PROTOCOL TITLE 'Empowering patients to Improve Safety in Polymedication'

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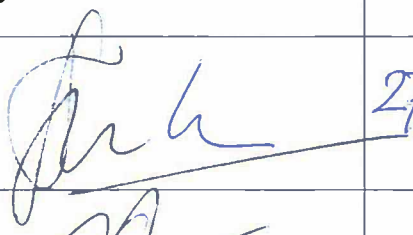
Head of Department: Henk-Jan Guchelaar, PharmD, PhD Professor of Clinical pharmacy		27/9/24
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
ADR	Adverse Drug Reaction
AE	Adverse Event
AI	Artificial Intelligence
CCMO	Central Committee on Research Involving Human Subjects, in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DDGI	Drug-drug-gene interaction
DDI	Drug-Drug Interactions
DNA	Deoxyribonucleic Acid
DPWG	Dutch Pharmacogenomics Working Group
eCRF	Electronic Case Report Form
EU	European Union
FAIR	Findable, Accessible, Interoperable, Reusable
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
HC	Healthcare
ICH-GCP	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP)
LUMC	Leiden University Medical Centre
MAF	Minor Allele Frequency
METC LDD	Medical Research ethics committee (MREC); in Dutch: Medisch-Ethische Toetsingscommissie (METC). LDD: Leiden, Den Haag, Delft
MMC	Medication Management Centre
MP	Data Management Plan
PGx	Pharmacogenomics
PoC	Proof Of Concept
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PROMs	Patient-Reported Outcome Measures
SAE	Serious Adverse Event
SNP	Single Nucleotide Polymorphism

SOP	Standard Operating Procedure
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation, or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor but referred to as a subsidising party.
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
UKA	University Hospital Aachen
UL	University of Ljubljana
UPAT	University of Patras
U-PGx	Ubiquitous Pharmacogenomics
UUID	Universal Unique Identifier
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: In current clinical practice, polypharmacy and patient empowerment are critical yet often overlooked. Polypharmacy, the chronic use of five or more drugs, poses risks such as adverse drug reactions and decreased medication adherence, especially in elderly and multimorbid patients. Despite the interconnected nature of drug-drug and drug-gene pro interactions, they are considered separately. Ignoring these interactions can be hazardous, yet clinical trials to investigate them are infeasible due to fast-growing complexity, variability among patients, high costs associated with large-scale studies, and ethical and logistical challenges. Consequently, there is a substantial knowledge gap in managing complex medication regimens in real-life scenarios and providing guidelines to enhance patient empowerment and drug safety. The SafePolyMed project aims to develop a patient-centred framework to define, assess and manage drug-drug, drug-gene and drug-drug-gene interactions. This framework, a web-based medication management centre, will support patients in managing their therapy-related health data, enhancing education and empowerment, and improving patient safety.

Objective: To assess the impact of the developed medication management centre on patient empowerment in polypharmacy patients, thereby improving drug safety. Secondary objectives are to explore if the tool is able to identify patients at risk for a drug-drug-gene interaction and lower the adverse drug event rate.

Study design: The study is a proof of concept study conducted at four institutes located in Germany, Greece, Slovenia and The Netherlands. Polypharmacy patients will use the medication management centre (MMC), which provides curated, patient-specific information about drug interactions and PGx. To assess patient empowerment, patients will receive questionnaires during a 12 week follow-up period.

Study population: 120 subjects with polypharmacy (defined as the chronic use of 5 or more drugs) of at least 18 years of age, with a first prescription for one of 10 index drugs. The study will be performed at 4 different sites (Leiden (NL), Patras (GR), Ljubljana (SL), Aachen (DE)) to represent different clinical settings across Europe. Each site will recruit 30 patients.

Intervention: The MMC that provides patient centred information on drug-drug interactions and pharmacogenetics affecting personal polytherapy. The MMC will show a selection of high quality publicly available information such as details on different types of medications, including their uses, side effects and instructions for use, in the language of the patient. This information is targeted at an individual patient's medication profile to inform patients to better understand and deal with their personal health information, with regard to drug therapy. Patients in the Netherlands, Slovenia and Greece also will receive their PGx profile to further personalise the MMC experience.

Main study parameters/endpoints: The primary outcome is the sense of empowerment and health literacy for participants before and after use of the MMC. Secondary outcomes include an evaluation of the drug-drug-gene interactions and adverse drug events in the study populations compared to matched historical controls.

Nature and extent of the burden and risks associated with participation, benefit, and group relatedness: Patients are exposed to the regular treatment. In addition, patients will receive questionnaires at baseline, two, and twelve weeks regarding the use and experience of the medication management centre, and a close-out interview at week twelve. In addition, 10ml of blood will be collected during a venipuncture for pharmacogenetic analyses.

Benefits include having access to the medication management centre for the duration of the study. Additionally, patients will receive their PGx profile. This can be used to individualize drug treatment, based on the Dutch Pharmacogenetics Working Group (DPWG) guidelines.

Overall, minimal risks are expected for subjects as they will receive normal clinical care. Information from the MMC will be a curation of existing publicly available data. Any information regarding DDIs and DGIs will be supplemented with a disclaimer that the patient should not adjust their treatment without talking to a healthcare provider.

1. INTRODUCTION AND RATIONALE

Adverse drug reactions (ADRs) are a major burden to our healthcare (HC) and economic systems. In the European Union (EU) alone, approximately 197,000 deaths annually are attributed to ADRs.(1) Polypharmacy, multimorbidity and genetic heterogeneity can affect drug efficacy, raise the risk for ADRs and consequently increase healthcare costs. This issue is exacerbated by the growing prevalence of polypharmacy (the chronic use of five or more medications concomitantly) which affects 26 to 40% of elderly European citizens.(2)

Public education on drug intake, polypharmacy, and individual medication risks remains insufficient. This contributes to weakened patient security, poor medical adherence, and suboptimal therapy outcomes.(3; 4) Elderly individuals, polymedicated patients, and those with multiple chronic conditions often face challenges in managing their health, potentially leading to increased healthcare needs. Systematic documentation of health status using patient-reported outcome measures (PROMs) is crucial for early identification of ADR-related issues and enhancing communication between patients and healthcare providers. A comprehensive approach involving patient education and active participation in documenting therapy-related health status can empower patients, improve treatment outcomes, and reduce ADRs.(5; 6)

The SafePolyMed project aims to develop a patient-oriented framework for defining, assessing, and managing drug-gene product interactions (DGIs) and drug-drug interactions (DDIs). This framework will support patients in managing their therapy-related health data, improving education, patient empowerment, and patient safety. Tools for PROM management, DDI information, and DGI information will be integrated into a web-based Medication Management Centre (MMC). This tool will help patients manage and monitor their therapies, educate them about their therapy, thereby empowering the patients by creating a sense of participation in the decision process when it comes to the management of their diseases. The information in this tool is curated publicly available information. Moreover, novel tools that uses machine learning and mechanistic modelling techniques using relevant real-world datasets to assess patients at risk for ADRs have been developed but are not yet clinically validated. These tools can be integrated into the MMC to show interconnectability but are not yet validated and therefore not reported to patients or used for drug management, this is a separate part of the overarching SafePolyMed consortium. Additionally, the MMC will be used to collect patient-reported outcomes.

To assess the impact of the developed medication management centre on patient empowerment in polypharmacy patients to improve drug safety, we will execute a transnational proof-of-concept study.

2. OBJECTIVES

2.1 Primary objective

The primary objective is to assess the impact of the developed medication management centre on the patient empowerment of polypharmacy patients, thereby improving drug safety.

2.2 Secondary objective

To investigate if the medication management centre is able to identify patients at risk for a drug-drug-gene interaction. Moreover, it will be investigated whether integrating the MMC into healthcare will lower the adverse drug event rate compared with matched historical control.

3. STUDY DESIGN

3.1 Overall study design

This study is a multi-centre, open-label study to assess the impact of the developed MMC in combination with the developed risk score algorithms, patient-reported outcome tool, and model-based precision dosing tool on patient empowerment of polypharmacy patients, thereby improving drug safety. In the study, a total of 120 patients will be enrolled in The Netherlands, Greece, Slovenia, and Germany (30 patients per country). The study subjects will be followed for 12 weeks. At set time intervals (2 and 12 weeks) the subjects will be asked to complete a validated questionnaire through the eClinical Data Management Platform Castor (table 1), for which the patients receive an email and a reminder through the MMC. These questionnaires collect information on the experience with the MMC, clinical monitoring, clinical outcome, and adverse events.

Table 1. Overview of the questionnaires during the 12-week follow-up. The baseline questionnaire comprises of 97 questions, the 2-week questionnaire of 133 questions and the 12-week questionnaire of 206 questions. All questionnaires are adaptive.

	Baseline questionnaire	Adaptive questionnaire in the MMC at time point:	
		2 weeks	12 weeks
Experience			
Usability		x	x
Health literacy	x		x
Clinical monitoring			
Comorbidities and allergies	x		
Concurrent medication and herbal remedies (through patient diary)	x	x	x
Clinical outcome			
Drug adherence	x	x	x
Quality of Life	x		x
Adverse events			
Patient reported ADR		x	x
Assessment of ADR severity		x	x
Pharmacogenomics			
DNA sample collection	x		

The baseline questionnaire will additionally comprise questions covering in- and exclusion criteria, demographics, recruitment information, previous PGx test results, comorbidities and allergies, and the level of health literacy before use of the MMC. In total, the baseline questionnaire consists of 97 questions. The questionnaire offered two weeks after inclusion in the study consists of 133 questions. The last questionnaire, offered 12 weeks after inclusion in the study, consist of 206 questions. All questionnaires are adaptive meaning that the length and duration of the questionnaire depends on the answers of the participants.

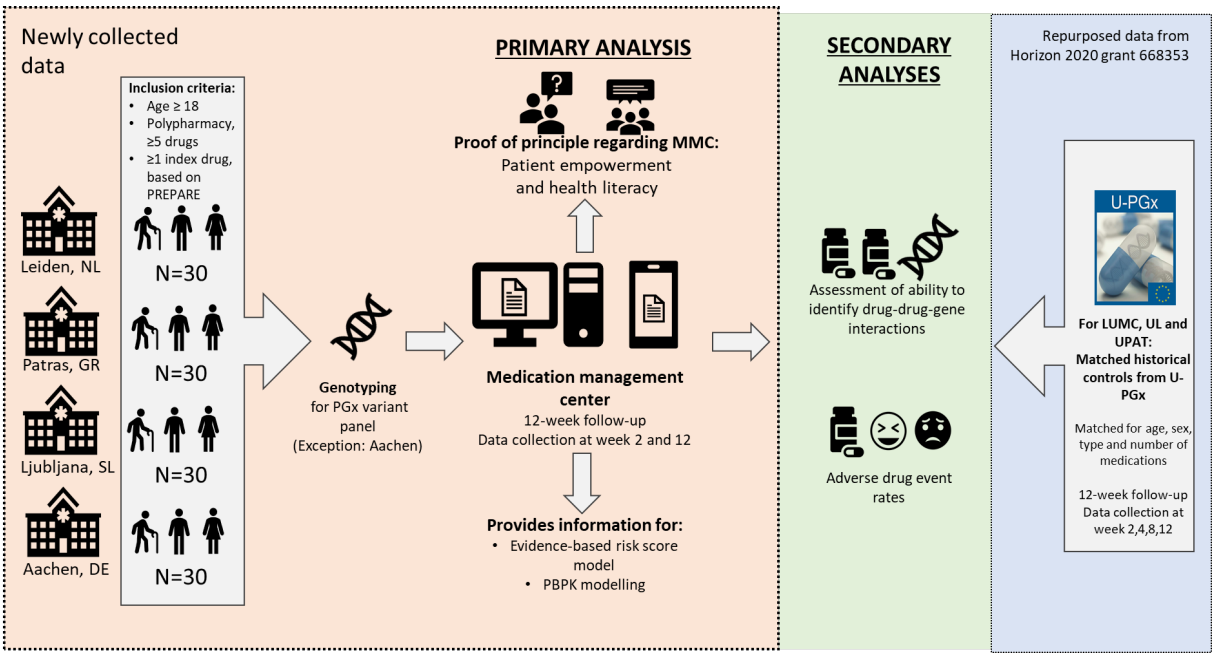
Effectiveness in the prevention of ADRs and the ability to identify drug-drug-gene interactions will be explored as a secondary endpoint by comparing results of the pilot study with those obtained from matched historical controls obtained from the control arm of the U-PGx project. This control arm is suitable as historical control group for the EmPaSafe study because of its alignment in key aspects, allowing for meaningful comparisons:

- Genotyped but not empowered with PGx Data: Participants in the U-PGx control arm were genotyped retrospectively, meaning their PGx information was available but not actively utilized in their care. This setup provides a unique baseline to assess the effectiveness of the MMC and the empowerment of EmPaSafe patients with PGx data, as we can analyse whether access to their genetic information and medication adjustments reduces ADRs and improves drug efficacy.
- Comparable Follow-up and Monitoring Protocols: The U-PGx control arm and the EmPaSafe study share similar follow-up methods, including regular monitoring for ADRs and the use of similar questionnaires. This similarity minimizes variation in data collection processes, allowing us to more directly compare ADR prevalence and other outcomes between the two groups.
- Matching for Key Variables: The control group will be matched to EmPaSafe participants based on age, sex, and type and number of medications, controlling for these variables in the analysis. This matching enhances the comparability of the two cohorts and strengthens the reliability of conclusions drawn about the impact of empowering patients with PGx data through the MMC.

Using the U-PGx control arm as a historical comparison thus allows EmPaSafe to evaluate the added value of PGx-informed care without needing a concurrent control group, streamlining the study while leveraging pre-existing data to explore the MMC's role in improving medication safety and personalization.

The EmPaSafe study design is depicted in figure 1.

Figure 1. Design of the EmPaSafe study.



Of note: UKA does not have the ability to genotype and will also not be able to report PGx results in a clinical setting and act upon it due to the German regulations. Due to the Arzneimittelgesetz, which consists of strict regulations for clinical research that deal with drug effects (e.g., safety, efficacy, and pharmacokinetics), and the Gendiagnostikgesetz, which are regulations concerning pharmacogenetic diagnostics, it is not allowed to study actionable variants that are not in use in German clinical practice. However, the inclusion of data from the German site offers critical insights that enhance the robustness and applicability of the EmPaSafe study results. Although regulatory restrictions in Germany limit the use of PGx results to cases with specific medical indications, the observations gathered from the German cohort remain highly valuable for the study, contributing to broader objectives beyond PGx data alone. Below are three primary ways in which including the German population will provide valuable information to the EmPaSafe study:

- Comparability with the Target Population: The German cohort primarily consists of elderly, polymedicated patients—a group closely resembling the primary target population of the EmPaSafe study. These patients typically have complex medication regimens and could greatly benefit from improved medication safety and personalized care. By including data from this population, we enhance the comparability of findings across the study's international sites, including those in the Netherlands, Slovenia, and Greece, allowing us to evaluate the consistency of our results across diverse patient populations and contexts.
- Insights into Patient Empowerment and Health Literacy: The purpose of the MMC within EmPaSafe extends beyond the use of PGx information alone; it aims to increase patient

empowerment and health literacy in medication management. Although PGx data usage is limited in Germany, the MMC still enables us to gather valuable information on how the tool impacts patients' understanding of, and engagement with, their medication. This is particularly useful to assess the broader functionality of the MMC as a patient-support resource, providing insights into its effectiveness in enhancing patient empowerment and health literacy independent of PGx information.

- Enhanced Generalizability of Findings: By collecting data from Germany, a region with distinct legal, healthcare, and cultural contexts, we improve the generalizability of our study's results. This allows us to analyse whether the MMC's effectiveness in promoting patient empowerment and health literacy is consistent across different healthcare systems and regulatory frameworks. Such insights are essential for evaluating the potential applicability of the MMC in other European countries, especially those with similar regulatory constraints on PGx data usage.

In summary, the German site provides valuable data that extends beyond PGx-specific analysis. The inclusion of this site enables a comprehensive evaluation of the MMC's impact on patient empowerment, health literacy, and the general functionality of the tool across different European healthcare settings. This international perspective is essential for understanding the potential for broader implementation of EmPaSafe within Europe.

3.2 Patient journey

The patient journey starts when the patient receives a first prescription for one of the index drugs (see table 3). Upon enrolment, patients get access to the MMC. The day of the first prescription is considered T=0.

- Medication Management Centre

The MMC will offer patients curated, personalised information regarding DDIs and DDGIs and a patient diary to manage and monitor their drug therapy. Additionally, the MMC will remind the patients by email to complete a questionnaire through the eClinical Data Management Platform Castor These questionnaires collect information on the experience with the MMC, clinical monitoring, clinical outcome, and adverse events, according to the schedule in table 2. Patients can report ADRs in the medication management centre through patient reported outcome measures (PROMs) in the patient diary. More information regarding the MMC can be found in section 5.1.1.

- PGx profile

Additionally, the patients in The Netherlands, Greece and Slovenia will donate DNA by a blood sample by a venipuncture or through saliva, and will be genotyped within two weeks for our panel of 26 variants in 4 pharmacogenes (LUMC, UPAT and UL). The results of this PGx test

will be communicated through the MMC. Patients will be stimulated to share these results with their healthcare providers. This approach is used due to the patient centred nature of our study and MMC approach. Physicians will not receive any specific additional results other than what the patients share with them.

At the end of the 12-week study period, patients will have a semi-structured close out interview with the research nurses regarding the experience of the medication management centre.

- Gene and variant selection

The genes that will be tested are CYP2C19, CYP2C9, CYP2D6 and SLCO1B1 (see also Appendix 3). These all have actionable recommendations in the DPWG guidelines and are related to drugs frequently used in outpatients with polypharmacy. The selection of the genes is based on the drugs that were selected to be index drugs. Additionally, testing these genes is technically feasible and readily implemented in Leiden, Patras and Ljubljana. Updates in the guidelines of the DPWG will be taken into account during the project.

The variants chosen to study align with those studied by the Ubiquitous Pharmacogenomics (U-PGx) consortium. See Appendix 3 for the full pharmacogene and variant panel.

- Genotyping

The method used to genotype the variants is up to the recruiting sites themselves. They must meet the following criteria: 1) test for the updated variant panel and 2) participate in proficiency testing programme to ensure quality of genotyping.

3.3 Data collection procedures

T=0 is defined as the day the patient initiates the index drug (table 3). During the 12-week follow-up period, the patients will receive surveys at baseline, 2 weeks and 12 weeks and a semi-structured close-out interview at week 12. Patients are requested to complete the surveys within a week. In case a patient discontinues the index drug within the 12-week follow-up period, the follow-up will continue as initially anticipated. The questionnaires will be provided to the patients through the medication management centre.

The data collected by the surveys is summarized in table 2. The MMC will collect: 1) Data entered by patients: demographic information, medical information, symptom diary, 2) Data created by the MMC and its tools: medication plan assessed with its safety risks (DDIs, DGIs, risk score, dosing information) and 3) statistical information collected by the system about the usage of the system by individual patients, sub-cohorts and the whole cohort.

All data will be entered into an electronic Case Report Form (eCRF), which guarantees consistency of data collection procedures. Data will be used exclusively in a pseudonymous fashion and data protection will be guaranteed according to international regulations. Local, independent internal monitors will guarantee data integrity and data homogeneity across all four implementation countries by risk-based monitoring of a random sample of the collected data. The research team will collect and store patient contact information (e-mail address, telephone number, name, and study-ID number) in a separate, local file (national subject identification code list).

4. STUDY POPULATION

4.1 Population (base)

Polypharmacy patients of any ethnicity, which are over 18 years of age and within routine care receiving a first prescription for one of the index drugs (see table 3), are eligible to participate in the study. The participating centres will **focus on, but are not limited to**, recruiting within a specific therapeutic area that cover both in- and outpatient settings (see table 2). This diverse population is a reflection of the general polypharmacy population which allows us to assess the use of the MMC in this diverse and heterogenous group of patients.

Table 2. Centres participating to the study, with corresponding recruitment of patients. The centres are not limited to recruiting patients within these specific therapeutic areas and can also include patients outside them.

Site	Therapeutic focus for treatment	Number of patients included in total	Country/ Language
LUMC	Leiden University Medical Centre will involve community pharmacies in Leiden to recruit patients.	30	The Netherlands/ Dutch
UPAT	Psychiatric patients will be recruited from the psychiatric clinic of the General University Hospital of Patras.	30	Greece/ Greek
UL	Primary care patients will be recruited from three primary health care centres (Community Health Centre Ljubljana, Family Medicine Clinic KUS and Health Institute Zdravje)	30	Slovenia/ Slovenian
UKA	Polypharmacy patients from different fields of medicine, above 60 years of age will be recruited in UKA's outpatient unit for clinical pharmacology.	30	Germany/ German
Total for study		120	

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Polypharmacy defined as the use of 5 or more drugs
- Start usage of at least one index drug according to the list in table 3. See Appendix 4.
- Subject must be ≥ 18 years old
- Subject is able and willing to take part and be followed-up for at least 12 weeks
- Subject is able to donate blood or saliva
- Subject has signed informed consent

Table 3. List of index drugs eligible for inclusion, based on their presence in the U-PGx cohort. For all these drug-gene combinations, an actionable DPWG guideline is available. See also Appendix 4.

Drug name	Gene
Amitriptyline	CYP2D6
Atorvastatin	SLCO1B1
Citalopram	CYP2C19
Codeine	CYP2D6
Escitalopram	CYP2C19
Paroxetine	CYP2C9
Sertraline	CYP2C19
Simvastatin	SLCO1B1
Tramadol	CYP2D6
Venlafaxine	CYP2D6

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Pregnancy or lactating
- Life expectancy estimated to be less than three months by treating clinical team
- Unable to consent to the study
- Unwilling to take part
- Subject has no fixed address
- Subject has previously been genotyped for PGx genes
- Subject has no current general practitioner
- Subject is, in the opinion of the Investigator, not suitable to participate in the study
- Estimated glomerular filtration rate (MDRD) of less than 15 ml/min per 1,73m2
- Patients with advanced liver failure (stage Child-Pugh C)

4.4 Sample size calculation

As this is a proof-of-concept (PoC) pilot study, the sample size is aimed at showing the impact of the use of the MMC on patient empowerment and exploring associations, rather than statistically significant relations. Therefore, no formal sample size and power calculation is done. A number of 30 participants per site is the number of subjects that we estimate to be sufficient to investigate the impact of using the medication management centre and associated tools.

To explore potential effectiveness of the tool, results will be compared with those of matched historical controls obtained from the control arm of the U-PGx project. While the study is not aimed at or powered for statistical comparisons, we are in the unique position to have a access to a substantial cohort of comparable patients. Controls will be matched for age, sex and type and number of mediations. These results will help to design a larger study to perform a formal statistical analysis of the effect of the medication management system and associated tools.

5. TREATMENT OF SUBJECTS

5.1 Investigational strategy

In this study, participants will be granted access to the MMC. This tool provides personalised patient-centred information on drug-drug interactions (DDIs) and PGx affecting polytherapy.

5.1.1 The medication management centre

All patients participating in the EmPaSafe study will gain access to the Medication Management Center (MMC), a digital platform developed to empower patients with information and enhance medication safety, particularly in cases of polymedication. The MMC's primary purpose is to serve as an educational resource that provides tailored, patient-specific insights into drug-drug interactions (DDIs) and drug-drug-gene interactions (DDGIs) based on individual pharmacogenomic (PGx) profiles. These insights aim to support adherence to therapy, improve patient outcomes, and mitigate risks associated with complex medication regimens.

The MMC annotates each patient's medication plan with curated safety information sourced from validated guidelines, including those from the Dutch Pharmacogenetics Working Group (DPWG), and trusted public databases such as the ABDA-Database. By offering personalized, high-quality content, the MMC helps patients understand their therapies and the potential risks associated with their medications. It also provides tools for reporting health concerns, such as adverse drug reactions (ADRs), through integrated patient-reported outcome measures (PROMs).

A core feature of the MMC is its emphasis on patient engagement. The platform equips users with the knowledge to have meaningful discussions with healthcare providers, thereby fostering collaborative decision-making. However, the MMC strictly serves an informational purpose; it neither facilitates self-adjustment of medication nor replaces professional medical advice. This distinction ensures compliance with regulatory requirements and underscores its role as an educational rather than a diagnostic tool.

The MMC also includes advanced functionalities that may shape the future of personalized medicine. These include exploratory tools, such as machine learning models and mechanistic risk assessments, designed to analyse real-world data for predicting adverse drug reactions (ADRs). While these tools are not yet clinically validated, they represent the innovative potential of integrating cutting-edge technologies into medication management.

By enabling patients to record their experiences in health diaries and providing access to curated, reliable information, the MMC empowers individuals to actively participate in their healthcare. This approach not only improves medication safety and adherence but also aligns

with the broader goals of the SafePolyMed project: enhancing the safety and effectiveness of polytherapy through patient-centred innovation.

It's important to note that all information provided by the MMC is publicly available and curated by the experts working on the SafePolyMed project. While the MMC and its tools serve to empower patients, they are not medical devices and do not replace professional medical advice or therapy adjustments. See also Appendix 2.

5.1.2 Questionnaires

The baseline questionnaire will comprise questions regarding demographics, in- and exclusion criteria, and comorbidities. Additionally, standardized questionnaires will be offered to the patients at 2 and 12 weeks after initiation of the index drug to obtain information about health behaviour, drug use, ADRs (PRO-CTCAE), quality of life (SF-36), MMC experience and health literacy (HLS-EU-Q47). The questionnaires are adaptive meaning that based on the provided answers only relevant follow-up questions will be asked to minimize the burden. Lastly, a semi-structured close-out interview will be held at week 12 to gather information on the experience with the MMC.

6. INVESTIGATIONAL PRODUCT

Not applicable

6.1 Name and description of investigational product(s)

Not applicable

6.2 Summary of findings from non-clinical studies

Not applicable

6.3 Summary of findings from clinical studies

Not applicable

6.4 Summary of known and potential risks and benefits

Not applicable

6.5 Description and justification of route of administration and dosage

Not applicable

6.6 Dosages, dosage modifications and method of administration

Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

Not applicable.

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

Not applicable.

7.4 Summary of known and potential risks and benefits

Not applicable.

7.5 Description and justification of route of administration and dosage

Not applicable.

7.6 Dosages, dosage modifications and method of administration

Not applicable.

7.7 Preparation and labelling of Non-Investigational Medicinal Product

Not applicable.

7.8 Drug accountability

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Proof of principle-study focused on assessing the impact of the developed MMC on patient empowerment in polypharmacy patients in order to improve drug safety. The primary endpoint is the sense of empowerment and health literacy for participants before and after use of the MMC. The endpoint consists of:

- Patient capacities, beliefs or resources including self-efficacy, sense of meaning and coherence about their condition, health literacy, perceived control and feeling respected by their healthcare providers.
- Activities or behaviours (things patient do) e.g., participate in shared decision-making by taking an active role and making informed decisions about their health and healthcare, self-manage and monitor their condition by choosing meaningful and realistic goals and taking steps to achieve those goals, participate in collective activities such as patient support or advocacy groups, and search for information about their health condition e.g., on the internet.

Literature shows that effective patient-provider communication, access to health information, a supportive healthcare environment and educational interventions can be listed as the main drivers for patient empowerment.(7-10) The health literacy questionnaire (HLS-EU-Q47) includes questions regarding these main drivers, but also the mentioned capacities, beliefs and resources, as well as activities or behaviour regarding patient empowerment. Health literacy can therefore be used as a proxy for patient empowerment.(11; 12) The questionnaire is validated in all four local languages (Dutch, German, Greek and Slovenian). The questionnaire is divided into three domains: health care (16 questions), disease prevention (15 questions) and health promotion (16 questions). These domains are subdivided into 4 categories: Accessing information, Understanding information, Appraising information and Applying information. Together, these domains cover 47 questions. The scores for the domains will be calculated using the instrument's scoring rules. For the questions incorporated in the questionnaire. Each question will have 5 responses: 1 = Cannot do or always difficult, 2 = Usually difficult, 3 = Sometimes difficult, 4 = Usually easy and 5 = Always easy.(11) A cut off of ≥3 was determined to quantify empowerment because scores of 1 to 3 on each item indicate a level of difficulty ('cannot do or always difficult', 'usually difficult' or 'sometimes difficult'). Descriptive statistics will be performed to analyse the results. An average score of ≥3 is defined as 'empowered' and serves as endpoint. Secondary, the growth in empowerment will be quantified, specifying the change in scores. The overall score will be evaluated to assess whether the endpoint has been

achieved, and the analysis will take into account both proportions and the magnitude of growth in empowerment.

A semi-structured close-out interview to obtain information on the patient experience of the medication management centre will be held. This interview can be divided into six sections: General experience with the MMC, Usability of the MMC, Patient empowerment, Impact, App features and functionality and Suggestions for improvement. All sections contain two to three questions each. This semi-structured close-out interview should be performable within an hour.

The interviews will be performed on a random sampling basis, until the saturation point is reached. This method allows for the collection of sufficient, diverse insights while minimizing redundancy.(13; 14) The interviews will be recorded using voice recorders and transcribed using ATLAS.ti to be able to analyse the responses.

The responses will then be categorized using a framework-analysis to capture higher-order concepts (e.g. “more involved in decisions” and “understood medication better” may form the category ‘Empowerment’ while “easy to navigate” and “intuitive layout” may form the category ‘Usability Strengths’). After that, we will develop overarching themes based on these categories (e.g. “The MMC improves patient empowerment through enhanced medication understanding”). The analysis will be performed according to AMEE-guide No. 164. The analysis will start deductively, using the existing framework, while allowing space for inductive insights to emerge, such as new themes or patterns that arise from the data.(15) Analysis of the responses will be performed within ATLAS.ti, To ensure accurate and consistent coding, we will implement agreement sessions where team members will collaboratively review and align their coding approaches. The findings from these interviews will be compared to questionnaire results to identify convergence or divergence.

8.1.2 Secondary study parameters/endpoints (if applicable)

Secondary analyses are aimed at defining the ability of the MMC to accurately identify patients at risk for a drug-drug-gene interaction. The effect of integrating the MMC into healthcare on the incidence of adverse drug events compared to matched historical controls from the U-PGx cohort will also be assessed.

Baseline demographics and clinical monitoring:

- Demographic measurements
- Current and past medical history
- Comorbidities
- Global Health Score
- Co-medication
- Renal function
- Liver function

Secondary clinical outcome:

- Total number of ADEs (related to index and subsequent drugs)
- Dose adjustments to index drug
- Drug cessation (and reason for discontinuation)
- Additional drugs that are prescribed during follow-up
- Routine drug levels (only those that are collected routinely) as a proxy for exposure
- Patient-reported drug adherence

8.2 Randomisation, blinding and treatment allocation

No randomization will be applied. The Dutch, Slovenian and Greek patients will receive the MMC with PGx testing. The German patients will get access to the MMC, but will not receive any PGx testing. We will test the user experience.

8.3 Study procedures

See also Section 3. Patients matching inclusion criteria as described in Section 3 will be invited to participate. If a patient agrees and provides IC, they are asked to complete a baseline questionnaire (table 1). All patients will be provided access to the MMC. In The Netherlands, Greece and Slovenia, 10 ml blood will be collected during a venipuncture or with saliva using saliva collection kits designed for DNA purification. The participants will then be genotyped for *CYP2C9, CYP2C19, CYP2D6,* and *SLCO1B1*. All participants will gain access to the MMC, where participants that are genotyped will receive the PGx results. Questionnaires collecting data on the patient experience, clinical monitoring, clinical outcome, and adverse events will be collected at 2 and 12 weeks through the eClinical Data Management Platform Castor, for which the patients receive an email. The questionnaire and genetic information will be used for the descriptive statistical analysis of the main study endpoints.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable, there are no specific criteria for withdrawal. The national principal investigator can decide to withdraw a subject from the study for urgent medical reasons.

The eCRF will have a specific page that enables the type of withdrawal to be classified precisely, and where possible the individual reason to be documented. Types of withdrawal from which can be selected:

- Complete withdrawal (none of the patient's data can be used, e.g., because the subject wants to fully withdrawal/wrong initial drug etc.)
- Withdrawal from remaining follow-up only (patient consents for the study to use their data which has already been collected, but they decline to continue to be followed-up OR patient did not use index drug for at least 7 consecutive days)
- Lost to follow-up (the subject does not specify that they decline further follow-up, they are unable to be contacted)
- Partial withdrawal (e.g., withdraw from ever using the patient-reported online monitoring system, but happy to be contacted by research team)
- Death

8.5 Replacement of individual subjects after withdrawal

Individual subjects will not be replaced after withdrawal, unless the participant is loss-to-follow-up before the first questionnaire.

8.6 Follow-up of subjects withdrawn from treatment

If a patient does not reply to attempts of contact, every effort will be made to contact the patient. If a patient wishes to withdraw, the reason for discontinuation will be noted, if the patient agrees. The date and reason (if disclosed) will be noted in the eCRF. How missing data is handled in the analyses will be described in the statistical analysis plan.

Participants will be given two options: 1) complete withdrawal, 2) withdrawal from follow-up only. Additionally, we can offer the patients the choice whether or not to report the PGx results back to them.

8.7 Premature termination of the study

The study will be terminated prematurely when the safety of participants cannot be guaranteed. No additional safety issues are expected in the study, and therefore no criteria have been

defined for premature termination of the study. When terminated prematurely the participants will be informed and the PGx results will be shared with the Dutch, Greek and Slovenian participants.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance with section 10, subsection 4 of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs and SAEs

9.2.1 Adverse events (AEs)

AEs reported by the patient will be followed up until they have abated, or until a stable situation has been reached, as done within the realm of routine clinical care. AEs will be monitored via patient reporting through the medication management centre.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission or prolongation of hospitalization will not be considered as a serious adverse event.

All national principal investigators have the responsibility for safety within their own country. The local investigators will report SAEs to the national principal investigators, who in turn will report it to their national spontaneous reporting system within 7 days of first knowledge SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study, as defined in the protocol.

9.4 Data Safety Monitoring Board (DSMB) / Safety Committee

The MMC is not designed for the patients to adjust their treatment on their own. Rather, it is a collection of curated, publicly available information tailored to their personal polytherapy. Additionally, it is up to the healthcare providers to follow the DPWG guidelines and incorporate PGx testing results into their prescriptions. Therefore, no additional safety issues are expected.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

Descriptive statistics will be used to describe the primary outcome.

10.2 Secondary study parameter(s)

Descriptive statistics will be used to describe the secondary outcomes.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The EmPaSafe study will be conducted according to the study protocol, applicable regulatory requirements, the ethical principles of the Declaration of Helsinki (2013, see for the most recent version: www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO), and in accordance with national law and legislation.

11.2 Recruitment and consent

It is the responsibility of the national Principal Investigators to obtain ethical approval or favourable opinion in writing of the study protocol and protocol amendments, the patient information leaflet, and the informed consent form from the before enrolment of any subject into the study.

Recruitment will differ per site. In the Netherlands, recruitment will involve the LANA pharmacies as well as the outpatient pharmacy of the Leiden University Medical Center (LUMC). All participating pharmacies will receive information about the study during a site initiation visit. Pharmacies will identify eligible polypharmacy patients and pharmacies will identify eligible polypharmacy patients and verbally inform eligible patients about the EmPaSafe study. If patients are interested to participate, the pharmacy will provide the patient information leaflet. Within 2 work days, a researcher from the LUMC will call the patient to provide further information about the study and answer questions. Upon agreement by the patient, an ICF will be provided. The patient inclusion will be managed by the LUMC research team. The study team is also available for any questions both during recruitment and throughout the study.

11.3 Benefits and risks assessment, group relatedness

Subjects undergo a small, extra burden. Firstly, 10 ml additional blood will be collected during a venipuncture. Secondly, subjects have to complete questionnaires at T=0, T=2 and T=12 (T in weeks). Lastly, the subjects will be contacted at T=12 for a close-out interview. No extra visits to the clinic are necessary.

Benefits to subjects in the study include having access to the medication management centre for the duration of the study. Additionally, Dutch, Greek and Slovenian participants will receive their PGx profile. This can be used to individualize drug treatment, based on the DPWG guidelines.

Overall, minimal risks are expected for subjects as they will receive normal treatment.

11.4 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study. The METC LDD did provide liberation of the subject insurance.

11.5 Incentives

No financial compensation will be offered; the only things that can be considered as incentive are the access to the medication management centre for the duration of the study, and the PGx profile that will be obtained for all participating subjects.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The members of the SafePolyMed consortium are committed to open access and open science. To achieve this, data stewardship according to the FAIR principles (https://www.go-fair.org/fair-principles/) is crucial. Therefore, we developed a data management plan (DMP) using the Horizon Europe DMP Template, in compliance with regulation 2016/679. The DMP includes details on: (i) handling of research data during and after the project; (ii) types of data to be collected; (iii) application of data methodology and standards; (iv) methods for sharing and accessing data; and (v) data curation and preservation strategies. The plan will outline the project's organizational and technical procedures for data collection, reuse, storage, retention, destruction, privacy, and confidentiality. The DMP, confirmations, and related support documents were submitted to the EU as a deliverable.

Clinical data and associated metadata will be stored in a structured, searchable format in a publicly accessible database. Individual entries will be identifiable by a generated unique identifier (UUID) and a standardized version number using semantic versioning (major, minor, and patch version numbering). Changes to existing entries will receive a new UUID, and version updates will follow standard semantic versioning conventions. The database will be searchable by keywords and critical endpoints. Metadata will include information about study design, cohort, administration protocol, and data origin. The acquired patient materials such as blood or saliva, as well as the obtained clinical data will be stored for 15 years, in accordance with the ICH-GCP and EU-directives.

12.2 Monitoring and Quality Assurance

Local, internal monitors will perform the monitoring of the EmPaSafe study, according to the monitoring plan which will be written before initiation of the study. Monitoring will occur at regular intervals to oversee the progress of the study, ensure the wellbeing of study subjects, ensure accuracy and completeness of study data, and monitor compliance with the study protocol, SOPs, ICH-GCP and the Declaration of Helsinki, EU directives and applicable regulatory requirements.

12.3 Amendments

All amendments will be notified to the METC that approved the protocol. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority but will be recorded and filed by the sponsor.

12.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last questionnaire. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The clinical study report will form of manuscripts intended for publication in a medical or scientific journal. Publications will be conform the 'CCMO-notitie Publicatiebeleid.'

12.7 Funding statement

The SafePolyMed project receives funding from the European Union's Horizon Europe Research and Innovation Programme under Grant Agreement No. 101057639.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

Medication management centre

A potential issue of concern is for patients to adjust their therapy without consulting a health care provider, basing the adjustments on notifications of interactions. To overcome this concern, we will repeatedly inform the patients not to act upon notified interactions themselves, and to always consult a health care provider before adjusting the therapy.

Collection of clinical data

To mitigate the threat of poor collection of clinical data, we will implement a central web-based database including eCRFs.

Ethics

The risk that ethical aspects cannot be managed within the project is extremely low as we will be proactive and managing the ethical issues prospectively. As soon as a potential problem would appear, it will be managed by open discussion within the consortium and finding external advice. Therefore, a Scientific Advisory Board has been commissioned to advise on the development of the protocol to ensure a scientifically sound method (see Appendix 5).

Changes over time

A potential threat is that during the project the panel of drugs and genetic variants will change. For example, new drugs for which genetic testing is recommended may be marketed, drugs may be removed from the market, or a genetic test may become mandatory. In addition, new genetic variants may be identified that are not in the current panel. At this moment it is difficult to judge if and how fast these developments will proceed. The discovery of novel genetic variants can easily be addressed by incorporating them in the genotyping platform which is open and flexible by design. Moreover, the project is planned to span a period of 7 months so no major changes are expected.

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15. Appendices

15.1 Appendix 1: Contact information

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15.1 Appendix 2: MDR/IVDR exemption

The Medication Management Centre (MMC) does not fall under the Medical Device Regulation (MDR) nor the In Vitro Diagnostic Regulation (IVDR) for several reasons.

First, the primary role of the MMC is to serve as an educational and informational platform rather than a tool for diagnosis or treatment. The MMC presents curated, publicly available information regarding DDIs, DDGIs, and PGx, which patients are responsible for interpreting. Patients can use this information to discuss relevant results with their healthcare providers, but the MMC itself does not make any diagnostic or therapeutic decisions. Importantly, PGx test results are displayed on a separate screen within the same application, reinforcing the fact that the MMC does not function as a diagnostic tool or directly influence treatment.

Additionally, the MMC does not impact clinical decision-making. It merely enhances patient knowledge by acting as a smart viewer that aggregates and merges data from different databases. This data is presented in a user-friendly way for patient review and understanding, but it does not directly lead to medical interventions. Healthcare professionals remain responsible for all clinical decisions, ensuring that the MMC does not pose any undue risk to patients. Any mistakes in the presentation of information do not result in incorrect treatments, as the final responsibility rests with the healthcare provider.

The MMC's role as an informative platform also means it does not meet the MDR nor the IVDR definition of a medical device nor IVDR, which covers instruments or software intended for diagnostic or therapeutic purposes. The MMC provides educational support to polypharmacy patients without performing independent diagnostic or therapeutic functions. Although it allows patients to ADRs through patient-reported outcome measures (PROMs), it does not replace professional medical advice or facilitate therapy adjustments. In short, the MMC serves to empower patients by providing access to relevant information, but it remains separate from clinical decision-making processes, thus falling outside the scope of the MDR and IVDR.

Moveover, the study will be submitted under the Dutch Medical Research Involving Human Subjects Act (WMO). This will ensure the safety and rights of the participants, addressing any potential risks. Thus, any concerns regarding patient safety are covered within this regulatory framework, independent of MDR or IVDR requirements.

In summary, the MMC is primarily a viewer that compiles information for patient use and does not independently impact treatment or diagnostic decisions. Therefore, it does not fall under the scope of the MDR or IVDR. While the MMC does not currently meet the criteria for MDR or IVDR compliance, its regulatory status may need to be re-evaluated if future developments include direct clinical decision-making or therapeutic adjustments.

15.2 Appendix 3: Gene and variant panel

Gene	Name	dbSNP	Allele	Functional status	DPWG guide-line	References	Note
CYP2C9	CYP2C9*2	rs1799853	*2	Reduced	Yes	(1)	
	CYP2C9*3	rs1057910	*3				
	CYP2C9*5	rs28371686	*5				
	CYP2C9*11	rs28371685	*11				
CYP2C19	CYP2C19*17	rs12248560	*17	Increased	Yes	(1; 2)	
	CYP2C19*9	rs17884712	*9	Reduced			
	CYP2C19*4A/B	rs28399504	*4A/B				
	CYP2C19*8	rs41291556	*8				
	CYP2C19*2	rs4244285	*2	Inactive			
	CYP2C19*2	rs4986893	*3				
	CYP2C19*5	rs56337013	*5	Reduced			
	CYP2C19*10	rs6413438	*10				
	CYP2C19*6	rs72552267	*6				
CYP2D6	CYP2D6*3	rs35742686	*3	Inactive	Yes	(1-8)	
	CYP2D6*3 CYP2D6*5	rs3892097; rs1065852	*4				
			*5				Whole gene deletion
	CYP2D6*6	rs5030655	*6				
	CYP2D6*8	rs5030865	*8				
	CYP2D6*9	rs5030656	*9	Reduced			
	CYP2D6*10	rs1065852	*10				
	CYP2D6*14	rs5030865	*14				Previously known as 14A
	CYP2D6*17	rs28371706	*17				
	CYP2D6*41	rs28371725	*41				
	CYP2D6*114	rs5030865; rs1065852	*114				Previously known as 14B
SLCO1B1	VKORC1	rs9934438	1173C>T	Reduced	Yes	(10)	

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15.3 Appendix 4: Index drugs

To select the index drugs for EmPaSafe, we analysed the incidence of prescription of the 39 index drugs within the PREPARE study. From this analysis, we selected the top 20 drugs prescribed at each centre (LUMC, UPAT, UL). In table 4 below. Coloured cells indicate the overlapping drugs.

Table 4. Overview of the top 20 drugs prescribed at each centre in the PREPARE study.

LUMC		UL		UPAT	
Name	Occurrence	Name	Occurrence	Name	Occurrence
Simvastatin	252	Sertraline	247	Sertraline	241
Metoprolol	200	Escitalopram	220	Escitalopram	215
Flucloxacillin	146	Haloperidol	213	Haloperidol	212
Atorvastatin	145	Venlafaxine	193	Aripiprazole	189
Clopidogrel	130	Aripiprazole	189	Venlafaxine	189
Tramadol	84	Tramadol	172	Tramadol	172
Citalopram	80	Citalopram	141	Citalopram	141
Codeine	67	Tacrolimus	112	Simvastatin	66
Amitriptyline	60	Simvastatin	66	Atorvastatin	51
Nortriptyline	32	Atorvastatin	52	Paroxetine	48
Tacrolimus	28	Paroxetine	48	Capecitabine	43
Sertraline	27	Capecitabine	46	Tamoxifen	29
Escitalopram	25	Amitriptyline	30	Amitriptyline	26
Fluorouracil	24	Tamoxifen	29	Zuclopenthixol	25
Venlafaxine	22	Zuclopenthixol	25	Clomipramine	24
Oxycodone	15	Clomipramine	24	Codeine	7
Tamoxifen	15	Fluorouracil	9	Flucloxacillin	7
Flecainide	13	Codeine	7	Carbamazepine	4
Paroxetine	12	Flucloxacillin	7	Pimozide	3

The 10 drugs that overlapped most, with the highest prevalence in the cohort, were selected as the index drugs for the EmPaSafe study. These are listed in table 5 below.

Table 5. Overlapping drugs with highest prevalence in the PREPARE study.

Drug	Related gene	Incidence PREPARE LUMC	Incidence PREPARE UL	Incidence PREPARE UPAT
Amitriptyline	CYP2D6 / CYP2C19	60	30	26
Atorvastatin	SLCO1B1	145	52	51
Citalopram	CYP2C19	80	141	141
Codeine	CYP2D6	67	7	7
Escitalopram	CYP2C19	25	220	215
Paroxetine	CYP2C9	12	48	48
Sertraline	CYP2C19	27	247	241
Simvastatin	SLCO1B1	252	66	66
Tramadol	CYP2D6	84	172	172
Venlafaxine	CYP2D6	22	139	189

15.4 Appendix 5: Scientific Advisory Board

The EmPaSafe Scientific Advisory Board consists of experts from academia, industry, and patient advocacy. This board provides strategic guidance and expertise to ensure the study's scientific rigor and relevance.

- Professor Munir Pirmohamed (University of Liverpool): An eminent pharmacologist with extensive research in drug safety, pharmacogenetics, and personalized medicine.
- Sabrina Grigolo (EUPATI): A leading figure in patient advocacy, representing the European Patients' Academy on Therapeutic Innovation, with a strong focus on patient involvement in research and healthcare decision-making.
- Dr. Valerie Nock (Boehringer Ingelheim): A senior researcher with profound experience in drug development and clinical research from a leading pharmaceutical company.
- Dr. Uros Urleb (Novartis): A prominent scientist in the field of drug discovery and development, contributing valuable insights from his extensive work in the pharmaceutical industry.
- Professor Søren Brunak (University of Copenhagen): A pioneer in bioinformatics and systems biology, known for his innovative work in integrating biological data to advance personalized medicine.

The collective expertise of this board ensures that the EmPaSafe study adheres to the highest standards of scientific excellence, patient-centred care, and innovative research methodologies. Their diverse backgrounds and comprehensive knowledge support the study's goal of improving medication safety and patient empowerment through advanced technological solutions.