UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Pharmacy Faculty

Department of Clinical Pharmacology

Kamila Urbańczyk

Dissertation for the degree of
Doctor of Pharmacy

Integrated Medicines Management –

A pilot randomized study assessing the provision of complex clinical pharmacy services in Polish healthcare system

Zintegrowane zarządzanie farmakoterapią – pilotażowe badanie randomizowane oceniające kompleksowe świadczenie usług farmacji klinicznej w polskim systemie ochrony zdrowia

Supervisiors:
Prof. dr hab. Anna Wiela-Hojeńska
Department of Clinical Pharmacology, Wroclaw Medical University

Prof. Michael Scott
Medicines Optimisation Innovation Centre, Northern Ireland

Wrocław 2025

Acknowledgements

I would like to begin by expressing my heartfelt gratitude to my supervisors, whose guidance and belief in me have shaped both my career and my outlook on life.

*To **Prof. Anna Wiela-Hojeńska**, you have been like a second mother to me - only in the professional realm of clinical pharmacy. Your compassionate leadership, generosity of spirit, and ability to inspire have left a profound mark on me. You have been a constant source of encouragement, showing me not only how to be a better pharmacist, but also a better person.*

*To **Prof. Mike Scott**, thank you for your unwavering support over the years, for setting the highest standards of best practice, and for motivating me to continually strive for excellence. My thanks also go to the Medicines Optimisation Innovation Centre, and in particular to the irreplaceable **Anita Hogg**, whose kindness, expertise, and encouragement have been invaluable companions on this journey.*

Contents

I. Introduction 5

II. Aims and objectives 7

III. Theoretical part 8

1. Clinical pharmacy - concept and definition 8

2. Clinical pharmacy services 9

3. Clinical pharmacy services around the world - current status 15

4. Clinical pharmacy and clinical pharmacy services in Poland 19

5. Integrated medicines management model 21

5.1. Admission 22

5.2. Medicines reconciliation 22

5.3. Medicines review 23

5.4. Inpatient monitoring and counselling 27

5.5. Discharge 28

5.6. Follow-up 29

V. Material and methods 29

1. Study planning 29

2. Study design 30

3. Patient selection and randomisation 30

4. Intervention 31

4.1. Admission 33

4.2. Inpatient monitoring and counselling 33

4.3. Discharge 33

5. Outcome measures 34

6. Data collection and statistical analysis 43

VI. Results 43

1. Demographics and selection criteria 43

2. Incidence of unplanned visits and length of hospital stay 45
3. Drug related interventions and quality of pharmacotherapy 48
4. Economic evaluation 53
5. Patient and healthcare staff satisfaction 59
VII. Discussion 61
1. Incidence of unplanned visits and length of hospital stay 63
2. Drug related interventions and quality of pharmacotherapy 66
3. Economic evaluation 68
4. Patient satisfaction 71
5. Critical appraisal and limitations 71
VIII. Conclusions 72
IX. List of tables 73
X. List of figures 74
XI. Summary 75
XII. Summary in Polish 76
XIII. List of abbreviations 78
XIV. References 79

I. Introduction

Contemporary pharmacotherapy is often complex. It takes into account both the appropriate use of medications and the prevention of their adverse effects, the management of existing drug-related complications, and the treatment of coexisting pathological conditions. The optimization of pharmacotherapy therefore requires extensive knowledge of the mechanisms of action, pharmacokinetic properties, and toxicity of the drugs used, as well as precise monitoring of the consequences of their effects. Managing treatment is not only about the appropriate selection of medications but also about the continuous monitoring of the patient's health, educating the patient and their family members or caregivers, and collaboration among various specialists. This is particularly difficult in relation to elderly patients [1].

The process of aging results in a growing occurrence of chronic illnesses and the subsequent development of multimorbidity, which in turn intensifies the demand for medication usage and often leads to polypharmacy. Consequently, due to the increasing proportion of elderly individuals, the prevalence of polypharmacy is on the rise [2]. In the year 2015, approximately 5% of the population in Organization for Economic Co-operation and Development (OECD) countries was aged 80 years and above. This percentage is projected to double by the year 2050 [3]. It is noteworthy that multimorbidity significantly increases with age - a study conducted in Scotland revealed that multimorbidity was prevalent in as many as 81.5% of individuals aged 85 years and older, with an average of 3.02 comorbidities [4]. Kardas et al. showed that the occurrence of polypharmacy, which is determined by the dispensing of five or more medications, varied between 21.8% during the months of January to June in 2019, and 22.4% during the months of July to December for the whole population of Poland. However, for individuals aged 65 years and above, the corresponding figures were 62.3% and 62.9%, respectively [5]. The previously mentioned data is noteworthy, particularly considering the most recent Eurostat report that ranks Poland as the European Union's second-fastest-aging society [6].

Medications serve as the predominant intervention to prevent, manage, and treat disease. The optimal selection of multidrug regimens can become considerably complicated, especially in the case of very old and frail patients. Nevertheless, medications also possess the capacity to cause harm. The World Health Organization (WHO), through its 3rd Global Patient Safety Challenge on Medication Safety, endeavours to reduce the extent of preventable harm associated with medications on a global scale by 50% within a five-year timeframe [7]. When considering the economic impact, it has been estimated that the mismanagement of

polypharmacy leads to a significant contribution, of the order of 4%, to the world's total avoidable costs, which are as a result of sub-optimal medicine use. This equates to a total of US$18 billion annually, accounting for 0.3% of the overall global health expenditure. However, it is worth noting that these costs could potentially be avoided through the implementation of appropriate polypharmacy management. The European Union funded iSIMPATHY (Stimulating Innovation Management of Polypharmacy and Adherence in The Elderly) project outlined that: “With up to 11% of unplanned hospital admissions being attributable to harm from medicines and over 70% of these being due to elderly patients on multiple medicines, there are significant opportunities to reduce this burden by timely and effective interventions” [4].

In addition, non-compliance with prescribed medication is a significant element associated with the phenomenon of polypharmacy. This lack of adherence can be categorized as either intentional or unintentional. Both scenarios become more prevalent as the number of medications prescribed increases, and it has been established that there is a positive relationship between noncompliance and the quantity of drugs being consumed [2]. Research shows that a significant proportion of patients with chronic health conditions, ranging from 50% to 80%, exhibit non - adherence. The failure to adhere to prescribed medication regimens can have serious consequences, for example it has been estimated to contribute to 48% of asthma-related deaths, an 80% heightened risk of mortality in individuals with diabetes, and a 3.8-fold increased risk of death following a heart attack [4]. The issue of non-adherence appears to be notably evident in Central and Eastern European (CEE) nations. A multinational investigation revealed that a substantial proportion of Polish patients, amounting to 57.6%, and Hungarian patients, totaling 70.3%, acknowledged non-compliance with regard to their chronic treatment. In contrast, the corresponding figures for Western European countries varied from 24.1% in the Netherlands to 41.5% in England [8].

The challenges for healthcare systems, as alluded to above, must also be analyzed within the framework of a growing scarcity of healthcare practitioners in many European nations. The deficiency in numbers, specifically among nurses and physicians, pose significant challenges, and the outlook for the future is even more concerning. For example, whilst Estonia, Latvia, Poland, and Slovakia have seen a small rise in the number of medical practitioners and nursing professionals per 1,000 inhabitants in the previous two decades this is not adequate to meet the actual requirement. The importance of this issue can be recognized in the OECD 2021 report “Health at a glance”: "In general, nations that allocate more funds towards healthcare and

possess greater quantities of healthcare personnel and additional resources exhibit improved health results, superior quality, and enhanced accessibility to medical services" [3].

The urgent need for a new paradigm in healthcare system architecture is evident in the light of these issues. In the year 2020, the Committee of Ministers of the Council of Europe put out a resolution concerning the execution of pharmaceutical care with the aim of enhancing the well-being of patients and the efficacy of health services [9]. Clinical pharmacy services (CPS) present a viable solution to many of above challenges. Countries that have implemented CPS are currently achieving a multitude of advantages, including but not limited to, improved drug utilization, better drug safety, enhanced medication adherence and cost-avoidance. These benefits ultimately contribute to the greater sustainability of their healthcare systems. Unfortunately, Poland is still amongst those countries with a poor level of CPS development [10].

II. Aims and objectives

Despite the benefits of clinical pharmacy services demonstrated in numerous publications and their implementation in many countries around the world, Poland has still not achieved nationwide implementation. There is also a lack of scientific data at the national level showing the benefits of including a pharmacist in the patient facing activities. Therefore, this thesis aimed to determine if pharmacist input at each stage of hospitalization, from admission to discharge (Integrated Medicines Management – IMM), can result in an enhanced level of patient care when compared to standard care as measured by a number of clinical and economic outcomes. Given the aforementioned, the pilot study was designed with objectives to:

1) Compare the incidence of hospital, emergency department and other unscheduled visits after discharge from hospital during the 6 months follow-up period between IMM and standard of care.
2) Compere the length of stay (LoS) in hospital in both groups – IMM and control.
3) Evaluate the IMM service by determining the frequency and type of interventions performed, their acceptance and influence on the quality of pharmacotherapy.
4) Assess the perception of the IMM service by both patients and healthcare professionals
5) Estimate the potential financial benefits of the IMM service.
6) Assess the feasibility of a definitive, multicentre trial in Polish health care system setting.

III. Theoretical part

1. Clinical pharmacy - concept and definition

Clinical pharmacy arose in the 1960s as an area of practice, education and research. It began in the United States of America (USA) at the University of Michigan and at the University of Kentucky with the pioneering work of David Burkholder, Paul Parker, and Charles Walton. It evolved from a lack of satisfaction and full benefit with old pharmacy practice patterns and the need for specialists having comprehensive knowledge of the therapeutic use of medicines. Over time, pharmacists realized that rather than concentrating just on supply and manufacture, they also needed to ensure that medications were used appropriately to enhance patient outcomes [11]. Efforts were then subsequently made to shift the paradigm and commencing with changing the education process. The University of Southern California implemented the Doctor of Pharmacy degree (Pharm.D.) program with residencies in clinical pharmacy in 1950 and it has been gradually implemented at other universities since then [12]. In 1968 the Committee on the Curriculum of the American Association of Colleges of Pharmacy adopted the following official definition: “Clinical Pharmacy is that area within the pharmacy curriculum which deals with patient care with emphasis on drug therapy. Clinical Pharmacy seeks to develop a patient-oriented attitude. The acquisition of new knowledge is secondary to the attainment of skills in inter-professional and patient communications [13].” However, the most cited definition was later formulated by the American College of Clinical Pharmacy (ACCP) and in its abridged form is as follows: “Clinical pharmacy is defined as that area of pharmacy concerned with the science and practice of rational medication use [14].”

In Europe, the United Kingdom (UK) has always been a pioneer in this field. In 1970 the Noel Hall report of the working committee on the Hospital Pharmaceutical Service in Great Britain was a facilitator for change in hospital pharmacy practice. It stated that pharmacists have a role in ensuring safe and cost-effective use of medicines directly on the hospital wards. Further, the committee appointed by the Nuffield foundation in 1983 suggested that clinical pharmacy practice should be established in all hospitals [15]. The United Kingdom Clinical Pharmacy Association (UKCPA) describes clinical pharmacy as encompassing the knowledge, skills and attitudes required by pharmacists to contribute to patient care. The most recent definition formulated by the European Society of Clinical Pharmacy (ESCP) states: “Clinical pharmacy aims to optimize the utilization of medicines through practice and research in order to achieve person-centered and public health goals” [16].

It is evident from the above definitions, stated by a number of different organizations, that in essence, clinical pharmacy is a field in which pharmacists provide patient care that maximizes the benefits of drug therapy and encourages health and illness prevention. The new direction in pharmacy includes education and professional practice focused on the drug, its preparation, and dispensing to individual patients. It follows the pharmaceutical care concept and, so to guarantee the best possible outcomes for patients, combines a compassionate approach with specific therapeutic expertise, experience, and judgement. In order to ensure safe and efficient drug administration, clinical pharmacists collaborate with doctors and other healthcare professionals as essential members of healthcare teams. Clinical pharmacy also has a responsibility as a field to help create new knowledge that further improves health and quality of life [16].

2. Clinical pharmacy services

Clinical pharmacy services (CPS) encompass a wide range of patient-oriented activities aimed at optimizing medication therapy and improving patient care and treatment outcomes. CPS have evolved significantly over the years. In most developed countries, CPS are provided across the care continuum –in hospitals, general practice, palliative care or care homes. In hospitals, clinical pharmacists play a pivotal role in ensuring the safe and effective use of medications. They collaborate closely with other healthcare professionals to conduct medicines reconciliation, comprehensive medication reviews, identify drug-related problems (DRPs), and provide tailored recommendations to optimize therapy outcomes. In General Practice (GP) practices, CPS have become increasingly vital in managing chronic diseases and promoting medication adherence. Clinical pharmacists work with general practitioners to conduct medication reviews, educate patients about their medications, and provide valuable insights into potential drug interactions and adverse effects. Figure 1 adapted from Onatade et al. presents the relationships between clinical pharmacy, pharmaceutical care and medicines optimization and includes examples of CPS [17].

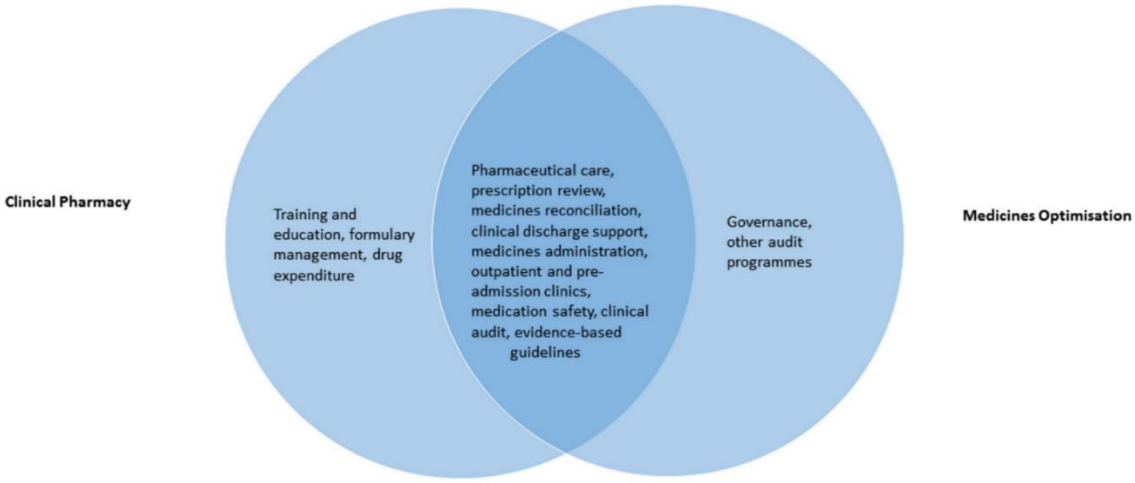

Figure 1. Relationships between clinical pharmacy, pharmaceutical care and medicines optimization prepared by Onatade et al. [17].

ECHO model - the Economic, Clinical, and Humanistic Outcomes, offers a comprehensive perspective on drugs and medical treatments. It illustrates the value of pharmaceutical services in conjunction with conventional clinical results derived from more recent metrics of quality and economic efficiency. CPS have been shown to have positive impacts on all these aspects - economic, clinical, and humanistic outcomes [17–22].

Economic evaluations of clinical pharmacy services are challenging due to the heterogeneity of the tasks undertaken, differences in healthcare systems and documenting the overall process. Nevertheless, available data show numerous opportunities for cost-savings thanks to CPS [17–22]. Table 1 presents some examples of research conducted on this topic around the world from 2015 to 2020 based on a literature review identifying clinical pharmacy services provided for hospital inpatients conducted by the author of this thesis as part of the postgraduate degree assignment. To focus on hospital setting, research papers relating to outpatient clinics, ambulatory care or nursing homes were excluded. Only studies published in English language assessing any type of economic value of described interventions and presenting estimate of monetary benefits were included in further assessment. Therefore, papers focusing solely on clinical outcomes were excluded. The following databases were screened: PubMed, Academic Search Complete, Google Scholar. Search terms included „clinical pharmacy" or „clinical pharmacist" plus „cost", „economic", „evaluation" or „benefit". This shows that regardless of type of CPS performed or department profile, a pharmacist can generate savings on different levels – direct cost reduction thanks to managing the medicines, cost avoidance due to prevention of adverse drug events (ADEs), reduction in LoS in hospital and readmissions [23–40].

In terms of clinical outcomes, CPS have been found to be effective in reducing readmission rates, emergency department visits, adverse drug events, and drug-related problems, as well as decreasing the length of hospital stay [18,41]. Additionally, clinical pharmacy services have been shown to improve therapeutic outcomes, such as reducing HbA1c levels and blood pressure, and humanistic outcomes, including medication adherence, knowledge, and health-related quality of life [42,43]. However, further rigorous studies with appropriate study designs are still needed to provide stronger evidence of the impact of clinical pharmacy services on different outcomes [18,19].

Compared to the other two aspects, there has been somewhat less work undertaken on the aspect of humanistic outcomes. Studies primarily assess two of them: health-related quality of life (HRQoL) and patient satisfaction. Due to difficulties in utilizing this measure, there is inconsistent evidence about correlation of CPS with HRQoL, despite the fact that satisfaction is high in the majority of publications. Nevertheless, new data from the iSIMPATHY project evaluated the relationship between gaining Quality-Adjusted Life Years (QALY) during medication reviews and addressing DRPs with a positive outcome [44–46].

Table 1. Table 1. Examples of research papers assessing the economic aspects of CPS [23–40].

First author	Year of publication	Pharmacist intervention	Setting	Period	Outcome measures	Results
Michalets et al.	2015	Complex: providing comprehensive care for ICU patients	Hospital in USA, ICU	24 months	Cost-avoidance due to ADEs prevention	Total cost savings of $2 118 426 not including pharmacist's salary
Onatade et al.	2016	Medicines reconciliation: unintentional discrepancies detected by pharmacy staff conducting MR on admission	Hospital in UK	6 full days	Cost-avoidance due to ADEs prevention	Costs avoided of £29 604–£68 718 (€36 412–€84 522)
Rychlickova et al.	2016	Medicines optimization: monitoring of DRPs and interventions on few hospital wards	Hospital in Czech Republic	12 months	Cost-avoidance due to ADEs prevention	Cost savings of approximately $287 000
Chen et al.	2017	Medicines optimization: introduction of pharmacist to nephrology unit for one full day and review of prescription	Hospital in China, nephrology department	total of 24 months	Decrease in medicines costs and cost-avoidance due to ADEs prevention	Cost avoidance of NT$6 686 338
Lee et al.	2017	VTE: monitoring interventions on venous thromboembolism prophylaxis	Tertiary teaching hospital in UK, medical and surgical department	1,5 months	Cost-avoidance due to appropriate VTEP	Estimated cost saving of £517 522/annum
Declaye et al.	2018	DOACs: prescriptions review by pharmacist	University hospital in Belgium	total of 12 months	Cost-avoidance due to thromboembolic/ haemorrhagic events prevention	Net benefit of €3 631
Renaudin et al.	2018	Complex: Correcting medication errors and recording interventions during daily activities	University hospital in France, orthopaedic and trauma department	2 months	Cost-avoidance due to ADEs prevention	Net benefit of €11 864

Malfara et al.	2018	Medicines optimisation: DRPs identified while participation in patient care rounds and daily pharmacotherapy monitoring	Hospital in Brazil, paediatric ICU	12 moths	Decrease in medicines costs	Cost saving of R$ 15 118.73 (US$ 4 828.00) not including pharmacist's salary
Bosma et al.	2018	Medicines optimisation: monitoring of DRPs and interventions on ICU	Two hospitals in the Netherlands, ICU	total of 9 months	Decrease in medicines costs and cost-avoidance due to ADEs prevention	Net cost benefit of €119 for one hospital and €136 for the other hospital per accepted intervention
Guruge et al.	2018	Complex: interventions during medication reconciliations, medication reviews and discharge medicines review together with patient's education	Hospital in Sri Lanka	6 months	Cost-savings on reduction of medication related readmissions	Net cost benefit of $17 661
Dryden et al.	2019	Medicines optimisation: Correcting drug related problems and recording interventions while reviewing emergency department patients	University affiliated tertiary care hospital in Canada, emergency department	1 month	Decrease in medicines costs and cost-avoidance due to ADEs prevention	Cost savings of $159 439
Leache et al.	2019	Antimicrobials: DRPs and interventions to optimise therapy	University hospital in Spain, ICU	4 months	Decrease in medicines costs	Cost savings of €10 905

Sjölander et al.	2019	Complex: interventions during medication reconciliations, medication reviews, and participation in ward rounds	Two hospitals in Sweden, internal medicine and orthopedic department	2 months	Cost-savings on the basis of readmission avoidance/reduction	Savings for subgroup €267 900/annum and €184 000 on the total sample
Chen et al.	2019	Medicines optimisation: monitoring of DRPs and interventions on hematology unit	Hospital in Taiwan, hematology unit	total of 24 months	Decrease in medicines costs and cost-avoidance due to ADEs prevention	Net benefit of NT$1 754 880
Sukkha et al.	2020	Antimicrobials: pharmacist's interventions regarding renal dosing	Hospital in Thailand, 8 departments	total of 15 months	Decrease in medicines costs and cost-avoidance due to ADEs prevention	Direct cost saving €5 114.11, cost avoidance €863.47
Buckley et al.	2020	Albumins: development of guidelines, education and monitoring of albumin use by pharmacist	University medical center in USA, general ward	total of 24 months	Decrease in medicines costs	Cost savings of $421 455
Ramesh et al.	2020	Medicines optimisation: monitoring DRPs and interventions on general surgery ward	Hospital in India, general surgery department	8 months	Cost-savings on LOS, readmissions, laboratory monitoring/medical procedure, decrease in medications cost	Cost saving of Rs. 207 134.7
Muñoz-Pichuante et al.	2020	Complex: DRPs and interventions recorded during daily activities in ICU	Hospital in Chile, ICU	2 months	Cost-avoidance due to interventions based on literature-sourced data	Net benefit of $252 620

ADE – adverse drug event; DOAC – direct acting anticoagulant; DRP – drug related problem; ICU – intensive care unit; LoS – length of Stay; MR – medicines review; VTEP – venous thromboembolism prophylaxis;

3. Clinical pharmacy services around the world - current status

As described above, the USA plays and has played a pioneering role within this field. The ACCP outlines that clinical pharmacists work in collaboration with other healthcare professionals to deliver comprehensive medication management and that care is coordinated across systems of care as patients transition in and out of various settings. The services provided include in-depth assessment of the patient, detailed evaluation of medication therapy, development, and implementation of a care plan, follow-up evaluation and medication monitoring. In addition to these functions, they may also serve as educators, researchers, mentors, administrators, managers, policy developers, and consultants. Moreover, this role requires specialized advanced education and training - accredited residency training or equivalent post-licensure experience [47].

Neighbouring Canada has also developed CPS to a high level and produced the Canadian Consensus on Clinical Pharmacy Key Performance Indicators to measure progress for a particular clinical pharmacy activity. These include 8 core services:

- medication reconciliation on admission,
- pharmaceutical care plan,
- drug therapy problems,
- interprofessional patient care rounds,
- patient education during hospital stay,
- patient education at discharge,
- medication reconciliation at discharge,
- bundled patient care interventions [48].

In contrast, in Latin America the uptake of CPS is more variable with Brazil being the most advanced. Services provided range from pharmacotherapeutic monitoring of patients to interdisciplinary collaboration in managing critically ill hospitalized patients [49].

In Australia, The Society of Hospital Pharmacists of Australia has also developed a number of CPS standards:

- medication reconciliation,
- assessment of current medication management,
- clinical review,
- therapeutic drug monitoring and adverse drug reaction management,
- contributing to the medicines management plan,
- providing medicines information,

- facilitating continuity of medication management on discharge or transfer,
- participating in interdisciplinary ward rounds and meetings,
- training and education,
- participating in research [50].

A "Pharmacy Forecast Australia 2023: Report" indicates that they will be also investing in pharmacist-led hospital outpatient clinics and non-dispensing, prescribing pharmacists in primary healthcare [51]. New Zealand adapted similar CPS as in Australia with additional attention to Therapeutic Drug Monitoring (TDM) [52]. When looking more broadly at the West Pacific Region, a considerable proportion of hospitals have implemented CPS. Large numbers reported participation in ward rounds, taking medication history or discharge counselling [53].

However, in South Asia CPS are also still evolving and are mostly limited to providing traditional services such as dispensing medicines. In individual cases, interventions performed by the pharmacists are related to education and counselling of patients including, among others, disease monitoring, treatment optimization, and medication adherence [54]. In relation to the Middle East CPS are still developing and only some of the services are provided [55]. Similar challenges with a lack of sufficient implementation also exist in Africa [56].

While CPS are well established in many countries worldwide, there are regional differences in the uptake of these services within Europe [10]. The United Kingdom in many respects serves as the gold standard. Similarly to the situation in the USA, clinical pharmacists are engaged in direct patient care on wards to monitor and advise on the use of medicines within multiprofessional teams in the hospital setting [17]. As an example, Northern Ireland has defined the following set of CPS standards for provision of services to inpatients:

- medicine history interview and medicines reconciliation,
- medicine therapy monitoring,
- prescription monitoring and review,
- prevention, detection, assessment and management of adverse drug reactions,
- prevention, assessment and management of drug interactions,
- therapeutic drug monitoring,
- prevention, identification, management and reporting of medication incidents,
- multidisciplinary working,
- provision of medicines information advice by pharmacists,
- discharge,
- patient medicine education [57].

To avoid gaps in care, CPS are also available in other settings. Various services are offered in GP practices, from medication reviews, management of long-term conditions or repeat prescribing requests up to care home and domiciliary visits [58]. However, clinical pharmacy practice encompasses even more aspects such as production of guidelines and policies, training, and education of other healthcare professionals [17]. Moreover, the UK is currently changing pharmacy education by integrating pharmacist independent prescribing into the undergraduate Master of Pharmacy (MPharm) degree and foundation year. It means that from 2026 all pharmacy graduates will be able to prescribe medicines following registration [59].

In addition to the UK in the European context Ireland, Norway, Netherlands, Belgium, Denmark, Spain, Portugal, France, Finland and Luxembourg also reported to a higher extent to have either daily visits on the wards by pharmacists or having pharmacists working at least 50% of their time on the ward. This is also connected with providing more patient oriented activities like patient visits at admission and patient counselling at discharge [60].

The current status of Central and Eastern Europe shows greater variability. In Slovenia CPS are fully reimbursed in three different settings: clinical pharmacist consultancy in primary care, seamless care system in hospitals (including medication reconciliation at admission, medication reconciliation at discharge, personal medication card before discharge and home dispensing) and a clinical pharmacist as a mandatory team member in the psychogeriatric team in psychiatric hospitals. In the Czech Republic CPS has been successfully implemented in both hospitals and GP practice. By way of contrast, patients in other countries such as Poland, Croatia, Bulgaria, Slovakia, Latvia, Estonia or Serbia do not have access to most CPS due to the lack of sufficient development of clinical pharmacy practice. Summary of differences can be seen in table 2 [10].

Table 2. Summary of data about details of CPS in CEE countries [10].

Country	Professional education in Clinical Pharmacy included in:		Hospital-based Clinical Pharmacy services	Outpatient Clinical Pharmacy services	National association of Clinical Pharmacy	Specialization, duration of the training
	Undergraduate training	Postgraduate training				
Austria	No	Yes	Yes Reimbursed	N/A	N/A	N/A
Entity of Bosnia and Herzegovina - Republic of Srpska	Yes, but optional	Yes, 3 years	Available in two hospitals Reimbursed	Available in selected places Not reimbursed	N/A	Yes, 3 years

Bulgaria	Yes	Yes	Yes Not reimbursed	N/A	N/A	Yes, 3 years
Croatia	Yes	Yes	N/A	N/A	Section for clinical pharmacy under Croatian pharmaceutical society as well as the committee for clinical pharmacy under Croatian pharmaceutical chamber	Yes
Czech Republic	Yes	Yes	Yes Reimbursed	Yes Reimbursed	Section of Clinical Pharmacy of the Czech Pharmaceutical Society and Czech Professional Society of Clinical Pharmacy	Yes, 5 years
Estonia	Yes	Yes	N/A	N/A	Not available, existing within Estonian Society of Hospital Pharmacists	N/A
Greece	No	Yes	N/A	N/A	N/A	N/A
Hungary	Yes	Yes	Yes Not reimbursed	N/A	Hungarian Society of Hospital Pharmacist Hungarian Chamber of Pharmacists (hospital and clinical pharmacy section) National Healthcare Service Centre (Hospital and clinical pharmacy section)	Yes 3 years

Latvia	Yes	Yes, 2.5 year	Available in 5 hospitals Not reimbursed	N/A	Section at the Pharmacists' Society of Latvia	Yes, 2.5 years
Poland	Yes	Yes	Yes, only in a few hospitals Not reimbursed	N/A	Yes, Polish Society of Clinical Pharmacy	Yes, 3 years
Serbia	Yes	No	Yes, only in a few hospitals Not reimbursed	Yes, only in a few hospitals Not reimbursed	The Section of Hospital pharmacists and Section of Pharmaceutical Care within the Pharmaceutical Association of Serbia	Yes, 3 years
Slovakia	Yes	Yes	Available Reimbursement for TDM laboratory items only	Available on demand. Not reimbursement	Section of Clinical Pharmacy, Slovak Pharmaceutical Association	Yes, 3 years
Slovenia	Yes	Yes	Yes Reimbursed	Yes Reimbursed	The Section of Clinical Pharmacists, which is organised as one of the sections of the Slovenian Pharmaceutical Society	Yes 3 years

N/A – not applicable

4. Clinical pharmacy and clinical pharmacy services in Poland

Although the first initiatives related to clinical pharmacy in Poland date back to the 1970s, the concept of involvement in direct patient care rather than procurement and dispensing is still evolving. Scientific symposia on clinical pharmacy were organized in different cities since 1973. First clinical pharmacy specialists, with the program changing over the years, obtained their certification in 1980s. This was also a period when textbooks were published describing the clinical pharmacy profession [61].

Nevertheless, national potential has been gradually built due to the inclusion of clinical pharmacy as a subject in undergraduate education. Additionally, pharmacists can complete a postgraduate specialization which currently lasts 3 years. A definite increase in the importance

of the pharmacist's role and gradual development of CPS has been observed over the past few years. In 2020 the Polish Society of Clinical Pharmacy was established and released the first Polish standard in clinical pharmacy (Medicines reconciliation) with more being currently developed. Further, a national consultant for clinical pharmacy was appointed with subsequent appointments of regional consultants for some of the Polish regions. Moreover, the Pharmacy Profession Act entered into force in 2021 and for the first time a definition of clinical pharmacy services with the possibility of forming clinical pharmacy teams [10,61,62].

In 2020 the Ministry of Health (MoH) released a report describing pharmaceutical care in community pharmacies with further steps in 2022 to prepare a report about CPS which was successfully published the same year [63,64]. This latter document described 5 main services suggested for hospitals: medicines reconciliation, medicines review, patient education, therapeutic drug monitoring, specialized medicines service (including high-risk oncology therapies and other specialist treatments dispensed from hospitals). The report also included the option of providing CPS in GP practice and long-term care facilities with the assumption being that care should be available across different healthcare settings [64].

Currently there are no formal requirements in place to employ clinical pharmacists and CPS are not reimbursed. Most activities are undertaken by pharmacists working in hospital pharmacy who are motivated to devote part of their time to clinical duties which usually include one of the services – medicines reconciliation, medicines review, TDM, consultation or patient education [10,61]. To date and to the authors own knowledge, there are at least 3 hospitals with established separate clinical pharmacy teams within their hospital structure providing different services depending on local arrangements. In the Polish setting, few studies have been undertaken in relation to the described potential roles for the pharmacist and their benefits or the pharmacist's perspective of patient safety [65,66]. There has been only one published piece of work regarding the inclusion of a CPS fully integrated into a multidisciplinary ward team. Urbanczyk et al. reported that the pharmacist performed 1349 interventions over a 1-year period in The Regional Specialist Hospital in Wroclaw (RHW), 97% of which were accepted by physicians. The most frequent type of intervention was drug discontinuation, followed by the addition of a new or missing drug and the change of the administration route. The study reported a cost-benefit ratio of 1:9.5, and the predicted cost savings on direct medications and the cost-avoidance resulting from the prevention of Adverse Drug Events (ADEs) were 30 000 zloty ($8306, €7035) and 318 835 zloty ($88 271, €74 766), respectively. However, CPS have to date not included care at discharge from hospital and any follow-up [67].

5. Integrated medicines management model

The concept of Integrated Medicines Management has been proposed as a mechanism to enhance medication effectiveness and safety. It's delivered by a clinical pharmacist at all three stages of inpatient care (admission, inpatient stay and patient discharge). The service includes, but is not limited to medicines reconciliation, medicines review, therapeutic drug monitoring, reviewing of clinical status and laboratory results during the hospital stay, patient education with amended medicines list when leaving hospital. The concept of IMM has been well documented in the existing literature. The phrase "comprehensive medicines management" is also used to describe this concept. Furthermore, it may also be characterized by the term "seamless care," which refers to the delivery of services across the whole care continuum [41,68,69].

In 2006 Schnipper et al. conducted a randomized controlled trial (RCT) and described reduction of medicines related adverse events during 30 days of follow-up after hospital discharge [70]. The key quality improvements were also demonstrated by Scullin et al. in Northern Ireland, that is, a reduction in the LoS, an increased time to readmission and a reduction in the number of readmissions to hospital within a 12-month period [41]. In Sweden, IMM led to major reductions in morbidity and drug-related readmissions in an elderly population [71]. The process of Lund-IMM medication reconciliation, conducted during both admission and discharge, along with a medication review, proved to be a cost-effective measure and resulted in increased usefulness when compared to standard care. This was primarily due to the prevention of hospital readmissions caused by drug-related issues [72,73]. The implementation of an IMM program in the field of oncology in Turkey led to a decrease in the occurrence of DRPs [74]. In Taiwan the introduction of such a system enhanced patient safety and optimized the utilization of medication by augmenting the reporting of medication errors and reducing the quantity of medications administered [75]. Similar benefits resulting from the implementation of the IMM model were made in Norway thus improving overall patient survival during the observation period [76].

In the Polish healthcare system, a coordinated care model has been implemented in the primary care setting encompassing complex care being offered to patients. However, at the time of writing of this dissertation it does not include the involvement of a pharmacist [77]. Further parts of the model describe possible elements of an IMM service in the hospital setting.

5.1. Admission

At the stage of admission to hospital when the patient is being taken care of by the ward staff, two key CPS can be provided – medicines reconciliation (MRec) and medicines review (MR) [41,57].

5.2. Medicines reconciliation

MRec plays a pivotal role in guaranteeing the safety of patients through the identification of deliberate and unintended inconsistencies in medications during transition of care [78]. A Cochrane review revealed that a significant portion of patients, specifically 55.9%, are susceptible to experiencing one or multiple inconsistencies in their medication regimen during the process of transitioning between different healthcare settings. This occurs even with the implementation of standard healthcare practices. As healthcare becomes more complex—with various providers and the introduction of telehealth—effective communication is more important than ever to ensure that medicines are reconciled correctly. Therefore, the fundamental principles of medicines reconciliation encompass the gathering of comprehensive data regarding the medications that a patient is taking. Such data is collected from multiple sources including from the patient, their family members, and all healthcare providers who have been involved in the patient's care during transitions of care. Although numerous healthcare practitioners are equipped to carry out medicines reconciliation, pharmacists possess the necessary knowledge and expertise and are best placed to rapidly and efficiently identify any inappropriate alterations in medication and avoid medication errors [62,78,79].

The following steps represent the best practice process for medicines reconciliation:

I. Creating the best possible medication history (BPMH) with the aim of using at least two information sources - complete list including all prescription and non-prescription medicines (herbal medicines, supplements, vitamins etc.) used by the patient, including the dose, frequency, formulation and route of administration
II. Comparing the BPMH with medicines prescribed on admission and identifying discrepancies;
III. Classifying discrepancies and taking the appropriate action by resolving them together with physician and documenting interventions [62,78].

Paper based templates can be used to document the medicines list and interventions, but considering current preferences, an electronic form would be more appropriate. MRec should be ideally conducted at each episode of transfer of care within 24h to assure safety. Therefore, it can take place both on admission to the emergency department or other hospital department,

when transferring patient between departments and at discharge. MRec should be undertaken for every patient. However, when inadequate resources make it impractical to reconcile medications for every patient, patient groups may be given priority in order to guarantee that the service is accessible to those who are most vulnerable to medication errors. Examples of high-risk factors and medicines are listed in table 3 [62,78,79].

Table 3. Examples of high-risk factors related to patients and high-risk medicines setting the priority for MRec [62,78,79].

Examples of high-risk factors	Examples of high-risk medicines
• Age > 65 years old • Number of medicines taken ≥ 5 or more • Taking high-risk medicines • Repeated hospitalizations • Insufficiency of main organs (liver, kidneys) • Frailty syndrome • Cognitive impairment • Short life expectancy	• Medicines with narrow therapeutic index ex. digoxin • Anti-platelets • Anticoagulants • Immuno-suppressants • Opioids • Anti-epileptics • Anti-parkinsons medicines • Insulins • Hypnotics

5.3. Medicines review

There is complementarity in the literature regarding the definition of medicines review (MR) services, with various proposals having been put forth. The Pharmaceutical Care Network Europe (PCNE) characterizes MR as a "structured assessment of a patient's medications with the purpose of optimizing their use and enhancing health outcomes. This involves identifying drug-related issues and suggesting appropriate interventions." Different types of MR can be identified according to “Room for review” guidance and PCNE, depending on setting, patient needs, sources of information used and pharmacist’s skills [80–82]. Table 4 adapted from Clyne et al. presents 3 most common types of MR [83].

Table 4. Main types of MR according to Clyne et al. [83].

Type of review	Purpose of the review	Requires patients to be present	Access to patient notes	Includes all prescription medicines	Includes prescription, complementary and over-the-counter medicines	Review of medicines and/or condition
Type 1 Prescription review	Address technical issues related to the prescription	No	Possibly	Possibly	No	Medicines
Type 2 Concordance and compliance review	Address issues related to patients medicines taking behaviour	Usually	Possibly	Possibly	Yes	Medicines use
Type 3 Clinical medication review	Address issues relating to the patient's use of medicines in the context of their clinical condition	Yes	Yes	Yes	Yes	Medicines and condition

However, PCNE further divides type 2 MR into 2 subtypes – 2a and 2b [80]. The issues that MR aims to address encompass medicine-medicine interactions, certain side effects, atypical dosages, concerns with adherence, interactions between medicine and food, efficacy-related matters, untreated medical conditions, and the employment of treatments without a specific indication [81]. With regards to the PCNE definition of MR and, this particular type of evaluation is only viable in scenarios 2b and 3 of MR, wherein the patient is physically present and able to provide relevant information [80,81]. In the context of IMM and assuring high-quality and safety of care in hospital, type 3 MR is the most suitable tool to address complex clinical scenarios, and it should be offered on admission in conjunction with MRec [69,81]. Similarly, as with MRec, attention should be given to the development of prioritization or screening methods in order to enhance the utilization of MR and personalize the service for individuals who would derive the greatest benefit [81].

It is worth commenting that medicines use review (MUR), often mentioned when discussing pharmaceutical care, as being a variant of MR and represents the collaboration between pharmacists and patients to enhance their utilization of medicines, accommodate their preferences, and maximize their conformity to prescribed medications. This particular service holds significance for individuals affected by polypharmacy, particularly those enduring chronic illness, and also encompasses those confronted with established challenges related to adherence [81].

As indicated within the description of type 3 MR, the analysis ofa broad set of details is necessary to optimize pharmacotherapy. Therefore, it should be conducted in a methodical manner in order to avoid overlooking substantial problems with a patient's medicines. Moreover, a range of tools can be employed to facilitate this procedure. NO TEARS is an acronym proposed by Lewis that covers several areas that should be considered when performing an MR. Description of elements of this tool are the following: Need and indication, Open questions, Tests and monitoring, Evidence and guidelines, Adverse events, Risk reduction or prevention, Simplification and switches [84].

In turn, the "7Steps" Medication Review process is a strategy for analyzing complex pharmacotherapy by implementing 7 steps, within which key questions are asked about the medicines used by the patient. It was first proposed by the Scottish Government Model of Care Polypharmacy Working Group in 2012 and further used in the European iSIMPATHY project [42,85]. In comparison to the NO TEARS technique it puts even more significance on the position and role of the patient in the treatment procedure by giving appropriate weighting to

mutually establishing plans for subsequent therapy [42,85]. Table 5 presents the 7Steps approach adapted from iSIMPATHY [42].

Table 5. Detailed description of 7Steps approach adapted from iSIMPATHY [42].

Domain	Steps		Process
Aims	**1.**	What matters to the patient problems	**Review diagnoses and identify therapeutic objectives with respect to:** ➢ Identify objectives of drug therapy ➢ Management of existing health problems. Prevention of future health concerns
Need	**2.**	Identify essential drug therapy	**Identify essential drugs (not to be stopped without specialist advice)** ➢ Drugs that have essential replacement functions (e.g. thyroxine) ➢ Drugs to prevent rapid symptomatic decline (e.g. drugs for Parkinson's disease, heart failure)
	3.	Does the patient take unnecessary drug therapy?	**Identify and review the (continued) need for drugs** ➢ What is medication for? ➢ with temporary indications ➢ with higher than usual maintenance doses ➢ with limited benefit/evidence of its use in general ➢ with limited benefit in the patient under review
Effectiveness	**4.**	Are therapeutic objectives being achieved?	**Identify the need for adding/intensifying drug therapy in order to achieve therapeutic objectives** ➢ to achieve symptom control ➢ to achieve biochemical/clinical targets ➢ to prevent disease progression/exacerbation ➢ is there a more appropriate medication that would help achieve goals
Safety	**5.**	Does the patient have ADR/ Side effects or is at risk of ADRs/ side effects? Does the patient know what to do if they're ill?	**Identify patient safety risks by checking for** ➢ is the targets set for the individual appropriate ? ➢ drug-disease interactions ➢ drug-drug interactions ➢ monitoring mechanisms for high-risk drugs ➢ risk of accidental overdosing **Identify adverse drug effects by checking for** ➢ specific symptoms/laboratory markers (e.g. hypokalaemia) ➢ cumulative adverse drug effects ➢ drugs that may be used to treat side effects caused by other drugs
Cost-effectiveness	**6.**	Is drug therapy cost-effective?	**Identify unnecessarily costly drug therapy by** • Consider more cost-effective alternatives (but balance against effectiveness, safety, convenience)

Patient centeredness	**7.**	Is the patient willing and able to take drug therapy as intended?	**Does the patient understand the outcomes of the review?** • Consider Teach back technique **Ensure drug therapy changes are tailored to patient preferences by** • Is the medication in a form the patient can take? • Is the dosing schedule convenient? • Consider what assistance the patient might have and when this is available • Is the patient able to take medicines as intended **Agree and communicate plan** • Discuss with the patient/carer/welfare proxy therapeutic objectives and treatment priorities • Decide with the patient/ carer/ welfare proxies what medicines have an effect of sufficient magnitude to consider continuation or discontinuation • Inform relevant healthcare and social care carers, changes in treatments across the care interfaces

After conducting MRec and MR according to chosen guidelines, identified drug related problems should be discussed with the physician together with suggested actions that need to be taken for their resolution. The whole process requires full documentation as detailed in the MRec section. Different templates can be adapted depending on local preferences and setting [81].

5.4. Inpatient monitoring and counselling

IMM and complex CPS assume intensive supervision throughout the hospital stay. Although MRec and MR are performed on admission, a patient's clinical status can change rapidly. Therefore, additional input is also needed from the clinical pharmacist. Several CPS can be distinguished during hospitalization [41,57].

Most importantly the pharmacist, as a valuable member of the healthcare team should participate in ward rounds and clinical meetings to provide input to patient care. Multidisciplinary work is described as bringing additional value in the available literature. Drug treatment should be evaluated on a daily basis. This regular review process is essential to ensure that the prescribed medication remains appropriate, effective, and safe for the patient. By analyzing the therapeutic goals, pharmacists can evaluate the progress and determine if any

adjustments or modifications are necessary to optimize the treatment regimen. Furthermore, the examination of relevant laboratory results and other monitoring parameters provides valuable insights into the patient's response to the drug, allowing for the identification of potential adverse effects or the need for dosage adjustments [41,48,57].

Therapeutic drug monitoring, for those agents with a narrow therapeutic index, is another service element that provides an extra degree of accuracy to the treatment process, enabling monitoring the drug's concentration in the patient's blood and making informed decisions based on the individual's therapeutic range. This ensures optimal dose selection with the highest therapeutic advantage and the least adverse outcomes. In addition, pharmacists provide input regarding the appropriate timing for sample collection, the necessary dose modification, as well as the robust monitoring of laboratory findings and the consequential therapeutic effects. This comprehensive approach to reviewing drug treatment ensures that patients receive the most appropriate and personalized care, with a focus on achieving optimal therapeutic outcomes while minimizing any potential risks or complications during inpatient stay [41,57]

Clinical pharmacists can also offer counselling, which is specifically customized to the unique requirements of every single patient. The primary objective of such counselling is to concentrate on medications that have been initiated or halted, medications that pose a higher level of risk, the utilization of medical devices, and any other circumstances where it is deemed vital to provide pharmaceutical guidance and expertise. Medicines information advice can also be provided to various healthcare professionals [41,57]. Moreover, pharmacists play a crucial role in actively participating in prevention, detection, assessment, management and reporting of adverse drug reactions. Surveillance and evaluation of the utilization of medication therapy in patients also includes the identification and management of potential and current drug interactions. Whenever pharmacists provide CPS during a patients hospital stay, all findings should also be discussed with the physician and documented [57].

5.5. Discharge

Before a patient is discharged from the hospital, the pharmacist takes the time to carefully review their current treatment plan. This includes looking for any potential issues with their medications. The pharmacist also works closely with other healthcare professionals, making sure everyone is on the same page to ensure that the patient's care continues smoothly after they leave the hospital. During this critical evaluation, the pharmacist verifies the clinical accuracy and appropriateness of all medications that have been prescribed upon the patient's discharge. This thorough examination encompasses an assessment of the patient's current medications and

any modifications that may have been made to the treatment plan, along with a comprehensive understanding of the underlying reasons for such changes. In the primary care context, a pharmacist also makes sure that all the information needed to maintain the patient's medicine supply is simple to find. Special attention is given to any monitoring requirements. A copy of every relevant detail is kept in the patient's medical records or in the appropriate location to ensure a thorough record of this essential data. The pharmacist assumes the responsibility for ensuring that the patient or caregiver is thoroughly educated on the specific medicines prescribed to them, taking into consideration their appropriateness, and furthermore, provides them with continuous reinforcement regarding the utmost importance of adhering strictly to the prescribed treatment plan, particularly in cases where there exists a risk factor or a previous history of non-compliance. Patients are supplied with comprehensive information, either via verbal communication or in written form, presented in a manner that is easily understandable and accessible. Additionally, pharmacists play an integral role in the facilitation of multidisciplinary patient education initiatives, such as cardiac rehabilitation or respiratory rehabilitation. To guarantee that crucial discharge information was promptly shared across the primary/secondary care interface, a copy of the discharge summary can be sent to the patient's general practitioner and designated community pharmacy, depending on the healthcare system arrangements [41,48,57].

5.6. Follow-up

Depending on the local arrangements and staffing, IMM can also include a follow-up after discharge. Most centres plan a telephone call in a pre-defined time period – 7 days up to 2 months after the patient has left the hospital. The patient, next of kin, or carer is contacted to make sure the information regarding the patient's current drug management had been correctly understood and to address any associated issues, worries, or enquiries [71,86].

V. Material and methods

1. Study planning

The IMM service was designed in cooperation with the Medicines Optimization Innovation Centre (MOIC) and Antrim Area Hospital (AAH) in Northern Ireland which has years of experience in implementing and maintaining this concept [41]. Additionally, MOIC has participated in advancing CPS in other countries such as Norway or Sweden [71,87]. For

completeness the available literature was analyzed to search for similar approaches. In this context, a modified solution was gradually implemented in a 500-bed Regional Specialist Hospital in Wroclaw with the aim of adjustment to the Polish context. Starting between 2017/2018, patients were offered CPS on admission and during hospital stay in the Vascular Surgery Department and an evaluation of this approach was undertaken [67]. This was preceded by a 2-month visit of the author (pharmacist) in AAH to gain hands on experience. Since 2019 collaborative efforts have been made to introduce IMM as it offers multiple benefits for patients and the healthcare system. The author graduated from the Advanced Clinical Pharmacy Program at Queen's University Belfast in 2020. After the COVID-19 pandemic, local experience and expansion of the team by an additional pharmacist allowed the extension of the service by the General Surgery Department.

2. Study design

Set against this background and context a randomized controlled pilot study was proposed to verify whether IMM can be successfully implemented within the Polish healthcare system and provide the basis for a further multicentre RCT. CONSORT 2010 statement (extension to randomized pilot and feasibility trials) was used to guide a detailed description of the study together with a template for intervention description and replication (TIDieR) checklist [88,89]. The research was approved by the Ethics Committee of Regional Hospital in Wroclaw (approval number KB 1/2022). All participants provided written informed consent or verbally informed consent if written informed consent was not possible. The study team consisted of one specialist clinical pharmacist and one pharmacy graduate. It was conducted from November 2022 to April 2023 in the Vascular and General Surgery Departments (with two months break). The criteria for progression to a definitive trial were recruitment of 40% of patients identified as eligible and retention of 75% of participants at 6-month follow-up.

3. Patient selection and randomisation

Pharmacists were screening admissions to both surgical departments daily from Monday to Friday for patients meeting the following inclusion criteria:

- ≥18 years old and an acute admission to the hospital fulfilling at least one of the following criteria:
    - taking ≥4 medicines
    - taking high risk medicines listed in the medicines reconciliation standard of the Polish Society of Clinical Pharmacy [62]

- medicine related admission to the hospital within the last 12 months
- chronic kidney or liver disease
- after solid organ transplantation

Exclusion criteria:

- age below 18 years old
- pregnant
- resident of long-term care facility
- unable to express informed consent to participate in the research
- expected survival less than 6 months

Patients eligible for inclusion in the study who gave informed consent to participate were grouped in pairs. Randomization was performed by sealed envelope technique. One of the healthcare staff working within the surgical departments who did not take care of recruited patients was asked to choose the envelope starting with the patient admitted earlier according to the hospital's electronic system. Within each pair one patient was assigned to the control group (standard care provided by hospital) and the other one to the IMM group (care enhanced by complex clinical pharmacy services).

4. Intervention

Each patient who was assigned to the IMM group received comprehensive CPS. This care was provided by a dedicated project pharmacist who remained actively involved in the patient's treatment journey during each of the three distinct stages, namely, admission, inpatient monitoring and counselling, and discharge. It is important to emphasize that this degree of care was provided with the highest dedication and professionalism, guaranteeing that the patients' requirements were satisfied, and their health was protected during their whole stay. Patients falling into the control group received standard hospital care as usual without additional pharmacist input. However, if the doctor asked for a consultation around a specific issue regarding this patient group, the pharmacist provided help and each intervention was documented. The study design is further presented on the Figure 2.

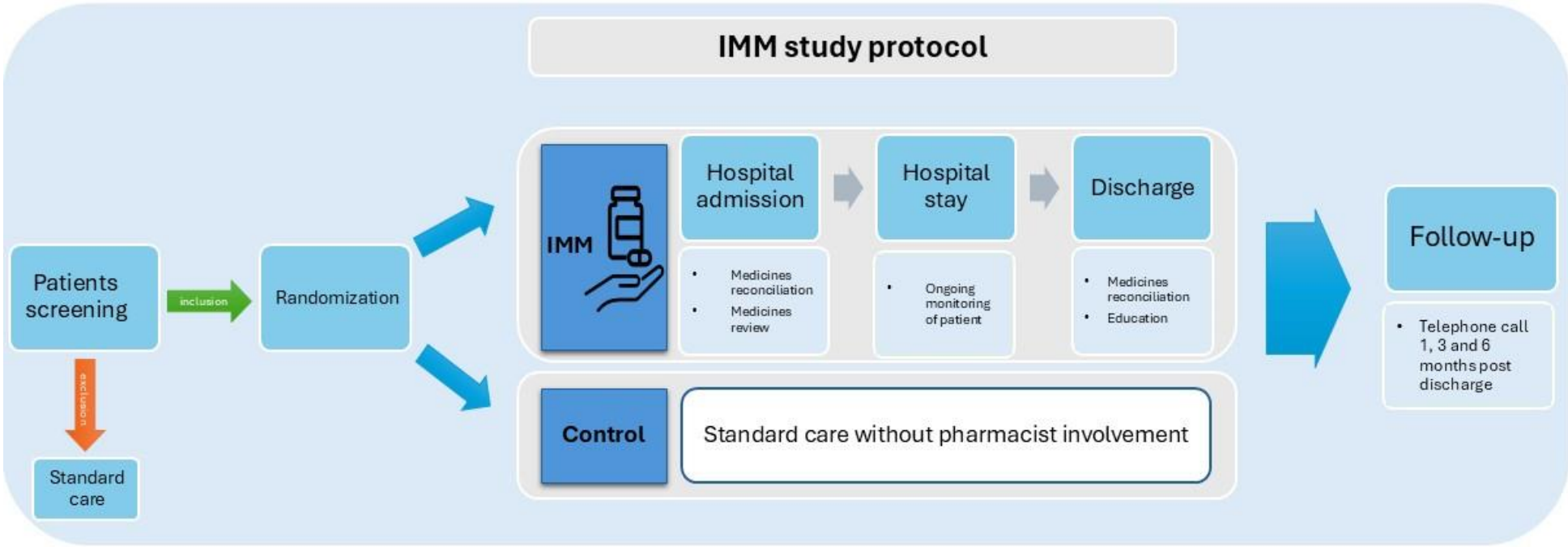

Figure 2. Graphic representation of study design.

4.1. Admission

Demographic information and prior medical history were gathered through the utilization of a registration form for patients. The clinical pharmacist established an accurate record of the medications used by the patient, employing a variety of sources. These sources encompassed the patient's documents, the patient's general practitioner, the patient's personal supply of medications, and information obtained directly from the patient or their caregiver. Additionally, any pertinent data regarding allergies, side effects, and adherence to prescribed medications was compiled during this phase. This process adhered to the established standard for medication reconciliation as formulated by the Polish Society of Clinical Pharmacy. In the event that any discrepancies arose with the list of prescriptions provided by the hospital, they were promptly addressed. Following this, a level 3 medicines review was conducted in accordance with the 7Steps methodology as outlined in the Scottish Polypharmacy guidance [85]. Any drug-related issues that were identified, along with proposals for potential interventions, were subsequently discussed with the physicians, who then made any necessary adjustments to the patient's pharmacotherapy. All interventions were documented.

4.2. Inpatient monitoring and counselling

Throughout the duration of their hospitalization, patients were provided with further comprehensive CPS. The drug treatment administered to the patients was evaluated on a daily basis, with key consideration given to the desired therapeutic outcomes, pertinent clinical status and laboratory findings, and, when deemed appropriate, therapeutic drug monitoring. To ensure continuous improvement, all interventions were documented and recorded. The clinical pharmacists also dedicated their efforts to delivering personalized counselling that was tailored to meet the specific needs of each patient and the current needs of healthcare staff. Counselling was primarily focused on drugs that had been newly initiated or discontinued, proper utilization of medical devices, and various other scenarios where pharmaceutical advice was necessary. Every drug-related intervention was documented.

4.3. Discharge

Upon discharge, the pharmacist engaged once again in the process of conducting medicines reconciliation, ensuring accuracy and consistency in the list of medications, which was then agreed upon with the doctor. Subsequently, a detailed medicines record sheet was crafted by the pharmacist for each individual patient, outlining all prescribed medications along with

explicit dosage instructions. Following the presentation of this comprehensive document, the patient received an extensive counselling session in which they were given vital information and assurance, stressing the significance of understanding and appreciating the recommended regimen. Furthermore, the medicines record sheet also encompassed details such as any modifications made to the patient's medication regime, being a comprehensive reference guide for both the patient and healthcare professionals. If any intervention occurred at this stage it was documented. In order to ensure the best possible patient outcomes and care quality, our systematic evaluation aimed to find and fix any inconsistencies or areas where the drug management procedure may be improved.

After this procedure, the patient was given a structured questionnaire designed to find out how they felt about this new service. Patients completed the form themselves, but when patients were having difficulties the completion of this questionnaire was overseen by the pharmacist who had not been directly involved in the patient's care during their hospitalization.

5. Outcome measures

The primary objective was the incidence of unplanned visits during the 6 months after discharge from hospital. This was analysed by follow-up phone calls in defined time periods namely – 1 month, 3 months and 6 months after discharge. Details were obtained from the patient or family member regarding any incidents that occurred within observation period: ED or hospital admission, GP visit, other unscheduled visits, dates, reason and outcome of the incidents.

The secondary objective was to look at LoS in the hospital with the data being obtained from the patient electronic records and comparing the IMM group with standard care.

To further evaluate this model including the payer, patient and healthcare staff perspective, a number of different factors were analysed. The type of DRPs and interventions from admission to discharge were recorded according to the classification prepared by the French Society of Clinical Pharmacy (presented in Table 6 and 7) together with the acceptance rate of the interventions by the physicians [90].

Table 6. Classification of DRPs prepared by French Society of Clinical Pharmacy [90].

1.1	Nonconformity to guidelines or contraindication	• Nonconformity of the drug choice compared to the accepted guidelines for example drug not held before surgery • Nonconformity of the drug choice compared to guidelines for example another drug has a better benefit/risk ratio or a better cost/efficacy ratio according to current guidelines • There is a physio-pathologic contra-indication for the prescribed drug for example the patient is asthmatic and was prescribed beta-blockers • Prescription of drug which is known to evoke allergy in patient • Allergy status/sensitivity not recorded in the documents or on patient's drug list
1.2	Untreated indication	• Valid indication without drug prescription • A new symptom is not being treated • A drug is missing after patient transfer/meds record changes/admission • The patient was not given any pre-medication or prophylactic treatment • A synergistic or corrective drug should be added to the ongoing treatment
1.3	Subtherapeutic dosage	• Dose too low in this specific case (daily dose) • Length of the treatment too short. (for example: antibiotic prescription for 5 days instead of 10 days)
1.4	Supratherapeutic dosage	• Supratherapeutic dose: Dose too high in this specific case • There is a risk of accumulation of the drug • Duplicate prescription: the same active substance is prescribed several times (for example: oral acetaminophen and the oral association of dextropropoxyphene/acetaminophen)
1.5	Drug without indication	• No justified indication for the drug • The drug is prescribed for too long (for example: antibiotics prescribed for 15 days)

		• Therapeutic redundancy: prescription of two different molecules from the same therapeutic class
1.6	Drug interaction	• A drug interferes with another drug and can lead to a modified pharmacological impact (over or under expressed)
1.7	Adverse drug effect	• The patient presents with an adverse drug effect with an adequate dosage (clinical, biological, or kinetic effect)
1.8	Improper administration	• The drug is adequate, but the mode of administration is not appropriate • Another route may be more effective or less costly for the same effectiveness • The mode of administration is not adequate (reconstitution, dilution, length of administration) • Inappropriate drug form • Incomplete formulation (dosage missing, etc.) • Inappropriate timing of administration
1.9	Failure to receive drug	• Physicochemical incompatibility between several injectable drugs: there is a risk of precipitation between drugs during infusion • Patient's non-compliance • Drug not available
1.10	Drug monitoring	• The patient is not suitably or sufficiently followed up: lab tests, kinetics, symptoms (glycemia, EKG, blood pressure, blood concentration of specific drugs, etc.)

Table 7. Classification of interventions related to DRPs prepared by French Society of Clinical Pharmacy [90].

2.1	Addition of a drug or continuation	• Addition of a new drug to ongoing treatment • Addition of a missing drug • Continuation of withheld or missed drug
2.2	Drug discontinuation	• Discontinuation of a drug without any substitution • Drug withheld

		• Prevention of administration of a drug which is known to evoke allergy in patient
2.3	Drug switch	• Switch from the currently administered drug to another drug • Substitution for a generic drug or a therapeutic equivalent (according to the local formulary) • Switch following a validated protocol • Switch for another drug better suited to the case
2.4	Change of administration route	• Parenteral/oral switch ➢ Alternative drug with equivalent effectiveness and possible oral administration ➢ Alternative oral form of a parenteral drug with the same bioequivalence • Choice of a route of administration better suited to the case
2.5	Drug monitoring/Patient monitoring	• Drug monitoring: INR, kalaemia kinetics, symptoms, etc • Discontinuation/Request for a new lab test or monitoring • Discontinuation/request for a new dosage of a specific drug • Highlighting allergy status on patient's drug list
2.6	Administration mode optimisation	• Timing of administration ➢ Distribution of doses according to food intake, to drug–food, drug–drug interactions (without modification of the dose) ➢ Information on the drug regimen (for example: take on an empty stomach, take during meals, take in the standing position, etc.) • Data on administration procedure (for example: mode of reconstitution, of dilution, length of infusion, etc.)
2.7	Dose adjustment	• Dose adjustment for a drug with a narrow therapeutic index, according to its blood level, with renal and hepatic data, or other lab test • Dose adjustment according to the patient's weight, age, clinical status • Dose increase/decrease according to regular medicines list

An expert panel made up of a senior clinical pharmacist, a cardiologist, and a surgeon further independently evaluated the performed interventions using the Eadon scale shown in Table 8 to assess their importance [91]. The latter two medical staff did not participate in the patients' actual treatment. Any disagreement was resolved by consensus.

Table 8. Description of the Eadon scale [91].

Eadon grade	Description
Grade 1	Detrimental to patient's well being
Grade 2	No significance for patient care
Grade 3	Significant but does not lead to an improvement in patient care
Grade 4	Significant and results in an improvement in the standard of care
Grade 5	Significant & prevents a major organ failure or adverse reaction of similar importance
Grade 6	Potentially lifesaving

The following categories corresponding to Eadon grades were applied, based on the Nesbit et al. approach, where a scoring system allows estimation of the interventions and adverse drug reaction (ADR) occurrence: 0.00 - no harm expected (Grade 2), 0.01 - very low (Grade 3), 0.10 - low (Grade 4), 0.40 medium (Grade 5), and 0.60 - high (Grade 6) [91,92]. By multiplying the potential harm coefficient by the number of interventions allocated to each category and the cost of hospitalization based on the assumption that a medication error could prolong hospitalization by two days based on data from published literature, the potential cost of resolving the ADR was calculated [93,94]. Additionally, the methodology applied by Mair et al. utilizing QALY's was used [42]. According to Campbell et al., a potentially fatal DRP can result in an average loss of 2.7 QALYs. Therefore, interventions assessed with Eadon grades and the Nesbit et al. method were used to estimate total QALY gain for the IMM group [95].

The quality of pharmacotherapy was evaluated by a senior pharmacist looking both at the admission and discharge medicines lists for each patient, employing the Patient-Centred Medicines Appropriateness Index (PC-MAI) – modified version of Medicines Appropriateness Index (MAI). This systematic assessment aimed to better envisage the potential influence of CPS on identifying and addressing any discrepancies or opportunities for improvement in the medication management process, ensuring optimal patient outcomes and quality of care. It

involves 8 key questions about each medicine taken by the patient, including over the counter and "as needed" medicines. Answers A, B, C are marked for each question where A suggests appropriate treatment, B marginal acceptance of the appropriateness and C corresponds to inappropriateness. Z means that additional information would be required to properly answer the questions for example. documents from GP practice. Table 9 presents the assessment system [42,96].

Table 9. PC-MAI patient form including questions with possible answers.

1. Is there an indication for the drug?	A_____ Indicated	B_____	C_____ Not Indicated	Z DK
Comments:				
2. Is the medication effective for the condition in this individual?	A_____ Effective	B_____	C_____ Ineffective	Z DK
Comments:				
3. Is the dosage correct?	A_____ Correct	B_____	C + or C - Incorrect	Z DK
Comments:				
4. Are the directions practical?	A_____ Practical	B_____	C_____ Impractical	Z DK
Comments:				
5. Are there clinically significant drug-drug interactions?	A_____ Insignificant	B_____	C_____ Significant	Z DK
Comments:				
6. Are there clinically significant drug-disease/condition interactions?	A_____ Insignificant	B_____	C_____ Significant	Z DK
Comments:				
7. Is there unnecessary duplication with other drug(s)?	A_____ Necessary	B_____	C_____ Unnecessary	Z DK
Comments:				
8. Is the duration of therapy acceptable/appropriate?	A_____ Acceptable	B_____	C_____ Unacceptable	Z DK
Comments:				

DK – do not know

For items coded as inappropriate (C), the following weights apply for individual criterion to calculate a summated PC-MAI score per drug presented in Table 10.

Table 10. Scoring system for medicines appropriateness assessment.

Criterion	Relative weight applied to inappropriate ratings
1. Is there an indication for the drug?	3
2. Is the medication effective for the condition in *this* individual?	3

3. Is the dosage correct?	2
4. Are the directions practical?	1
5. Are there clinically significant drug-drug interactions?	2
6. Are there clinically significant drug-disease interactions?	2
7. Is there unnecessary duplication with other drugs?	1
8. Is the duration of therapy acceptable?	1

To calculate a weighted MAI score per patient, MAI scores are added for each drug in the patient's regimen. Therefore, the maximum score is 15, and the minimum = 0 [42,96].

In addition, the pharmacist evaluated patient opinion based on the adapted Patient Satisfaction with Pharmacist Services Questionnaire (PSPSQ 2.0), which utilized a 4-point, Likert-type scale for assessment [97]. It comprised following questions:

1. Pharmacist addressed my health concerns
2. Pharmacist was professional in interaction
3. Pharmacist explained information that I can understand
4. Pharmacist checked if I understood
5. Pharmacist spent as much time needed
6. Pharmacist made sure I understood following the drug regimen
7. Pharmacist provided useful recommendations on taking my meds
8. Pharmacist made recommendations for my overall health
9. Pharmacist worked with me to manage my med related issues
10. Pharmacist was caring and kind in his interactions
11. Pharmacist encouraged me to achieve my treatment goals
12. Pharmacist made me comfortable in my interactions
13. Pharmacist was respectful during our interactions
14. Pharmacist was committed in improving my health
15. I could trust my pharmacist on the information provided
16. I was satisfied with my pharmacist for overall care provided

As part of the evaluation of the CPS, healthcare staff opinions were gathered to check acceptance, perceived value, and recommendations for service improvement. A carefully

selected sample of medical professionals was chosen because of the study's pilot status and small team size. This group included junior physicians, senior physicians, and nurses that interacted with the pharmacist. Participants were invited to share their perspectives through open-ended, semi-structured interviews. The interview guide included broad questions regarding the perceived impact of the service, integration into the clinical team, and potential areas for role refinement and expansion. Interviews were conducted in a conversational manner to encourage feedback. Responses were transcribed and subsequently examined for recurrent themes through thematic content analysis.

Economic analysis was conducted from the hospital and healthcare system perspective. The above-described data collected and described above has created a basis for further analysis. Local hospital data regarding costs were extracted for different types of incidents, taking into account the research population: hospital stay at specific departments, emergency department visit, and specialist visit. Cost calculations for specific departments were based on a number of patient cases for a certain type of visit, mean patient stay or time of visit and total cost of services provided. The cost of a single patient visit in primary health care in Poland, from the perspective of the health care system is not calculated as a per-visit unit cost, but rather within a capitation-based system. This means that the GP receives a monthly payment for each registered patient, regardless of how many visits that patient makes. Assuming that a patient has an average of 2–3 visits per year, the estimated cost of one visit can be estimated. However, this is only an approximation as national insurance does not pay for individual visits, but for overall care of the population. Due to patient recruitment and follow-up during the years 2022 and 2023, costs were obtained for both periods and mean values were used to describe the costs. Although some patients were hospitalized in other facilities, costs for the Regional Hospital in Wroclaw were adapted to assure consistency of estimation and avoid gaps in follow-up data. Available benchmarking values provided by an external consulting company to RHW show that spending can differ between hospitals by approximately 10%.

The costs extracted allowed estimation of cost-avoidance for the primary outcome – that is the additional healthcare use in the follow-up period. To estimate the potential influence of the intervention on the healthcare system and for the hospital department on an annualised level, extrapolation of the costs were further performed for acute admissions at the vascular surgery and general surgery department with assumption that only 60 to 80% would meet the inclusion criteria for the IMM service (predicted on the basis of local registry of DRPs and interventions).

For LoS in hospital, bed day costs were obtained for the two departments included for both years 2022 and 2023. Differences in this value allowed the estimation of the potential cost-avoidance for this parameter. Similarly as with the primary outcome, extrapolation was conducted to check the impact of shortening the LoS for a specific department, at an annual level, if 60 to 80% would receive IMM service based on current pilot data.

Moreover, the economic data regarding bed day costs were utilized to assess the potential cost-avoidance related to the interventions undertaken. The following categories corresponding to Eadon grades were applied, based on the Nesbit et al. approach, where a scoring system allows estimation of the interventions and adverse drug reaction (ADR) occurrence: 0.00 - no harm expected (Grade 2), 0.01 - very low (Grade 3), 0.10 - low (Grade 4), 0.40 medium (Grade 5), and 0.60 - high (Grade 6) [91,92]. By multiplying the potential harm coefficient by the number of interventions allocated to each category and the cost of hospitalization based on the assumption that a medication error could prolong hospitalization by two days based on data from published literature, the potential cost of resolving the ADR was calculated [93,94].

Additionally, the methodology applied by Mair et al. with utilizing QALY was used [42]. According to Campbell et al., a potentially fatal DRP can result in an average loss of 2.7 QALYs. Therefore, interventions assessed with Eadon grades and Nesbit et al. method were used to estimate total QALY gain for the IMM group [95]. To further clarify the potential benefit of the IMM service for healthcare system, Incremental Cost Effectiveness Ratio (ICER) in connection to assessed QALY gain due to the interventions performed and salary was calculated. In Poland, the value of one QALY is established based on three times the gross domestic product (GDP) per capita. These values are updated annually by the Agency for Health Technology Assessment and Tariff System based on data from the Central Statistical Office. For the purpose of this research, values from 2022 and 2023 were applied to determine the willingness to pay threshold. Following formular was used utilizing the study data when calculating the ICER for IMM [98]:

$$ICER = \frac{C_1 - C_0}{E_1 - E_0}$$

Where:

- C_1 – total cost of the intervention (for IMM the cost of employing pharmacist for the time necessary to make the intervention) [PLN],
- C_0 – total cost of standard treatment (here assuming $C_0 = 0$ if the only additional cost come from pharmacist salary) [PLN]

- $E_1 - E_0$ – total QALY gain based on interventions assessment [QALY]

As the outcome measure was utility-based (QALYs), this ICER is specifically an incremental cost-utility ratio (ICUR) [98].

Next, in order to calculate the cost-benefit ratio in relation to different types of cost-avoidance categories, the minimal annual salary for the pharmacist and clinical pharmacy specialist employed in hospital setting was included as defined by Polish legislation [99].

6. Data collection and statistical analysis

Data collection was performed using custom Libre Office Base (The Document Foundation. (2020). LibreOffice 7.0 (Version 7)) database. The patient outcome data, together with details including gender, age, recruitment into the study, past medical history, pharmacy interventions data were recorded, and further conversion was executed to summarize all metrics in a Microsoft Excel® 2016 (Microsoft Corporation 186 Redmond, USA) spreadsheet. Statistical analyses were performed using TIBCO Software Inc. (2017) and Statistica version 13b. All continuous variables with normal distribution are represented with the mean ± standard deviation. Whereas continuous variables without normal distribution are presented as median (interquartile range). The groups were compared using Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables are presented as frequencies and percentages and were analyzed using the chi-square test or Fisher's exact test, where appropriate. Statistical significance was set at $p < 0.05$. The goal of this pilot study was to collect data from 30 patients in each trial arm, in accordance with guidelines for pilot studies [100,101].

VI. Results

1. Demographics and selection criteria

Based on the criteria above, during the recruiting period 142 acute admissions in the two departments were reviewed for eligibility in total. However, 5 declined participation. After assessment, 60 patients meeting the inclusion criteria were randomly assigned to the IMM or control group. Further allocation and patient flow through the pilot is shown in Figure 3. One patient in the intervention group was lost to follow-up as it was not possible to contact him by phone after discharge. However, his health insurance was active during the 6-month period meaning that was not deceased.

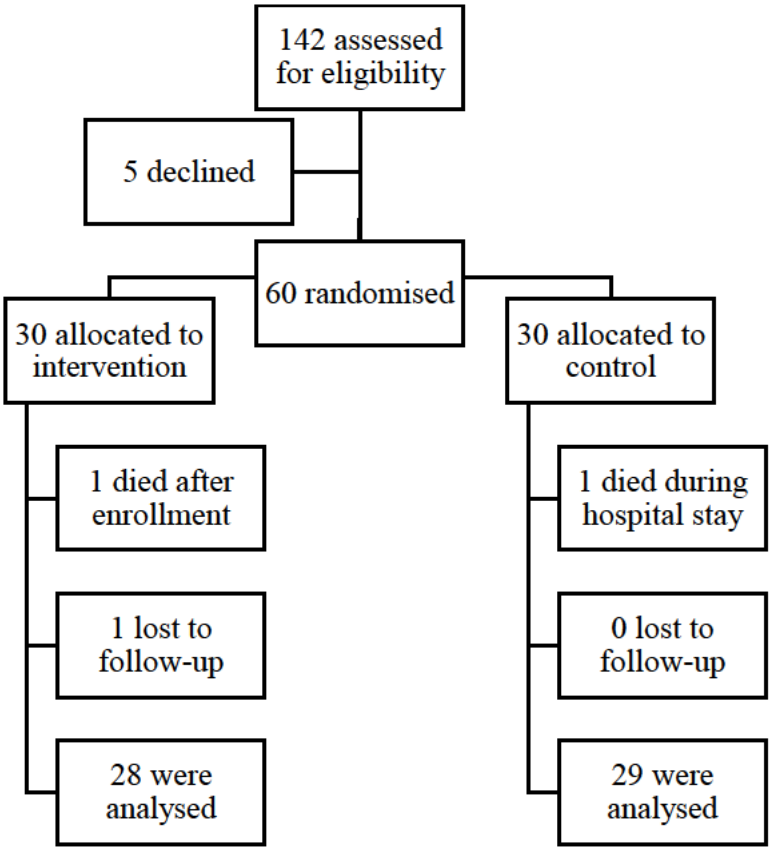

Figure 3. Patient flow diagram within the study.

The groups were well balanced in terms of age, sex, number of medicines and comorbidities burden. Recruitment from both departments was also uniform. Detailed characteristics are presented in Table 11.

Table 11. Characteristics of patients by group status at randomization.

Variable	IMM group (n=30)	Control group (n=30)	Total (n=60)	p
Age (mean ± SD)	70.30 ± 10.67	70.33 ± 11.68	70.32 ± 11.09	0.9908
Female sex - n (%)	11 (36.67%)	13 (43.33%)	24 (40%)	0.7925
Weight [kg] - (mean ± SD)	78.76 ± 16.15	75.77 ± 13,94	77.24 ± 15.02	0.4490
Height [cm] - (mean ± SD)	70.30 ± 10.67	70.33 ± 11.68	70.32 ± 11.09	0.9494
BMI [kg/m^2] - (mean ± SD)	27.49 ± 4.88	26.48 ± 4.07	26.98 ± 4.47	0.3942
Vascular Surgery - n (%)	16 (53.3%)	14 (46.7%)	30 (50%)	0.80
General Surgery - n (%)	14 (46.7%)	16 (53.3%)	30 (50%)	
eGFR < 30	1 (3.45%)	5 (17.24%)	6 (10.34%)	0.19

[mL/min/1.73 m^2] - n (%)				
Creatinine [md/dl] - median (IQR)	0.95 (0.8 – 1.38)	1.08 (0.77 – 1.46)	0.97 (0.78 – 1.42)	0.78
No. of medicines on admission - median (IQR)	8 (6 - 11)	6 (4 - 8)	8 (5 - 9)	0.01
Age-adjusted CCI score - median (IQR)	5 (4 - 6)	5 (4 - 7)	5 (4 - 7)	0.65
5 most prevalent comorbidities				
hypertension	15 (50%)	19 (63.33%)	34 (56.67%)	0.58
diabetes	15 (50%)	15 (50%)	30 (50%)	1
hyperlipidaemia	15 (50%)	15 (50%)	30 (50%)	1
heart failure	7 (23.33%)	11 (36.67%)	18 (30%)	0.53
atrial fibrillation	6 (20%)	10 (33.33%)	16 (26.67%)	0.51
Surgery				
no surgery	11 (36.67%)	12 (40%)	23 (38.33%)	0.94
abdominal surgery	5 (16.67%)	4 (13.33%)	9 (15%)	
limb ischemia	11 (36.67%)	12 (40%)	23 (38.33%)	
other	3 (10%)	2 (6.67%)	5 (8.33%)	

2. Incidence of unplanned visits and length of hospital stay

A total of 59 patients were analysed with regards to primary outcome and 60 patients in respect of LoS. Data related to the primary outcome, that is the incidence of hospital, emergency department and other unscheduled visits after discharge from hospital during the 6 months follow-up period are summarized in Table 12. Within the IMM group 4 patients experienced additional episodes of care, whereas in the control group 17 patients experienced additional episodes of care (meaning that some patients experienced more than 1 episode).

Table 12. Summary of outcomes over 6 months follow-up period.

Variable	IMM group	Control group	Total
Additional episodes of care – general summary			
Number of ED visits not resulting in hospitalization	1	7	8
Number of Hospital readmissions	3	16	19
Number of ambulatory specialist visits	0	7	7
Number of GP visits	2	7	9
Total number of additional episodes of care	6	37	43
Drug related additional episodes of care			
Drug related ED visits not resulting in hospitalization	0	2	2
Drug related hospital visits	0	7	7
Drug related GP visits	1	6	7
Drug related clinic visits	0	7	7
Total drug related visits	1	22	23

A Chi-squared test for total visits was performed, and a p-value less than 0.05 indicated that there were significantly more incidents within the control group. The majority of events in the observation period required hospitalization. However, when using the Fisher test to assess the different types of episodes of care in the follow-up period, there were no statistically significant differences between IMM and the control group. Incidents were further assessed, to examine whether it was drug-related (DR), both by pharmacist and medical doctor. This revealed 1 DR GP visit in the IMM group which was connected with nose bleeding in a patient on acenocumarol. In contrast, within the control group 22 episodes were accounted as possibly DR. Among those, 13 were resolved via the GP or an ambulatory visit. The remaining 9 incidents required hospital admission. Detailed description of the nature of additional episodes of care are presented in Table 13 and 14. When considering only DR incidents, statistical significance was also observed between the groups with $p < 0.05$.

Furthermore, during the follow-up period, 3 patients from the control group died (1 within 1 month - cardiovascular, 1 within 3 months - cardiopulmonary arrest and 1 within 6 months – infection and respiratory failure). No deaths were recorded within the IMM group after discharge.

Table 13. Drug related visits during follow-up period with their reasons.

Type of episode of care	IMM group	Control group
GP	• Nose bleeding	• 5 x pain related to the surgical site • Uncontrolled hypertension
Ambulatory specialist visits	-	• Dizziness • Pain related to surgical site • 2 x Nose bleeding • Uncontrolled hypertension
ED visits	-	• Fall • Pain related to the surgical site
Hospital admissions	-	• Pulmonary embolism and antipsychotics overdose • 2 x Heart failure decompensation • Digoxin intoxication requiring pacemaker implantation • Acute upper limb ischemia • Acute lower limb ischemia • Dizziness and head injury

Table 14. Non-DR reasons of additional visits during follow-up period.

Type of episode of care	IMM group	Control group
GP	• Anaemia	• Rash
Ambulatory specialist visits	-	• Weakness • Surgical site infection
ED visits	• Anaemia	• 4 x worsening of lower limb ischemia • Cardiopulmonary arrest

Hospital admissions	• 2 x acute pancreatitis • Diabetic foot	• 5 x worsening of chronic limb ischemia – amputation or further amputation • Pneumonia • 2 x peritonitis • Surgical site infection

The length of hospital stay analysis showed significant differences between the groups – p = 0.0372. Patients' median LoS in the IMM group was 5 days (with IQR 3-7; n = 30) vs. 7 days (with IQR 5-10; n = 29) in the control group. The total median length of stay was 6 days (IQR 4-8).

3. Drug related interventions and quality of pharmacotherapy

In total, 273 DRPs were identified by the pharmacists for the IMM group (n = 29; exclusion of 1 patient – died after enrolment) during their index admission with a corresponding number of interventions which were fully accepted by physicians. The most common interventions were drug additions or continuation (n = 138), drug discontinuations (n = 45) and dose adjustments (n = 38). Thus, a mean of 9.1 interventions were performed for each patient over the course of the hospital stay for the 30 patients being discharged. Detailed data are presented within Table 15 and Table 16.

Table 15. Types of identified DRPs for IMM group and their numbers.

DRP category	Example	No. of DRPs
Another drug has a better benefit/risk ratio or a better cost/efficacy ratio according to current guidelines	Ondansetron is recommended for PONV instead of metoclopramide	13
Drug should not be currently continued	Dapagliflozin should be held before surgery	5
There is a physio-pathologic contraindication for the present drug	Patient has creatinine clearance below 30 ml/min and receives metformin	13

The patient is not suitably or sufficiently followed-up: lab tests, kinetics, symptoms	Lack of vancomycin TDM	24
A drug is missing after patient transfer/meds record changes/admission	Lack of patient regular medicines ex. betablocker, insulin, inhalers	63
A new symptom is not being treated	Patient reports pain and has no analgetic	33
A synergic or corrective drug should be added to the ongoing treatment	Thiamine is lacking in TPN	15
The patient was not given any premedication or prophylactic treatment	Lack of enoxaparin after surgery	12
Valid indication without drug prescription	Patient has hypercholesterolemia and no statin in the regiment	10
Dose too low in this specific case	Dose of the antibiotic is too low when considering indication and renal function	19
Duplicate prescription	Paracetamol is prescribed alone and in combination with tramadol	4
Dose too high in this specific case	Patient was taking 5 mg of bisoprolol instead of prescribed 10 mg	16
There is a risk for accumulation of the drug	Dose of antibiotic is too high when considering renal function	2
No justified indication for the drug	Oxycodone prescribed based on outdated drug history	6
The drug is prescribed for too long	GKS was temporarily introduced and should be discontinued few days ago	2
The patient presents an adverse drug reaction with an adequate dosage	Bleeding on DOAC	3
Another route may be more effective or less costly for the same effectiveness	Patient can take PPI orally, but prescribed IV	17

Inappropriate drug form	Patient was using SR form of indapamide, but prescribed standard release	4
Inappropriate timing of administration	Levothyroxine taken with food	4
Incomplete formulation	Patient was taking metformin twice a day, but prescribed only once a day	5
Drug not available	Rosuvastatin not available	4
Patient's non-compliance	Patient was not using prescribed inhaler for asthma	2

PONV – postoperative nausea and vomiting; TDM – therapeutic drug monitoring; TPN – total parenteral nutrition; GKS - glucocorticosteroid; DOAC – direct oral anticoagulant; PPI – proton pump inhibitor; IV- intravenous.

Table 16. Types of interventions performed for IMM group and their numbers.

Type or intervention	Example	No. of interventions
Addition of a missing drug	Addition of the missing drug for example. betablocker, insulin, inhalers	51
Addition of a new drug to the ongoing treatment	Addition of a statin due to untreated indication	68
Continuation of withheld or missed drug	Continuation of withheld antiplatelet	19
Discontinuation of a drug without any substitution	Discontinuation of analgesic due to lack of pain	36
Drug withheld	Dapagliflozin withheld before surgery	9
Substitution for a generic drug or a therapeutic equivalent	Statin substitution for the one available in the formulary	4
Switch for another drug better suited to the case	Change of antibiotic according to microbiology results	4
Switch from the currently administered drug to another drug	Change to a different betablocker	2

Choice of a route of administration better suited to the case	Patient has nausea – recommendation for IV analgesics	4
Parenteral/oral switch - Alternative drug with equivalent effectiveness and possible oral administration	Switch from IV to oral PPI	8
Parenteral/oral switch - Alternative oral form of a parenteral drug with the same bioequivalence	Switch from IV to oral ciprofloxacin	2
Discontinuation/request for a new dosage of a specific drug	Change of vancomycin dose based on TDM	2
Discontinuation/Request for a new lab test or monitoring	Monitoring the set of parameters when patient on TPN	9
Drug monitoring: INR, kalaemia, kinetics, symptoms, etc	Repeated potassium measurement due to hypokalaemia and concurrent digoxin use	8
Timing of administration - Distribution of doses according to food intake, to drug–food, drug–drug interactions	Change of levothyroxine administration for empty stomach	6
Timing of administration - Information on the drug regimen	Information how to administer phosphates IV	3
Dose adjustment according to the patient's weight, age, clinical status	Adjusting enoxaparin dose according to patient weight	12
Dose adjustment for a drug with a narrow therapeutic index	Adjusting vancomycin dose according to TDM result	7
Dose increase/decrease according to regular medicines list	Reduction of prescribed bisoprolol dose according to regular patient's dose	19

TDM – therapeutic drug monitoring; TPN – total parenteral nutrition; PPI – proton pump inhibitor; IV-intravenous.

The interventions performed were further assessed using the Eadon scale to examine clinical importance [91]. The majority of interventions made were of grade 4 standard as presented in Figure 4. No interventions were assigned as being detrimental to patient's health.

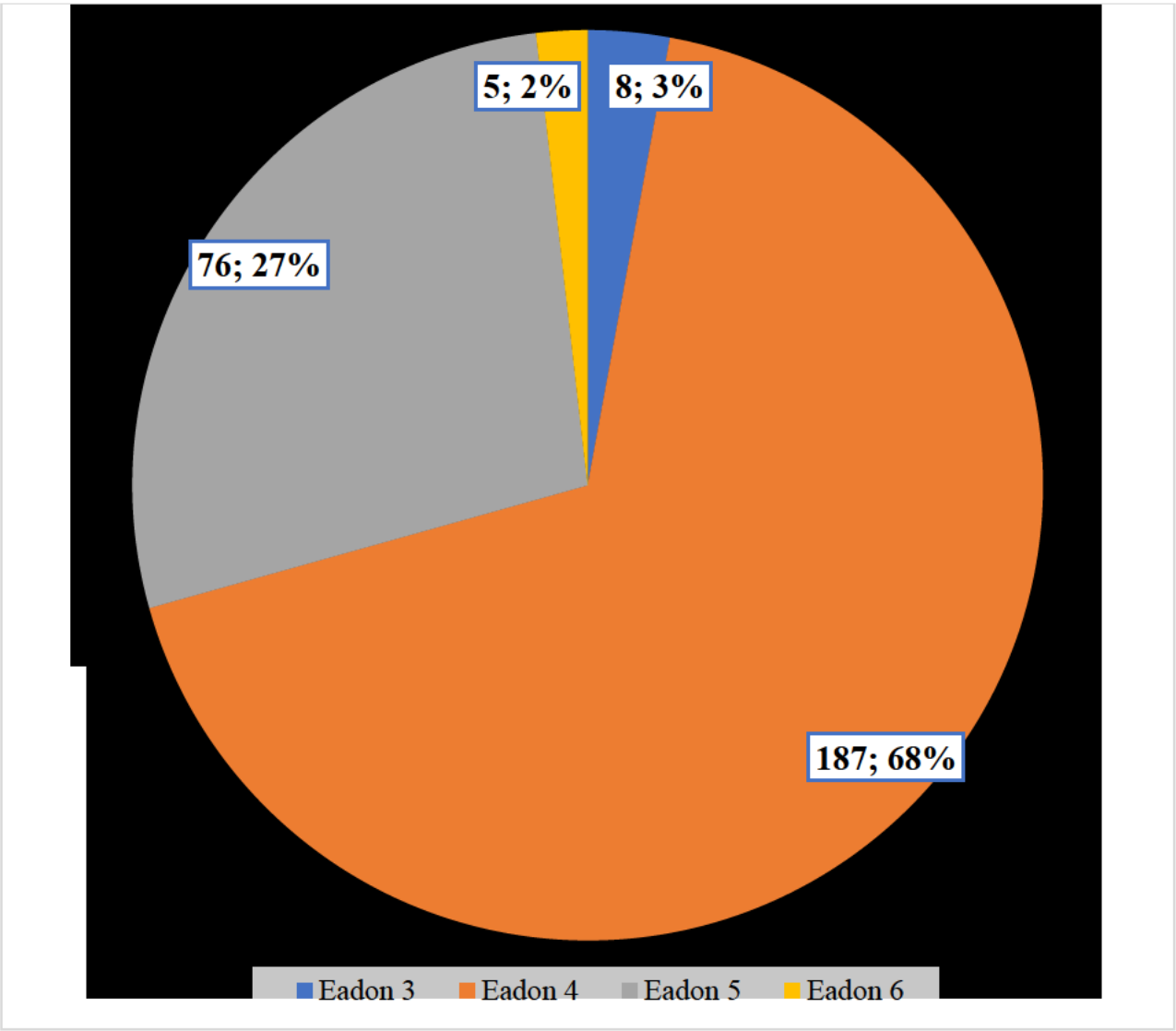

Figure 4. Results of assessment of pharmacist's interventions according to Eadon scale [91].

Table 17 presents the results of the verification of the quality of pharmacotherapy using the PC-MAI tool. Only medicines assumed to be taken by the patient on a regular basis when discharged were assessed, omitting therapy recommended for a defined period related to hospitalization, for example, continuing the course of antibiotics. However, the pharmacist reviewed and helped in formulating the discharge letter for all IMM patients. The appropriateness of the prescribed medicines improved over the course of hospital stay – median score 8.03 on admission versus 0.48 at discharge with a concomitant decrease in the total number of medicines.

Table 17. Chart comparing changes between PC-MAI scores on admission vs. at the discharge.

Value	Admission (n=29)	Discharge (n=29)	p
Number of patients analysed	29	29	-
Total number of drugs	265	240	-
Mean number of drugs (mean ± SD)	9.14 ± 8.41	8.28 ± 7.70	0.0214
PC-MAI score - median (IQR) (mean ± SD)	5 (0-12) 8.03 ± 6.30	0 (0-0) 0.48 ± 0.03	0.0003
The highest PC-MAI value	31	13	-

4. Economic evaluation

An economic analysis was conducted from both the hospital and the healthcare system perspective. Considering the primary endpoint, patients from the control group did experience significantly more episodes of care during the follow-up period. Table 12 in the results section shows the exact numbers of visits in both groups. Furthermore, patients from the control group were hospitalised for an estimated additional 248 days after being discharged from our facility (exact data were not available for 3 hospital stays due to difficulties in obtaining the necessary information during the telephone conversation). In contrast, within the IMM group, there were 33 additional days in hospital that occurred during the follow-up period. This relates both to DR and non-DR episodes.

Assessment of the costs from a healthcare system perspective has indicated that the IMM group required additional care, resulting in extra spending of 198.12 PLN (DR) and 17 030.20 PLN (non-DR), while for control group it was 75817.55 PLN (DR) and 70551.71 (non-DR). The estimated numbers cover only the expected costs for the patients included in the pilot study as shown in Table 18.

Table 18. Description of estimated costs for different episodes of care during follow-up period within study group based on data from the Regional Specialist Hospital in Wroclaw.

Type of episode of care in follow-up period	Mean cost of episode of care for one patient [PLN]	Cost for control group [PLN]		Cost for IMM group [PLN]	
		DR	Non-DR	DR	Non-DR
General Surgery Department	5 610.70	0	22 442.80	0	16 832.10
Vascular Surgery Department	15 075.58	30 151.16	15 075.58	0	0
Cardiology Department	10 888.28	43 553.12	0	0	0
Nephrology Department	8 166.18	0	32 664.72	0	0
Emergency Department*	520.46	4684.14	7 286.44	0	2 081.84
Laryngology outpatient clinic	173	346	0	0	0
Cardiology outpatient clinic	209.94	419.88	209.94	0	0
Vascular surgery outpatient clinic	158.67	158.67	158.67	0	0
GP visit	198.12	1188.72	0	198,12	198.12
Total		**75 817.55**	**70 551.71**	**198.12**	**1 7030.20**

DR – drug related; non-DR - non drug related; *For purpose of cost calculation both ED visits not resulting and resulting in hospital admission were included;

However, if extrapolating the potential costs for the control group to acute admissions of patients hospitalized at both the vascular surgery and general surgery departments and assuming

that between 60 to 80% would meet the inclusion criteria for the IMM service (predicted on the basis of local registry of DRPs and interventions), this would yield potential cost avoidance as presented in Table 19 if only including DR incidents.

Table 19. Potential annual cost avoidance for the healthcare system resulting from preventing additional episodes of care connected with DR incidents if 60 to 80% of acutely admitted patients from the vascular and general hospital departments received IMM.*

Type of department	Total number of acute admissions in 2022	Total number of acute admissions in 2023	Estimated range of cost-avoidance for 2022 [PLN]	Estimated range of cost-avoidance for 2023 [PLN]
Vascular Surgery	476	386	732 554.40 – 995 562.86	605 494.64 – 807 326.19
General Surgery	1704	1537	2 672 960.80 – 3 563 947.73	2 410 998.09 – 3 214 664.12

* For the purpose of drafting the potential scale of the savings, calculations assume that the total number of patients in the control group (29) generated costs for DR incidents of 75 817,55 PLN (not differentiating between departments) and estimates by using proportion what would be the cost if 60-80% of acute admissions would be generating further cost for the healthcare system after the index hospital stay.

From the hospital perspective, LoS was recorded for both groups as a secondary endpoint, enabling assessment of potential cost avoidance. Based on data extracted concerning the costs of bed days at the departments of vascular and general surgery between 2022/2023 and the reduction of LoS in IMM group by 2 days, the anticipated savings would reach 43 166,86 PLN for 29 patients as presented in Table 20.

Table 20. Cost savings due to shortened LoS in IMM group.

Type of department	Number of patients included	Mean cost of bed day in 2022 [PLN]	Mean cost of bed day in 2023 [PLN]	Mean cost avoidance for IMM group [PLN]*
Vascular Surgery	13	901,28	865.49	22 968.14
General Surgery	16	589,53	672.89	20 198.72
			Total	**43 166.86**

*Mean cost of a bed day was estimated based on 2022 and 2023 data, multiplied by 2 (number of bed days avoided according to current results) and the number of patients included in the intervention.

Table 21 illustrates the potential annual cost savings if this reduction were extended to acute admissions in vascular and general surgery, provided that 60-80% of those patients met the IMM service's inclusion criteria.

Table 21. Potential cost avoidance for the hospital resulting from shortening the LoS by 2 days if 60 to 80% of acutely admitted patients from the chosen hospital departments received IMM.

Type of department	Number of acute admissions in 2022	Number of acute admissions in 2023	Estimated range of cost-avoidance for 2022 [PLN]	Estimated range of cost-avoidance for 2023 [PLN]
Vascular Surgery	476	386	514 813.21 – 686 417.62	400 896.91 – 534 529.22
General Surgery	1704	1537	1 205 463.21 – 1 607 284.28	1 241 070.72 – 1 654 760.96

Another method was implemented to estimate potential cost-avoidance as a result of the service provided by pharmacists where Eadon grades were applied and combined with the Nesbit et al. approach, allowing estimation of ADR occurrence [91,92]. The results presented in Table 22 show that the IMM service provided for the intervention group could lead to approximate savings of between 65 872,66 – 92 190,47 PLN.

Table 22. Summary of data used to calculate possible cost-avoidance due to DRP prevention by a pharmacist.*

Risk of DRP and its coefficient	No. of interventions	Estimated range of cost avoidance [PLN]**
High risk - 0,6	5	3 787.24 – 5 300.33
Medium risk - 0,4	76	38 377.33 -53 710.05
Low risk - 0,1	187	23 607.11 – 33 038.75
Very low risk - 0,01	8	100.99 – 141.34
No harm - 0	0	0
Total	**276**	**65 872.66 – 92 190.47**

* By multiplying the potential harm coefficient by the number of interventions allocated to each category and the cost of hospitalization based on the assumption that a medication error could prolong hospitalization by two days based on data from published literature, the potential cost of resolving the ADR was calculated [93,94]; ** Based on a mean cost of bed day in 2022/2023 for vascular and general surgery departments; range represents estimation depending on the type of department where the intervention was performed.

Next, Eadon grades assigned to performed interventions in IMM group together with average value of QALY for specific importance of the intervention were utilized to calculate the potential QALY gain within the intervention group [91,95]. Based on applied methodology, patients receiving pharmacist input could potentially benefit from an additional 20,1045 QALY (0,693 QALY/patient). Data used for calculations are presented in Table 23.

Table 23. Summary of data used to calculate the potential QALY gain for IMM group.

Eadon grades*	No. of interventions	Average QALY**	Total QALY for specific Eadon grade
Potentially lifesaving	5	2.705	13.525
Very significant: prevents a major organ failure or adverse reaction of similar importance	76	0.0755	5.738

Significant: improves patient care	187	0.0045	0.8415
Significant: does not improve patient care	8	0	0
No significance to patient	0	0	0
Detrimental to patient	0	-	
Total	**276**	**-**	**20.1045**

*Grades assigned based on Eadon scale [91]; ** Average QALY loss connected to certain incidents were based on Campbell et al. [95].

To calculate the ICER and then the cost-benefit ratio, the minimum annual salary for both the pharmacist and clinical pharmacy specialist was included as defined by Polish legislation with estimation of the payment for the period of performing the study [99]. Details are presented in Table 24.

Table 24. Summary of pharmacist salary depending on level of education and time period.

Level of pharmacist education	Annual salary in 2022 [PLN]	Annual salary in 2023 [PLN]	Salary within 4 months of effective patient's enrolment [PLN]
Clinical pharmacy specialist	87 655.92	98 238.36	30 982.38
Pharmacist	72 027.36	80 735.04	25 460.40

Data on salary and estimated QALY gain for the IMM group were used to calculate the potential ICER.

$$ICER = \frac{C_1 - C_0}{E_1 - E_0}$$

Where:

- C_1 = 56 442,78 PLN (total cost of the intervention where for IMM it was the cost of employing both the pharmacist and clinical pharmacy specialist for the time of performing the intervention)
- C_0 = 0 PLN (total cost of standard treatment; here assuming $C_0 = 0$ if the only additional cost arises from the pharmacist's salary)
- $E_1 - E_0$ = 20,1045 QALY (the total QALY gain based on the assessment of the interventions)

Therefore, when including the study environment and performing of the intervention by both the pharmacist and the clinical pharmacy specialist, the following ICER could be achieved:

$$\boldsymbol{ICER \approx 2\,807,47\ \text{PLN/QALY}}$$

However, when considering the real-life work environment and including only the clinical pharmacy specialist performing the intervention the ICER would be:

$$\boldsymbol{ICER \approx 1541,17\ \text{PLN/QALY}}$$

If looking at the values for one QALY in Poland which were 175 926 PLN in 2022 and 217 641 PLN for 2023, the investment in the IMM service to achieve one QALY gain is much lower than the willingness to pay threshold (WTP) defined at the national level. As the outcome measure was utility-based (QALYs), this ICER is specifically an incremental cost-utility ratio (ICUR) [98,102].

After considering all monetary values associated with the IMM service and the cost of the pharmacist's employment, attempts to assess the cost-benefit ratio were undertaken. When considering that drug related episodes of care could be avoided in the control group, LoS in hospital could be shortened and interventions could additionally bring a calculated level of cost-avoidance, the cost-benefit ratio for IMM would be 1:3-4 in this setting when both the pharmacist and the clinical pharmacy specialist are providing it and 1:6-7 if only the clinical pharmacy specialist would be involved.

5. Patient and healthcare staff satisfaction

All patients in the IMM group filled in the questionnaire to assess their opinion about the care provided by the pharmacist. Results showing the responses to the 16 questions are shown

in Figure 5. Only responses “agree” and “definitely agree” from the 4-point Likert-type scale were reported by patients. It shows that the service was well received.

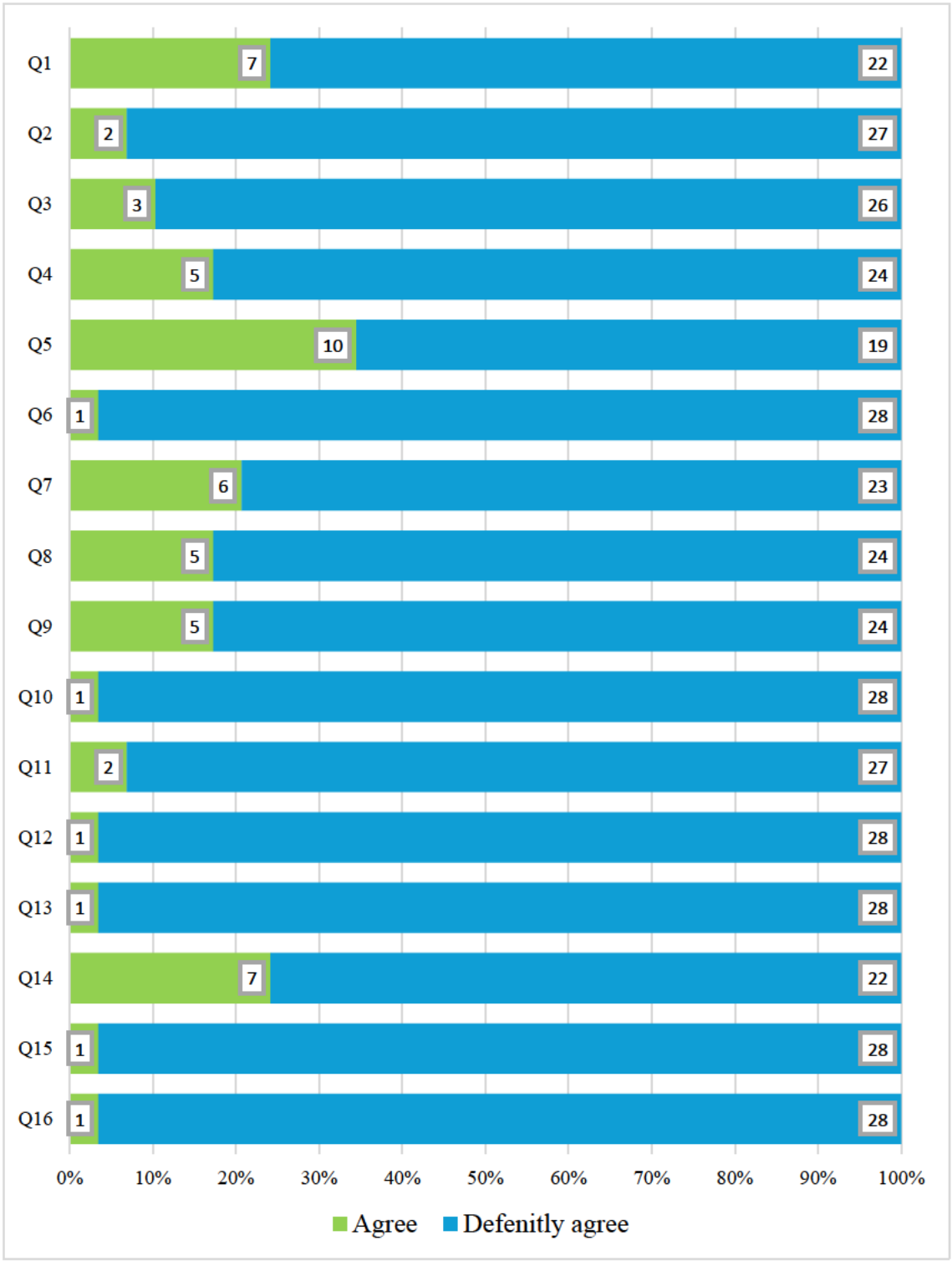

Figure 5. Results of the questionnaire given to the IMM group assessing patient opinion about the service provided by the pharmacist.

A few patients agreed to give a comment about the service received and the examples are presented in Figure 6.

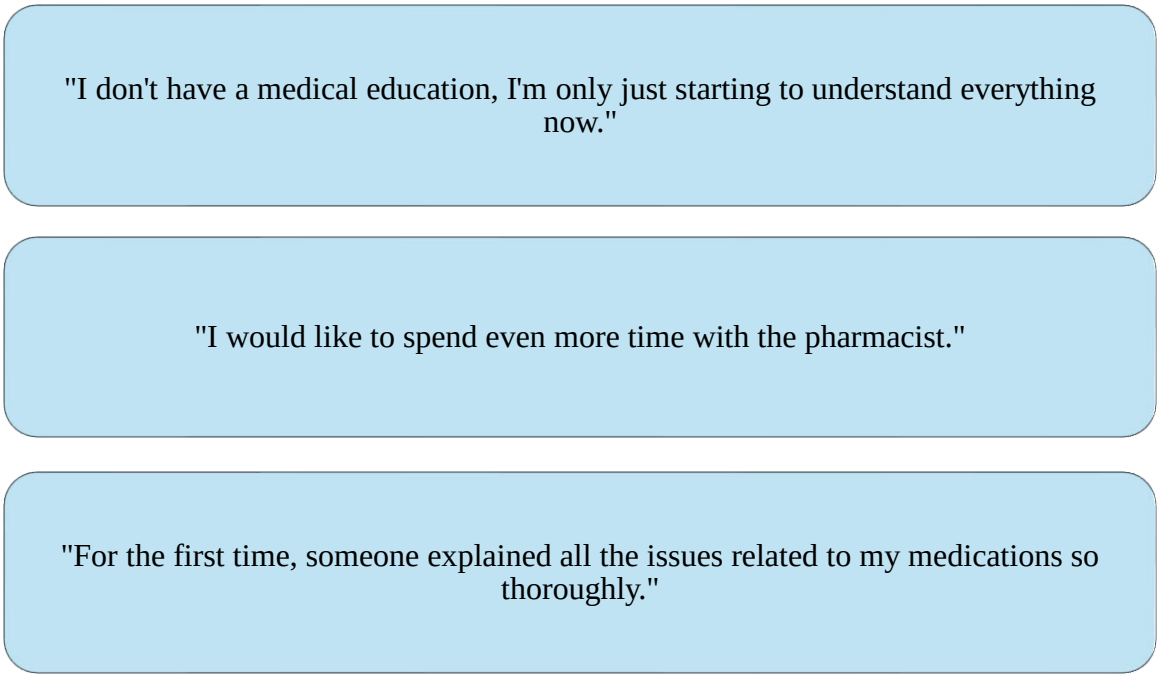

Figure 6. Selected opinions of patients about the IMM.

The CPS was viewed favourably by healthcare professionals, according to an analysis of the interview data. High levels of satisfaction were reported by participants from both professional groups – physicians and nurses, who often mentioned that they could not envision going back to a workflow without pharmacist involvement. As a crucial component of the multidisciplinary team, the pharmacist helped with clinical decision-making and the quality of patient care.

In order to improve scope clarity and promote interprofessional collaboration, participants recommended that the pharmacist's ongoing duties be more clearly stated. Interestingly, there was broad support for expansion of the pharmacist's role, especially with regard to prescribing. According to the respondents, pharmacists should first be given the authority to make changes to prescription charts and prescribe certain drugs, including analgesics, in accordance with well-defined procedures. This was viewed as a way of improving efficiency, reducing prescribing delays, and optimizing patient outcomes.

VII.Discussion

Numerous studies have evaluated the role of CPs in direct patient care, including the model of comprehensive service provision in the hospital setting [19,41,71,72,86,87,103–107]. Kaboli et al. performed a systematic review and concluded that clinical pharmacists in inpatient settings positively affect patient care by preventing adverse drug events and optimizing therapeutic

outcomes [103]. This is further supported by Skjøt-Arkil et al. (2018), who reported that multifaceted pharmacist-led interventions improve clinical outcomes, such as reductions in medication errors and hospital readmissions, by addressing the complex needs of hospitalized patients [105]. Moreover, the Lund Integrated Medicines Management (LIMM) model has been shown to enhance medication appropriateness and reduce drug-related hospital revisits. The model, which involves comprehensive medication reviews and interdisciplinary collaboration, directly addresses issues such as medication errors, inappropriate prescribing, and suboptimal drug therapy, contributing to improved patient health outcomes [72]. Similarly, a study by Gillespie et al. in elderly patients demonstrated that pharmacist-led interventions were associated with reduced morbidity and hospital admissions, highlighting the beneficial impact of targeted pharmacist interventions in this vulnerable population [71]. A systematic review and meta-analysis by Deng et al. revealed that medication therapy management services can lead to substantial economic benefits. These services not only reduce the incidence of costly adverse drug events but also minimize unnecessary hospital admissions and readmissions [19]. In the context of comprehensive medication reviews and post-discharge follow-up, a study by Kempen et al. (2021) found that hospital-based IMM services resulted in significant reductions in healthcare utilization, demonstrating that investing in clinical pharmacy services can result in cost savings for both hospitals and healthcare systems [86].

The economic value of IMM services extends beyond direct healthcare savings. Scullin et al. explored how the routine implementation of IMM services improved the quality of care for patients and led to better resource allocation within hospital systems. Pharmacist-led interventions have been shown to enhance patients' quality of life by reducing the burden of adverse drug reactions and improving medication adherence. In particular, older adults, who are at higher risk for polypharmacy and medication-related complications, benefit significantly from pharmacist-led medication management [104,106]. These services contribute to improved patient satisfaction by empowering individuals to better understand their medications, manage their conditions, and engage in shared decision-making with their healthcare providers [87]. By providing comprehensive medication management, pharmacists help minimize the risks associated with inappropriate medication use, leading to better health outcomes and enhanced patient well-being [107].

In this pilot randomized controlled trial, we have investigated the possible outcomes of integrating a clinical pharmacist into the medical team within a hospital. Overall, our findings are in accordance with the findings reported above. The IMM service that was introduced resulted in a decreased number of unplanned visits in the follow-up period and a shorter LoS.

In line with previous studies, the continuing care enabled the resolution of multiple DRPs and enhanced the quality of pharmacotherapy with concomitant savings and positive feedback both from patients and healthcare professionals. Collectively, these data demonstrate that the primary and secondary outcomes were possible to achieve, and this pilot shows that the model is feasible with encouraging preliminary effects of IMM on improving patient outcomes.

1. Incidence of unplanned visits and length of hospital stay

Unplanned hospital visits, readmissions, and prolonged hospital stays are major challenges faced by healthcare systems worldwide, leading to increased healthcare costs, resource strain, and suboptimal patient outcomes. These issues are often associated with medication mismanagement, including adverse drug reactions, incorrect drug therapy, and poor medication adherence. IMM, with multidisciplinary teams led by clinical pharmacists, has been increasingly recognized as a solution to address these challenges [19,71,103,105].

The systematic review performed by Kaboli et al. revealed that thanks to pharmacist involvement readmission rates, ICU transfers, test use, and costs were either reduced or not affected [103]. Another review analyzing multifaceted interventions performed by CP in the hospital setting showed that among 16 studies investigating either ED visits, readmissions or drug-related hospital visits, 7 studies reported a significant positive difference [105]. According to Scullin et al., IMM patients had a longer time to readmission (20 days) and a considerably lower rate of readmission throughout a 12-month follow-up period [104]. Hellström et al. found that the implementation of the LIMM model resulted in a 50% reduction in drug-related hospital revisits in the intervention group when compared to the control group, highlighting the effectiveness of pharmacist-led interventions in reducing unnecessary hospital visits [72]. Patients 80 years of age or older who received a thorough medication review that included follow-up after hospital discharge experienced a 16% decrease in hospital visits the following year, according to an earlier randomized clinical trial carried out in Sweden. Readmissions due to ADEs were cut by 80% [71]. A similar pattern of results was obtained within our study indicating that provision of complex CPS has the potential to significantly reduce the incidence of additional episodes of care. It can be noted that in our sample of patients, the difference between the study group and the control group in terms of additional episodes of care during the follow-up period was even more pronounced than in the cited studies. However, the small sample size and single-centre nature of the study do not allow for definitive comparisons and require further verification in a multicentre study. Nevertheless, this measure can be used as one of the endpoints in further trials.

In contrast to the above findings, comprehensive medication reviews combined with post-discharge follow-up did not reduce the number of unscheduled hospital stays, according to research by Kempen et al. conduced later also in Sweden [86]. Similarly, in Norway the major endpoints of time to readmission or mortality within a year were not significantly impacted by pharmacist-led medication management. Although, during the 21–40-month follow-up, a statistically significant improvement in overall survival was noted [87]. This shows that it can be difficult to determine how a medication management strategy affects clinically significant endpoints in individuals with multiple comorbidities and complex drug regimens. Influencing hospital readmission rates and other urgent medical treatment may be challenging in this group. Moreover, many different factors can influence readmissions over such a long follow-up period as 12 months. For this reason, in the current study, we decided on a six-month observation period with a particular focus on drug-related incidents. The structure of the healthcare system and the current level of CPS implementation at various levels of care may also be significant in the context of achieving improvements in additional care incidents. Currently within the Polish healthcare system there is significant work being undertaken focussing on better coordination of care and shifting activity from secondary to primary care. Taking this into account IMM has the capability of improving this process.

Reducing the length of hospital stay is crucial for improving patient flow and reducing healthcare costs [103,105]. Correlation between CPS and LoS has been already explored based on datasets from the 1990s with a positive outcome [108]. Scullin et al. reported that IMM implementation led to a 2-day reduction in hospital stay duration, compared with standard care [41]. A pilot study examining transition of care with pharmacist engagement confirmed LoS reduction in the intervention group (4 days [3-8] with pharmacist vs. 7 days [4-20] standard of care) [109]. Similar outcomes were achieved in this pilot study - median LoS in the IMM was 5 days vs. 7 days in control group. Therefore, a reduction by 2 days corresponds with what has been achieved in previous studies [41].

Moreover, when considering the surgical field a recent systematic review and meta-analysis by Naseralallah et al. evaluated the impact of pharmacist-led interventions on clinically important outcomes in perioperative settings. In 25 reported studies it was found that in 11 of them, the LoS was significantly impacted by pharmacist care as opposed to standard care according to pooled data. These findings underscore the effectiveness of pharmacist-led interventions in improving perioperative patient outcomes. However, when it comes to a lack of correlation, authors indicated that one or more of the following characteristics were primarily present: (1) There was only one pharmacy service provided during the perioperative period

(mostly medication reconciliation); (2) the intervention was not continuous; and (3) the patient was not contacted prior to admission to optimize drug management [110]. This summarizes the differences that may be present in the literature and favours the more comprehensive approach such as IMM, even within a dynamic and demanding surgical setting. It is also in line with the fact that transfer of care exposes patients to a higher risk of errors [7]. Therefore, LoS is similarly a challenging measure as the incidents of additional episodes of care within follow-up period to reliably connect in with CPS. Within IMM we have enrolled patients being acutely admitted, due to the initial challenging clinical status, LoS would differ in this group when the comparison is made with planned admissions. One of the patients within the IMM group was hospitalized for around 90 days but did not have any additional unscheduled visits within 6 months. This may indicate that a long hospital stay was necessary due to the patient's health condition, and it is difficult in this situation to argue about the possibility of shortening it which may in fact be detrimental to the patient.

Apart from that, differences in research results regarding the impact of clinical pharmacy on additional episodes of care and hospital LoS may arise from the heterogeneity of service delivery models and the varying levels of integration of the pharmacist within the therapeutic team. Significant influence is also generated by the characteristics of the studied population - particularly the degree of complexity of clinical cases and the presence of comorbidities. Methodological diversity further complicates the unequivocal interpretation of results. Systemic factors, such as hospital work organization or local therapeutic protocols, which may modify the effectiveness of pharmaceutical interventions, should also be taken into account. Finally, the impact of other concurrently implemented interventions should not be overlooked, as this may lead to difficulties in entirely attributing the effect of reduced hospitalization to clinical pharmacy alone.

Although some difficulties exist in establishing the value of CPS, evaluating the impact of health system–level factors is essential for the effective implementation of clinical pharmacy services. Understanding organizational, structural, and policy-related determinants allows for tailored integration strategies that maximize clinical and economic outcomes. Despite the above challenges, the overall influence of CPS on the system remain positive when summarizing the effects of implemented services and its significance based on the evidence generated to date [19,71,103,105].

2. Drug related interventions and quality of pharmacotherapy

Clinical pharmacy services play a pivotal role in optimizing medication therapy and reducing DRP's. Numerous studies have demonstrated that pharmacist interventions significantly contribute to the resolution of DRPs, improving medication appropriateness, and ultimately enhancing patient outcomes across various healthcare settings. The prevalence of DRPs is particularly high among multimorbid patients, those receiving polypharmacy, and elderly individuals, necessitating pharmacist-led medication management strategies to mitigate risks and improve treatment efficacy [71,72,110–116].

For example, Garin et al. conducted a cross-sectional study in which they assessed 1602 hospitalized patients. The overall prevalence of DRP's was high across all medical specialties (45.1%). The two main categories of issues that led to DRP's were drug efficacy and adverse responses with drug and dose selection the most common reasons. In 74.1% and 4.81% of instances, interventions were approved and the DRP was fully or partially resolved. This finding underscores both the high burden of DRPs in clinical practice and the significant role of pharmacists in mitigating these problems [111]. Similarly, Deawjaroen et al. performed a prospective observational study in hospitalized patients in Thailand. In all, 257 patients experienced 316 avoidable DRPs. With 32.3% of all DRPs, the most common cause was not receiving medication treatment despite an existing indication. Therefore, starting a medication was the most common intervention (34.0%). Overall, 95.8% of interventions were accepted [113]. When it comes to the surgical area, AbuRuz et al. showed that within RCT in a general surgery department with a relatively small intervention group (63 patients), pharmacists were able to identify 545 DRPs, mostly related to efficacy and safety issues, which were corrected with an acceptance rate of 90% by surgeons [117]. Further in 149 vascular surgery patients, Martinez Lopez et al. performed 481 interventions with 85% being agreed and implemented thanks to cooperation with the medical team [118]. The current results present 273 DRPs and interventions for 29 patients with a full acceptance rate by medical colleagues. The types of interventions performed were comparable to previous studies (most frequently drug addition or continuation, drug discontinuation and dose adjustment), confirming that with such a level of pharmacist engagement pharmacotherapy can be optimized to a wide extent. However, the high acceptance can be associated with such a small pilot group therefore not generating arguable clinical scenarios and overall better local experience of the healthcare professionals in cooperating within the multidisciplinary team. Within a study performed in 2017 at the vascular surgery department of RHW, 1349 interventions in 901 patients were suggested of which 97%

were accepted by surgeons. At that time CPS was newly implemented, thus potentially creating more debate about clinical decisions due to the novelty of this approach with medical colleagues [67].

Focusing on high-acuity settings, Albayrak et al. evaluated intensive care unit (ICU) patients in a Turkish university hospital. During the study period, 151 patients in total were involved. The total number of DRPs was 206, with 108 patients having at least one DRP. The majority of DRPs were caused by drug selection (40.29%) and dose selection (54.36%). With a rate of 56.79%, dose change accounted for the largest percentage of interventions. Finally, 98% of all interventions were accepted and implemented [116]. In the emergency department, Miarons et al. evaluated pharmaceutical interventions and reported that a total of 529 interventions for 390 patients were performed during the study period, with an acceptance rate of 84.9%. The researchers also undertook an economic analysis which demonstrated that these interventions not only improved patient safety but also resulted in significant cost savings [115]. These data illustrate that even in critically ill and challenging populations - where medication regimens are often complex and in the context of a fast-pace environment - clinical pharmacists can effectively detect and manage DRPs. We have only assessed the surgical field with satisfactory level of DRPs resolution, but the above outcomes suggest that it would be feasible to conduct similar assessments within other departments as discussed above.

Implementation of the IMM concept allows pharmacists to supervise patients at all stages of hospital care and enables them to perform interventions during the whole period, not only on admission or at discharge. Lea et al. identified as many as 3826 DRPs in 193 patients with an acceptance rate of 91% [87]. Whereas Scullin et al. performed 1628 interventions for 294 IMM patients. In contrast, Gillespie et al. detected 476 DRPs in 182 patients with a 75% acceptance rate which can be seen to be somewhat less than in papers mentioned above, but still being a significant value [71]. Considering that these were full scale trials with higher number of patients involved, we would expect a similar increase with bigger patient populations. Another fact to consider is how the DRPs were classified and what was counted as an intervention. In contrast to a paper from Norway where the Pharmaceutical Care Network Europe's classification was used, we have utilized French categories [87,90]. This can generate some difficulties with comparing solely the number of DRPs. However, the importance of these interventions represents a substantial value. In Northern Ireland, 75% of them were scored as 4 according to Eadon criteria. Similarly in this study, 69% were graded as "Significant and results in an improvement in the standard of care", confirming that the majority of them were of importance.

The integration of CPS into healthcare has been demonstrated to also improve medication prescribing. One of the key measures used to assess this is MAI and its patient-centered adaptation, the PC-MAI. Studies evaluating the impact of clinical pharmacy services on MAI and PC-MAI scores provide compelling evidence of their role in enhancing medication management, particularly in the elderly and polypharmacy patients [42,119–124]. Lund et al. showed that: "each inappropriately rated item with a modified MAI weight of 1 (eg, drug without indication) increased ADE risk by 13%, and each item with a weight of 2 (eg, drug-disease interaction) increased the risk by approximately 26%" [124]. Although, Krisch et al. described difficulties in addressing what constitutes a clinically significant change [122].

A broader synthesis provided in a Cochrane review about polypharmacy in older people included 5 research papers comparing the post-interventional mean MAI-score and finding a 3.88 point lower score for the intervention groups [121]. The iSIMPATHY Evaluation Report provides compelling evidence that clinical pharmacy interventions can improve PC-MAI scores by a mean of 13.8 points (92% of patients had a decrease in PC-MAI scores between pre- and post-review), reinforcing the value of incorporating patient-specific factors into the evaluation of medication appropriateness [42]. Among IMM patients, Scullin et al. observed a change from mean 5.81 points pre-review to mean 3.64-point post-review [104]. Within this pilot, patients in IMM group also experienced a mean change in PC-MAI score from 8.03 to 0.48 which is consistent with results achieved in other studies. It indicates that improvement in the quality of pharmacotherapy is possible within surgical departments with pharmacist assistance, despite most of the work in such units being focused on surgical procedures rather than medical conditions.

3. Economic evaluation

Strong evidence of the therapeutic and financial advantages of clinical pharmacy services has been presented in a growing body of research spanning several decades [17–22]. Early economic evaluations, such as those conducted by Schumock et al., laid the groundwork by systematically reviewing the economic outcomes of CPS. These trials established important indicators such as cost avoidance and a decrease in adverse medication events [22]. More advanced methodologies, such as cost-benefit, cost-effectiveness, and cost-utility studies, were used in later evaluations by Perez et al. and Touchette et al. respectively to measure financial advantages in diverse healthcare contexts [20,21]. According to Gallagher et al., who conducted a comprehensive analysis of the effects of clinical pharmacist interventions on hospital inpatients, these interventions can significantly reduce hospital expenditures by reducing

medication mistakes and improving drug treatment management. Moreover, they have pointed out that “judgement may have been reached that established clinical pharmacy services are in general cost-effective and further research into them is unlikely to be necessary” [18]. More recent works offer up-to-date data from both the UK and international contexts. These studies demonstrate that clinical pharmacy services improve humanistic outcomes by improving patient satisfaction and quality of life in addition to generating economic savings through direct cost reductions [17,19]. According to the iSIMPATHY project results, the maximum preventable inpatient costs in each country would be £24.7 million (€28.9 million) for Ireland, £11.0 million (€12.9 million) for Northern Ireland, and £36.0 million (€42.1 million) for Scotland if thorough medication reviews were offered to all patients over 65 (over 75 in Northern Ireland) who were taking five or more medications [42]. In respect of the reviewed literature, the cost-benefit ratio of CPS remains positive. However, comparisons of clinical pharmacy services is still difficult due to the lack of consistency in reporting results, differences in healthcare systems and at times the poor quality of research [17–22].

As discussed above when elaborating on primary and secondary outcomes, one of the main economic advantages of IMM is the reduction in overall healthcare costs, achieved through decreasing hospital readmissions, emergency department visits, LoS and adverse drug events. Although, because of the complex character of this approach, it is challenging to assess all of the aspects [19,41,71,72,86,87,103–107]. The LIMM model demonstrated both cost savings and enhanced value relative to normal treatment, mostly due to the prevention of drug-related hospital readmissions [73]. When examining ED visits and hospital readmissions, Gillespie et al. found that the intervention group's overall cost per patient was $230 less than the control group's after accounting for the full cost of comprehensive pharmacist care [71]. Sjolander et al. has documented savings per year to be €267 900 on the DR readmissions for the subgroup without heart failure, and €184 000 on readmissions for the total number of patients. Extrapolated data for the whole country were estimated to be €10 million, and €6.9 million, respectively [35]. This is consistent with our findings where additional care episodes throughout the follow-up period resulted in potential expenditures of 146 369,26 PLN for the control group and 17 228,32 PLN for the IMM group. Unfortunately, not all studies take into account the various types of costs to fully compare the monetary value of interventions. For example Scullin et al. has achieved similar reductions in LoS by 2 days, but the assessment of cost-saving is lacking [41,104]. At the same time, an estimated 43 166,86 PLN was potentially saved for the IMM group by as a result of the LoS decrease within our pilot. Additionally, the functioning of

the healthcare system and its financing, along with currency differences, complicate this comparison.

To further assess the potential cost avoidance associated with CPS, various methodologies were employed in the literature, but most of them use the approach which is based on ADE prevention [94,95,125]. Several authors have categorized interventions following the framework proposed by Nesbit et al. and subsequently estimated the costs of adverse drug events using figures reported by Bates et al. [92,94]. However, the cost estimates date back to 1997 and are based exclusively on U.S. data. Alternative approaches to cost-avoidance estimation include the SCHARR model and the microcosting method developed by Rottencolber et al. [95,125]. Rychlickova et al. presented a possible cost reduction of about US$287,000 for a sample of pharmacist interventions (275) in Czech Republic. However, national statistics were used to determine the time required to resolve an adverse incident [25]. UK analysis of ADEs that had been prevented has proven savings of £75 249 for 116 resolved problems due to MRec with SCHARR including country specific costs [24]. In contrast, a previous study at RSH showed cost avoidance of 318 835 PLN ($88 271, €74 766) for 1311 interventions [67]. A similar method was used to estimate the cost savings for pharmacist input within IMM study where 276 interventions produced potential savings of around 65 872,66 – 92 190,47 PLN. With a lack of more specific national data on ADEs, our costing approach was more conservative than the one presented by the teams from other countries assuming that the LoS would be prolonged only by 2 days in our setting. Moreover, healthcare system reimbursement and costing differ across Europe. All the studies, however, consistently demonstrate the cost savings linked to clinical pharmacy services [24,25,67]. To better understand and compare the savings due to CPS, costs of the service need to be included. Compared to previous studies that have revealed cost-benefit ratios of 1:1-5 when analyzing different pharmacist interventions, this current study's ratio also fits within this range [25,29,36]. However, when including different employment costs it could rise to even 1:7. Previous research conducted in the vascular surgery department at the RSH, achieved a ratio of 1:9 [67].

To properly assess the economic worth of clinical pharmacy services, quality-adjusted life years should be used in conjunction with both incremental cost-effectiveness and incremental cost-utility ratios. The ICUR, as a type of ICER, measures both the amount and the quality of life gained, whereas the ICER offers a reliable and consistent measure of incremental cost per unit of health benefit. Since they allow for comparability across therapies, disease areas, and locations, QALYs are commonly acknowledged as the gold-standard outcome in health

technology assessment [18,98,126]. A systematic review conducted by Price et al. showed that among analyzed studies, 57 were either dominant or cost-effective when considering a defined willingness-to-pay threshold per QALY [126]. Similarly, within this pilot study, the intervention achieved an ICER of 1541.17 - 2807.47 PLN/QALY which is well below the national WTP cut off level.

4. Patient satisfaction

Recent advances in clinical pharmacy have redefined traditional roles, shifting the focus from medication dispensing to an integrated, patient-centred approach. Yuliandani et al. indicates that structured pharmacist–patient interactions - such as personalized medication therapy management and tailored counselling sessions - are critical in enhancing patient satisfaction. This systematic review underscores that clear communication, professional expertise, and patient involvement in decision-making are pivotal determinants of satisfaction, leading to improved adherence and therapeutic outcomes [44]. These findings are supported by the iSIMPATHY evaluation report, which demonstrates that active engagement by clinical pharmacists in addressing drug-related concerns significantly elevates patient perceptions of care quality [42]. Despite these encouraging findings, the literature also notes that it might be difficult to ensure consistency in patient satisfaction ratings across various clinical settings [44]. These findings align with patient satisfaction reported within our pilot study. All of the patients within the intervention group expressed positive feedback about their IMM experience. Although, some patients expressed that they would wish that the pharmacist could spend even more time with them to talk about their pharmacotherapy.

5. Critical appraisal and limitations

Several limitations need to be highlighted to fully assess and interpret the results. Since this was a pilot study, the primary outcomes were based on a small group of patients. Limited numbers reduce statistical power, increasing the risk of type II errors. Due to that fact subgroup analyses may be underpowered. Therefore, as assumed at the beginning, this approach should be tested in a larger group and progressed to full scale RCT. In addition, in this scenario a more automated approach to assignment to control or intervention group would need to be employed. Secondly, pharmacist experience can be listed as another important factor. Within this study, the team consisted of one junior pharmacist and one clinical pharmacy specialist with more than 5 years of experience. Considering that CPS are evolving in Poland and IMM can be provided by professionals with different level of expertise, the results can differ in a bigger

scale. The study was also conducted in a specific clinical setting of a general and vascular surgery department. This limits the external validity of the findings and further research would need to include other areas or else increase the number in both control and intervention groups as these patients are heterogenous in terms of their comorbidities profile.

Moreover, due to the fragmented documentation across the Polish healthcare system, some information about patient health status can be lacking which poses a challenge both in terms of recruitment and description of the patient population. An additional obstacle is monitoring during the follow-up period. The details obtained were based on telephone calls to patients and their families. Therefore, details cannot always be accurate, and patients and carers may not have the medical knowledge to appropriately describe the clinical situation. Direct data from the national insurance institution would be more trustworthy if possible to extract. Some of the cost-avoidance calculations are based on assumptions about the attribution of DRPs. While it can limit the conclusiveness of the economic benefits, this method is widely used in the available literature. In a full-scale trial both currency and Purchase Power Parity need to be included together with a sensitivity analysis to compare the data with reports from other countries.

A large-scale research project should also include more patient reported outcome measures (PROMs), for example by incorporating the Euro-Quality of Life Questionnaire [127]. The healthcare system perspective is crucial when evaluating the new service, but different factors related to patient needs and improvement in wellbeing is also of utmost importance. Healthcare staff opinion could be collected in a more objective way in order to avoid any bias by sending out questionnaires to physicians and nurses.

VIII. Conclusions

In conclusion, IMM services led by clinical pharmacists are essential in improving clinical, economic, and humanistic outcomes in hospital settings. These services optimize medication therapy, reduce adverse drug events, enhance patient quality of life, and provide substantial economic benefits through reduced hospitalizations and healthcare utilization. The growing body of evidence supporting the effectiveness of IMM services underscores the importance of clinical pharmacists in modern healthcare teams and their pivotal role in improving patient care. As healthcare systems continue to evolve, the integration of IMM services should be prioritized to maximize the benefits of pharmaceutical care for all patients.

The above-described research allows us to provide a following conclusions:

1) The incidence of hospital, emergency department and other unscheduled visits after discharge from hospital during the 6 months follow-up period was significantly lower in the IMM group. The length of hospital was significantly shorter in the IMM group.
2) The pharmacist contribution was also visible and reflected in, minimized drug-related problems, and improved pharmacotherapy quality, which is of importance for maintaining safety and high standards of provided care.
3) Furthermore, both patients and healthcare professionals expressed high satisfaction with pharmacist involvement, reinforcing the necessity of expanding pharmacist-led interventions in hospital settings.
4) Enhanced cost-effectiveness is expressed in reduced costs for the healthcare system due to less episodes of care, reduced cost for hospital, thanks to shorter LoS and to the estimated cost of resolving DRPs in advance. The cost-benefit ratio remains positive even when including the costs of providing the IMM.
5) The pilot trial identified that a definitive trial is feasible. There were very small numbers of missing data at baseline and at 6 months post recruitment in both trial arm.

IX. List of tables

Table 1. Table 1. Examples of research papers assessing the economic aspects of CPS [23–40]. 12
Table 2. Summary of data about details of CPS in CEE countries [10] 17
Table 3. Examples of high-risk factors related to patients and high-risk medicines setting the priority for MRec [62,78,79] 23
Table 4. Main types of MR according to Clyne et al. [83] 24
Table 5. Detailed description of 7Steps approach adapted from iSIMPATHY [42] 26
Table 6. Classification of DRPs prepared by French Society of Clinical Pharmacy [90] 35
Table 7. Classification of interventions related to DRPs prepared by French Society of Clinical Pharmacy [90]. 36
Table 8. Description of the Eadon scale [91]. 38
Table 9. PC-MAI patient form including questions with possible answers. 39
Table 10. Scoring system for medicines appropriateness assessment. 39
Table 11. Characteristics of patients by group status at randomization. 44
Table 12. Summary of outcomes over 6 months follow-up period. 46

Table 13. Drug related visits during follow-up period with their reasons. 47
Table 14. Non-DR reasons of additional visits during follow-up period. 47
Table 15. Types of identified DRPs for IMM group and their numbers. 48
Table 16. Types of interventions performed for IMM group and their numbers. 50
Table 17. Chart comparing changes between PC-MAI scores on admission vs. at the discharge. 53
Table 18. Description of estimated costs for different episodes of care during follow-up period within study group based on data from the Regional Specialist Hospital in Wroclaw. 54
Table 19. Potential annual cost avoidance for the healthcare system resulting from preventing additional episodes of care connected with DR incidents if 60 to 80% of acutely admitted patients from the vascular and general hospital departments received IMM.* 55
Table 20. Cost savings due to shortened LoS in IMM group. 56
Table 21. Potential cost avoidance for the hospital resulting from shortening the LoS by 2 days if 60 to 80% of acutely admitted patients from the chosen hospital departments received IMM. 56
Table 22. Summary of data used to calculate possible cost-avoidance due to DRP prevention by a pharmacist.* 57
Table 23. Summary of data used to calculate the potential QALY gain for IMM group. 57
Table 24. Summary of pharmacist salary depending on level of education and time period... 58

X. List of figures

Figure 1. Relationships between clinical pharmacy, pharmaceutical care and medicines optimization prepared by Onatade et al. [17]. 10
Figure 2. Graphic representation of study design. 32
Figure 3. Patient flow diagram within the study. 44
Figure 4. Results of assessment of pharmacist's interventions according to Eadon scale [91].52
Figure 5. Results of the questionnaire given to the IMM group assessing patient opinion about the service provided by the pharmacist. 60
Figure 6. Selected opinions of patients about the IMM. 61

XI. Summary

Introduction: To date, numerous studies have demonstrated the positive impact of clinical pharmacy services (CPS) on the healthcare system. Unfortunately, CPS are still underdeveloped and underutilised in Poland. This study aimed to determine whether the involvement of a pharmacist at each stage of hospitalization - from admission to discharge - can improve the level of patient care in the Polish healthcare system, as measured by a range of clinical and economic outcomes.

Material and methods: In this prospective pilot randomized controlled trial (RCT), patients acutely admitted to the vascular and general surgery departments of the Regional Specialist Hospital in Wroclaw who met the eligibility criteria were randomly assigned to either an integrated medicines management (IMM) service group or a regular hospital care group. The IMM service involved the provision of a complex clinical pharmacy service covering three stages of patient hospitalization: medicines reconciliation and review at admission, inpatient monitoring and counselling, and medicines reconciliation with education at discharge. After leaving the hospital, both groups were followed-up at three time points: 1, 3 and 6 months post-discharge. The primary outcome measure was the incidence of hospital and unscheduled visits (emergency department visits, readmissions, GP and specialist care [total and drug- related]) after discharge from hospital during follow-up period. The secondary objective included the length of stay (LoS) in the hospital. Moreover, in the IMM service group the frequency and type of interventions, their acceptance and influence on the quality of pharmacotherapy, in hospital complications, and the perception of the service by both patients and healthcare professionals together with estimating the potential financial benefits of the service were evaluated.

Results: After assessment, 60 patients who met the inclusion criteria were randomly assigned to either the IMM or control group. Of these, 58 completed the follow-up period, while 1 was lost to follow-up. Both groups were similar in context of both age and sex. Additional health care system visits occurred significantly more often in the control group than in the IMM group – 39 vs. 6 ($p<0.05$). The length of hospital stay analysis showed significant differences between the groups – $p = 0.0372$. Patients' median LoS in the IMM group was 5 days (with IQR 3-7; $n = 30$) vs. 7 days (with IQR 5-10; $n = 29$) in the control group. In total, 273 DRPs were identified by the pharmacists for the IMM group during their index admission with a corresponding number of interventions which were fully accepted by physicians. The majority of interventions made were of grade 4 according to Eadon scale. The appropriateness of the prescribed

medicines improved over the course of hospital stay – median Patient Centred – Medicines Appropriateness Index score was 8.03 on admission versus 0.48 at discharge with a concomitant decrease in the total number of medicines. In the control group, additional care episodes during the follow-up period generated potential costs amounting to 146 369,26 PLN, while in the IMM group, these costs amounted to 17 228,32 PLN. The savings associated with the reduction of LoS for the study group were estimated at 43 166,86 PLN. On the other hand, the pharmacotherapy interventions generated potential savings of 65 872,66 – 92 190,47 PLN with a simultaneous gain in Quality of Life (QALY) of 20,1045. Thus, the intervention achieved an Incremental Cost Effectiveness Ratio of 1541.17 - 2807.47 PLN/QALY and a cost-benefit ratio of 1:3-7 depending on the level of costs considered. Pharmacist involvement was well perceived by both patients and healthcare professionals.

Conclusions: Implementation of the IMM is possible in the Polish health care system, and a pilot study has demonstrated the potential positive impact of clinical pharmacy services on defined endpoints and additional metrics. The result should be further verified in a multicentre randomized trial.

XII. Summary in Polish

Wstęp: Liczne badania wykazały wielowymiarowe korzyści dla systemu opieki zdrowotnej płynące z usług farmacji klinicznej (UFK). Niestety, UFK są nadal słabo rozwinięte i niewykorzystane w Polsce. Niniejsze badanie miało na celu ustalenie, czy w polskim systemie opieki zdrowotnej wkład farmaceuty na każdym etapie hospitalizacji, od przyjęcia do wypisu, może skutkować poprawą poziomu opieki nad pacjentem, mierzoną szeregiem mierników klinicznych i ekonomicznych.

Materiał i metody: W ramach prospektywnego pilotażowego badania randomizowanego pacjenci przyjęci w trybie nagłym na oddziały chirurgii naczyniowej i ogólnej Wojewódzkiego Szpitala Specjalistycznego we Wrocławiu, spełniający kryteria kwalifikacji, zostali losowo przydzieleni do grupy zintegrowanego zarządzania farmakoterapią (ZZF) lub standardowej opieki szpitalnej. Usługa ZFF obejmowała świadczenie kompleksowych usług farmacji klinicznej obejmujących każdy z trzech etapów hospitalizacji pacjenta: koncyliację lekową i przegląd lekowy przy przyjęciu, monitorowanie i doradztwo w trakcie hospitalizacji oraz przygotowanie listy leków z edukacją przy wypisie. Po opuszczeniu szpitala obie grupy były monitorowane w trzech punktach czasowych: 1, 3 i 6 miesięcy. Pierwszorzędowym punktem końcowym była częstość nieplanowanych wizyt i hospitalizacji w trybie nagłym (wizyty na

oddziale ratunkowym, ponowne przyjęcia do szpitala, opieka lekarza rodzinnego i specjalistyczna [łącznie i związana z lekami]) po wypisie ze szpitala w okresie obserwacji. Drugorzędnym celem była długość pobytu w szpitalu. Ponadto w grupie usług ZZF oceniono częstotliwość i rodzaj interwencji, ich akceptację i wpływ na jakość farmakoterapii, postrzeganie usługi przez pacjentów i pracowników ochrony zdrowia, a także oszacowano potencjalne korzyści finansowe wynikające z usługi.

Wyniki: W toku badania włączono 60 pacjentów spełniających kryteria, którzy zostali losowo przydzieleni do grupy ZFF lub kontrolnej. Spośród nich 58 osiągnęło okres obserwacji, w tym 1 nie odpowiadał na próby kontaktu. Obie grupy były podobne pod względem wieku i płci. Dodatkowe epizody opieki miały miejsce istotnie częściej w grupie kontrolnej niż w grupie ZZF – 39 vs. 6 ($p<0,05$). Analiza długości pobytu w szpitalu wykazała istotne różnice między grupami – $p = 0,0372$. Mediana czasu hospitalizacji pacjentów w grupie ZZF wynosiła 5 dni (z IQR 3-7; n = 30) vs. 7 dni (z IQR 5-10; n = 29) w grupie kontrolnej. Łącznie zidentyfikowano 273 problemów lekowych dla grupy ZZF podczas ich hospitalizacji z odpowiadającą liczbą interwencji, które zostały w pełni zaakceptowane przez lekarzy. Większość wykonanych interwencji była stopnia 4 według skali Eadona. Jakość farmakoterapii również uległa poprawie w trakcie pobytu w szpitalu – mediana wskaźnika Patient Centered – Medicines Appropriatness Index wyniosła 8,03 przy przyjęciu w porównaniu do 0,48 przy wypisie, przy jednoczesnym zmniejszeniu całkowitej liczby leków. W grupie kontrolnej dodatkowe epizody opieki w okresie obserwacji wygenerowały potencjalne koszty w wysokości 146 369,26 zł, podczas gdy w grupie IMM koszty te wyniosły 17 228,32 zł. Oszczędności związane z redukcją długości pobytu w szpitalu w grupie badanej oszacowano na 43 166,86 zł. Z drugiej strony, interwencje dotyczące farmakoterapii wygenerowały potencjalne oszczędności w wysokości 65 872,66 – 92 190,47 zł przy jednoczesnym przyrostem długości życia skorygowanej o jakość (Quality-Adjusted Life Year - QALY) o 20,1045 QALY. W ten sposób interwencja osiągnęła wskaźnik efektywności kosztowej (Incremental Cost Effectivness Ratio - ICER) wynoszący 1541,17 - 2807,47 zł/QALY oraz wskaźnik koszt-korzyść wynoszący 1:3-7, w zależności od poziomu rozważanych kosztów. Zaangażowanie farmaceutów było dobrze postrzegane przez pacjentów i pracowników ochrony zdrowia.

Wnioski: Realizacja ZZF jest możliwa w polskim systemie opieki zdrowotnej, a badanie pilotażowe wykazało potencjalny pozytywny wpływ usług farmacji klinicznej na zdefiniowane punkty końcowe oraz dodatkowe mierniki. Wynik powinien zostać dodatkowo zweryfikowany w wieloośrodkowym badaniu randomizowanym.

XIII. List of abbreviations

AAH Antrim Area Hospital

ACCP American College of Clinical Pharmacy

ADE adverse drug event

ADR adverse drug reaction

BPMH best possible medication history

CEE Central and Eastern Europe

CPS clinical pharmacy service

DOAC direct acting anticoagulant

DR drug-related

DRPs drug-related problems

ED Emergency Department

ESCP European Society of Clinical Pharmacy

GDP gross domestic product

GKS glucocorticosteroid

GP General Practice

HRQoL health-related quality of life

ICER Incremental Cost Effectiveness Ratio

ICU intensive care unit

ICUR incremental cost-utility ratio

IMM Integrated Medicines Management

iSIMPATHY Stimulating Innovation Management of Polypharmacy and Adherence in The Elderly

IV intravenous

LoS length of stay

MAI Medicines Appropriateness Index

MoH Ministry of Health

MOIC Medicines Optimization Innovation Centre

MPharm Master of Pharmacy

MR medicines review

MRec medicines reconciliation

MUR medicines use review

OECD Organization for Economic Co-operation and Development

PC-MAI Patient-Centred Medicines Appropriateness Index

PCNE Pharmaceutical Care Network Europe

PONV postoperative nausea and vomiting

PPI proton pump inhibitor

PROMs patient reported outcome measures

PSPSQ Patient Satisfaction with Pharmacist Services Questionnaire

QALY Quality Adjusted Life Years

RCT randomized controlled trial

RHW Regional Specialist Hospital in Wroclaw

TDM Therapeutic drug monitoring

TPN total parenteral nutrition

TPN total parenteral nutrition

UK United Kingdom

UKCPA United Kingdom Clinical Pharmacy Association

USA United States of America

VTEP venous thromboembolism prophylaxis

WHO The World Health Organization

XIV.References

1. Kurczewska-Michalak, M.; Lewek, P.; Jankowska-Polańska, B.; Giardini, A.; Granata, N.; Maffoni, M.; Costa, E.; Midão, L.; Kardas, P. Polypharmacy Management in the Older Adults: A Scoping Review of Available Interventions. *Front Pharmacol* 2021, *12*.

2. Kardas, P.; Lewek, P.; Matyjaszczyk, M. Determinants of Patient Adherence: A Review of Systematic Reviews. *Front Pharmacol* 2013, *4 JUL*, doi:10.3389/fphar.2013.00091.

3. OECD Health at a Glance 2021 Available online: https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-2021_ae3016b9-en (accessed on 10 August 2025).

4. Mair, A.; Fernandez-Llimos, F.; Alonso, A.; Harrison, C.; Hurding, S.; Kempen, T.; Kinnear, M.; Michael, N.; McIntosh, J.; Wilson, M. *Polypharmacy Management by 2030: A Patient Safety Challenge. 2nd Edition. Coimbra: SIMPATHY Consortium*; 2017; Vol. 2nd;

5. Kardas, P.; Urbański, F.; Lichwierowicz, A.; Chudzyńska, E.; Kardas, G.; Czech, M. Prevalence and Age Structure of Polypharmacy in Poland: Results of the Analysis of the National Real-

World Database of 38 Million Citizens. *Front Pharmacol* 2021, *12*, 1–9, doi:10.3389/fphar.2021.655364.

6. Eurostat Population Structure and Ageing Available online: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Population_structure_and_ageing (accessed on 24 June 2025).

7. World Health Organization The Third WHO Global Patient Safety Challenge: Medication Without Harm Available online: https://www.who.int/patientsafety/medication-safety/en/ (accessed on 23 August 2020).

8. Morrison, V.L.; Holmes, E.A.F.; Parveen, S.; Plumpton, C.O.; Clyne, W.; De Geest, S.; Dobbels, F.; Vrijens, B.; Kardas, P.; Hughes, D.A. Predictors of Self-Reported Adherence to Antihypertensive Medicines: A Multinational, Cross-Sectional Survey. *Value in Health* 2015, *18*, 206–216, doi:10.1016/j.jval.2014.12.013.

9. Committee of Ministers Resolution CM/Res(2020)3 on the Implementation of Pharmaceutical Care for the Benefit of Patients and Health Services Available online: https://go.edqm.eu/ResPhCare20203 (accessed on 22 March 2023).

10. Urbańczyk, K.; Guntschnig, S.; Antoniadis, V.; Falamic, S.; Kovacevic, T.; Kurczewska-Michalak, M.; Miljković, B.; Olearova, A.; Sviestina, I.; Szucs, A.; et al. Recommendations for Wider Adoption of Clinical Pharmacy in Central and Eastern Europe in Order to Optimise Pharmacotherapy and Improve Patient Outcomes. *Front Pharmacol* 2023, *14*, doi:10.3389/fphar.2023.1244151.

11. MILLER, R.R. History of Clinical Pharmacy and Clinical Pharmacology. *The Journal of Clinical Pharmacology* 1981, *21*, 195–197, doi:10.1002/j.1552-4604.1981.tb05699.x.

12. Carter, B.L. Evolution of Clinical Pharmacy in the USA and Future Directions for Patient Care. *Drugs Aging* 2016, *33*, 169–177, doi:10.1007/s40266-016-0349-2.

13. Kamian, F.D. The Clinical Pharmacy Program in a Community Hospital Setting : An Integral Part of the Educational Process Available online: https://scholarlycommons.pacific.edu/cgi/viewcontent.cgi?article=2896&context=uop_etds (accessed on 10 August 2025).

14. American College of Clinical Pharmacy The Definition of Clinical Pharmacy. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 2008, *28*, 816–817, doi:10.1592/phco.28.6.816.

15. Auta, A.; Maz, J.; Strickland-Hodge, B. Perceived Facilitators to Change in Hospital Pharmacy Practice in England. *Int J Clin Pharm* 2015, *37*, 1068–1075, doi:10.1007/s11096-015-0153-9.

16. Dreischulte, T.; van den Bemt, B.; Steurbaut, S. European Society of Clinical Pharmacy Definition of the Term Clinical Pharmacy and Its Relationship to Pharmaceutical Care: A Position Paper. *Int J Clin Pharm* 2022, *44*, 837–842, doi:10.1007/s11096-022-01422-7.

17. Onatade, R.; Appiah, S.; Stephens, M.; Garelick, H. Evidence for the Outcomes and Impact of Clinical Pharmacy: Context of UK Hospital Pharmacy Practice. *European Journal of Hospital Pharmacy* 2018, *25*, e21–e28, doi:10.1136/ejhpharm-2017-001303.

18. Gallagher, J.; McCarthy, S.; Byrne, S. Economic Evaluations of Clinical Pharmacist Interventions on Hospital Inpatients: A Systematic Review of Recent Literature. *Int J Clin Pharm* 2014, *36*, 1101–1114, doi:10.1007/s11096-014-0008-9.

19. Deng, Z.-J.; Gui, L.; Chen, J.; Peng, S.-S.; Ding, Y.-F.; Wei, A.-H. Clinical, Economic and Humanistic Outcomes of Medication Therapy Management Services: A Systematic Review and Meta-Analysis. *Front Pharmacol* 2023, *14*, doi:10.3389/fphar.2023.1143444.

20. Touchette, D.R.; Doloresco, F.; Suda, K.J.; Perez, A.; Turner, S.; Jalundhwala, Y.; Tangonan, M.C.; Hoffman, J.M. Economic Evaluations of Clinical Pharmacy Services: 2006-2010. *Pharmacotherapy* 2014, *34*, 771–793, doi:10.1002/phar.1414.

21. Perez, A.; Doloresco, F.; Hoffman, J.M.; Meek, P.D.; Touchette, D.R.; Vermeulen, L.C.; Schumock, G.T. Economic Evaluations of Clinical Pharmacy Services: 2001–2005. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 2009, *29*, 128–128, doi:10.1592/phco.29.1.128.

22. Schumock, G.T.; Meek, P.D.; Ploetz, P.A.; Vermeulen, L.C. Economic Evaluations of Clinical Pharmacy Services 1988-1995. *Pharmacotherapy* 1996, *16*, 1188–1208, doi:https://doi.org/10.1002/j.1875-9114.1996.tb03049.x.

23. Michalets, E.; Creger, J.; Shillinglaw, W.R. Outcomes of Expanded Use of Clinical Pharmacist Practitioners in Addition to Team-Based Care in a Community Health System Intensive Care Unit. *American Journal of Health-System Pharmacy* 2015, *72*, 47–53, doi:10.2146/ajhp140105.

24. Onatade, R.; Quaye, S. Economic Value of Pharmacy-Led Medicines Reconciliation at Admission to Hospital: An Observational, UK-Based Study. *European Journal of Hospital Pharmacy* 2018, *25*, 26–31, doi:10.1136/ejhpharm-2016-001071.

25. Rychlickova, J.; Saloun, J.; Gregorova, J. Evaluation of Clinical Pharmacists' Interventions in the Czech Republic. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 2016, *35*, 84–90, doi:10.14108/j.cnki.1008-8873.2016.06.012.

26. Chen, C.-C.; Hsiao, F.-Y.; Shen, L.-J.; Wu, C.-C. The Cost-Saving Effect and Prevention of Medication Errors by Clinical Pharmacist Intervention in a Nephrology Unit. *Medicine* 2017, *96*, e7883, doi:10.1097/MD.0000000000007883.

27. Lee, E.H.; Bray, V.; Horne, R. Developing an Economic Case of Clinical Pharmacists' Interventions on Venous Thromboembolism Prophylaxis Through Service Evaluation. *J Res Pharm Pract* 2017, *6*, 106–113, doi:10.4103/jrpp.JRPP_16_160.

28. Declaye, C.; Sennesael, A.L.; Larock, A.S.; Spinewine, A.; Krug, B. Partial Economic Evaluation of Clinical Pharmacy Interventions on the Prescription of Direct Oral Anticoagulants in a Teaching Hospital. *European Journal of Hospital Pharmacy* 2018, *25*, e66–e69, doi:10.1136/ejhpharm-2016-001024.

29. Renaudin, P.; Coste, A.; Audurier, Y.; Berbis, J.; Canovas, F.; Jalabert, A.; Castet-Nicolas, A.; Mercier, G.; Villiet, M.; Dagneaux, L.; et al. Clinical, Economic, and Organizational Impact of the Clinical Pharmacist in an Orthopedic and Trauma Surgery Department. *J Patient Saf* 2018, *Publish Ah*, 1–7, doi:10.1097/pts.0000000000000539.

30. Malfará, M.; Pernassi, M.; Aragon, D.; Carlotti, A. Impact of the Clinical Pharmacist Interventions on Prevention of Pharmacotherapy Related Problems in the Paediatric Intensive Care Unit. *Int J Clin Pharm* 2018, *40*, 513–519, doi:10.1007/s11096-018-0632-x.

31. Bosma, B.E.; van den Bemt, P.M.L.A.; Melief, P.H.G.J.; van Bommel, J.; Tan, S.S.; Hunfeld, N.G.M. Pharmacist Interventions during Patient Rounds in Two Intensive Care Units: Clinical and Financial Impact. *Neth J Med* 2018, *76*, 115–124.

32. Guruge, L.; Shanika, T.; Jayamanne, S.; Wijekoon, N.; Coombes, J.; Perera, D.; Mohamed, F.; Coombes, I.; Silva, A. De; Hamilton, A. Ward-Based Clinical Pharmacists and Hospital Readmission : A Non- Randomized Controlled Trial in Sri Lanka. 2018, 155–164, doi:10.2471/BLT.17.198366.

33. Dryden, L.; Dewhurst, N.F. Integration of a Clinical Pharmacist into a Canadian, Urban Emergency Department: A Prospective Observational Study. *International Journal of Pharmacy Practice* 2019, *27*, 175–179, doi:10.1111/ijpp.12481.

34. Leache, L.; Aquerreta, I.; Aldaz, A.; Monedero, P.; Idoate, A.; Ortega, A. Clinical and Economic Impact of Clinical Pharmacist Interventions Regarding Antimicrobials on Critically Ill Patients. *Research in Social and Administrative Pharmacy* 2020, *16*, 1285–1289, doi:10.1016/j.sapharm.2019.07.006.

35. Sjölander, M.; Lindholm, L.; Pfister, B.; Jonsson, J.; Schneede, J.; Lövheim, H.; Gustafsson, M. Impact of Clinical Pharmacist Engagement in Ward Teams on the Number of Drug-Related Readmissions among Older Patients with Dementia or Cognitive Impairment: An Economic Evaluation. *Research in Social and Administrative Pharmacy* 2019, *15*, 287–291, doi:10.1016/j.sapharm.2018.05.006.

36. Chen, P.-Z.; Wu, C.-C.; Huang, C.-F. Clinical and Economic Impact of Clinical Pharmacist Intervention in a Hematology Unit. *Journal of Oncology Pharmacy Practice* 2020, *26*, 866–872, doi:10.1177/1078155219875806.

37. Sukkha, S.; Rattanavipanon, W.; Chamroenwit, B.; Sanganurak, M.; Nathisuwan, S.; Chaikledkaew, U.; Kongwatcharapong, J. Quality Assessment and Cost Saving of Renal Dosing Recommendation by Clinical Pharmacists at Medical Wards in Thailand. *Int J Clin Pharm* 2020, *42*, 610–616, doi:10.1007/s11096-020-01016-1.

38. Buckley, M.S.; Agarwal, S.K.; Lansburg, J.M.; Kopp, B.J.; Erstad, B.L. Clinical Pharmacist–Led Impact on Inappropriate Albumin Utilization and Associated Costs in General Ward Patients. *Annals of Pharmacotherapy* 2021, *55*, 44–51, doi:10.1177/1060028020935575.

39. Westerlund, T.; Marklund, B. Assessment of the Clinical and Economic Outcomes of Pharmacy Interventions in Drug-Related Problems. *J Clin Pharm Ther* 2009, *34*, 319–327, doi:10.1111/j.1365-2710.2008.01017.x.

40. Muñoz-Pichuante, D.; Villa-Zapata, L. Benefit of Incorporating Clinical Pharmacists in an Adult Intensive Care Unit: A Cost-saving Study. *J Clin Pharm Ther* 2020, *45*, 1127–1133, doi:10.1111/jcpt.13195.

41. Scullin, C.; Scott, M.G.; Hogg, A.; McElnay, J.C. An Innovative Approach to Integrated Medicines Management. *J Eval Clin Pract* 2007, *13*, 781–788, doi:10.1111/j.1365-2753.2006.00753.x.

42. Mair, A.; Kirke, C.; Scott, M.; Michael, N.; Kanan, Y.; Law, S.; Scullin, C.; Fleming, G.; Hyder Skinner, N.; Kyle, D. ISIMPATHY Evaluation Report Available online: https://www.isimpathy.eu/uploads/iSIMPATHY_Evaluation_report_ver8_online.pdf (accessed on 2 March 2025).

43. Saini, S.; Kaur, H.; Pant, M.; Joshi, Y. Role of Clinical Pharmacy Services in Healthcare System. *Asian Journal of Pharmaceutical and Health Sciences* 2023, *12*, 2757–2760, doi:10.5530/ajphs.2022.12.28.

44. Yuliandani, Y.; Alfian, S.D.; Puspitasari, I.M. Patient Satisfaction with Clinical Pharmacy Services and the Affecting Factors: A Literature Review. *Pharmacia* 2022, *69*, 227–236, doi:10.3897/pharmacia.69.e80261.

45. Pickard, A.S.; Hung, S.Y. An Update on Evidence of Clinical Pharmacy Services' Impact on Health-Related Quality of Life. *Annals of Pharmacotherapy* 2006, *40*, 1623–1634, doi:10.1345/aph.1G653.

46. Loh, Z.W.R.; Cheen, M.H.H.; Wee, H.L. Humanistic and Economic Outcomes of Pharmacist-Provided Medication Review in the Community-Dwelling Elderly: A Systematic Review and Meta-Analysis. *J Clin Pharm Ther* 2016, *41*, 621–633, doi:10.1111/jcpt.12453.

47. American College of Clinical Pharmacy Standards of Practice for Clinical Pharmacists. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 2014, *34*, 794–797, doi:10.1002/phar.1438.

48. Fernandes, O.; Toombs, K.; Pereira, T.; Lyder, C.; Bjelajac Mejia, A.; Shalansky, S.; Al-Sukhni, M.; Gerges, S.; Sohal, S.; Gorman, S. Canadian Consensus on Clinical Pharmacy Key Performance Indicators: Quick Reference Guide Available online: https://www.cshp.ca/sites/default/files/files/publications/Official Publications/CPKPI/CSPH-Can-Concensus-cpKPI-QuickReferenceGuide_June_2017.pdf (accessed on 10 August 2025).

49. Zavaleta-Monestel, E.; Serrano-Arias, B.; Milano-Gil, A.; Sanchez-Solis, C.; Arroyo-Monterrosa, D.A.; Muñoz-Pichuante, D.; Morales-Vallespin, J.; Diaz-Madriz, J.P.; Viñas-Veliz, M.; Dalmaso-Neto, S.; et al. Insights into Clinical Pharmacy Practice in Latin America. *JACCP: Journal Of The American College OF Clinical Pharmacy* 2023, *6*, 1103–1116, doi:10.1002/jac5.1854.

50. SHPA Committee of Speciality Practice in Clinical Pharmacy. Overview: Standards of Practice for Clinical Pharmacy Services. *Journal of Pharmacy Practice and Research* 2013, *43*, 91–93, doi:10.1002/j.2055-2335.2013.tb00894.x.

51. The Society of Hospital Pharmacists of Australia; American Society of Hospital Pharmacy; Omnicell Pharmacy Forecast Australia 2023: Report Available online: https://shpa.org.au/publicassets/a9a9fc94-3a62-ee11-912e-00505696223b/Pharmacy-Forecast-Australia-2023.pdf (accessed on 11 January 2024).

52. New Zeland Hospital Spharmacists' Association Standards of Practice for New Zealand Hospital Pharmacy Services Available online: https://nzhpa.org.nz/assets/Uploads/NZHPA-Standards-of-Clinical-Practice-June-2019.pdf (accessed on 11 January 2024).

53. Penm, J.; Chaar, B.; Moles, R. Clinical Pharmacy Services That Influence Prescribing in the Western Pacific Region Based on the FIP Basel Statements. *Int J Clin Pharm* 2015, *37*, 485–496, doi:10.1007/s11096-015-0084-5.

54. Shrestha, S.; Shrestha, R.; Ahmed, A.; Sapkota, B.; Khatiwada, A.P.; Christopher, C.M.; Thapa, P.; KC, B.; Blebil, A.Q.; Khanal, S.; et al. Impact of Pharmacist Services on Economic, Clinical, and Humanistic Outcome (ECHO) of South Asian Patients: A Systematic Review. *J Pharm Policy Pract* 2022, *15*, 37, doi:10.1186/s40545-022-00431-1.

55. Obaid, D.; El-Dahiyat, F.; Babar, Z.U.D. Pharmacy Practice and Clinical Pharmacy Research in the Middle East: A Scoping Review of Studies from Bahrain, Iraq, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, United Arab Emirates, and Yemen. *J Pharm Policy Pract* 2022, *15*, doi:10.1186/s40545-022-00434-y.

56. Njuguna, B.; Berhane, H.; Ndemo, F.A.; Opanga, S. Scaling up Clinical Pharmacy Practice in Africa: Current Challenges and the Future. *JACCP: JOURNAL OF THE AMERICAN COLLEGE OF CLINICAL PHARMACY* 2020, *3*, 966–972, doi:10.1002/jac5.1297.

57. Mccusker, E.; Scott, M.; Boyce, T.; MacIntyre, J.; Friel, A. Northern Ireland Clinical Pharmacy Standards Available online: https://www.health-ni.gov.uk/sites/default/files/publications/dhssps/northern-ireland-clinical-pharmacy-standards-2013.pdf (accessed on 10 August 2025).

58. Savickas, V.; Foreman, E.; Ladva, A.; Bhamra, S.K.; Sharma, R. Pharmacy Services and Role Development in UK General Practice: A Cross-Sectional Survey. *International Journal of Pharmacy Practice* 2021, *29*, 37–44, doi:10.1111/ijpp.12653.

59. Girvin, B.; Sims, L.; Haughey, S. Empowering Future Pharmacists - Embedding Prescribing in the United Kingdom Pharmacy Undergraduate Degree. *Curr Pharm Teach Learn* 2023, *15*, 334–339, doi:10.1016/j.cptl.2023.04.010.

60. Frontini, R.; Miharija-Gala, T.; Sykora, J. EAHP Survey 2010 on Hospital Pharmacy in Europe: Parts 4 and 5. Clinical Services and Patient Safety. *European Journal of Hospital Pharmacy* 2013, *20*, 69–73, doi:10.1136/ejhpharm-2013-000285.

61. Bryla, A.; Urbańczyk, K.; Stachowiak, A.; Burkacka, M.; Steczko, M.; Wiela-Hojeńska, A. Clinical Pharmacy – at What Stage Are We in Poland? *Farm Pol* 2020, *76*, 175–182, doi:10.32383/farmpol/121064.

62. Polish Society of Clinical Pharmacy Medicines Reconciliation (Koncyliacja Lekowa) Available online: https://ptfk.pl/wp-content/uploads/2021/11/PTFK_standard_koncyliacji_lekowej_wydanie-I.pdf (accessed on 10 August 2025).

63. Polish Ministry of Health Raport Opieka Farmaceutyczna. Kompleksowa Analiza Procesu Wdrożenia. Available online: https://www.gov.pl/web/zdrowie/opieka-farmaceutyczna---raport (accessed on 28 March 2023).

64. Polish Ministry of Health Rozwiązania w Zakresie Farmacji Klinicznej Oraz Działalności Farmaceutów w Podmiotach Leczniczych Available online: https://www.gov.pl/web/zdrowie/raport-2022-rozwiazania-w-zakresie-farmacji-klinicznej-oraz-dzialalnosci-farmaceutow-w-podmiotach-leczniczych (accessed on 10 August 2025).

65. Gajda, A.; Gajda, M.; Fedorowicz, O.; Karolewicz, B. Identification of the Area of Services Provided by the Clinical Pharmacist in Patient Care after Kidney Transplantation. *Farm Pol* 2018, *74*, 709–715, doi:10.32383/farmpol/118619.

66. Fedorowicz, O.; Rypicz, Ł.; Wiela-Hojeńska, A.; Jaźwińska–tarnawska, E.; Witczak, I. Application of Novel Pharmacists' Risk in Pharmacotherapy (PHARIPH) Scale for Identification of Factors Affecting the Safety of Hospital Pharmacotherapy—An Observational Pilot Study. *Int J Environ Res Public Health* 2022, *19*, doi:10.3390/ijerph19031337.

67. URBAŃCZYK, K.; WNĘK, P.; ROLEDER, T.; WITKIEWICZ, W.; MCCAGUE, P.; SCOTT, M.; WIELA-HOJEŃSKA, A. Optimized and Cost-Effective Pharmacotherapy of Vascular Surgery Patients: Evaluation of Clinical Pharmacy Service. *Italian Journal of Vascular and Endovascular Surgery* 2022, *29*, 74–79, doi:10.23736/S1824-4777.22.01534-0.

68. Zerovnik, S.; Lipovec, N.C.; Locatelli, I.; Kos, M. Seamless Pharmaceutical Care in Slovenia. *Farm Vestn* 2018, 211–218.

69. Burnett, K.M.; Scott, M.G.; Fleming, G.F.; Clark, C.M.; Mcelnay, J.C. Effects of an Integrated Medicines Management Program on Medication Appropriateness in Hospitalized Patients. *American Journal of Health-System Pharmacy* 2009, *66*, 854–859, doi:10.2146/ajhp080176.

70. Schnipper, J.L.; Kirwin, J.L.; Cotugno, M.C.; Wahlstrom, S.A.; Brown, B.A.; Tarvin, E.; Kachalia, A.; Horng, M.; Roy, C.L.; McKean, S.C.; et al. Role of Pharmacist Counseling in Preventing Adverse Drug Events after Hospitalization. *Arch Intern Med* 2006, *166*, 565–571, doi:10.1001/archinte.166.5.565.

71. Gillespie, U.; Alassaad, A.; Henrohn, D.; Garmo, H.; Hammarlund-Udenaes, M.; Toss, H.; Kettis-Lindblad, Å.; Melhus, H.; Mörlin, C. A Comprehensive Pharmacist Intervention to Reduce Morbidity in Patients 80 Years or Older: A Randomized Controlled Trial. *Arch Intern Med* 2009, *169*, 894–900, doi:10.1001/archinternmed.2009.71.

72. Hellström, L.M.; Bondesson, Å.; Höglund, P.; Midlöv, P.; Holmdahl, L.; Rickhag, E.; Eriksson, T. Impact of the Lund Integrated Medicines Management (LIMM) Model on Medication Appropriateness and Drug-Related Hospital Revisits. *Eur J Clin Pharmacol* 2011, *67*, 741–752, doi:10.1007/s00228-010-0982-3.

73. Ghatnekar, O.; Bondesson, Å.; Persson, U.; Eriksson, T. Health Economic Evaluation of the Lund Integrated Medicines Management Model (LIMM) in Elderly Patients Admitted to Hospital. *BMJ Open* 2013, *3*, 1–9, doi:10.1136/bmjopen-2012-001563.

74. Umar, R.M.; Apikoglu-Rabus, S.; Yumuk, P.F. Significance of a Clinical Pharmacist-Led Comprehensive Medication Management Program for Hospitalized Oncology Patients. *Int J Clin Pharm* 2020, *42*, 652–661, doi:10.1007/s11096-020-00992-8.

75. Chen, K.-L.; Hunag, C.-F.; Sheng, W.-H.; Chen, Y.-K.; Wang, C.-C.; Shen, L.-J. Impact of Integrated Medication Management Program on Medication Errors in a Medical Center: An Interrupted Time Series Study. *BMC Health Serv Res* 2022, *22*, 1–14, doi:10.1186/s12913-022-08178-w.

76. Lea, M.; Mowé, M.; Molden, E.; Kvernrød, K.; Skovlund, E.; Mathiesen, L. Effect of Medicines Management versus Standard Care on Readmissions in Multimorbid Patients: A Randomised Controlled Trial. *BMJ Open* 2020, *10*, doi:10.1136/bmjopen-2020-041558.

77. Polish Society of Family Medicine Coordinated Care in Primary Care in Poland Available online: https://ptmr.info.pl/opieka-koordynowana-w-poz/ (accessed on 10 February 2024).

78. International Pharmaceutical Federation Medicines Reconciliation A Toolkit for Pharmacists Available online: https://www.fip.org/file/4949 (accessed on 16 September 2023).

79. WHO The High 5s Project Medication Reconciliation Implementation Guide Available online: https://www.who.int/publications/m/item/high5s-implementation-guide-medication-reconciliation (accessed on 16 September 2023).

80. Griese-Mammen, N.; Hersberger, K.E.; Messerli, M.; Leikola, S.; Horvat, N.; van Mil, J.W.F.; Kos, M. PCNE Definition of Medication Review: Reaching Agreement. *Int J Clin Pharm* 2018, *40*, 1199–1208, doi:10.1007/s11096-018-0696-7.

81. International Pharmaceutical Federation Medication Review and Medicines Use Review A Toolkit for Pharmacists Available online: https://www.fip.org/file/5100 (accessed on 10 August 2025).

82. Task Force on Medicines Partnership and The National Collaborative medicines Management Services Programme Room for Review: A Guide to Medication Review - the Agenda for Patients, Practitioners and Managers. Available online: https://medicines-partnership.org/medication-review/room-for-review (accessed on 16 September 2023).

83. Clyne, W.; Blenkinsopp, A.; Seal, R. A Guide to Medication Review 2008 Available online: https://www.cff.org.br/userfiles/52%20-%20CLYNE%20W%20A%20guide%20to%20medication%20review%202008.pdf (accessed on 10 August 2025).

84. Lewis, T. 10-Minute Consultation: Using the NO TEARS Tool for Medication Review. *Br Med J* 2004, *329*, 434, doi:10.1136/sbmj.0410362.

85. Scottish Government Polypharmacy Model of Care Group Polypharmacy Guidance, Realistic Prescribing 3rd Edition Available online: https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/04/Polypharmacy-Guidance-2018.pdf (accessed on 20 November 2022).

86. Kempen, T.G.H.; Bertilsson, M.; Hadziosmanovic, N.; Lindner, K.J.; Melhus, H.; Nielsen, E.I.; Sulku, J.; Gillespie, U. Effects of Hospital-Based Comprehensive Medication Reviews Including Postdischarge Follow-up on Older Patients' Use of Health Care: A Cluster

Randomized Clinical Trial. *JAMA Netw Open* 2021, *4*, doi:10.1001/jamanetworkopen.2021.6303.

87. Lea, M.; Mowé, M.; Molden, E.; Kvernrød, K.; Skovlund, E.; Mathiesen, L. Effect of Medicines Management versus Standard Care on Readmissions in Multimorbid Patients: A Randomised Controlled Trial. *BMJ Open* 2020, *10*, doi:10.1136/bmjopen-2020-041558.

88. Eldridge, S.M.; Chan, C.L.; Campbell, M.J.; Bond, C.M.; Hopewell, S.; Thabane, L.; Lancaster, G.A.; Altman, D.; Bretz, F.; Campbell, M.; et al. CONSORT 2010 Statement: Extension to Randomised Pilot and Feasibility Trials. *The BMJ* 2016, *355*, doi:10.1136/bmj.i5239.

89. Hoffmann, T.C.; Glasziou, P.P.; Boutron, I.; Milne, R.; Perera, R.; Moher, D.; Altman, D.G.; Barbour, V.; Macdonald, H.; Johnston, M.; et al. Better Reporting of Interventions: Template for Intervention Description and Replication (TIDieR) Checklist and Guide. *BMJ (Online)* 2014, *348*, doi:10.1136/bmj.g1687.

90. Allenet, B.; Bedouch, P.; Rose, F.X.; Escofier, L.; Roubille, R.; Charpiat, B.; Juste, M.; Conort, O. Validation of an Instrument for the Documentation of Clinical Pharmacists' Interventions. *Pharmacy World and Science* 2006, *28*, 181–188, doi:10.1007/s11096-006-9027-5.

91. Eadon, H. Assessing the Quality of Ward Pharmacists' Interventions. *International Journal of Pharmacy Practice* 2011, *1*, 145–147, doi:10.1111/j.2042-7174.1992.tb00556.x.

92. Nesbit, T.W.; Shermock, K.M.; Bobek, M.B.; Capozzi, D.L.; Flores, P.A.; Leonard, M.C.; Long, J.K.; Militello, M.A.; White, D.A.; Barone, L.D.; et al. Implementation and Pharmacoeconomic Analysis of a Clinical Staff Pharmacist Practice Model. *American Journal of Health-System Pharmacy* 2001, *58*, 784–790, doi:10.1093/ajhp/58.9.784.

93. Classen, D.C.; Pestotnik, S.L.; Evans, R.S.; Lloyd, J.F.; Burke, J.P. Adverse Drug Events in Hospitalized Patients: Excess Length of Stay, Extra Costs, and Attributable Mortality. *J Am Med Assoc* 1997, *277*, 301–306, doi:10.1001/jama.277.4.301.

94. Bates, D.W.; Spell, N.; Cullen, D.J.; Burdick, E.; Laird, N.; Petersen, L.A.; Small, S.D.; Sweitzer, B.J.; Leape, L.L. The Costs of Adverse Drug Events in Hospitalized Patients. *J Am Med Assoc* 1997, *277*, 307–311, doi:10.1001/jama.277.4.307.

95. Campbell, F.; Karnon, J.; Czoski-Murray, C.; Jones, R. A Systematic Review of the Effectiveness and Cost-Effectiveness of Interventions Aimed at Preventing Medication Error (Medicines Reconciliation) at Hospital Admission Available online:

https://www.eprescribingtoolkit.com/wp-content/uploads/2013/11/PatientSafetyMedsSystematicReview.pdf (accessed on 3 June 2025).

96. Hanlon, J.; Schmader, K.; Samsa, G.; Weinberger, M.; Uttech, K.; Lewis, I. A Method for Assess Drug Therapy Appropriateness. J Clin Epidemiol. *J CUB Epiaemiol* 1992, *45*, 1045–1051.

97. Sakharkar, P.; Bounthavong, M.; Hirsch, J.D.; Morello, C.M.; Chen, T.C.; Law, A. V. Development and Validation of PSPSQ 2.0 Measuring Patient Satisfaction with Pharmacist Services. *Research in Social and Administrative Pharmacy* 2015, *11*, 487–498, doi:10.1016/j.sapharm.2014.10.006.

98. Agencja Oceny Technologii Medycznych i Taryfikacji Wytyczne Oceny Technologii Medycznych (HTA, Ang. Health Technology Assessment) Available online: https://www.aotm.gov.pl/wp-content/uploads/2020/07/20160913_Wytyczne_AOTMiT-1.pdf (accessed on 24 June 2025).

99. Ustawa z Dnia 26 Maja 2022 r. o Zmianie Ustawy o Sposobie Ustalania Najniższego Wynagrodzenia Zasadniczego Niektórych Pracowników Zatrudnionych w Podmiotach Leczniczych Oraz Niektórych Innych Ustaw Available online: https://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=WDU20220001352 (accessed on 24 June 2025).

100. Lancaster, G.A.; Dodd, S.; Williamson, P.R. Design and Analysis of Pilot Studies: Recommendations for Good Practice. *J Eval Clin Pract* 2004, *10*, 307–312, doi:10.1111/j..2002.384.doc.x.

101. Lewis, M.; Bromley, K.; Sutton, C.J.; McCray, G.; Myers, H.L.; Lancaster, G.A. Determining Sample Size for Progression Criteria for Pragmatic Pilot RCTs: The Hypothesis Test Strikes Back! *Pilot Feasibility Stud* 2021, *7*, doi:10.1186/s40814-021-00770-x.

102. World Bank Group GDP per Capita - Poland Available online: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=PL (accessed on 20 July 2025).

103. Kaboli, P.J.; Hoth, A.B.; McClimon, B.J.; Schnipper, J.L. Clinical Pharmacists and Inpatient Medical Care. *Arch Intern Med* 2006, *166*, 955, doi:10.1001/archinte.166.9.955.

104. Scullin, C.; Hogg, A.; Luo, R.; Scott, M.G.; McElnay, J.C. Integrated Medicines Management - Can Routine Implementation Improve Quality? *J Eval Clin Pract* 2012, *18*, 807–815, doi:10.1111/j.1365-2753.2011.01682.x.

105. Skjøt-Arkil, H.; Lundby, C.; Kjeldsen, L.J.; Skovgårds, D.M.; Almarsdóttir, A.B.; Kjølhede, T.; Duedahl, T.H.; Pottegård, A.; Graabæk, T. Multifaceted Pharmacist-led Interventions in the Hospital Setting: A Systematic Review. *Basic Clin Pharmacol Toxicol* 2018, *123*, 363–379, doi:10.1111/bcpt.13030.

106. Brajković, A.; Bićanić, L.A.; Strgačić, M.; Orehovački, H.; Ramalho-de-Oliveira, D.; Mucalo, I. The Impact of Pharmacist-Led Medication Management Services on the Quality of Life and Adverse Drug Reaction Occurrence. *Pharmacy* 2022, *10*, 102, doi:10.3390/pharmacy10050102.

107. Brajković, A.; Bosnar, L.; Nascimento, M.M.G. Do; Prkačin, I.; Balenović, A.; Ramalho de Oliveira, D.; Mucalo, I. Healthcare Utilisation and Clinical Outcomes in Older Cardiovascular Patients Receiving Comprehensive Medication Management Services: A Nonrandomised Clinical Study. *Int J Environ Res Public Health* 2022, *19*, doi:10.3390/ijerph19052781.

108. Bond, C.A.; Raehl, C.L.; Franke, T. Interrelationships among Mortality Rates, Drug Costs, Total Cost of Care, and Length of Stay in United States Hospitals: Summary and Recommendations for Clinical Pharmacy Services and Staffing. *Pharmacotherapy* 2001, *21*, 129–141, doi:10.1592/phco.21.2.129.34105.

109. Saleh, J.; El Nekidy, W.S.; Hisham, M.; Elrefaei, H.; Abidi, E.; AlTakruri, M.; Kalagieh, O.; Alzaabi, S.; Atallah, B.; Chehab, O.; et al. Impact of Pharmacist-Led Transitions of Care Model on Length of Hospital Stay and 30-Day Readmission Rates at a Quaternary Care Hospital: A Pilot Study. *JAPhA Practice Innovations* 2024, *1*, 100015, doi:10.1016/j.japhpi.2024.100015.

110. Naseralallah, L.; Koraysh, S.; Aboujabal, B.; Alasmar, M. Interventions and Impact of Pharmacist-Delivered Services in Perioperative Setting on Clinically Important Outcomes: A Systematic Review and Meta-Analysis. *Ther Adv Drug Saf* 2024, *15*, doi:10.1177/20420986241260169.

111. Garin, N.; Sole, N.; Lucas, B.; Matas, L.; Moras, D.; Rodrigo-Troyano, A.; Gras-Martin, L.; Fonts, N. Drug Related Problems in Clinical Practice: A Cross-Sectional Study on Their Prevalence, Risk Factors and Associated Pharmaceutical Interventions. *Sci Rep* 2021, *11*, doi:10.1038/s41598-020-80560-2.

112. Peled, O.; Vitzrabin, Y.; Beit Ner, E.; Lazaryan, M.; Berlin, M.; Barchel, D.; Berkovitch, M.; Beer, Y.; Tamir, E. Acceptance Rate of Clinical Pharmacists' Recommendations—an Ongoing Journey for Integration. *Front Pharmacol* 2023, *14*, doi:10.3389/fphar.2023.1253990.

113. Deawjaroen, K.; Sillabutra, J.; Poolsup, N.; Stewart, D.; Suksomboon, N. Characteristics of Drug-Related Problems and Pharmacist's Interventions in Hospitalized Patients in Thailand: A Prospective Observational Study. *Sci Rep* 2022, *12*, doi:10.1038/s41598-022-21515-7.

114. Albayrak, A.; Başgut, B.; Bıkmaz, G.A.; Karahalil, B. Clinical Pharmacist Assessment of Drug-Related Problems among Intensive Care Unit Patients in a Turkish University Hospital. *BMC Health Serv Res* 2022, *22*, doi:10.1186/s12913-022-07494-5.

115. Miarons, M.; Marín, S.; Amenós, I.; Campins, L.; Rovira, M.; Daza, M. Pharmaceutical Interventions in the Emergency Department: Cost-Effectiveness and Cost-Benefit Analysis. *European Journal of Hospital Pharmacy* 2021, *28*, 133–138, doi:10.1136/ejhpharm-2019-002067.

116. Albayrak, A.; Başgut, B.; Bıkmaz, G.A.; Karahalil, B. Clinical Pharmacist Assessment of Drug-Related Problems among Intensive Care Unit Patients in a Turkish University Hospital. *BMC Health Serv Res* 2022, *22*, doi:10.1186/s12913-022-07494-5.

117. Aburuz, S.; Jaber, D.; Basheti, I.; Sadeq, A.; Arafat, M.; Alahmad, M.; Said, A. Impact of Pharmacist Interventions on Drug-Related Problems in General Surgery Patients: A Randomised Controlled Trial. *European Journal of Hospital Pharmacy* 2021, *28*, E72–E78, doi:10.1136/ejhpharm-2020-002206.

118. Martínez López, I.; Do Pazo-Oubiña, F.; Lozano Vilardell, P. Atención Farmacéutica Integral a Los Pacientes de Un Servicio de Cirugía Vascular. *Farmacia Hospitalaria* 2011, *35*, 260–263, doi:10.1016/j.farma.2011.02.005.

119. Spinewine, A.; Swine, C.; Dhillon, S.; Lambert, P.; Nachega, J.B.; Wilmotte, L.; Tulkens, P.M. Effect of a Collaborative Approach on the Quality of Prescribing for Geriatric Inpatients: A Randomized, Controlled Trial. *J Am Geriatr Soc* 2007, *55*, 658–665, doi:10.1111/j.1532-5415.2007.01132.x.

120. West, L.M.; Cordina, M.; Cunningham, S. Clinical Pharmacist Evaluation of Medication Inappropriateness in the Emergency Department of a Teaching Hospital in Malta. *Pharmacy Practice (Internet)* 2012, *10*, 181–187, doi:10.4321/S1886-36552012000400001.

121. Patterson, S.M.; Cadogan, C.A.; Kerse, N.; Cardwell, C.R.; Bradley, M.C.; Ryan, C.; Hughes, C. Interventions to Improve the Appropriate Use of Polypharmacy for Older People. *Cochrane Database of Systematic Reviews* 2014, *2014*, doi:10.1002/14651858.CD008165.pub3.

122. Krisch, L.; Mahlknecht, A.; Bauer, U.; Nestler, N.; Hempel, G.; Osterbrink, J.; Flamm, M. The Challenge to Define a Relevant Change in Medication Appropriateness Index Score in Older Adults – An Approach. *Br J Clin Pharmacol* 2020, *86*, 398–399, doi:10.1111/bcp.14167.

123. Hanlon, J.T.; Schmader, K.E. The Medication Appropriateness Index at 20: Where It Started, Where It Has Been, and Where It May Be Going. *Drugs Aging* 2013, *30*, 893–900, doi:10.1007/s40266-013-0118-4.

124. Lund, B.C.; Carnahan, R.M.; Egge, J.A.; Chrischilles, E.A.; Kaboli, P.J. Inappropriate Prescribing Predicts Adverse Drug Events in Older Adults. *Annals of Pharmacotherapy* 2010, *44*, 957–963, doi:10.1345/aph.1M657.

125. Rottenkolber, D.; Hasford, J.; Stausberg, J. Costs of Adverse Drug Events in German Hospitals - A Microcosting Study. *Value in Health* 2012, *15*, 868–875, doi:10.1016/j.jval.2012.05.007.

126. Price, E.; Shirtcliffe, A.; Fisher, T.; Chadwick, M.; Marra, C.A. A Systematic Review of Economic Evaluations of Pharmacist Services. *International Journal of Pharmacy Practice* 2023, *31*, 459–471, doi:10.1093/ijpp/riad052.

127. EuroQol Group EQ-5D-3L Available online: https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-3l/ (accessed on 10 August 2025).