat het ook allemaal klopt. Het is echt de samenwerking binnen elkaars specialisme.	Making aware/controling	Collaboration	Keep expertise	Collaboration
P6	Wij vertrouwen ook op het kunnen van de apotheek. Dat zij snappen hoe het werkt en waar ik het op baseer. Ik vertrouw op hun experise, want je zult wel moeten, want die kennis heb ik niet. Ik denk ook niet dat ik dat kan begrijpen.	Trust	Collaboration	Multidisciplinarity	Collaboration
P6	Tijd om het om het te leren gebruiken en feedback vanuit de apotheker, want uiteinde zijn zij zijn diegene die dat dan kunnen doen.	Learning together	Collaboration	Making aware/controling	Collaboration
P1	Adjust dosing, but not like precisely like not like a precise dose for each patient. More like, do I need dose adjustment for a certain population? Implement our research to clinical practice.	Precise dosing	Platform	Implementation	Platform
P1	There's so much variabilities in clinic and from a model of but I only see the one interesting or the challenging part as a modeler. More models are necessary to cope with the variations	Lots of models needed	Platform	Time-consuming	Platform
P1	I think for weight, age, those kind of things, it's possible to adjust change in age or change in renal function or like liver function change. And I think that that will be fine to use through a platform.	Covers easy cases	Platform		
P1	I think that this is quite handy for people who don't really understand the modelling part	Understandable/ easy to use	Platform		
P2	Wanneer bloedspiegels zijn afgenomen. En sommige covariaten, wat afhankelijk is van het geneesmiddel, dus nierfunctie, gewicht, leeftijd en dan krijg je eigenlijk daar uit simulaties te zien. En dan kan je ook de volgende doseringen erin zetten en dan kan je zien hoever vancomicine bijvoorbeeld of een bepaald target gehaald wordt, dus daar baseert de ziekenhuisapotheker het advies naar de arts toe op voor de volgende dosering	Precise dosing	Platform	Interdisciplinarity	Platform
P2	Maar je kan al als het een infuus is kan je kort, lang de dosering aanpaste. Je kan allemaal verschillende situaties te uithalen.	Flexible	Platform		
P2	Er moet een bepaalde training of iets dergelijks aan af moeten gaan voordat het bruikbaar is voor anderen. Ik denk dat er dan educatie moet zijn, zowel voor ziekenhuis, apothekers als artsen, en hoe je dit kan gebruiken in de praktijk in welke situaties dit meerwaarde heeft. Uhm. En dat kan in principe gewoon heel makkelijk geïmplementeerd worden in een specialisme wanneer zij nog aan het leren zijn.	Training needed	Platform	Learning together	Collaboration
P2	Ik denk dat het intuïtief moet worden. Dus net zoals Excel, dat je op een paar knopjes klikt of dat je gewoon je klik dingen aan van dit is de dosering is de nierfunctie. Uhm. Euhm. En dat het snel moet werken voor een arts, hij heeft andere dingen te doen. En die heeft geen niet echt tijd om met allemaal van een muis werkt niet en mwpharm moet met pijltjes werken en dus hartstikke jaren 90 of zelfs daarvoor. Dus dat dat gaat niet werken. Het moet echt heel duidelijk,	Fast in use	Platform	Intuitive	Platform

	overzichtelijk, simpel en snel zijn met gewoon knopjes die ze aankunnen klikken en een concreet resultaat.				
P2	Eigenlijk dat je zelf niet eens zou hoeven spelen met de doseringen, maar dat die dosering als een uitkomst eruit rolt. Als jij aangeeft wat jouw effectiviteit zou moeten zijn als het aan jou.	Providing dosing advice	Platform		
P3	Het moet heel erg praktisch zijn en het moet echt een klinische vraagstelling dienen, in plaats van dat het soms zo is kan gebeuren dat je zelf iets heel interessant vindt, maar wat een klinisch die op dat moment de meerwaarde niet ervan inziet. En dat heeft mij echt doen denken vanuit klinische vraagstelling	Serving clinical purpose	Platform	Interdisciplinarity	Platform
P3	Maar ik geloof wel in in dat het praktisch moet blijven en praktisch inzetbaar moet zijn.	Practical in use	Platform		
P3	Ik leg wel eens wat uit over een voorbeeld van een populatiePK model en dat je dan variabiliteit kan aantonen en die kan proberen te verklaren met klinische parameters. Maar daar houdt het wel op. Daar laat ik het dan een beetje bij, want ik ga niet praten over hoe ingewikkeld is om soms naar de shrinkage te kijken en al dat soort dingen.	Understandable/ easy to use	Platform	Keep expertise	Collaboration
P3	Ik vind dat heel fijne programma's omdat je als je kritisch blijft kijken naar modellen, je die natuurlijk gewoon in zo'n programma kan zetten en daarmee ook weer voorspellingen kan doen. Dus ik vind dat een hele goede programma's om ons op weg te helpen in doseren adviezen.	Precise dosing	Platform	Practical in use	Platform
P3	Voor InsightRX wordt het op zich wel wat internationale manier geupdate met zijn modellen, dat is voor mwFarm niet altijd. Die loopt nogal eens van achter. Ja, en dat vind ik dan soms wel jammer dat je dan. Dus je moet echt de literatuur eigenlijk goed bijhouden. Eigenlijk moet je echt één iemand hebben die dat als ze ook als takenpakket erbij neemt van het updaten van die modellen? Ja, voor alle patiëntengroepen is dat wel een en een tijds intensieve taakje, maar merk bijvoorbeeld wel dat wel steeds belangrijker ga vinden	Up-to-date	Platform	Time-consuming	Platform
P3	Maar ik geloof wel dat je altijd kritisch moet denken van is de populatie in dat programma mwfarm of insightrx, is dat een afspiegeling van mijn populatie. Toch heb ik het idee dat dat autonomie heel erg versterkt juist, want je hebt een soort ehm, een tool die echt iets tot meer inzicht leidt terwijl je zelf blijft nadenken. En dat vind ik heel mooi.	Clinical awareness	Platform	Autonomy	Platform
P4	Medieval, dat is een van de grotere volgens mij van de voorschrijft systemen die zijn ontwikkelt. En daar zie je dat ze je gewoon heel de lijst van heel wat patiënten allemaal heeft. Om dat echt al tien verschillende middelen zijn en interactie daarin ietsje vaak ook wel nog. En als je het voorschrijft, dan krijg je die pop-up wanneer er interactie is.	Serving clinical purpose	Platform	Up-to-date	Platform
P4	Of het wordt een zo'n ingewikkeld model dat ik denk dat het ook qua tijd, tijd investering, teveel is want het is echt bizar druk soms. Dat dat gaat elkaar schuren.	Time-consuming	Platform		
P5	waar ik meteen aan denk is dat er een koppeling is tussen mijn patiëntendossier. Of dat die koppeling mogelijk is. Dus dat het gewicht, de leeftijd, dat het allemaal in ieder geval gekoppeld kan worden. Dus dat dat gewoon dat er heel	Efficiency	Platform	Up-to-date	Platform

	efficiënt gebeurt. Dus precies dat zal wel heel mooi zijn als voorschrijver niet al die data van die desbetreffende patiënt nog hoeft in te vullen. Maar dat wanneer jij een patiënt opzoekt dat je er op klikt en dat eigenlijk dat er allemaal uitkomt rollen.				
P5	Erg overzichtelijk, zeker volgens mij wat links staat. Dat wordt dus zou fantastisch zijn als dat uit je gewoon medisch patiëntendossier wordt, hij eruit wordt gehaald. Ehm ja. En ook ik vind ik hou van grafieken, houdt het goed overzichtelijk en zie je duidelijk dat het goed gaat.	Understandable/ easy to use	Platform	Efficiency	Platform
P5	Hmm dus een goed ICT systeem met een goede koppeling en een overzichtelijk dashboard zoals dit net, dat lijkt me wel handig. En verder. Ja, ik denk toch echt wel flink wat uitleg van hoe gaat het dan? Bewijs dat dit bijdraagt aan een kwaliteit van leven waar het bij mij in mijn werk natuurlijk altijd op draait.	Training needed	Platform	Proof	Platform
P6	Eigenlijk moeten ze iets hebben van dat je zou dan kunnen bedenken van hoe gaan we een systeempje maken waarin we aan de apotheken kunnen aangeven van nee, dit is anders dan wat we in een normale situatie doen. Waar dan ook de patiëntengegevens bijgevoegd zijn. Want ik heb vaak weinig tijd en geen idee over wie het gaat.	Efficiency	Platform	Fast in use	Platform
P6	Het in één in een systeem geïmplementeerd wordt zijn aan de aan het eind van het systeem komt er bij mij, er verander niks maar op de achtergrond gebeurt er heel veel. Ja euh, dan is dat meerwaarde. Ja. En als dat ertoe leidt dat wij makkelijker met elkaar kunnen communiceren en om ter voorkoming eva het aantal probleem, ja, dan is dat gunstig.	Understandable/ easy to use	Platform	Efficiency	Platform
P6	Als je dat gaat inbouwen, wil ik het liefst van mijn computer het advies hebben. Dat ik het medicijn kies, en de computer dan de dosering op basis van de karakteristieken van de patient. Ik wil zelf nadenken of een specialist die wil altijd zelf nadenken over wat ie voorschrijft zeker. Maar wat dan wel ideaal zijn is dat de computer uiteindelijk zegt: nou ja, bij deze mevrouw Jansen is toch wel verstandig om iets lager te gaan doseren.	Precise dosing	Platform	Autonomy	Platform
P6	Op moment dat dat door het platform te bouwen, bij iedereen die bij die data die op een patiënt zich maar vastgeplakt zijn en dat iedereen erbij kan. Ja dan zorgt er liever voor dat je zorg een stuk veiliger en specifieker is.	Interdisciplinarity	Platform	Safe	Future perspective
P1	I think there are a lot of countries for example Asia where the pharmacokinetic modelling, which we showed, is not so developing, but they still want to use this kind of information to improve that clinic. So I do think it will be useful for those countries	International	Future perspective		
P2	In de ideale wereld zou je zo'n model willen gebruiken in om doses limiting toxiciteit te voorspellen voor die stof in combinatie behandeling om met MEK HER remmers, want dat je ziet bij steeds meer vormen van kanker dan die behandelingen een rol gaan spelen. En ze geven allebei bijvoorbeeld heel veel diarree. En dat is wel een reden waarom mensen stoppen met de behandeling. En met zo'n model kan je wel gaan onderzoeken van is het dan beter om de MEK remmer te verlagen of de PANHER	Limiting toxicity	Future perspective	A lot of models needed	Future perspective

	remmer? Maar of is het beter om continu of intermitted van vijf dagen op vijf dagen af? Waarbij over dat soort dingen zou je dan mee kunnen onderzoeken en dan zou je kunnen proberen mensen op de behandeling te houden. Maar daar is meer data nodig.				
P2	Dus het zou ook fijn zijn als ik niet gewoon overal continu achteraan moet gaan, want anders gebeurt het letterlijk gewoon niet.	Autonomy	Future perspective	Making aware/controling	Collaboration
P3	Dus ik geloof wel dat het uiteindelijk voor iedereen is maar dat we dat moeten aantonen, beginnend bij de speciale patiëntengroepen.	Extended scope patient groups	Future perspective		
P3	Ik denk ook wel dat dat de toekomst eigenlijk nu al is en ook wel echt blijft, dat we het steeds eigenlijk meer moeten gaan updaten voor speciale patiënten populaties. Dat zal ook wel echt gaan gebeuren in de toekomst	Lot of models needed	Future perspective		
P3	en we weten dat de fysiologie van de zwangere vrouw heel anders is. En we doseren nog steeds empirisch en conform als niet zwanger. En dat vind ik heel raar, want we weten dat de klaring echt heel anders is. In het derde trimester weten we dat verdeling is volume heel anders is. En we kijken eigenlijk alleen naar veiligheid voor de feutes. Wat natuurlijk superbelangrijk is. Maar we kijken niet naar, bereiken we nu goede targets bij zwangere patiënten? Ik denk dat we er echt wel voor formularia gaan krijgen, vooral voor zwangere patiënten.	Extended scope patient groups	Future perspective		
P4	Ik denk dat daar zo beter zou zijn als daar hun doseringen beter uitgezocht, beter onderzocht zouden worden en beter aangepast aan mijn patiënten. een juiste behandeling hebt zal diegene waarschijnlijk ook minder snel terugkomen en dus uiteindelijk goedkopere zorg geleverd kunnen worden	Precise dosing	Future perspective	Affordable care	Future perspective
P5	Zeker hoe meer gepersonaliseerd je kunt voorschrijven ook, ja, hoe beter het is. Dus dat is wel de toekomst ja.	Precise dosing	Future perspective		
P6	Alle patiënten één keer per jaar en de medicatie controleren. En dat je ook aan het eind van de rit weet dat elk jaar iedereen geevaluseerd is, dus dat ik altijd vanuit gaan dat het goed is dat het goed is.	Up to date	Future perspective		
P6	Dat zou mooi zijn. Dus als je elk medicijn wat je voorschrijft, ja patiënt specifieke dosering heeft. Dat zorgt ervoor dat je zorg een stuk veiliger en specifieker is.	Precise dosing	Future perspective	Safety	Future perspective

Supplementary F. Focus group protocol

Focus group protocol

Introduction to the topic

Nowadays, the development of models for model informed precision dosing (dosing based on what the body does with the drug) is very upcoming, since the use of such models would reduce the chance of a patient reaching an exposure leading to toxicity. For a lot of drugs, busulfan in this study's case, a platform is developed to describe the concentration-time and elimination profiles for a specific dose, creating the ability to fully personalize dosing based on patient characteristics. The busulfan dosing process is still mainly based on the patient's body weight, despite the availability of model informed precision dosing platforms. Practitioners are used to dose patients based on long-existing protocols, which they know by

heart, and which are very easy to use. Because of unidentified reasons, they do not use such available platform and stick to the old protocol, risking a decrease in efficacy of busulfan treatment and increasing the risk of toxicity in a patient. To be able to make use of population model informed precision dosing implemented in a platform, a clear communication and collaboration between the pharmacometrician and practitioner is necessary.
This project aims to describe the difficulties in the communication and collaboration between pharmacists and pharmacometricians (for example, what causes practitioners to stick to the old protocol instead of using the platform) and describe what practitioners and pharmacometricians need in their collaboration through the platform, meaning what elements are needed in the platform to improve the pharmacists' practice and to create a learning platform for both parties. These adjustments to improve the platform are meant to make it more accessible, applicable, less time-consuming, and more attractive to be used and improved constantly.
One example of a MIPD platform is this platform of InsightRX, where the patient characteristics are seen left, the dosing regimen that can be adjusted in the middle, and the graph showing the concentration-time profile and the target concentration over time to check of the choosing dosing regimen fits the target exposure (show recycled sample as used in interview protocol Appendix C).
In a previous phase of the project, I interviewed several professionals in each discipline. The analysis of these interview led me two main subjects, that I would like to discuss in this focus group. During the analysis of the interviews, I coded all the quotes of the participants and then after combined all these codes and related them to a specific topic. This led me to some codes that were perceived as being most important for that topic by these participants. In the focus group, I would like to obtain all your point of views, beliefs, and attitudes regarding the specific topics by asking you what you would perceive as most important. I have written down several codes (page 4) on these pieces of papers, of which you select the 5 most important and subsequently will rank them from being 1 to 5 (5 being most important) whenever I give a situation case. The first ranking per case will be about the collaboration, and the second and third will be about the use of a dosing platform. You are allowed to discuss during this ranking with your own discipline. Then after we will discuss in a group the results and I will ask some related questions. The discussion will be fully confidential and in the analysis no names will be used. Is this all clear to you or do you have any questions?

Setting the rules for the discussion
Before starting the discussion, would like to set some rules in order to make the group discussion go as fluently and comforting as possible. The rules will be: 1) listen to each other and the moderator; 2) only one person is talking at the same time during the plenary discussion; 3) let your team members speak and listen to them while discussing the ranking together; and 4) respect other participants in the conversation in their opinions and their explanations.

Ranking the cases based on codes from the interview
The topics further tested and studied include the collaboration between the pharmacists and pharmacometricians and the use of the platform. Your attitudes towards these themes will be tested through 1 introductory course case, 2 dosing cases, and the summarized topics as a whole. Then after a short discussion will be started regarding the answers of the interviews and a couple of questions will be asked.

1. **Introductory course before using improved MIPD platform**
   Before pharmacists and pharmacometricians are able and allowed to make use of a MIPD platform, an introductory practicum needs to be passed. Both disciplines meet up one morning to go through the introduction of the two portals of the platform, where they interact to pass the instruction.

   On the morning of the course, a pharmacist is linked to a pharmacometrician. They start the course and first, the portal for the pharmacists opens and let both the pharmacists and pharmacometricians see its features including explanations. The course starts with the overview of all patient numbers corresponding to one specific patient. Clicking on patient number 0, corresponding to the introductory patient, the portal is brought to the dashboard of that hypothetical patient. On the dashboard, they see how the characteristics and genomic information of the patient is entered and can be renewed based on the latest data. Furthermore, an overview of medication patient 0 is currently using is shown combined with a list of medication previously used. A prescription can be added by clicking on the plus-button, where the drug, in this studies case Busulfan, that the

pharmacists would like to prescribe can be added. Then, the pharmacist explains the pharmacometrician based on what they decides on what drug and corresponding dosing for that patient, showing each step of their decision making (literature/Farmaceutisch Kompas e.g.). That decided dosing regimen can be filled in to be tested or can be calculated by the platform based on the characteristics/genome information. Looking at the concentration-time graph showing the target concentration and the concentration caused by the specific dosing regimen for busulfan, the pharmacometrician can explain how to interpret such a graph and how to know whether your concentration is sufficient or needs to be adjusted. If the dosing regimen is sufficient, the drug can be signed as prescribed, which subsequently will be sent to the portal of the pharmacometrician.

The hypothetical prescription is sent to the portal of the pharmacometrician, which leads the course to the portal of the pharmacometrician, where an overview of the dosing regimen as prescribed by the pharmacist is shown. The pharmacometrician can see on what the dosing is based, what characteristics are important and whether the information on the patient is up to date. Then after, to check the dosing regimen, all implemented models for this drug are shown on the dashboard. The pharmacometrician checks if the model, necessary to base patient 0's dose on, is developed and implemented. This feature of different models causes a pop up in the course where a short explanation in lay language is given on how a model is developed and what should be included to validate. The pharmacists and pharmacometrician discuss these different models, where the pharmacometrician answers the questions asked by the pharmacist and explains how they approach these models and base their dosing on such model. After deciding the dosing regimen is sufficient, they can click on the accept button and the recipe for the regimen will be sent to the pharmacy. Whenever the models are not up to date, raising the idea that the dosing will be insufficient, the pharmacometrician does research on the dose, while contacting the pharmacist to discuss. When the discussed dose is entered and accepted, the MIPD platform sends the prescription to the pharmacy.

2. Busulfan for chronic myeloid leukaemia

Erik is a 56-year-old male who is admitted for a matched related bone marrow transplant for chronic myelogenous leukaemia in chronic phase, resistant to multiple tyrosine kinase inhibitors (TKIs). His conditioning regimen is the busulfan/fludarabine regimen, which is:

Fludarabine 30 mg/m2/day IV every 24 hours on days -7, -6, -5, -4, -3
Busulfan dosed to target AUC IV every 24 hours on days -6, -5, -4, -3

Dose 1 of targeted busulfan started on 1-APR-2022 at 4 mg/kg. According to his transplant care team, the desired cumulative busulfan exposure range is 80 to 100 mgxh/L over the 4 days of busulfan administration. Cumulative exposure is defined as area under the curve (AUC) over all days of busulfan conditioning. There are no known significant drug interactions.

Only one dose adjustment will be made based on Dose 1 pharmacokinetic analysis. The new dose will start with Dose 2 and continues through Dose 4. Thus, Dose 1 is based on Erik's actual body weight combined with the desired cumulative busulfan exposure, while subsequent doses are based on pharmacokinetic sample analysis of Dose 1.

Characteristics Erik:
Actual body weight: 80.1 kg
Adjusted ideal body weight: 71.3 kg
Height: 171.6 cm

Busulfan Dose 1 administered: 285 mg Infusion start time: 8:00	

Infusion stop time: 11:00	
Actual sample collection times (24:00)	Measured plasma concentrations (ng/mL)
1) 11:02	3990
2) 11:15	3662
3) 12:30	2784
4) 14:00	2040
5) 16:04	1279

Dose 1 is administered on the 1st of April by his treating pharmacist. To determine the subsequent doses, the pharmacist's assistant takes samples at five timepoint after infusion. Pharmacokinetic sampling is conducted as followed:

Using the results of the pharmacokinetic analysis of Dose 1, the following doses can be determined. The pharmacist enters the patient characteristics obtained from the pharmacokinetic analysis of Dose 1 in the dashboard of that specific patient on the portal for pharmacists of the MIPD platform. They enters the expected dosing regimen based on possibilities of the hospital, and then after a dose for Dose 1 to Dose 4 comes out. The pharmacists checks whether this fits the target concentration-time profile. The recipe for this dosing regimen is send to the portal of the pharmacometrician of the platform. The pharmacometrician check the prescribed doses through the platform making use of the cumulative target exposure and patient characteristics, expressed in pharmacokinetic data, as determined from sample analysis. The pharmacometricians then rejects and changes or accepts the dosing regimen as described by the pharmacists. Dose 2 infusion needs to start at 8:00 the following day, meaning Dose 2 calculations and preparations need to be conducted beforehand. Therefore, pharmacometrician communicates Dose 2 calculations and preparation instructions to pharmacist on time.

3. Tamoxifen for ER-positive, HER2 negative metastatic breast cancer and CYP2D6*4/*4

Karen is a 68-year-old postmenopausal Caucasian female diagnosed with metastatic ER-positive, HER2 receptor negative breast cancer. Bone scan shows positive uptake in the spine and right scapula; brain and liver scans are negative for metastatic breast cancer. All laboratory values, including complete blood count and liver function tests, are within normal limits. Currently taking gabapentin for musculoskeletal pain due to fibromyalgia. Patient is not taking any other medications. The practitioner chooses to prescribe the oral drug tamoxifen, since no significant drug interactions are found.

Dose 1 used for Month 1 is based on the body surface area of Karen. The desired exposure of tamoxifen is reached by a dose given once daily ranging from 4 to 200 mg/m2 body surface area. The usual starters dose is set to be 20 mg once daily.

Characteristics Karen:
Actual body weight: 68.2 kg
Height: 169.6 cm
BSA: 1.79 m^2

Karen's genomic Information: CYP2D6*4/*4 (poor metabolizer)

The treating physician of Karen enters the characteristics and genomic information of Karen into the MIPD platform and estimates a dosing of 20 mg of tamoxifen per day for the first month, since is the most common starting dose and the target exposure would be reached based on Karen's BSA. However, after entering the estimated dosing regimen of 20 mg per day, the pharmacist checks the concentration-time profiles in his/her MIPD portal, which shows the concentration of tamoxifen is too low to reach target exposure. The platform gives a warning to increase the dosing regimen, since the CYP2D6*4/*4 decreases the effectivity of tamoxifen. The platform suggests increasing dosing regimen of tamoxifen to 40 mg per day for the first month to reach target exposure. The prescription is sent to the pharmacometricians portal, who checks the concentration-time profile of Month 1. They checks whether the right models are implemented in MIPD platform, to make sure the platform

predicted the increased starting dose of 40 mg per day based on BSA and Karen's genomic information correctly. The pharmacometricians accepts the 40 mg per day for 30 days prescription and sets a reminder to check the dosing regimen for the following months.

4. The collaboration between pharmacists and pharmacometricians.

5. The platform for decision-making in dosing regimen.

   Discuss the results with the participants based on what the interviewees thought were more important.

Asking the questions
The following questions were shortly discussed to obtain insights on what to focus on in describing recommendations. The questions aim to test the establishment of a collaboration through the platform.

1. What are the first things to mind when you think of the collaboration, both on the practical introduction and the platform, as discussed? Positive or negative aspects?
2. What are your general feelings about this dosing platform? What is something you would like to learn about it?
3. What are your general feelings about collaborating with the other discipline through a dosing platform as explained in the introduction? Suggestions on how to approach this collaboration or what changes would you recommend?
4. What would you like to get from the other discipline in collaborating through the platform? And what would you like to give the other discipline back?
5. How do you think this collaboration towards an introductory course would affect the overall collaboration and use of the platform?
6. Do you expect to use such a platform in the future? Why or why not?
7. Do you feel like any aspects or issues about this collaboration and/or platform have not been addressed and are important to address?

To encourage participants to elaborate on their answers, some probing questions were formulated:

- Why do you feel like this?
- What do you think about it?
- How would you do it differently?
- How would like to see it differently?
- What could be worse?
- What could be better?

Closing focus group by everyone commenting upon the discussion
The discussion will be closed after everyone spoke their hearts. The question leading to the end of the discussion will be:
Since we are at the end of the discussion, I would like to ask you whether you still have something you would like to share regarding these topics.
Then after, finish up the discussion by thanking the participants and explain how their input will be used in the study.

Codes regarding collaboration:
Clarity
Compromising
Connecting
Correct ratio giving/taking
Decision-making
Discussions
Efficiency
Expectation management
Giving/taking advice
Inefficient

Interdisciplinarity
Keep expertise
Learning together
Making aware/controlling
Multidisciplinarity
Trust

Codes regarding platform:
Autonomy
Clear
Clinical awareness
Covers easy cases
Efficiency
Fast in use
Flexible
Implementation
Interdisciplinarity
Intuitive
Lots of models needed
Model overview
Proof
Practical in use
Precision dosing
Serving clinical purpose
Simulating different situations
Time-consuming
Training needed
Understandable/easy to use
Up to date

Supplementary G. Focus group quote-theoretical framework relation

Quote	Discipline	Proposed implementation	Theoretical framework element
Voorbeeld hierin ook wel gewoon de discussie dat je kunt discussiëren waarom iemand iets doet. Binnen dit platform dus dat je kunt zeggen van oké maar ja, leuk en aardig dat jij die dosering baseert op literatuur. Maar waarom? En wat haal je eruit? En hoe weet je dat dan?	Pharmacometrician	Collaboration	Interdisciplinary learning
Voor de gevallen als ze dan weten en uit het hoofd doen, hebben ze in principe zo'n model niet nodig. Maar het is wel perfect voor zeldzame gevallen en dat soort dingen.	Pharmacometrician	Platform	Interdisciplinary collaboration and technology acceptance
Dat is het ook zo dat op het moment dat je uit je hoofd doet en je vult het in, dan geeft het platform gewoon aan oh dit is goed, prima, schrijf maar voor. Wanneer je alles toevoegt is het ook weer extra data zeg maar, waardoor alles up to date blijft.	Pharmacometrician	Platform	Technology acceptance
Ehm, ik denk dat het uiteindelijk ook efficiency oplevert. Maar wel als er daadwerkelijk tijd in geïnvesteerd wordt.	Pharmacometrician	Platform	Technology acceptance
Misschien wel, want als jij vindt dat zij en jij moet hen vertrouwen, maar zij moeten jou ook	Pharmacometrician	Collaboration	Interdisciplinary collaboration

vertrouwen. Ook op het moment dat jij toelicht wat zo'n model precies weet je inhoud. Moeten zij jou wel kunnen vertrouwen? Dus ik ben het daar mee eens.			
Misschien ook wel expectation management. Maar dat hoort dan wel een beetje bij Trust. Deze beïnvloeden elkaar, maar ook de keep expertise zit in de expectation management en heeft trust nodig om te kunnen waarborgen.	Pharmacometrician	Collaboration	Interdisciplinary collaboration
Voor een pharmacometrician**, d**us iemand die die modellen implementeert, dat die ook kan zien van oké, maar welke modellen zijn er dan allemaal? En hoe maak ik gebruik van verschillende modellen?	Pharmacometrician	Platform	Technology acceptance
Ja, en laten we eerlijk wezen efficient is ook gewoon belangrijk, want zo'n cursus moet vooral ook een beetje praktisch gericht zijn. Ook dat lijkt me vrij belangrijk.	Pharmacist	Collaboration	Interdisciplinary collaboration
Dat je gelijk in zo'n introductie aantrekkelijk maakt om het ook gebruiken voor straks in de echte case.	Pharmacometrician	Collaboration	Technology acceptance
En learning together**,** hebben we dat? **Ma**ar dat hebben we eigenlijk al een beetje met dat je elkaar leert kennen zeg maa**r**. Ja, da**t is** een beetje alles **met** connect**.**	Pharmacist	Collaboration	Interdisciplinary learning
Je gewoon heel graag duidelijk wil hebben wat het doel is van een e-learning of wat het doel is van een introductie van een introductiepracticum. Als je dat helder is wat ze van jou verwachten, dat het helder is wat je ervan kan verwachten. Dat komt ook later in expectations management. Maar je kan gewoon ja, zeg maar een beetje concreet taalgebruik. Dat helpt ons gewoon heel erg. Want anders als het niet duidelijk is hoe het werkt en als niet duidelijk is wat de bedoeling is, dan haak je gewoon heel snel af als je er online een training moet volgen	Pharmacists	Collaboration	Interdisciplinary collaboration
Dat je ook gewoon eens weten hoe het aan de andere kant er aan toegaat zeg maar, aan de hand van het platform dat jij niet gebruikt. En daarbij zeg maar connecting dat je dus ook een gezicht hebt bij die andere kant en weet wat iemand voor expertise of achtergrond heeft	Pharmacist	Collaboration	Interdisciplinary learning
Binnen ons veld, en dus zeker een ziekenhuis zien wij heel vaak mensen in consult. Dit is het moment dat jij iemand met meer expertise op dat veld om advies vraagt. Dan ga ik eigenlijk per definitie van uit dat die er meer voor weet dan ik en dat die dus gelijk heeft. Dus Trust is voor mij iets wat er gewoon al is.	Pharmacist	Collaboration	Interdisciplinary collaboration
Ik kan me voorstellen en het als je een relatief nieuw beroep hebt of iets in de coderings wereld waar wij gewoon echt helemaal niks verslappen. Maar dan is het veel moeilijker om in te schatten wat voor expertise heeft iemand? En in hoeverre kan ik die modellen van die persoon vertrouwen zeg maar? Ik snap precies wat dat voor jullie. Vanuit de andere kant doet het meer misschien belangrijker is.	Pharmacist	Collaboration	Interdisciplinary learning
Maar dan bij de platformen. Is dus echt die proof. Dus echt de eh het bewijs dat het werkt. Ehm. En dat vonden wij dus juist eigenlijk het belangrijkst van het platform, omdat je gewoon moet kunnen aantonen dat het werkt. En nu liggen die bewijzen er wel, maar ze moeten ook overgebracht worden.	Pharmacometrician	Platform	Technology acceptance
Want juist die modelleerder zijn nog heel erg bezig met het overtuigen van het feit dat het iets is. Terwijl inderdaad jullie als je het gebruikt erop	Pharmacometrician	Collaboration	Interdisciplinary collaboration

vertrouwt dat het goed is, want het is goedgekeurd			
Vonden we het eigenlijk nog steeds de Clarity het belangrijkst omdat het gewoon duidelijk moet zijn van wat wordt dan inderdaad die dosis volgens het model? En wat kunnen we daarvan verwachten?	Pharmacist	Platform	Technology acceptance
Dus daarom vinden we die decision making belangrijk omdat het dus het is, er komt dan iets uit dat model. Maar is dat toch nog open voor discussie of onderling? Of is het dan gewoon wat het is? En wat wordt dan gedaan? Zeg maar? Die neemt dan de beslissing en heeft dan de verantwoordelijkheid slechts de regie daarover? Ja, dat vinden wij wel. Dat moet je dan wel goed van tevoren afspreken. Ja dus daarom was die decision making voor ons in dit proces onderling heel belangrijk omdat je daar afspraken over moet maken.	Pharmacist	Collaboration	Interdisciplinary collaboration
Ook multidisciplinair denk ik, zeker in zo'n oncologie geval. De behandeling voor die mensen is niet niks. Aan dit soorten behandelingen zit zo veel nadelen en bijwerkingen dat het ook wel belangrijk is om naast gewoon uberhaupt het doseren in de behandeling, dat je er ook iets meer holistisch kijkt naar wat kan die patiënt überhaupt nog aan kan. Bijvoorbeeld op zijn gewicht gebaseerd kan het allemaal wel, maar hij heeft zo ontzettend veel bijwerkingen van, accepteren we dit dan nog?	Pharmacist	Collaboration	Multi- and interdisciplinary collaboration
De samenwerking hangt af van hoe duidelijk het is wie wat doet en hoe ze samen te werk gaan	Pharmacist	Collaboration	Interdisciplinary collaboration
Dit is de dosering die we geven. Dat is altijd zo of zo en hij zegt dan maar bij deze patient doe je het anders of zo. En dat wordt aangepast. Maar ja, dat je daar in ieder geval wel een soort helderheid hebt in rollen, maar ook misschien inderdaad een beetje verwachting.	Pharmacist	Collaboration	Interdisciplinary collaboration
En daarom ook giving/taking advice. Dat is eigenlijk een beetje wat jullie denk ik bedoelde met keep expertise, want het is eigenlijk dat je van elkaar aanneemt dat de ander experts op zijn of haar gebied en daar ook zeer goed advies zal geven.	Pharmacist	Collaboration	Interdiscplinary learning/collaboration
Omdat we dat inderdaad allebei wel bij elkaar vandaan horen. Dus inderdaad. En qua platform is het op zich logisch inderdaad, de dingen moet gewoon duidelijk zijn voor jullie, want je moet het gewoon goed snel kunnen gebruiken.	Pharmacometrician	Platform	Technology acceptance
Je hebt natuurlijk weinig tijd, maar sommige dingen kosten nou eenmaal tijd en dus gewoon weet als ik hier nu iets in stop. En de moeite die ik doe levert iets nuttigs op. Dan vind ik het belangrijker dat het dat het de input output in balans is dan dat het per se alleen maar snel moet zijn. Snap je, want kwaliteit vind ik ook belangrijk. Daar zit een beetje, die efficiëntie vonden we daarom meer passend	Pharmacist	Platform	Technology acceptance
Flexibel, dat is ook eentje die we eerder niet hadden. Euhm. En dat dat kwam vooral eigenlijk omdat wij gewoon weten dat patiënten echt zijn uniek zijn en en dat er daarom ook gewoon echt wel eens een gevalletje is gaan komen die niet binnen de lijntjes passen. En misschien ook niet van jullie modellen.	Pharmacist	Platform	Technology acceptance
En f**a**st in in u**se**. Ik vind d**at** als ik zo'n introductie**course** moet volgen**, a**ls het langer dan tien minuten duurt voor te begrijpen, dan ben je mij echt kwijt.	Pharmacist	Collaboration	Technology acceptance
Model overview is, denk ik ook wel gewoon dat je	Pharmacist	Collaboration	Interdisciplinary learning

gewoon echt in het begin een beeld krijgt va**n** ja, wat doe je **ermee** uiteindelijk zeg maar. Dat je inderdaad in het begin wel gewoon eventjes **een** kijkje achter de schermen van het deel van het platform wat jij niet gebruikt. Vooral wat precies wat er zit. Want bereik je er uiteindelijk mee? Wat levert het op?			
Misschien **d**iscussion **ook** wel wat eerder. En op zich vind ik multidisciplinaire **o**ok nog wel belangrijk denk ik, omdat je naast dat je kijkt naar bijvoorbeeld de juiste doses ook moet kijken**, h**eeft iemand er last van? En nou ja, dat je op die manier is het iets patient breder neemt dan alleen **d**at doe je natuurlijk zo gewoon	Pharmacist	Collaboration	Multi- or interdisciplinary collaboration
Ik vind het gevoel van iets efficiëntst is anders dan het gevoel van wat ik persé snel moet zijn. Ja eens moet zich maar alle handelingen moeten doelmatig zijn. En dat het er dan misschien twee meer zijn is prima. Als het zich maar euhm ja ik weet niet ook efficient is.	Pharmacist	Platform	Technology acceptance