Models to optimise medication safety in elderly and oncology inpatients

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Abbreviations

ABDA	Federal Union of German Associations of Pharmacists (Bundesvereinigung Deutscher Apothekerverbände)
AC	APS-Doc® category “administration/compliance” nowadays called “adherence”
ADL	Activities of Daily Living
ADR	Adverse drug reactions
ADT	Working Group of German Tumour Centres (Arbeitsgemeinschaft Deutscher Tumorzentren)
AE	Adverse event
AMTS	Medication safety (Arzneimitteltherapiesicherheit)
AP	APS-Doc® category “administration”
APS-Doc®	German drug-related problem classification system for the hospital setting
ASCO	American Society for Clinical Oncology
BfArM	German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
B	Coefficient estimates
BMG	German Federal Ministry of Health (Bundesministerium für Gesundheit)
BMI	Body Mass Index
ca.	Circa, approximatelly
CDSS	Clinical decision support system
CDT	Clock Drawing Test
CG	Cockcroft-Gault
CGA	Comprehensive Geriatric Assessment
CHD	Coronary heart disease
CI	APS-Doc® category “contraindication”
CI	Confidence interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cr	Clinically relevant
CrCl	Creatinine Clearance rate
CRF	Case Report Forms
CTCAE	Common Terminology Criteria for Adverse Events

CTx	Chemotherapy
DART	Drug Associated Risk Tool
DDI	Drug-drug interactions
DI	Drug interactions
DKG	German Cancer Society (die Deutsche Krebsgesellschaft)
dl	Decilitre
DLBCL	Diffuse large B-cell lymphoma
DRP	Drug-related problem
DRR	Drug-related readmissions
DokuPIK®	System for documenting pharmaceutical interventions in the hospital setting (Dokumentation Pharmazeutischer Interventionen im Krankenhaus)
DOS	APS-Doc® category “dosage”
DRG	Diagnosis-related group (classification system of hospital cases)
DS	APS-Doc® category “dosage form/drug strength”
e	mathematical constant approximately equal to 2.718
e.g.	For example (exempli gratia)
ECOG	Eastern Cooperative Oncology Group
EK	Ethic Committee (Ethikkomitee)
EMA	European Medical Agency
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration
g	Gram
GFR	Glomerular Filtration Rate
GEKID	Association of Population-based Cancer Registries in Germany (Gesellschaft der epidemiologischen Krebsregister in Deutschland)
HFS	Hand-foot syndrom
HSCT	Hematopoietic stem cell transplantation
I	Item value
i.a.	Inter alia, among others
IADL	Instrumental Activities of Daily Living
IBM	International Business Machines Corporation
ICD	International Statistical Classification of Diseases
IND	APS-Doc® category “indication”
INR	Prothrombin time

IOM	Institute of Medicine
I_{pr}	Implemented pharmaceutical recommendations
IR	Implementation rate
IR	Incidence rate
IQR	Interquartile Range
kg	Kilogram
l	Liter
λ	Incidence rate per time unit
λ_o	Baseline incidence rate
m	Meter
µ	Micro (a factor of 10^{-6} in the metric system)
µ	Mean of expected DRP
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Mediq®	Interaction software in German language
mg	Milligram
min	Minute, Minimum
ml	Millilitre
MMSE	Mini-Mental State Examination
MRC	Medical Research Council
MSR	Medication safety review
n	number of items
NaCl	Sodium chloride chemical formula
NCC-MERP	National Coordinating Council for Medication Error Reporting and Prevention
NCI	National Cancer Institute
O	APS-Doc® category “other”
OTC	Over-the-counter
p	Potential
P	Probability
p-value	probability value, calculated probability
PI	Pharmaceutical intervention
PIM	Potentially inappropriate medication
PCNE	Pharmaceutical Care Network Europe
PR	Pharmaceutical recommendation
PRO	Patient-Reported Outcome

PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PROBE	Prospective Randomised Open, Blinded End-point
R-CHOP	Therapy treatment: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-EPOCH	Therapy treatment: rituximab, etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone
RA1	Research assistant 1
RA2	Research assistant 2
RCT	Randomised controlled trial
RS	Raw score
RTx	Radiotherapy
RWTH	Rhine-Westphalian Technical University (die Reinisch-Westfälische Technische Hochschule)
Rx	APS-Doc® category “drug”
S	Second
Scr	Serum creatinine
SOP	Standard Operating Procedure
SP	Study pharmacist
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SPSS	Statistical Package for the Social Sciences
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TDM	Therapeutic Drug Monitoring
T_{pr}	Total number of pharmaceutical recommendations provided
T	Offset
UK	United Kingdom
UKA	University Hospital RWTH Aachen (das Universitätsklinikum RWTH Aachen)
US	United States
VES-13	Vulnerably Elderly Survey
WHO	World Health Organization
X	Influential factors
ZfKD	German Centre for Cancer Registry Data (Zentrums für Krebsregisterdaten)

Preliminary note

The thesis is conducted in cooperation with the pharmaceutical care research group (at the clinical pharmacy department of the pharmaceutical institute of the University of Bonn, Germany) and the medication safety research group (hospital pharmacy of the University Hospital RWTH Aachen, Germany).

For the sake of clarity and to improve readability the use of the female form was largely forgone in the present study (e.g. the patient is referred to as “he”). Generally the respective wording also contains the female form. The two terms medicine and drug are used interchangeably. Furthermore, the author of this work was anxious to consider the copyright of all used texts, figures and data.

1 Introduction

Medicines have always been a mainstay of medical treatment for variety of different diseases. Physicians in Germany prescribed a total of 852 million drugs in 2015 [1]. As a matter of fact, there is additional large number of over-the-counter (OTC) drugs obtained in pharmacy without prescription. In total, more than 1.4 billion drug packages were delivered in Germany in 2015, of which 37 % were OTC drugs [2].

Before a drug is available on any market, it has to undergo a drug approval process by the ruling authority of a government. For instance, in the United States (US) there is the Food and Drug Administration (FDA), in European Union is the European Medical Agency (EMA) and in Germany there is the Federal Institute for Drugs and Medical Devices[1] (BfArM). During the approval process, ruling authority assesses and confirms the efficacy, safety and quality of respective medicinal product. Subsequently, the medicinal product enters the market and it can be prescribed [3-5].

Nevertheless, authorisation of medicines by the ruling authority does not imply that medicinal products on the market are risk-free. Any pharmacologically active drug may have side effects, so-called adverse drug reactions (ADRs). ADR is defined as a response to a drug that is noxious and unintended. It occurs at doses normally used [6, 7]. ADRs can be unavoidable in the intended use due to drug active mechanism. An example of this is the alopecia in chemotherapy, e.g. with doxorubicine. On the contrary, there are avoidable ADRs occurring when a drug is used incorrectly. Apart from ADRs, there are further problems and situations that may occur during the course of drug use. Any event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes is together defined as drug-related problem (DRP) [6, 7]. DRPs are ADRs, various types of interactions, under- or overdosing and non-adherence. Besides, DRPs include use of a drug without indication, absence of a drug despite an existing disease, inappropriate drug selection for certain high-risk patient group or existing contraindications. If a DRP could be avoided, i.e. an ADR that can be prevented by correct dose adjustment, then it is considered as medication error [6, 8]. To a great extent, medication errors are caused due to complexity of the entire medication process. Medication process includes, by definition, all stages of drug therapy from medication history to drug prescribing, patient counselling, OTC,

[1] German: Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM

drug distribution, delivery, administration, documentation, therapy monitoring and testing, as well as communication, medication reconciliation up to the outcome evaluation [6]. In different levels of the medication process, different participants are involved such as physicians, pharmacists, nurses, caregivers, relatives and patient himself. Each participant serves as a safety barrier, but at the same time as a potential hazard for development of a medication error [9]. A set of measures to ensure optimal medication process with the aim of reducing medication errors and thereby avoidable risks for a patient in drug therapy, is defined in Germany as **medication safety**[2] (AMTS) [6].

The global attention was drawn to medication safety at the beginning of the millennium when in 2000 the US Institute of Medicine (IOM) published the report "To Err Is Human: Building a Safer Health System". The report presented evidence demanded considerable improvement in patient safety. For the first time the frequency of preventable medical errors in the health care system was described. Two out of 100 patients admitted to American hospitals encounter preventable ADR, and up to 98,000 patients/year in the US die because of medical errors [10]. The subsequent report of the IOM estimated that 1.5 million preventable ADRs occur each year [11]. In the report from 2008, the World Health Organization (WHO) has also addressed the issue of patient safety underlining the need for research and intervention in the field. According to the report estimates between 7.5 % and 10.4 % of patients in acute care settings experience an ADR. ADRs alone lead annually to 140,000 deaths in the US. Further, the WHO estimated that from 28 up to 56 % of ADRs are preventable [12]. Results of a prospective observation study of 18,820 patients from England showed 6.5 % prevalence of ADRs leading to the hospital admission [13]. German ministry of health has recognised the problem and extrapolated that there is no difference between western countries, such as the US or the United Kingdom (UK) and Germany, regarding medication errors and ADRs [14]. A longitudinal analysis of routine ICD-10 data from 2003 to 2007 showed that an ADR complicated more than 5 % of hospital stays in Germany [15]. The modelling approach from 2007 estimated that total health care costs related to ADRs in outpatient care in Germany were € 816, where the mean cost per case was € 381. This illustrates the great potential for cost savings through increased medication safety [16]. The most frequent reported medication errors are

[2] German: Arzneimitteltherapiesicherheit (AMTS)

incorrect dosing, particularly disregarding renal function, then non-consideration of contraindications, neglecting allergies and various drug interactions [17].

Concepts to reduce medication therapy risk: medication safety

Available data on medical errors and drug-related problems is growing. Medication therapy is recognised as a high-risk process. As a result, nationally and internationally the development of concepts and strategies for risk reduction and patient safety is promoted.

In 2004 the World Alliance for Patient Safety was launched to improve patient safety worldwide and strengthen research in this area. For the first time heads of agencies, health policy-makers, representatives patients' groups and the WHO came together to advance the patient safety goal of "First do no harm", and reduce adverse health and social consequences of unsafe health care. Among other things, recommendations included more active patient involvement in the therapy and adequate patient education and counselling related to the medication therapy [18]. In 2017, WHO launched a global initiative The Global Patient Safety Challenge on Medication Safety to reduce severe, avoidable medication-associated harm world-wide by 50 % over the next five years. The Challenge aims to make improvements in each stage of the medication use process including prescribing, dispensing, administering, monitoring and use. WHO works toward providing guidance and developing strategies, plans and tools to ensure that medication process has the safety of patients at its core, in all health care facilities. Besides, the focus is to increase awareness among patients about risks associated with the improper use of medication [19].

The IOM published the report about preventing the medication errors. Besides electronic prescribing, they recognised pharmacists' participation in clinical rounds in hospitals and in medication management in outpatient care as effective prevention strategy. The report calls for a patient-oriented treatment where patients and corresponding medical care providers collaborate as partners, and patients continuously provide necessary information for safe and effective drug usage. Other recommendations were maintaining a complete list of patient's medications as well as checking their accuracy and appropriateness on a regular basis [11]. Recent Cochrane systematic review indicated medicines self-monitoring and self-management programmes were effective to improve medicines use, adherence, adverse events and clinical outcomes. The intervention to prevent ADRs and improve other key medicine-related outcomes had a pharmacist involved in medication management, medicines reviews and phar-

maceutical care services. However, the review underlined that this favourable intervention requires further investigation in order to be more certain of its effect [20].

In addition to transformation of care from provider-centred to patient-centred, models of care need to move from reliance on independent, individual performance excellence to interdependent, collaborative, multi-professional teamwork [21]. That represents a central point to enhance patient and medication safety [21, 22].

In Germany, the Federal Ministry of Health[3] (BMG) took the decisive step in 2007 to promote medication safety. They published the first action plan for improvement of medication safety. The aim was an establishment of a safety culture by raising awareness of risks of medication therapy, increasing cooperation between physicians and pharmacists, improving information on medicines, developing and implementing strategies for preventive risk management and initiating research on medication safety [14]. The action plan was valid for 2008 and 2009 and was then revised in two-year cycles. The current action plan was presented in June 2016 and is valid from 2016 until 2019. The focus of the current action plan is to foster awareness of medication safety among patients, physicians, pharmacists and caregivers, to improve information on medicines and intersectional communication about drug therapy as well as facilitation of medication safety research. A central point represents the need for greater involvement and information of the patient with regard to his medication therapy [22].

In 2012, the German Advisory Council for the Evaluation of Development in Health Care[4] published a special report. They concluded that cross-sectional care in the field of medication therapy can only be guaranteed if physicians have a complete overview of all currently used medicines. That includes OTC medication and, in some cases, also medicines formerly taken, e.g. cytostatic agents in tumour patients. The prerequisite for a safe medication therapy is a comprehensive drug history with review of interactions, dosages and dosage forms based on patient-specific characteristics. That implies characteristics such as renal function, weight, age, allergies and living conditions. Therefore, this information should be available in a standardised and clear format across sectors [23].

[3] German: Bundesministerium für Gesundheit (BMG) der Bundesrepublik Deutschland

[4] German: Sachverständigenrat zur Begutachtung der Entwicklung im Gesundheitswesen

There are activities with the same direction on the federal state level, too. For instance, the regional health conference in North-Rhine-Westphalia in 2012 addressed the importance of medication safety. In support with the regional Ministry of Health, specific recommendations for action were developed. Recommendations urged for implementation and evaluation of multi-professional models to ensure medication safety. Thereby, they drew attention to the value of a complete medication record and clearly defined roles within the multi-professional teams, especially for patients with polypharmacy [24] (commonly reported as use of five or more medications daily [25]). Further, in order to ensure adequate medication safety they defined the aim of pharmacotherapy management. The aim was precise allocation of tasks and responsibilities to all participants in a team. The task allocation should be in accordance with the complete medication record that is individually adjusted to each patient [24].

The coordinating group on implementation and updating of the action plan for improvement of medication safety[5] in Germany published a memorandum on research development in this field. Objectives of medication safety research included development of risk-minimizing interventions and implementation of effective interventions in the routine service. Special emphasis was laid on collaboration within medication process adjusted to requirements of the routine service [26]. One already successfully implemented measure is development of a uniform patient medication record. The uniform medication record was standardised on the national level [27]. From October 2016, the German Federal Government on E-Health Act has initiated that every insured person in Germany who receives at least three prescribed drugs at the same time is entitled to the standard national medication record issued by a physician [28]. On the other hand, there is still great room for improvement in terms of successful collaboration of multi-professional teams working in the medication process that is optimally adjusted to requirements of the routine service.

[5] German: Koordinierungsgruppe zur Umsetzung und Fortschreibung des Aktionsplans zur Verbesserung der Arzneimitteltherapiesicherheit in Deutschland (Aktionsplan AMTS)

2 Model I

Multi-professional medication safety model reducing drug-related readmission in care-dependent elderly - study protocol

2.1 Introduction

Background and rationale

In response to the National Research Council's report "To Err Is Human: Building a Safer Health System" considerable effort is undertaken to restructure the hospital environment to reduce risk of medical errors and maximize quality of healthcare delivery [10]. Quality driven improvements in health care have brought patient and medication safety into sharp focus. In patient-oriented health care high priority was given to reduction of errors and harm from medicines based on their safe use [29]. The German Ministry of Health (BMG) has recognized the relevance of medication errors for health care and published already four action plans to improve medication safety in Germany [22].

All medications carry risk of an ADR, but elderly patients are more prone to ADRs due to an increased disease burden and a corresponding complex medication therapy in conjunction with deteriorating organ function [30]. At least one in ten elderly patients will experience an ADR during their hospital stay [31]. In the US, patients with ADR had higher risk of spending additional days in the hospital and the adjusted median monthly cost of care was 1.90 times higher [32]. Moreover, poor communication of medical information among caregivers at transition points from inpatient to outpatient care was responsible for up to 20 % of ADRs [29]. Within the 45-day post hospitalisation period, 35 % of ADRs identified were deemed preventable, of which 32 % were characterized as serious [33]. In the UK, out of 100 patients readmitted to hospital within one year of discharge, 20 patients were readmitted due to a suspected ADR. Approximately 10 of these 20 patients exhibited ADRs, which were possibly preventable [34]. In Germany is estimated a rate of 3.8 % admissions where ADRs led directly to hospitalisation [35]. A German study on the internal medical ward estimated that the incidence of hospitalisation due to at least 'possible' serious outpatient ADRs was 3.25 %. Average treatment cost of a single ADR was € 2250. Considering the

proportion of 20 % of preventable cases this equals a saving potential of € 87 million per year [36].

There is clearly a need to reduce readmission rates to hospital. This is important in terms of patient care, medication safety and in relieving the burden on over-stretched hospitals. One of the essential strategies is to establish an active and effective collaboration model amongst health care professionals. The multi-professional collaboration represents a complex intervention consisting of several interacting components regarding behavioural adaptation required by those delivering or receiving the intervention and a certain degree of flexibility in the form of the designed intervention [37-39].

The worldwide attempts to evaluate and implement different multi-professional medication safety models in the hospital setting confirm how challenging the task is. Randomised controlled studies evaluating collaborative models with integrated medicines management service showed a reduced length of the hospital stay and prolonged time to readmission [40-42]. Further studies revealed more appropriate use of medicines during and after the hospital stay, improved patients' health-related quality of life [41], even 80 % reduction of drug-related readmissions and considerable economic benefit in one Swedish study [43]. A key benefit of these services was intra- and inter-sectorial partnership established between patients, their caregivers and a number of health care professionals [41, 43]. In Denmark, however, collaborative model with systematic medication review and medication counselling did not show any effect on in-hospital length of stay, readmission or mortality of elderly patients in a randomised control study. Interesting and quite likely critical point is relatively low clinicians' acceptance of medication changes recommended by clinical pharmacists and clinical pharmacologists. Less than half of the provided drug counselling resulted in changes in patients' medication. This fact has weakened the effect of the intervention and probably influenced study results in the direction of no difference [44]. Finally, a recent Cochrane systematic review of complex interventions using medication reviews in the hospital setting indicated uncertain evidence for their effect on mortality and hospital readmissions. However, the number of emergency department contacts was reduced compared to the standard care. The authors concluded that there is a need for new multi-professional medication safety intervention trials focussing on high-risk populations. The team performing medication review should include members that are competent to change patient medications. Moreover, well-described methods when conducting

the medication review, a long-term follow-up and a ward- or team-based cluster randomisation should be used [45].

Substantially highlighted evidence confirms that the diversity of methodological approaches and variability in individual level outcomes make it extremely hard to ensure strict standardisation of multi-professional medication safety models. Those practical and methodological struggles that any successful evaluation must overcome, have led to a consensus (i.e. the Medical Research Council (MRC) framework) among health science researchers in form of guidelines for the development and process evaluation, and criteria for evaluation of complex interventions [37-39]. In accordance with the consensus, the complex intervention of a multi-professional medication safety model may work best if tailored to the local circumstances. There are numerous studies describing the status quo, consequences and potential solutions of DRPs in German hospitals. Many German hospitals have started improving the local services to reduce DRPs and enhance medication safety. Examples were shown in the field of cardiology concerning better medication adherence [46], less readmissions in patients with ischemic stroke [47] and better quality of life for oncology patients [48].

To the best of our knowledge, there is no project in Germany which has developed and evaluated the multi-professional medication safety model in the hospital setting in order to comprehensively improve medication safety and quality of delivering healthcare by reduction of drug-related readmissions (DRRs). The project is at the University Hospital RWTH Aachen (UKA) where the basis of collaboration between physicians, nurses, pharmacists and patients was established through previous research work. The collaboration showed considerable potential and may undergo process evaluation.

Previous work on the model

Based on the evidence of medication safety issues in the existing literature worldwide, the need to determine local evidence was recognised. In the development study, a multi-professional medication safety model was proposed. The new complex intervention model (i.e. care team) had a pharmacist, in addition to the standard ward team of physicians and nurses. Thus, the collaborative complex intervention setting consisted of a patient, a physician, a nurse and a pharmacist having a close personal interaction, where the physician had the main responsibility and final decision about the patient's pharmacotherapy (Table 2.1) [49]. The model was assessed identifying DRPs on the

three medical departments at the UKA: urology, neurology and internal medicine III (gastroenterology and metabolic disorders) evaluation (Figure 2.1).

For 306 included patients 702 DRPs were detected. The collaborative multi-professional care team accepted 77 % of pharmacist recommendations on documented DRPs. The high acceptability and practicability of the model underlined benefit of multi-professional collaboration. As a result, a guideline for the comprehensive medication safety review (MSR) was developed [49]. The guideline represents a valuable contribution to the methodology of medication safety complex interventions. This guideline became part of the Standard Operating Procedure (SOP) for medication safety, developed for and used in the present evaluation study (Attachment Model I). It is, therefore, explained in detail in the section 2.2 Methods. Modelling the process showed patients' age and number of drugs as statistically significant risk factors [49]. Hence, in the further step focus was narrowed on elderly inpatients (patients 65 years of age or older). Results of initial testing in the development study encouraged further examination of model's key uncertainties in the pilot study. The key uncertainties were: feasibility of the intervention in other medical departments, on high-risk population, and effectiveness of the model on other patient-relevant outcomes during a long follow-up.

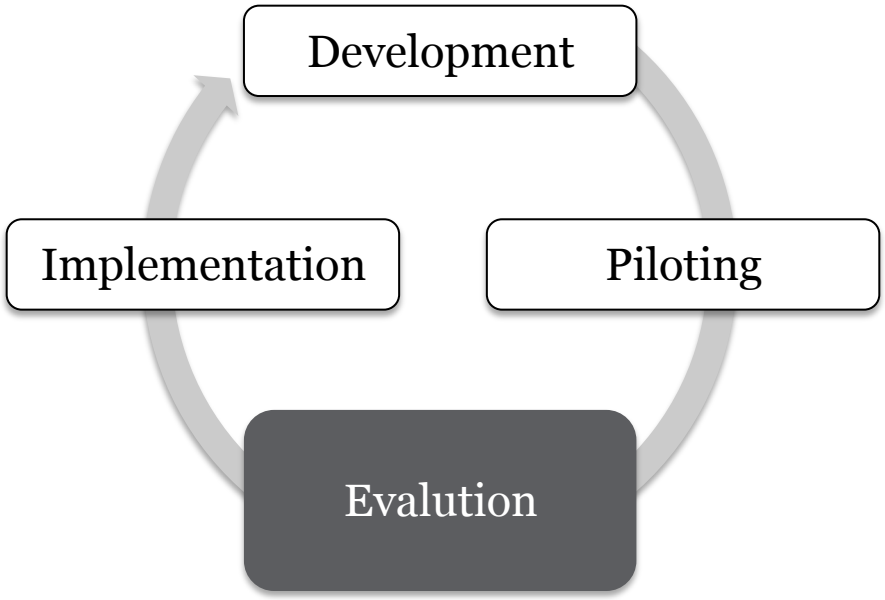


Figure 2.1: Development and evaluation process in accordance to the MRC guidelines

Table 2.1 Task description of each partaker of the multi-professional medication safety model

Partakers	Tasks of each partaker
Patient	Recipient of care continuously reporting and describing personal conditions, symptoms, feelings and wishes relevant to the treatment and drug therapy to the care providers
Nurse	A care provider who is a first 'inspector' of the patient treatment reactions, conditions and symptoms; continuously reporting them to attending physician and pharmacist, and applying physician's and pharmacist's recommendations according to the treatment plan
Pharmacist	A care provider who optimises use of medicines and improves health outcomes by providing pharmaceutical care [50] including a medication review based on medication history, medication reconciliation, medication safety checks, and recommendations on drug therapy to the medical team members
Physician	A care provider with main responsibility for provision of optimal and comprehensive medical care to the patient, working in close collaboration with other care providers; negotiates an agreement with the patient about the therapeutic objectives

Besides urology, neurology, internal medicine III (gastroenterology and metabolic disorders), another internal department was added at this stage: internal medicine I (cardiology, pulmonology and angiology) [51]. The intervention model and the comprehensive MSR were performed according to the previously defined assignments (Table 2.1) and guideline [49]. More suitable measures were chosen: preventable /ameliorable ADRs and DRRs. Preventable/ameliorable ADR is a fraction of DRPs that is potentially avoidable by medical teamwork. DRR represents a reliable patient-relevant, short- as well as long-term outcome. Follow-up period of 12 months was chosen [51]. Empirical evidence identified patients with dependent living situation as a vulnerable group for DRRs [52]. Hence, in the pilot study the focus was narrowed on nursing home residents and home-cared elderly admitted to the UKA [51].

Sixty participants were randomly assigned to either control group (standard care) or intervention group (multi-professional medication safety model). An independent and blinded outcome assessment panel made final decision on ADR causality, severity and preventability/ameliorability. In a two-step valuation procedure, the panel assessed 53 ADR-suspicious symptoms as ADRs. One third of ADRs was classified as preventable or ameliorable. Thirteen DRRs occurred during 12-month follow-up (7 patients in the control group vs. 3 patients in the intervention group – one patient in the intervention group was readmitted three times to the hospital). The time to DRR was longer in the intervention group than in the control group (1-year readmission rate under intervention: $\pi_{Intervention} = 0.1$; 1-year readmission rate under standard: $\pi_{Standard} = 0.3$; Figure 2.1: Log-rank-test, $p = 0.0684$). Statistical significant risk factors for DRRs were age, duration of initial hospital stay, and number of medication changes after discharge during 12-month follow-up. After adjusting for significant risk factors the multivariable Cox Proportional Hazard Model showed that the control group patients had 5.588 times more risk (Hazard Ratio = 5.588) to experience a DRR ($p = 0.0247$; KI: 1.245 – 25.085) [51, 53]. These results provided strong motivation to extend the study into an evaluation phase.

The multi-professional medication safety model, however, showed no difference in the number of medication changes, and in the number and type of potentially inappropriate medication. Further, there was no difference between treatment groups in the number and time-related occurrence of ADR [51, 53].

A notable tendency of reduction of DRR in the pilot study outlines a positive impact of the multi-professional approach on patient and medication safety. It calls to perform a full-scale evaluation of the multi-professional medication safety model in a larger study. Finally, the proposed model includes all currently lacking parameters in the existing literature recommended for future trials of complex interventions in the hospital setting [45].

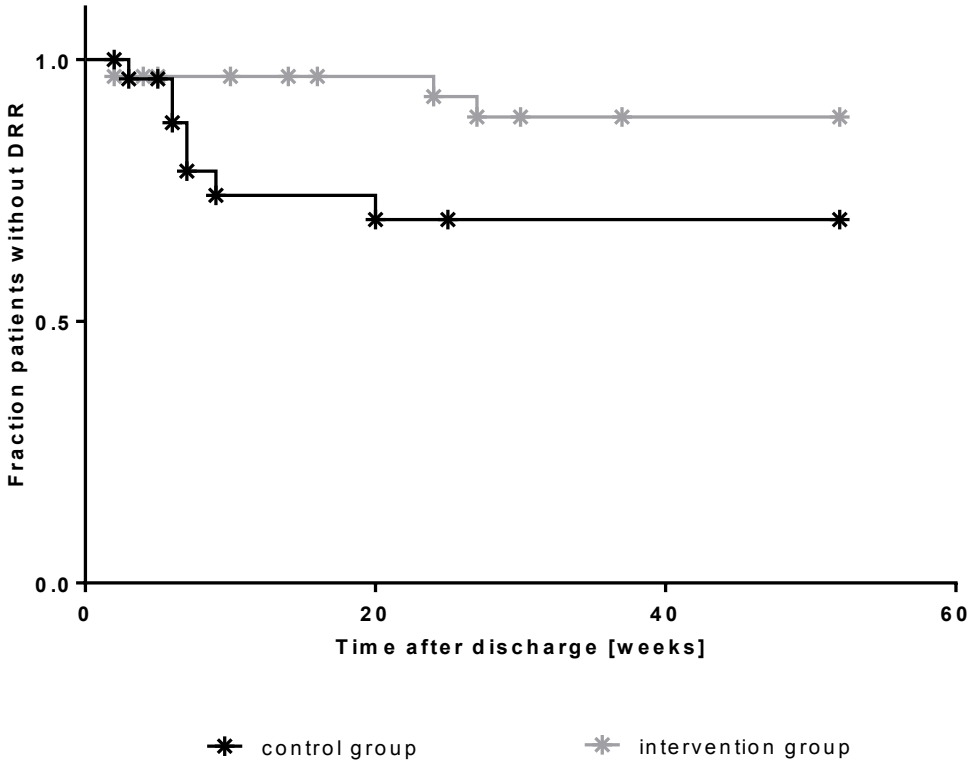


Figure 2.1: Kaplan-Meier-plot of the intention-to-treat-analysis for the primary outcome drug-related readmissions [51]

2.1.1 Objectives

The study aim is to assess the effectiveness and to evaluate the quality of the multi-professional medication safety model in the hospital setting.

Scientific objectives are:

1. To assess whether the **multi-professional medication safety model affects the time to DRR** (primary outcome);
2. To assess whether the multi-professional medication safety model affects the number of DRR (secondary outcome);
3. To evaluate the value of the multi-professional medication safety model to detect and resolve preventable or ameliorable ADRs (secondary outcome);
4. To evaluate the quality of the multi-professional medication safety model in light of internal model interaction and communication (secondary outcome).

2.2 Methods

The present study protocol is prepared according to the SPIRIT outline [37, 38]. The study is an open randomised controlled trial (RCT) supplemented by a qualitative evaluation of the intervention. The study consists of a holistic approach using quantitative methods to measure effects and qualitative methodology to assess interaction patterns and communication customs between partakers of the model.

The RCT part of the evaluation study represents PROBE design (Prospective Randomised Open, Blinded End-point) because it is a prospective study, which uses randomisation and has an open-label and blinded endpoint (i.e. outcome). Integrating qualitative methodologies in this case implies studying individuals in their natural setting to explain behaviour pattern. The mixed-methods approach uses multiple ways to explore the research problem and overcomes the limitations of a single design. Methods are combined in a way that enables gradual accumulation of know-ledge of how the intervention is delivered, and how and why it works (triangulation).

Study setting

The project is conducted in the academic hospital, UKA in Germany, on the four study departments: urology, neurology, internal medicine III (gastroenterology and metabolic disorders) and internal medicine I (cardiology, pulmonology and angiology). The study departments are the same as in the pilot study [51]. In hospitals team members can have daily in-person contact. Close contact of team members should assist in implementation of the multi-professional medication safety model in the routine practice.

2.2.1 Patient recruitment

Patients who fulfil the inclusion criteria are eligible to enter the study. The criteria is identical to the one in the pilot study [51]. In case of patient's mental disorder, their caregiver may be a surrogate decision maker. Beside the failure to meet inclusion criteria or unwillingness to participate in the study, patients will be excluded if they have already entered the study during preliminary stages.

The inclusion criteria:

- Patient is hospitalised at one of the project departments: urology, neurology, internal medicine III (gastroenterology and metabolic disorders) and internal medicine I (cardiology, pulmonology and angiology),
- Patient is 65 years of age or older,
- Patient requires daily-provided care (i.e. dependent living situation: nursing home/home-cared patients/Care Level I, II, III),
- Patient must stay a minimum of three days at UKA hospital,
- Patient has an existing medication therapy on admission,
- Patient gives an informed consent.

Recruitment procedure and Informed Consent

A recruitment procedure is planned for 12 months. The procedure and supporting documentation (information sheets and informed consent) are prepared according to the German legal requirements. Regular medical team on study wards informs their patients about the existing study and encourage their participation. Afterwards, the research assistant 1 (RA1) performs the structured recruitment interview in a way that the rights of potential participants are respected. Patients are verbally informed by RA1 as to what their participation involves and how the data is used. They have an opportunity to ask questions and considerably enough time to make their decision. Participation is voluntary. Patients are free to accept an invitation to participate in the project, as well as to opt out at any time. Stopping the participation would not affect further medical treatment, health care nor their rights in any way. Informed consent and project information leaflet are provided during the structured recruitment. Willingness to participate in the study and permission for data procession is confirmed by a written informed consent. For all patients who decide not to participate in the study, reasons are documented.

Sample size

Bio-statistical group of PD Dr. Nicole Heussen (UKA) performed the sample size calculation based on the results of the pilot study [51]. It was assumed a 1-year-readmission rate under intervention of 0.1 (exponential hazard 0.1054) compared to a 1-year-readmission rate under standard of care of 0.3 (exponential hazard 0.3567). All patients are simultaneously followed for one year. During the study period an expected dropout rate is 20 %. Acting on these assumptions, sample size of 69 patients per

group (i.e. 138 patients altogether) is required to obtain a power of at least 80 % for the Log-rank test comparing two survival curves with two-sided significance level of 5 %. All patients in the intervention group (69) are potential participants in qualitative assessment.

Randomisation

Block randomisation is implemented to secure unbiased effect estimates. The study is placed on four clinical departments with structural differences. The department differences have influenced DRP patterns in previous work [49]. As a result, randomisation is stratified with regard to the participating study clinical departments. Due to the low number of comparable study departments, there is no cluster randomisation.

After successful recruitment in the study, stratified blocked randomisation takes place. Randomisation list is generated using the R package randomizeR [54]. RA1 randomly assigns patients to either an intervention group or a control group. Implementation of randomisation is performed via opaque sealed envelopes.

Contamination effects

The risk of contamination effects between control and intervention patients is low because of the individualised pharmaceutical intervention (PI). Pharmacists have a special training before the study begins. The research team has an appropriate training too, in order to handle requests of control-group patients in a clear and respectful way. The research team provides sustained contact to control-group patients during their hospital stay.

Blinding

It is a non-blinded study. Nature of the intervention in the intervention group – patients' counselling, patients' education and close collaboration between ward-base members – does not allow the blinding of any of ward-team members (patients, physicians, nurses, pharmacists). Non-blinded study needs an objective assessment of the primary outcome. Therefore, an independent and blinded review committee performs the outcome assessment (2.3.3 Outcome assessment panel).

2.2.2 Participant timeline

The following schematic diagram (Table 2.2) represents the participants' timeline.

Table 2.2: Participant timeline

	STUDY PERIOD								
	Enrolment	Allocation	Post-allocation						Close-out
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	t_7
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
INTERVENTION GROUP:									
Medication history			X						
MSR			←	—	→				
Case conference			←	—	→				
Discharge counselling					X				
Patient interview					X				
Follow-up examination						←	—	—	→
CONTROL GROUP:									
Follow-up examination						←	—	—	→
ASSESSMENTS:									
Study geriatric assessment	X								
OUTCOME VARIABLES:									
ADR-suspicious symptoms			←	—	—	—	—	—	→
PIM				X					
DRP (intervention group only)			X	X					

Legend: MSR – medication safety review, ADR – adverse drug reaction, PIM – potentially inappropriate medication, DRP – drug-related problem, -t_1 – admission tot he UKA hospital, t_1 – within the first three days of the hospital stay, t_2 – inpatient stay, t_3 – hospital discharge, t_4 – one week after the hospital discharge, t_5 – two months after the hospital discharge, t_6 – six months after the hospital discharge, t_7 – 12 months after the hospital discharge

2.2.3 Geriatric assessment

Supplementary to physicians' and nurses' routine assessment of elderly patients, RA1 performs a geriatric assessment for all the recruited patients. The geriatric assessment in the study includes: functional assessment using the Vulnerably Elderly Survey score [55], cognitive assessment with the Mini-Cog tool [56] and ADR assessment with the GerontoNet ADR risk score [57]. The Vulnerably Elderly Survey identifies elderly patients at risk for health deterioration considering age, self-rated health, and limitations in physical function, and functional disabilities [55]. The Mini-Cog is a brief and sensitive screening tool designed to identify individuals at high-risk for dementia. It combines two simple cognitive tasks (three-item word memory and clock drawing) with an empirical algorithm for scoring [56]. The GerontoNet ADR Risk score helps identify elderly inpatients at risk of an ADR. It contains information about comorbidity, number of drugs, renal failure, heart failure, liver disease and previous ADRs [57].

2.2.4 Control group

Participants randomly allocated to the control group are treated according to the current medical standard of care, where a ward-based medical team includes physicians and nurses. Pharmacists are not included in the team. RA1 is responsible for control group patients and maintains a regular daily contact with them. Daily visits are part of patient retention strategy. RA1 documents ADR-suspicious symptoms and potentially inappropriate medication (PIM) from the PRISCUS list [58]. If any symptom of a serious or life threatening ADR occurs, the research team discusses the case with an attending physician. Shortly before the patients' discharge, RA1 meets the control-group patients and prepares them again individually for the upcoming follow-up.

2.2.5 Intervention group

Participants randomly allocated to the intervention group, are treated according to the multi-professional medication safety model. The complex intervention model, besides physicians and nurses, has a study pharmacist (SP) as an integrated part of the ward-based multi-professional health care team (Attachment Model I: SOP for medication safety). The SP provides pharmaceutical care throughout the patient's hospital stay. Pharmaceutical care is patient-centred, structured intervention that includes a close collaboration with other ward-based team members, as well as patients and their care-givers. It consists of different activities described in the following paragraphs.

Admission in this study represents the period of first three days in the hospital. It is t_1 in the participant timeline (Table 2.2), where medication history, and first medication safety review and case conference take place.

Medication history

Up on arrival on the study ward, SP assesses every study patient and takes his medication history. Medication history is the most accurate list of all home medications, prescribed and OTC drugs (including drug name, dosage, frequency, and route of administration), and the history of medication use (any known previous DRP). Various information sources are used to facilitate the accuracy of the medication history list e.g. patient's medical records in the hospital, prescriptions from primary care centres, communication with the responsible nurse, as well as communication with a patient and his caregiver.

Medication Safety Review

After completing the medication history, SP performs a comprehensive Medication Safety Review (MSR). In the MSR, patient's pharmacotherapy is reviewed and assessed according to the SOP for medication safety (Attachments Model I). For every DRP detected in the MSR that leads to PI, SP prepares pharmaceutical recommendation (PR).

The comprehensive review consists of certain assignments. Main assignments of the review are based on the guideline established in the development study [49]. Detailed description is presented in the SOP for medication safety (Attachments Model I):

1. Medication reconciliation: comparison of home medication list against the physician's admission order
2. Diagnosis-medication plausibility check
3. Search/check for known patient allergies
4. Review of renal function values
5. Review of hepatic function values
6. Review of all relevant laboratory values
7. Review of medication plausibility and contraindication
8. Review of drug dosages, interactions, adherence to the relevant guidelines, PIM;
9. Preoperative medication management
10. Review of medication in terms of planned examinations during the hospital stay
11. Check on duration of medication therapy
12. Patient counselling and education about medication, particularly about newly prescribed ones
13. Therapeutic Drug Monitoring (TDM) for drugs with a narrow therapeutic range

Case conference

The comprehensive MSR results in understandable and specific recommendation on each DRP leading to PI. From PRs it should be clear from which source the advice is based on. PRs are documented and added into the patient medical record. Furthermore, SP discusses the recommendation on patient's medication with the attending physician, and if needed with the attending nurse too, as part of a case conference. The case conference is performed during the routine work of attending physicians and nurses. As the patient's viewpoint is actively sought, the advice (PR) is given in a patient-centred manner. Lastly, the attending physician makes the final decision regarding the patient's medication.

Inpatient stay in this study represents patients' time in the hospital. It is t_2 in the participant timeline (Table 2.2), where SP performs comprehensive pharmaceutical care. Any change in the patient's pharmacotherapy calls for additional MSR (see above: Medication Safety Review) and adjustment of the medication plan. Should any DRP occur, SP assesses it. When the PI is needed, the DRP is documented and appropriate recommendation is provided. Accordingly, PRs are discussed with attending physicians and nurses (see above: Case conference) and the patient is counselled.

Discharge in this study represents the last two days in the hospital. It is t_3 in the participant timeline (Table 2.2). Before leaving the hospital, the study patient meets

SP again for a discharge counselling. The discharge counselling aims at educating the patient on changes in the medication plan and what should be considered in following ambulatory care. SP provides PR to the attending physician, too. It is proposed to add PRs in a discharge letter. The attending physician decides whether PRs are part of the discharge letter and has the responsibility to hand over the discharge letter to the patient. At discharge, research assistant 2 (RA2) interviews patients in the intervention group (2.2.7 Patient interview).

2.2.6 Follow-up

In order to assess the long-term effects of the multi-professional medication safety model, a 12-month follow-up is planned. It starts after the hospital discharge. RA1 contacts the study participants from both patient groups at four time points during the follow-up: one week after and then two, six and twelve months after the discharge. Time points in the follow-up schedule assessment are identical to those in the pilot study [51]. The schedule is developed after reviewing previous international studies and discussing it with the colleague [43] who successfully performed the follow-up study in the Swedish hospital.

Participants are asked about their current condition (including relevant vital parameters) and medication plan, laboratory test results, hospital visits and admission as well as reasons for admission (discharge letters when available), ADR-suspicious symptoms and any other new symptom/complaint (Table 2.3).

Dropout refers to a patient who has been originally recruited in the study, but withdrew before the completion of actual study time. Considering the low dropout rate of 1.6 % in the pilot study [51], it is unlikely that special measures are needed to adjust the drop outs.

Lost to follow-up refers to a patient who at one point in time was actively participating in the study, but was lost at the point of the follow-up. These patients can be lost for many reasons: they may have opted to withdraw from the study, they may have moved away from the particular study site during the study time, or became ill and unable to communicate or even passed away. In the pilot study [51] 20 out of 61 patients were lost to follow-up. In order to protect the patients and the integrity of the study outcome, RA1 should make a reasonable effort to ascertain reasons, while fully respecting

the rights of participating patients. If the cause of early cessation is independent of prognosis of the primary outcome, the data is considered as censored.

Table 2.3 Examinations during the follow-up period

EXAMINATIONS / TIME POINTS	Medication plan	Lab data	Hospital visit/ admission	ADR-suspicious symptoms	Any symptom/ complaint
1. One week after the discharge	✔	✔	✔	✔	✔
2. Two months after the discharge	✔	✔	✔	✔	✔
3. Six months after the discharge	✔	✔	✔	✔	✔
4. Twelve months after the discharge	✔	✔	✔	✔	✔

2.2.7 Patient interview

Individual assessment of patients' views and experiences in terms of communication with the model associates

Patient's perspectives are increasingly seen as important in informing the future of healthcare. Interviews provide an opportunity for this contribution. [59] All participants in the intervention group are potential participants for the individual interview. For those patients in the intervention group, where a caregiver as surrogate decision maker has signed the informed consent, the caregiver is a potential participant. At the hospital discharge, RA2 (further in this chapter referred as interviewer) provides to all participating patients or corresponding caregivers in the intervention group a semi-structured individual interview. This interview comprises both structured and open-ended questions. It represents the most appropriate interview form in this case, because it provides information on both: (a) predetermined structured measures and (b) a more detailed examination of pertinent views and experiences of participating patients.

(a) Quantitative evaluation of patients' satisfaction

Quantitative part of the interview contains closed questions about patients' satisfaction with the multi-professional model in terms of supervision and communication. Closed questions are documented in writing and have a range of predictable responses according to the five-point Likert rating scale [60], ordinal level.

(b) Qualitative evaluation of patients' experience and communication

Further, individual semi-structured interview contains open-ended questions about patients' experience and communication with the model. This part of the interview has an unpredictable range of responses. Participating patients or corresponding caregivers have an opportunity to express their own views in their own words [59]. According to the interview guide, qualitative enquiry provides a framework for the interview. The interview in the present study contains following open-ended questions and probing questions:

- Opinion/remark/comment about multi-professional team supervision
- Opinion/remark/comment about communication with the multi-professional team
- What would you particularly emphasize as an advantage of the teamwork?
- Have you experienced any difficulty in communication/supervision with physicians, nurses or pharmacists?
- What do you think has caused this difficulty?
- When did the difficulty occur?
- Has the difficulty with the medical team influenced your hospital stay?
- Did you consider taking any measures in order to solve the difficulty in communicating with the medical team?
- What would you improve in terms of communication/supervision of the multi-professional team?

If a patient tends to provide a very brief response, skilled interviewer (RA2) should ask for a clarification or more details in relation to any question so that the responses are more meaningful.

However, the actual direction and content of the interview in terms of discussed issues are determined by patients' experiences, views, and perceptions. The interviewer should discover what is important to the interviewed patient. It is up to the interviewer to use his skills to ensure that the interview fully explores these perspectives rather

than being influenced by his own agenda or preconceptions [59]. Finally, the interview is used to explore issues from patients' perspective in order to improve future communication between patients and multi-professional model associates. The individual interview with open-ended questions is digitally recoded and transcribed verbatim.

2.2.8 Focus group

Qualitative assessment of the multi-professional model interactions

A focus group is conducted to assess how the multi-professional model works. This group discussion is planned in form of a retreat after the intervention period is concluded. The retreat takes place outside of the daily setting, in a comfortable venue, free from distraction. Nine care providers are invited to participate: four clinicians and four nurses (one from each study department), and the SP. The interaction between participants that occurs in the focus group is the main difference in comparison with individual interviews and at the same time the key to a successful group discussion [61]. The interaction between contributing care providers may stimulate a wide-ranging discussion as participants stimulate each other. The care providers may change viewpoints on hearing arguments of the others. This is going to be used for generating information on collective views and meanings that lie behind those views, in order to gain an insight on how the model works. In the focus group, however, there may be a reluctance to express opposing viewpoints. Some participants may tend to dominate the discussion. Inevitably, as in any group there are more and less vocal members. Therefore, the facilitator (RA2) plans and adopts strategies and styles of questioning to promote and encourage wide participation, to elicit contribution from all participants, to value all contributions and treat all as equally valid [59]. The following interview structure is used:

Engagement questions: (1) How do you feel about working in the multi-professional model (in general)? (2) What do you consider as an advantage/disadvantage?

Exploration questions: (1) How do you assess communication within the model? Taking into account the way of interaction (face-to-face/E-mail/ phone), timing, colleague's motivation/interest in cooperation, equal and respectful partnership, and hierarchy. (2) Patient case discussion (a case from

	the intervention period, where the disagreement was met and reasons were not clear): where the disagreement occurred, why, how it was solved, what could be changed in the future. (3) Recommendations for the safety culture improvements within the model.
Exit questions*:*	(1) Is there anything else you would like to say about the function of the model?

The focus group is guided and monitored by a facilitator (RA2) trained in qualitative methods and guiding group discussions. The facilitator should facilitate group discussion, keeping it focussed without leading it. The co-facilitator (RA1) digitally records the focus group. In addition to the digital recording, notes are taken to document the non-verbal interaction. The recording is transcribed verbatim.

Patient is not part of the focus group because of the following aspects:

– Emotional – for the care-dependent elderly patients an additional meeting for the focus group after the official hospital discharge represents an emotional burden; even if the focus group takes place at the end of the hospital stay, which is the earliest possible point for its execution, an emotional burden caused by the prolongation of the hospital stay of patients is hardly favourable;

– UKA organisation – the focus group is not feasible during the time span when the intervention is provided and patients are hospitalised at the UKA, because of organisational issues of the daily health care routine and the additional intervention process.

2.3 Data management

Data collection

With the signed informed consent, patients' medical records are available for the project research team. All data is primarily collected in the Case Report Forms (CRFs) in paper form as in the pilot study [51] and then inserted into an electronic database that bio-statistical group of PD Dr. Nicole Heussen (UKA) has prepared particularly for this project stage of process evaluation. During the study process, the bio-statistical UKA group performs quality checks for the entered data in the database.

For the time being in the hospital, RA1 documents reasons for not participating in the study; and for participating patients demographic data such as age, gender; care and

living situation; weight and height; vital signs and laboratory values; functional status with the Vulnerable Elderly Survey [55]; cognitive status with Mini-Cog tool [56]; ADR risk factors such as comorbidity, number of drugs, liver disease, heart and renal failure, previous ADRs, with the GerontoNet ADR risk score [57]; reasons for admission; complete medication; ADR-suspicious symptoms and recommendation if needed (i.e. when the symptoms of ADR are present); PIM drugs from the PRISCUS list [58]; length of stay on the study department. RA1 treats all patients the same to assure reliability and validity of patient data.

Independently, SP has contact exclusively with the patients in the intervention group. For those patients, SP documents information about DRPs and PRs for DRPs; recommendations regarding PIM; acceptance of PRs by the physicians; time needed for the pharmaceutical care service.

RA2 digitally records patient interviews while RA1 records the focus group.

During the follow-up period the RA1 tracks and updates the medication plan, vital signs and laboratory values, document information about hospital visits, readmissions and ADR-suspicious symptoms of all patients in the same and predefined manner (2.2.6 Follow up).

Data monitoring

While the study is ongoing, RA1 is the person on-site to monitor the patient safety. If any symptom of a serious or life threatening ADR occurs, RA1 discusses the case firstly within the research team on-site, and then as quickly as possible with an attending physician.

Important step in the process of conducting the study is transcribing data from CRFs into electronic form. Double data entry will be applied. It is a widely used method consisting of two steps: an initial entry step and a verification step. An independent data-entry technician performs each step. Bio-statistical team of Ms Heussen supports the study at this stage, as they provide the electronic database too.

2.3.1 Study instruments

Vulnerably Elderly Survey (VES-13) [55] is an international function-based tool used to assess the risk of health deterioration of older adults by considering a number of factors including disabilities, age, self-reported health status and functional limita-

tions. This assessment is a 4-question, 13-item simple function-based questionnaire that is used in the study's geriatric assessment. *Validity:* The VES-13 correlates with the Comprehensive Geriatric Assessment (CGA) with a value of r = 0.4 and with the Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL) with a value of r = 0.5, showing it as a valid tool [62]. *Reliability:* Internal consistency for the VES-13 in the same study by Luciani et al. (2001) found a Cronbach's alpha of 0.9 when compared against the CGA. Sensitivity was reported to be 87 % and a specificity of 62% versus CGA, and 90 % and 70 % versus ADL/IADL scales. This shows that the VES-13 is a highly sensitive and predictive instrument of functional vulnerability.

Mini-Cog [56] is a brief, three-step cognitive screening instrument planned as a part of the geriatric assessment in the study. *Validity:* The Mini-Cog has proved to have a more superior discriminatory power (86.8 %) than either Clock Drawing Test (CDT) (72.6 %) or Mini-Mental State Examination (MMSE) (78.1 %) ($p < 0.01$ each) and had demonstrated to be the valid instrument to administer in the geriatric setting [63].

GerontoNet ADR risk score [57] is a practical tool for identification of elderly patients who are at increased risk for an ADR and a target for interventions aimed at reducing ADRs. The tool is used in the study's geriatric assessment. *Validity*: The area under the curve (AUC) showing an ability of the risk score to predict ADRs in the development sample was 0.70 (95 % CI 0.63 – 0.78) [57].

PRISCUS list [58] represents a list of potentially inappropriate medications for elderly patients. The list is defined particularly for the German market.

ID-Diacos® Pharma provides drug-interaction assessment as part of the local clinical decision support system (CDSS). Mediq® is a drug-interaction software for German speaking countries.

APS-Doc® [64] is a classification system for DRPs in the hospital setting in Germany. *Reliability:* Inter-ratter reliability in the same study was found to be substantial in the main categories (k = 0.68, 95 % CI 0.66 – 0.69) and moderate in subcategories (k = 0.58, 95 % CI 0.58 – 0.59). The tool is used during MSR in the intervention group.

2.3.2 Outcome variables

The following primary and secondary outcomes are defined as dependent variables for the quantitative analysis.

The primary outcome:

- Time to DRR during 12-month follow-up

The secondary outcomes:

- Number of DRRs during 12-month follow-up
- Number of ADRs during the hospital stay and 12-month follow-up
- Number of prescribed PIM drugs
- Number and type of DRPs in the intervention group
- Patient's satisfaction (Likert-type scale [60] as part of the patients' interview)

The following information will be used for qualitative analysis:

- Verbatim transcripts of patients' interviews
- Verbatim transcripts of the focus group

2.3.3 Outcome assessment panel

The ADR-suspicious symptoms and potential DRRs monitored for both patient groups are assessed further in an outcome assessment panel consisting of three external experts (outcome assessors). In the present study, ADR-suspicious symptoms were defined as symptoms occurring in plausible context of medication use including inherent ADRs, medication errors and changes in laboratory data in a clinically relevant manner. DRR was defined as re-hospitalization of a discharged patient due to an ADR in any hospital [53].

RA1 is responsible for organizing the panel. The research team and experts meet before the official start for an introduction of the outcome assessment procedure. The second meeting takes place after the data collection procedure is completed.

The outcome assessors are blinded. The procedure is planned as a two-step evaluation with an aim to characterise ADRs in terms of causality, severity and preventability/ ameliorability. The panel assesses ADR-suspicious symptoms and readmissions and

makes a final judgement. That means the panel assess whether ADR-suspicious symptoms are in fact ADRs and whether potential DRR are truly drug-related. The outcome assessment procedure uses the tools proposed in the pilot study [51, 53]. The ADR-suspicious symptoms are classified as 'no ADR', 'potential ADR' or 'ADR' according to Arimone et al. causality criteria [65]. The potential ADRs are further classified in seven causality levels: "ruled out", "unlikely", "doubtful", "indeterminate", "plausible", "likely", "certain". The causality levels "certain", "likely" and "plausible" are regarded as ADR. The approach from Schumock and Thornton [66] is used for assessment of preventability and ameliorability of ADRs. The preventable and ameliorable are finally categorised according to their severity using an algorithm from the National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) [67]. The algorithm has eight categories: from "no harm" through three "error, no harm" and three "error, harm" to the most severe one "error, death".

2.3.4 Statistical analysis

Statistical analysis is performed with support of the bio-statistical group of PD Dr. Nicole Heussen (UKA). The provided database uses pseudonymised data. RA1 is responsible for quantitative and RA2 for qualitative analysis.

The primary outcome is analysed using the stratified (by department) log-rank test. Sensitivity analysis uses the Cox-model (stratified by department) to assess the influence of single or groups of covariates (age, sex, living situation, comorbidity, length of stay on the study department, number of PIM, number of changes in medication during the follow-up, number of drugs during the stay on study department, GerontoNet ADR score, Vulnerable Elderly Survey score).

The analysis of the secondary outcomes is descriptive and explorative. It uses regression techniques (linear models for continuous outcomes (score results), logistic regression for binary outcomes, and Poisson regression for count data). As explained before, ADRs are analysed in the blinded panel (2.3.3 Outcome assessment panel).

The individual patient interviews and the focus group are digitally recorded and transcribed verbatim. The verbatim transcripts are analysed according to the Mayring's "Qualitative content analysis" [68]. The software MAXQDA is used. Rigor in qualitative analysis of the focus group and individual interviews is assured with multiple coding - two individual coding. Analyses are discussed and discrepancies are solved. In

case two researchers do not find an agreement, a third researcher should be added. In a structured discussion, hearing pros and cons of the two researchers, should assist in finding a final agreement. Moreover, another two independent individuals code 20 % of the transcripts additionally as a peer review.

2.4 Ethics and dissemination

Data protection: access to data and confidentiality

Participants' right to confidentiality is fully respected. The members of the project research team at the UKA have access to health and personal information of participants if and only if their informed consent is obtained. Participant files are stored in a secure and accessible place and manner. Participant names are stored separately and only members of the project research team at the UKA have access to identity codes. Patient names are omitted during the transcribing process (from CRFs) when inserted in the database. Local data entry enables fast correction of missing or inaccurate data. The data in the database is pseudonymised.

For qualitative analysis: when transcribing the recordings of patients' interviews and focus group personal data, e.g., names, are replaced with placeholders. After having checked the accuracy of the transcripts, the recordings are deleted.

Research results are available for public dissemination. The publication is with anonymous patient data only, where no patient data allows backtracking of patient's personal information.

Research Ethics approval

The proposed project follows the Declaration of Helsinki (2013). Despite the randomisation in the project, every patient receives the current standard of care treatment. The participation in the project is voluntary and only patients who have agreed on the informed consent and data processing are included in the project.

The local Ethics Committee is consulted throughout the project conduction. The Clinical Research Ethics Committee of the UKA formally reviewed and approved the project at the stage of the development and piloting (Internal file reference EK 195/11). The study protocol of the evaluation phase has not yet been submitted.

2.5 Discussion

Good cooperation between different professions is the core value in provision of health care. The goal of all health care providers is to maximize the quality of healthcare delivery and to minimise the treatment-associated risk as much as possible. Multi-professional care models have a great potential to enhance patient and medication safety. Some trends of improvement were observed in previous investigation of models of this kind [40-45], highlighting the important role of communication and inter-professional interaction. The present longitudinal evaluation study of multi-professional medication safety model should provide important insights into effectiveness of such a model and why it is effective.

Although, it was not planed to record any economic endpoint, the importance of reduction of drug-related readmission (primary endpoint) could be illustrated from the previous work on the model. Even though in the previous work the number of cases is low, there was a difference in duration of DRRs. The average duration of all DRRs was 19.8 days and an average duration of DRRs caused by preventable/ameliorable ADR was 13.4 days. Further, there was a tendency to prolong time to DRRs, especially early DRRs up to 10th week after the hospital discharge. [51] That demonstrates an enormous economic benefit should the developed model be implemented in the routine care. The suggested reduction of early DRRs is of long-term economic interest not only for the health-care system, but also for the hospitals in time of DRG-based reimbursement system. The discharging hospital is strained by early DRRs. The present model could lessen the burden. This proposal is complemented with the analysis by Rottenkolber et al. Analysing ADRs in patients of all ages on the internal medical ward, they showed that the average treatment costs of a single ADR were € 2250. Considering the proportion of 20 % of preventable cases, this equals a saving potential of € 87 million per year [36].

Limitations

The Hawthorne effect could have influenced the behaviour of physicians, nurses, patients and relatives. Care providers in our model are not blinded, which may encourage some of them to more attentive care in both patient groups and cause performance bias. No specific nurse or physician is trained. Instead the training takes place for the whole medical department. Given the high frequency of physician rounds, differences in provided health care are to be expected in every day routine work.

However, that should not influence the study procedure. Our trained research team (for this task RA1) documents outcome measures for both patient groups. RA1 treats patients equally, independently from the group patient has been allocated to. Finally, blinded outcome assessment panel assesses outcome measures and makes the final decisions about the primary and some of the secondary outcome measures. The two strategies should assure the objectivity of the study.

The follow-up interviews are not blinded and a detection bias may influence the results. A recall bias may be induced in the long follow-up, as patients or contact persons might not remember less severe events that happened long ago [53]. However, standardized questions are used in the follow-up interviews to control the potential bias.

UKA has not yet fully integrated CDSS in the routine work. That limits the generalisability of the model in the hospitals with different structures (e.g. with CDSS). Although, this assumption is arguable, the study does not provide mere comparison of the hospital's logistic and structural issues. Even though some local adjustment of the external application of our model might be needed, the study generates an in-depth insight of inter-professional issues providing how effective and fruitful communication and collaboration work. This embedded qualitative evaluation encourages transportability of the model.

Strengths and transportability of the model

The study is designed as a RCT with a long follow-up of 12 months underlining the need of high-quality and long follow-up trials, as stated in a Cochrane Review [45]. Parallel-group design is preferred to minimize possible time-dependent bias [53]. The equality of observation for both treatment groups is ensured through independent work of the SP and the RA1/RA2.

Our multi-professional model may serve as a convenient example for further research and implementation of multi-professional hospital care models in daily routine. After project completion study material will be available for the public. Particularly important are: The SOP with tasks for each model associate, the detailed guideline for the comprehensive MSR and CRFs (Attachments Model I: SOP for medication safety). On that basis it will be possible for other researchers to develop a comparable model in their local setting and structure trainings for model associates.

The qualitative output of the intervention is of great benefit not only for the local hospital rather for general improvements of the multi-professional teams, and patient

and medication safety. The qualitative output will answer: how to communicate with different professionals and how to communicate with a patient; where are potential stumbling stones – is that maybe hierarchy or time pressure; how would certain care providers prefer to interact with their colleagues; what kind of working environment has been developed so far; has culture of blame been broken down and how good is safety culture implemented; how do care providers think safety culture and patient safety may be improved? Those questions represent the general health care and multi-professional issues. They are going to be answered with the qualitative analysis and as a result, they are transportable in every other health care team. Interaction among different professionals has a general understanding. However, each local team should then adjust individually on account of logistic issues of their local setting.

Finally, wider generalisation of our model should support further multicentre evaluation and implementation of the multi-professional model. That is the most appropriate next step according to the MRC guidelines for evaluating complex interventions [37, 39]. This project outlines how to maximize effectiveness of health care and enhance patient and medication safety by reducing DRR. Thereby, it provides a starting point for the model conceptualisation.

3 Model II

Development of a prediction model to estimate the risk of drug-related problems on the oncology ward – pilot study

3.1 Introduction

Cancer in Germany

Cancer is the second most common cause of death in Germany after cardiovascular diseases [69]. Every year there are approximately 480,000 people diagnosed with cancer. Between 2002 and 2012, the absolute number of newly diagnosed cancer cases has increased by 13 % in men and 10 % in women. The 5-year prevalence in 2012 was 810,300 for men and 790,500 for women. According to the current state, every second man (51 %) and 43 % of all women develop cancer in the course of life. A further increase of incidence rate of about 20 % is expected by 2030 [70]. The estimate in the US even suggests a 45 % increase in cancer incidence by 2030 [71]. This is mainly due to the demographic change in population and improved early detection [70]. Despite increasing rate of disease in younger people, cancer remains a disease of age. The frequency increases sharply beyond the age of about 60 years. The median age of the disease is 69 years [69, 70]. But, the mortality rate of cancer patients has been continuously declining for several years. This is due to intensive research and development in the field of oncology and rising rate of available and effective antineoplastic drugs. Overall, the total number of cancer patients continues to rise steadily. The 5-year survival rate in 2011-2012 was 62 % for men and 67 % for women [70]. Therefore, it is to expect a growing number of cancer patients over 60 years that have to be treated over an increasingly longer period of time.

Complexity of cancer treatment

Cancer treatment has a special role in medication safety [72]. Cancer therapeutic area represents one of the most intensively researched areas. The market of available active ingredients is constantly growing. In 2016, the European Medicines Agency, EMA, approved 13 drugs for the treatment of solid tumours and haematological disorders, just slightly down from 16 novel oncology products approved in the year before. These

included immunotherapies, small molecules and even more traditional chemotherapy-based products. In the same year (2016), 18 already approved products received a positive evaluation, extending their indication or gaining approval for a new indication [73]. The complexity of therapies increases by the same degree but with simultaneous loss of clarity and comprehensibility.

Depending on underlying tumour, cytostatics with different mechanisms of action are usually used in combinations in order to increase the effect without increasing toxicity and to avoid occurrence of resistance [74]. This leads to a very complex therapy regimen with several different drugs that are administered simultaneously or sequentially and cyclically, intravenously or perorally for several weeks or months.

For example, the most widely used treatment for diffuse large B-cell lymphoma (DLBCL) is a combination of chemotherapy and monoclonal antibody rituximab. The treatment is called R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and it is usually given in 21-day cycles. In some cases another chemotherapy drug, etoposide, is added to the regimen, resulting in a drug combination called R-EPOCH. To treat patients with DLBCL whose disease is refractory or relapsed following the initial chemotherapy, high-dose chemotherapy coupled with hematopoietic stem cell transplantation (HSCT) is used [75].

The cytotoxic effect of most antitumoural drugs is not limited to the degeneration of tumour cells. It attacks every proliferating tissue in the body leading to a high toxicity [74]. Even if used as intended, it may cause a large number of ADRs that are partly dose-dependent or lead to treatment discontinuation. Some example are: a bone marrow apoplasty with the corresponding effects on the blood counts, such as neutropenia and anaemia, inflammation and ulcers of oral and gastric mucosa (mucositis, stomatitis) and alopecia. In addition, renal and hepatic impairment, severe nausea and vomiting, constipation or diarrhoea, fatigue, and other substance-specific ADRs such as neuropathy or ototoxicity may occur [74, 76]. Toxicity is less predictable in elderly patients, as a decline in organ function in some elderly can alter pharmacokinetics of many commonly used chemotherapeutic agents [77]. In spite of above-mentioned toxic properties of cytostatics, to assure acceptable quality of life compatible supportive measures are included in cancer treatment. These measures include i.a. supportive therapy with antiemetic substances such as 5-HT3 receptor antagonists, steroids and neurokinin-1 receptor antagonists during and after chemotherapy, the administration of colony-stimulating factors in neutropenia, the administration of allopurinol to avoid

urate nephropathy and administration of MESNA for the prevention of urotoxicity of cyclophosphamide. The adequate therapy of pain and the prevention and therapy of mucositis belong to the supportive therapy in cancer patients, too [75, 78, 79].

As mentioned before, the average age when the cancer disease is diagnosed for the first time is 69 years. Because of this relatively high age, at the beginning of therapy many patients suffer from other chronic diseases, called comorbidity. A cross-sectional study on prevalence of comorbidity in cancer patients with lung, prostate, breast or colon cancer showed that more than 80 % of 301 cancer patients included had at least one other disease. These were mainly cardiovascular and pulmonary diseases. The most common diseases were hypertension, arthritis, coronary heart disease (CHD) and diabetes mellitus [80]. The frequent occurrence of other diseases causes chronic use of other drugs. This phenomenon is called polypharmacy. On average, patients take five to nine drugs prescribed by physician before chemotherapy begins [81]. These are primarily antihypertensives, drugs for reducing plasma lipids and anticoagulants [82]. The drug therapy of comorbidity, complex chemotherapy, and supportive therapy together provide a variety of drugs that must be administered or taken regularly by cancer patients [81, 83]. In addition, it has been assessed that up to 35 % of patients use complementary oncological therapies. This includes a treatment supplementary to standard therapy, for example food supplements [84].

As organ performance diminishes with age, a further consequence of high age of cancer patients is a relatively large proportion of patients with impaired renal or hepatic function. A cohort study from France with over 4600 patients reported that over 16 % of cancer patients had a creatinine clearance less than 60 ml/min according to Cockcroft-Gault equation [85]. Older studies report a proportion of up to 33 % of cancer patients with a creatinine clearance below 80 ml/min [86]. Disregarding existing renal or hepatic impairment may lead to overdose and severe toxic effects of chemotherapy.

Increased risk of drug-related problems

Given above-mentioned points, it could be said that the number of cancer patients is rising. There are mainly elderly cancer patients. Over an increasingly extended period of time, these patients often need to take a variety of drugs with complex therapy regimens and partial serious toxic effects. In addition, these patients have a considerable proportion of organ function limitations. The risk of drug-related problems and medication errors is therefore particularly high in drug-related cancer therapy [72].

Results of a retrospective American study in the oncological-ambulatory area showed that medication errors occur at approximately 8 % of hospital visits, of which approximately 57 % had potential to cause harm [87]. After the group of psychoactive and analgesic drugs, cytotoxic drugs are the second most common cause of fatal medication errors [88]. In addition to adverse drug effects and incorrect dosing, drug interactions occur quite frequently resulting in excessive toxicity or reduced efficacy of tumour drug therapy. Interactions between drugs of chemotherapy and supportive therapy, therapy of companion disease and complementary therapies play a role, as well as interactions between medicines and additionally used food supplements or diets. It is particularly important to recognize this increasingly common problem in medical practice to avoid potentially hazardous effects. [72, 89-94]

Concepts to reduce risks in cancer drug therapy

In 2008 the German Ministry of Health (BMG) initiated the National Cancer Plan. Thereby, the BMG together with the German Cancer Society[6] (DKG), the German Cancer Aid[7] (DKH) and the Working Group of German Tumour Centres[8] (ADT), began a goal-oriented approach to improve the health-care situation for cancer patients in Germany. Certain fields of action were defined where an urgent action was needed, such as further development of oncological care structures and quality assurance. This includes, for example, improving the interdisciplinary cooperation and networking within oncological care to ensure cross-sectoral, integrated oncological care. Further defined field of action is strengthening patient orientation in therapy decision-making process by i.a. strengthening patient competency [95].

For this purpose, the establishment of multi-professional centres for cancer treatment, so-called “Comprehensive Cancer Centre” was launched. The development began with certification and support of top oncological centres by DKH. These centres provide i.a. an interdisciplinary cancer treatment for all types of cancer, interdisciplinary tumour boards and cancer-specific treatment pathways in form of guidelines [96]. Further, the DKG has certified specialised cancer centres in Germany. The certification criteria is very similar and involves an establishment of a quality management system [97]. The aim of these concepts is to promote standardisation of patient treatment.

[6] German: Deutsche Krebsgesellschaft, DKG
[7] German: Deutsche Krebshilfe, DKH
[8] German: Arbeitsgemeinschaft Deutscher Tumorzentren, ADT

Medication management and pharmaceutical care

Medication management where a pharmacist has an active role was seen in the field of oncology as well. On the oncological ward of Swedish university hospital, pharmacist's participation in morning rounds, medication checks and patient interviews resulted in detection of 114 DRPs in 58 patients, and drug therapy was subsequently optimised. The pharmacist's contribution was recognised and welcomed by participating physicians and nurses [98]. In Germany, several studies from Bonn were able to show the value of pharmacist's involvement in medication management. Intensified pharmaceutical care of cancer patients could improve adherence and persistence of the patients treated with peroral capecitabine [99, 100]. Often the therapy-limiting side effect of capecitabine is hand-foot syndrome (HFS). In addition to the adherence management, the patients were informed in writing and in oral form about their therapy and possible side effects, especially the HFS, and trained to take certain prophylactic and therapeutic measures. Although available recommendations were empirical only, intensive education and monitoring of patients in terms of HFS showed signs of a positive impact on the severity of HFS [101]. In the following study, influence of intensified care was investigated, including drug management on onset of nausea and vomiting under chemotherapy in patients with breast or ovarian carcinoma. Participating pharmacist trained study patients for prophylactic and therapeutic measures regarding the occurrence of nausea and vomiting during chemotherapy. Trainings were consistently repeated during the time of chemotherapy treatment. In addition, pharmacist carried out on a regular basis a review of medication on interactions, and an optimisation of antiemetic supportive therapy. The result was significant reduction in incidence of vomiting in the intervention group, i.e. significantly increased response to antiemetic prophylaxis [48]. Results showed that additional and intensified patient care provided by pharmacists in the context of medication management, could positively influence clinical endpoints, such as the occurrence of ADRs. Generally speaking, pharmaceutical care of oncologic patients during the medication management can identify and reduce medication errors and DRPs. These include, further, the avoidance of interactions, the reduction of ADRs and the increase in adherence [72]. Tasks and services performed within oncological and pharmaceutical care vary dramatically, ranging from medication history and optimisation of supportive therapy to development of therapeutic guidelines and optimal use of economic resources [102, 103]. For an effective implementation of pharmaceutical care in oncology, it is necessary to

provide a competence in the field of drug discovery, monitoring and patient counselling as well as an adequate training [104].

Assessment of risk for drug-related problems

During recent years, attempts were made to determine the risk factors for occurrence of DRPs. Risk factors are also referred to as predictors, covariates, risk indicators, prognostic factors, determinants, test results, or—more statistically—independent variables [105, 106]. According to a systematic review from 2016, ten most frequently reported risk factors associated with medication-related issues that may potentially lead to a hospital PI are as follows (ranked in descending order of frequency): prescription of certain drugs or classes of drugs, polypharmacy, elderly patients, female gender, poor renal function, presence of multiple comorbidities, length of patient stay, history of drug allergy or sensitivity, patient compliance issues, and poor liver function. These risk factors may be used to identify patients at risk, with a perspective of targeting PI in order to minimise risks concerning medicines and improve efficiency of pharmaceutical care service [107].

The following idea was to develop a tool for a fast and reliable identification of patients with present risk factors to direct pharmaceutical care approach at the patients at risk and thereby increase service efficiency and save resources. Different tools are available in the literature. Canadian researchers were pioneers developing self-administered questionnaires to identify patients at risk for medication-related problems in primary care [108-110] followed by the Australian [111] and US researchers [112, 113]. The team from Switzerland proved feasibility and acceptability of the developed tool: Drug Associated Risk Tool (DART). The DART is based on a combination of a systematic literature search, with the professional experience, and knowledge of a multidisciplinary expert panel. That enabled comprehensive finding of risk factors for DRPs representing real-life situation in the Swiss healthcare setting. The self-assessment questionnaire asks about patient's health, inquiring thereby about comorbidities such as renal/hepatic/cardiac disease, about certain medication and general about the medication use habit, compliance and tolerability. Although, it is a resource-saving tool with direct patient involvement, it has a limited validity. The tool limitations show the need for statements rephrasing in the questionnaire, validation in a more specific patient population and development of a scoring system [114].

In another hospital in Switzerland, clinical pharmacists performed efficient and rapid electronic screening of 500 patients to identify patients at risk of DRPs in preparation

for the ward round. The queries aimed at identifying patients receiving drugs such as cytochrome P450 inducers/inhibitors, those with renal impairment, those on digoxin with low serum potassium, those with intravenous anti-infectives and elderly patients with polypharmacy. The screening helped clinical pharmacist to prioritise their medication reviews and to optimise their workload and team's contribution. However, no external validation of the tool has been reported [115]. Finally, a Spanish research team, Urbina et al., designed and validated the first predictive score to detect DRP in hospitalised adults. The score has a scoring system and it is applicable in daily clinical practice. It contains following parameters: age > 60 years, Charlson index = 2, Number of drugs during hospitalisation >10 and certain major diagnostic categories. This strategy has contributed to optimisation of resources for drug treatment monitoring of general inpatient population in Spain [116].

However, all available tools refer to general inpatient population. To the best of our knowledge, no multivariable predictive model has been developed to estimate the risk of DRPs during the stay on the oncology ward. The multivariable predictive model (also commonly called "prognostic model" or "risk score" [105, 106]) may aid health care providers in their decision-making. Moreover, communication failures and knowledge gaps as shown in the literature underpin factors for the DRP occurrence. It is recommended that the DRP risk assessment is not performed separately, but rather accompanied by team optimisation [117].

Multi-professional teams

Given the complexity of modern drug therapy, an effective patient care is solely possible in a multi-professional cooperation [21, 118, 119]. Development and improvement of multi-professional cooperation is one of the objectives of current AMTS action plan of the BMG and the National Cancer Plan [22, 95]. Multi-professional teams include all professions involved in the medication process. In the hospital settings, these include physicians, pharmacists and nurses. Possible further cooperation partners in the field of oncology are nutritionists and psycho-oncologists. The structure of the team can vary depending on the setting, patient's needs and other resources. It is vital that a patient is seen and included as an indistinguishable member of the team [21]. Besides the common goal and mutual trust, clear distribution of roles and allocation of functions and responsibilities as well as effective communication, provide the basis of patient care in teams. Moreover, regular measurement of endpoints should be used to determine success of the multi-professional care [119].

Establishment of multi-professional treatment teams worldwide is a crucial component to ensure high-quality cancer patient care. For example, the American Society for Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) are calling for multidisciplinary cancer care. They have stated that optimal treatment of cancer should be provided by a team that includes, where appropriate, multidisciplinary medical expertise composed of medical oncologists, surgical oncologists, radiation oncologists, oncology pharmacists and palliative care experts, as well as oncology nurses and social workers. In this joint consensus statement about the quality of cancer treatment, it is stated that patients should also have access to counselling for their psychosocial, nutritional, and other needs [120].

A study, initiated within the clinical pharmacy group of the University of Bonn and conducted with collaborators on the national level, aimed at defining task allocation and responsibilities in a multi-professional cancer medication management. Using focus group meetings and the Delphi technique, tasks were identified and allocated to physicians, pharmacists and nurses. Members of the German Cancer Society assessed the acceptance of the proposed task allocation and perceptions on multi-professional teamwork. Total of 38 tasks were identified and allocated. Tasks allocated to a pharmacist were prevention of drug-related problems, and patient education and counselling for prophylaxis, therapy of ADRs as well as for dietary supplements and nutrition. Further tasks were encouraging adherence, preforming a drug interaction check, dose adjustment, adaptation of supportive therapy and conduction of drug history [121].

The existing scientific evidence shows benefits of multi-professional cancer teams when the pharmacist is included. However, the critical step towards the optimisation of treatment and quality of patient care is to transfer this evidence, guidelines and political demands into everyday practice [122, 123]. To ensure this, it has been suggested to start with optimisation of patient care and treatment process from the patient's point of view. That means evidence-based decision-making and improved communication between team participants, where patient is in the centre of attention. That is followed by the improvement of workflows in terms of communication and consultation, continuous review and enhancement of the process, primarily from the patient's point of view [123].

Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

An essential aspect in cancer clinical trials and oncology routine care is monitoring and documentation of toxicity and adverse events (AEs) to ensure patient safety and to provide safety data on medicinal products. With the complexity of cancer treatments, methods of AE reporting in clinical trials have evolved. AEs are usually reported using standard instruments such as the United States National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) or the Medical Dictionary for Regulatory Activities (MedDRA) [124, 125]. For systematically grading and reporting treatment-related toxicity in cancer clinical trials, CTCAE is the predominant system [126]. The latest version 4.03 of the CTCAE released by the NCI contains 790 items including laboratory tests, clinical events, and symptom evaluation [127, 128]. It represents a long-standing, empirically developed, comprehensive lexicon of symptoms often found in oncology [125]. It has been developed to facilitate recognition, assessment and documentation of AEs by clinical investigators [126]. The contribution is seen in standardisation and comparability of published study results. However, an underestimation of AE severity by healthcare professionals has been repeatedly demonstrated [129-132]. Interest to incorporate patient's perspective is thereby greatly expanding [124, 126, 133, 134]. Moreover, the empiric evidence showed that collection of this information directly from patients improves precision and reliability of symptomatic AE detection in trials [124, 129, 130, 132]. This type of self-assessment is referred to as "Patient-Reported Outcome (PRO)". According to the US FDA, PRO represent all reports on status of patient's health condition that comes directly from the patient, without interpretation of patient's responses by a clinician or anyone else [135]. Covering different aspects of AE reports, clinician-reported and patient-reported approaches are complementary [124, 127].

In closely related areas, such as evaluation of health-related quality of life, satisfaction with treatment and drug adherence, PRO has long been the gold standard in data collection [124, 136-138]. The FDA has therefore published a guide for industry to establish PRO as a standard for the collection of symptoms as endpoints [135]. Feasibility of symptom evaluation by patients has been confirmed several times, even with patients in the terminal phase of illness and with a high symptom burden [139-141].

To improve precision and patient-centeredness in capturing the symptomatic AEs, the NCI developed a library of PRO items to supplement the CTCAE, called the

Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) as it has been previously described [125, 142]. Of the 790 AEs in the CTCAE, 78 were identified as amenable to patient self-report. For each of these AEs, PRO items were created reflecting attributes of frequency, severity and interference with usual daily activities. One to three attributes were selected for any given AE depending on the content of the CTCAE criteria for that AE and the nature of that particular AE. In total, 124 individual items represent 78 symptomatic AEs currently in the PRO-CTCAE item library [143]. In order to transfer corresponding CTCAE symptoms into a patient-friendly version, medical terminology was removed and different educational levels of the patients were observed. Afterwards, items were optimised in a multicentre study with cognitive interviews to ensure item clarity, comprehension, and ease of response judgment in different patient populations [144]. English items were subsequently evaluated using both qualitative and quantitative techniques, and have demonstrated favourable measurement properties in terms of validity, reliability, and responsiveness [145]. To make PRO-CTCAE item questions available to scientists, physicians and patients worldwide, English items are gradually being translated into different languages. At present, certified translation is available in Danish, German, Italian, Japanese, Korean and Spanish. A Chinese, Czech, Dutch-Flemish, French, Greek, Hungarian, Polish, Portuguese, Russian and Swedish version are under development and are being tested [143].

A Swiss working group from Basel has translated English items into German language and linguistically validated in a sample of patients undergoing haematopoietic stem cell transplantation [146]. A German working group from Bonn went a step further. Of 124 items contained in the PRO-CTCAE German language item library, 31 were selected for validation and defined as a “core item set” [147]. Selected items reflect 14 symptomatic toxicities and were chosen on basis of their prevalence across cancer treatment types and disease sites [145, 148] and based on expert consultation [147]. The working group from Bonn showed first quantitative evidence of a subset of the PRO-CTCAE item library in German language. The core item set met accepted criteria with respect to item quality, reliability, and validity for use as a patient-reported measure of symptomatic toxicity in cancer clinical trials [147].

3.1.1 Study background

Back in 2014 in the University Hospital RWTH Aachen (UKA) in Germany, hospital pharmacy and department of haematology, oncology, hemostaseology and stem cell transplantation extended their cooperation from routine work into joint research. With an overall goal to optimise treatment and quality of patient care, a multi-professional team decided to tackle an issue of drug-drug interactions (DDIs) [149] - one of the most prominent issues among oncological patients where the role of pharmacist in other hospitals has shown to be beneficial [72, 89-94]. The research team at that time, aimed to assess number of clinically relevant DDIs in cancer patients on the local oncology ward by two independent clinical pharmacists. Over a period of seven weeks, 78 patient medical records were prospectively evaluated. DDIs were identified in Mediq® interaction software. As shown in the Table 3.1, clinical pharmacists and oncologists agreed which symptoms were clinically relevant to be reported (stated in the table as considered "X") and which were redundant being regularly controlled and adjusted on the oncology ward (stated in the table as not considered "—").

Mediq® interaction software alone reported a large amount of information not equally relevant to the daily clinical practice. The software evaluation provided 1180 of all DDIs, 15 DDIs per patient. Considering the physician-pharmacist agreement (Table 3.1), two clinical pharmacists assessed 456 DDIs (6 DDIs/patient) as clinically relevant. Selected DDIs with appropriate recommendations on each interaction, were fully accepted on the oncology ward and represented a useful supporting tool in the oncological routine practice [149].

Next step toward the overall goal was to establish an effective pharmaceutical care on the oncology ward as integrated part of the effective multi-professional ward-based team. These needs were recognised and the present pilot (feasibility) study was accordingly designed.

Table 3.1: Clinically relevant DDIs [149]

DDI effect	Clinical relevance*
Blood counts	X
Neurological function	X
Renal function	X
Skin reactions	X
Prolongation of the QT interval	X
Therapeutic drug level	X
Blood pressure	—
Blood sugar level	—
Electrolyte level	—

Legend: DDI effect: effect cased by drug-drug interaction; Clinical relevance: clinical relevance according to agreement between clinical pharmacist and oncologists in the local setting, X : considered effect, — : not considered effect, regularly controlled and adjusted on the oncology ward*

3.1.2 Objectives

In this feasibility study the aim was **to develop multivariable prognostic predictive model to estimate the probability of DRPs** (primary outcome) during the stay on the oncology ward.

In order to optimise pharmaceutical care service at the UKA oncology ward, following scientific objectives (secondary outcomes) were defined:

1. To assess number and type of DRPs leading to a PI;
2. To evaluate type of PIs provided and determine the implementation rate;
3. To assess PRO-CTCAE symptom burden.

3.2 Methods

3.2.1 Study design

The study was conducted as a prospective cohort. It was an open cohort as study patients entered and left the study at different time points. For the report of the cohort, STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement was used [150, 151]. Further, this was a feasibility study aiming to uncover strengths and weaknesses of the pharmaceutical care service provided on oncology ward. Prospect of future successful multi-professional cancer ward team should have been proposed. The primary outcome, a multivariable predictive model to estimate the probability of DRPs during the stay on the oncology ward, was reported according to the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) statement [105, 106].

The study was not a subject of German drug law[9] as individual drug therapies were not tested for efficacy and safety. Patients were treated with drugs approved to be on the market. Pharmaceutical team examined optimality of existing patient drug therapy. There were no changes to legal situation in regard to legal responsibilities. According to the German medical prescription regulation[10], medical staff continued to provide medical prescriptions [152]. Pharmaceutical care service offered by pharmacists was provided under section § 20 of Pharmacies' Operating Regulations[11]. According to these regulations, pharmacists are obliged to provide information and advice to patients, nurses and physicians about drug therapy, in particular regarding aspects of drug safety. This means pharmaceutical care is one of statutory pharmacist tasks. Although pharmacists advised attending physicians about drug therapy, physicians' decision about the patient drug therapy was not a subject of any restriction at any moment. PRs are based on published findings. Information on drug therapies is, therefore, concisely provided knowledge within the scope of patient drug therapy.

[9] German: das Arzneimittelgesetz
[10] German: die Arzneimittelverschreibungsverordnung (AMVV);
§§1-2 Regulation on Drug Prescription from December 21st 2005, amended by Article 1 of the Regulation from December 19th 2014
[11] German: die Apothekenbetriebsordnung (ApBetrO)

3.2.2 Setting

The study was conducted at the UKA. Cooperating partners in the hospital were the hospital pharmacy research group and the department of haematology, oncology, hemostaseology and stem cell transplantation (Internal medicine IV "IM42"). The department includes two wards: haematology-haemostasis and oncology ward and allogeneic stem transplantation ward. Additionally, there is an interdisciplinary tumour ambulatory service. The study was solely conducted on the haematology-haemostasis and oncology ward, hereinafter referred to as study ward.

On the study ward, every attending physician and nurse was part of the study, hereinafter referred to as medical (ward) team. The routine work on study ward was undisturbed. Pharmaceutical team providing intervention on the study ward consisted of a research pharmacist (author of this work) and an oncology pharmacist (from the oncology department of UKA hospital pharmacy).

3.2.3 Data management

Data collection

Electronic and paper patients' records were available to the pharmaceutical team. Paper patients' records stayed during the entire study procedure on the study ward. Research pharmacist collected anonymous data in paper form in study case report forms (CRF).

Anonymously collected data included: medication history data on admission, oncological and general demographic patient characteristics (CRF 1 Arznemittelanamnese), data for ADR risk score (CRF 0.1 The GerOnto ADR risk score) and answers on PRO-CTCAE survey (CRF 0.2 PRO-CTCAE). For each patient, relevant data for MSR was recorded, for example: laboratory parameters, vital signs, drug indication, and therapy plan (CRF 1 Arznemittelanamnese). Patient medication list (CRF 2 Stationäre Medikation) was updated daily during the stay on ward. The outcome of the MSR was presented in CRFs for DRPs (CRF 3 Datenerfassung Arzneimittelbezogene Probleme, and CRF 5 Empfehlungen aus der Medikationscheck). Besides, time exposure was tracked i.e. the time invested in patient recruitment, documentation and complete pharmaceutical care (CRF 4 Zeiterfassung für die Intervention). CRF templates are presented in Attachments Model II, Model II CFRs.

Data protection

Each study associate fully respected patients' right to confidentiality. Personal patient name was used during the stay on ward and continuous provision of pharmaceutical care. Research pharmacist had a patient list with patient number, name and date of birth used solely during the study time (CRF 0 Patientennummer in Attachments Model II/Model II CFRs). Once the data collection was completed, patient list was deleted and merely anonymous data was used for data analysis. Research results are available for public dissemination. The publication is going to be with anonymous patient data where it is not possible to track patient related data back to its origin in patient records.

The study follows the Declaration of Helsinki (2013) [153]. Current standard of care was provided to every patient. The study ward director signed the agreement confirming collaboration in the present study (Approval from the study ward in Attachments Model II). Within the study framework, pharmaceutical team provided drug therapy advice to the medical ward team and to patients. Pursuant to § 20 German Pharmacy work regulations (ApBetrO) that also applies to hospital pharmacists according to §1 ApBetrO, indicates that a pharmacist is obliged to provide information and advice on drugs. Planned pharmaceutical care was therefore an activity that belongs to the legal areas of a pharmacist's legal duties and no informed consent from patients was needed. The local Ethics Committee at the UKA was consulted throughout the project conduction, and formally reviewed and approved the study (Internal file reference EK 142/16, Ethic Committee opinion in Attachments Model II).

Data analysis

To perform a statistical data analysis and graphical data presentation, software Microsoft Excel® 2011 and IBM SPSS Statistics® 24 were used. Paper-based collected data was transferred into electronic data. Thereby a codebook was prepared defining and labelling each of the variables. For categorical data, numbers were assigned to each of the possible responses. Before starting an analysis, datasets were checked for errors [154]. The errors were found and corrected in the data file.

The collected data were investigated descriptively and explorative. The frequencies were calculated absolutely and relatively. Mean, median, standard deviation, range and interquartile range were included in data characterisation.

Descriptive statistics was used to describe the cohort (variable such as " age" "gender", "number of drugs", "body mass index"), oncology patient specific characteristics (such as "cancer type", "therapy regimen", "ECOG performance status", "CTx complexity") cohort subgroups, DDIs, variables of ADR risk score and the score itself.

3.2.4 Participants

The main focus of the study ward was diagnosis and treatment of haematological diseases (leukaemia, lymphoma, multiple myeloma, myeloproliferative neoplasms, myelodysplastic syndromes, aplastic anaemia, etc.) and oncological diseases with particular expertise in the area of the bronchial carcinoma, the head and neck tumours; sarcoma, brain tumours, and melanomas. According to the medical team on the study ward, majority of solid tumour patients on the ward were complex cases with advanced cancer, as patients with local not-advanced tumours were threated either on organ-specific wards (e.i. gynaecology, urology, surgery) or in ambulatory (outpatient) care.

In the time frame of four months, it was planned to enrol 100 eligible patients. Patients entered the study upon their arrival on the study ward and left the study when they were discharged from the study ward, either home/care facility or to another ward (internal/external). Participants' **inclusion criteria** was defined by:

- Minimum three-day stay on the study ward;
- Oncological/haematological main diagnosis;
- Existing drug therapy on admission.

An exclusion criterion was patient's prior participation in the study. There were no eligibility limitations with respect to the type of treatment currently being received or disease site.

Participant timeline

Table 3.2: Participants timeline

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3
ENROLMENT:					
Eligibility screen	X				
Allocation		X			
PHARMACEUTICAL CARE:					
Medication history			X		
Medication reconciliation			X		
Medication safety review			↔	↔	
Pharmaceutical recommendations*			↔	↔	
Discharge counselling*					X
MEASUREMENTS:					
Performance score			X		
ADR risk score			X		
Drug-drug interactions			X		
PRO-CTCAE			↔	↔	
DRP			↔	↔	

*Legend: **$-t_1$** – admission to the study ward; **t_1** – within the first three days of the hospital stay; **t_2** – inpatient stay**;** **t_3** – hospital discharge and study close-out**;** * – as the circumstances require; ADR – adverse drug reaction; PRO-CTCAE – Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; DRP – drug-related problem*

3.2.5 Intervention: pharmaceutical care

Pharmaceutical team in the present study consisted of oncology pharmacist (from the oncology department of UKA pharmacy) and research pharmacist (the author of this work). From admission to discharge pharmaceutical team provided pharmaceutical care on the study ward. Pharmaceutical care included extended medication history, medication reconciliation and ADR risk score calculation on admission, and medication safety review (MSR). MSR was performed on admission and repeated after every change in the pharmacotherapy. The review is based on the checklist of SOP for medication safety (Checklist AMTS Prüfung in Attachments Model I, SOP for medication safety) and adjusted to oncology patients including DDI assessment and PRO-CTCAE (3.2.6.2 DDI assessment and 3.2.6.3 PRO-CTCAE).

For any DRP leading to PI, detected during the MSR, pharmaceutical team suggested a potential solution. The solution for DRPs leading to PI was finalised in PR paper form. Pharmaceutical team discussed recommendations with the medical team on the study ward and if necessary with the patient. The PR was scanned in the internal patient documentation system.

Pharmaceutical team was available for consultation about new drug prescription and instruction for drug use. For any drug-related issue, pharmaceutical team was a contact person and an advisor to the medical team and patients on the study ward during the study time. Research pharmacist attended ward rounds at least once a week, and thereby additionally supervised study patients. Before a patient was discharged from the study ward, pharmaceutical team provided additional recommendations concerning drug therapy changes and instructions for their safe use in the outpatient care.

Medication history

In a personal pharmacist-patient discussion (or when needed with patient's care provider), the research pharmacist conducted extended medication history within first three days of patient's stay on the study ward – as early as routine workflow allowed it. For this purpose medication history documentation sheet was used (CRF 1 Arznemittelanamnese in Attachments Model II/Model II CFRs). Besides the basic demographic data, the aim was to collect as much information about patients' medication as possible: what he had used before the admission, all prescribed and over-the-counter medicines, recent previous ADRs and recent changes in drug therapy. The medication used

before admission to the study ward was home medication (if patient was admitted from home), or care-home medication (if patient was admitted from the care home facility), or medication from the last visited ward (if patient was admitted from the internal or external health care facility). The current medication prescribed on admission to the study ward was documented, too.

Medication reconciliation

The research pharmacist documented incomprehensible, or from the pharmaceutical side unsupported discrepancies between the pre-admission medication and admission ward medication in the comment field of the medication history documentation sheet (CRF 1 Arznemittelanamnese in Attachments Model II/Model II CFRs). For instance: when a patient had not voluntarily reported to the attending physician some over-the-counter medicine, or any medication or transmission error on admission. Research pharmacist suggested a solution for each discrepancy. Oncology pharmacist assessed the suggested solutions and made the final decision on clinical relevance. Clinically relevant discrepancies were treated as DRPs, and documented with their solutions in CRFs for DRPs (CRF 3 Datenerfassung Arzneimittelbezogene Probleme, and CRF 5 Empfehlungen aus der Medikationscheck in Attachments Model II/Model II CFRs).

Medication safety review

Information collected during medication history and medication reconciliation represented the basis for the MSR. Besides, pharmaceutical team used available patient records (paper form/internal UKA software). The review was conducted at the beginning of the hospital stay on the study ward, as well as every time the patient's drug therapy was changed. It considered the following steps:

- Plausibility review of each medication on patient's therapy plan (including indication, dosage, application of drug)
- Review of drug dosage, DDIs, contraindications
- Review of any potential ADR symptom
- Review of relevant laboratory data
- Adjustment review: review of allergies, renal and liver dysfunction and adjustment of doses, if required
- Review of TDM and adequate duration of drug therapy (e.g. antibiotic therapy)
- Review of medication before interventions (e.g. surgery)

- Review of a need for patient counselling, particularly if a new drug therapy is initiated

Further details are provided in the checklist of SOP for medication safety (Checklist AMTS Prüfung in Attachments Model I, SOP for medication safety). Supporting information tools available in the UKA pharmacy for resolving drug-related issues were: German prescribing information register Fachinfo-Service® (Summary of Product Characteristics), Micromedex DRUGDEX®, an updated drug knowledge portal, and interaction software: Mediq®, ID Diacos Pharma Check®, Lexicomp®.

Having all relevant information, each member of the pharmaceutical team independently assessed patient drug therapy. Research pharmacist and oncology pharmacist presented each other identified DRPs and discussed potential solutions. In case of disagreement the oncology pharmacist made a final decision, based on broader and longer experience on the study ward. Final decision of the pharmaceutical team on DRP leading to an intervention resulted in PR. Within first five days of the hospital stay, the first recommendation was provided, if there was need for any.

The recommendations contained explained DRP and an appropriate solution, and were also discussed on the study ward with the medical team, and if necessary with the patient. Having the PR in the paper form, physicians were able to go back to them at any time and include the relevant information in the patient letter. Exclusively the DRPs that led to PI ended in the PR and were tracked in the study documentation.

3.2.6 Study measures

Demographic and oncological variables

Basic demographic data was in continuous variables “age” and observation (study) time “time on the study ward”, and in categorical variables “gender”, existing “allergy”, “alcohol” consume and “smoking” habit. Oncological characteristics were distributed in categorical variables:

- “Cancer type” was divided into haematological or solid tumour patient group;
- “Cancer diagnosis” were according to the International Statistical Classification of Diseases (ICD) [155];

- "Therapy regimen" was a treatment option prioritised in lines of therapy: 1st line, 2nd line, 3rd line therapy, etc. A criteria how to assess therapy regimen was finalised with study physicians (Table 3.3);
- "Therapy plan" was divided into: palliative, curative and unclear therapy goal (where further diagnostics was needed);
- "Chemotherapy complexity" was divided into low, moderate or high complexity;
- "Chemotherapy cycle" was a number of a chemotherapy cycle of a patient;
- "Current chemotherapy" was whether a patient received chemotherapy during the study time (yes/no).

Table 3.3: Therapy regimen criteria

CRITERIA	THERAPY REGIMEN	COMMENTS
Chemotherapy (CTx) and radiotherapy (RTx)	1st line	Together one therapy line
After complete remission occurrence of new tumour type	1st line	Or any current therapy line
Autologous HSCT (Initial therapy, conditioning treatment (CTx/RTx), transplant (optional double transplantation), and maintenance therapy (optional))	1st line	All steps considered as a one therapy line
Disease relapse	2nd line	Or any following line
Disease progress	2nd line	Or any following line
Therapy switch (allergic reaction, adverse reaction, no respond on initial therapy choice)	2nd line	Or any following line

Number of prescribed drugs

In order to analyse the number of prescribed drugs, the drugs prescribed on the ward were counted (continuous variable "number of drugs"). Products containing more than

one active substance were considered as one drug. In the count, paused or discontinued drugs were not included. Change of drug dosage was not counted as a new prescribed drug. On contrary, change of the dosage form (e.g. change from intravenous to oral dosage form) was considered as a new prescription. Solutions carriers or agents for volume substitution (e.g. NaCl 0.9%, Ringer's solution) were not recognised as drugs. Medicines used both as food supplements as well as drugs (e.g. potassium, magnesium) were evaluated as drugs. Medical products such as saline nasal sprays, moistening eye drops, mouthwash etc. were also regarded as drugs.

Body Mass Index (BMI)

BMI is a measure for indicating nutritional status in adults. BMI is an estimate of body fat and a good gauge of risk for diseases that can occur with more body fat. The higher BMI is, the higher is the risk for certain diseases such as heart disease, high blood pressure, type 2 diabetes, gallstones, breathing problems, and certain cancers [156]. Although BMI can be used for most men and women, it does have some limits: it may overestimate body fat of athletes and others who have a muscular build, and it may underestimate body fat of older persons and others who have lost muscle [157]. BMI is defined [156] and accordingly calculated in the present study:

$$BMI = \frac{person's\ weight\ (kg)}{(person's\ height\ (m))^2}$$

BMI nutritional status is divided in ranges (Table 3.4) based on the effect that excessive body fat has on diseases and death. The ranges relate reasonably well to adiposity [156].

Table 3.4: BMI ranges [156]

BMI	Nutritional status
Below 18.5	Underweight
18.5 – 24.9	Normal weight
25.0 – 29.9	Overweight/Pre-obesity
30.0 – 34.9	Obesity (class I)
35.0 – 39.9	Obesity (class II)
Above 40	Obesity (class III)

Liver function

Total bilirubin in *µmol/l* (*mg/dl*), serum albumin in *g/dl* and prothrombin time (INR) prolongation in *s*, were information obtained from available UKA laboratory data. Diagnoses of ascites and hepatic encephalopathy were available in the patient medical records, when the disease was present. With these five parameters, the research pharmacist calculated Child-Pugh score and interpreted into the Child-Pugh class [158, 159] (Table 3.5 and Table 3.6). Given that this study was not focused on chronic liver diseased patients where the interpretation of Child-Pugh class in terms of survival is vital, this interpretation (Table 3.6) was irrelevant to the study results and it was omitted in the further discussion.

Table 3.5: Child Pugh score [158, 159]

Child –Pugh score			
Measures	1 point	2 points	3 points
Total bilirubin (*µmol/l*)	< 34 (< 2)	34 – 50 (2 – 3)	> 50 (> 3)
Serum albumin (*g/dl)*	> 3.5	2.8 – 3.5	< 2.8
Prothrombin time (INR) prolongation *(s)*	< 4.0	4.0 – 6.0	> 6.0
Ascites diagnosis	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy diagnosis	None	Grade I – II	Grade III – IV

Table 3.6: Child –Pugh score interpretation

Child –Pugh score interpretation			
Points	Class	One year survival	Two year survival
5 – 6	A	100%	85%
7 – 9	B	81%	57%
10 – 15	C	45%	35%

Renal function

The Creatinine Clearance rate (CrCl) and Glomerular Filtration Rate (GFR) were reviewed and documented during the MSR. In laboratory hospital data, Serum creatinine (Scr) and estimated GFR using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula were provided. The research pharmacist estimated CrCl using Cockcroft-Gault (CG) formula [160]:

$$CrCl = \left\{\frac{\left((140 - age) \times weight\right)}{72 \times Scr}\right\} \times 0.85\ (if\ female)$$

Where CrCl was in *ml/min*, age in *years*, weight in *kg* and Scr in *mg/dl*.

The stages of Chronic Kidney Disease (CKD) are mainly based on measured or estimated GFR. There are five stages (Table 3.7), however, the kidney function is normal in Stage 1, and minimally reduced in Stage 2 [161].

Table 3.7: CKD stages [161]

Stage	GFR*	Description
1	90 +	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease
2	60 – 89	Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease
3A 3B	45 – 59 30 – 44	Moderately reduced kidney function
4	15 – 29	Severely reduced kidney function
5	< 15 or on dialysis	Very severe, or end-stage kidney failure (sometimes call established renal failure)

** All Glomerular Filtration Rate (GFR) values are normalised to an average surface area of 1.73m²*

Eastern Cooperative Oncology Group (ECOG) performance status

Tumour board is a cancer treatment planning approach in which a number of doctors who are experts in different specialties review and discuss the medical condition and treatment options of a patient. Designed to optimise patient outcomes, tumour boards are essential to clinical decision-making and patient management.

ECOG performance status [162] was one of the parameters determined and documented for each patient on the tumour board. The grading system (Table 3.8) was developed to spur further standardization among researchers who design and evaluate cancer clinical research [163].

Table 3.8: ECOG performance status [162]

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50 % of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50 % of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

3.2.6.1 Adverse drug reaction risk score

Original version of ADR risk score [57] was translated into German and used as supporting measure for each patient on the study ward. Each score variable: diagnosed hearth failure, diagnosed liver disease, diagnosed renal failure, having four or more comorbidities, weights one point. If a patient had previous ADRs, it was scored two points. For the variable number of drugs, there was a following scoring criteria: lower or equal than five drugs – no points, six or seven drugs – one point, and more or equal than eight drugs – four points. This variable was called in the present study "number of drugs coded" and it is to be distinguished with the continuous variable "number of drugs". The maximum ADR risk score was 10 points. As suggested in the original study [57], the cut off point was 4 and patients with more than 5 points were considered

prone to ADRs. Thereby, score interpretation “ADR probable” and “ADR definite” were referred together as “high” ADR risk score (Table 3.9).

Table 3.9: ADR risk score interpretation

SCORE	ADR occurrence
0 point	Doubtful
1 – 4 points	Possible
5 – 8 points	Probable
9 – 10 points	Definite

3.2.6.2 Drug-drug interactions

During the MSR important step was assessment of DDIs. During this task, pharmaceutical team followed DDI assessment steps A – E (explained below) and provided clinically relevant PRs to attending physicians. Pharmaceutical DDI assessment steps were developed on basis on the previous work [149] and expanded in the present study. These steps were:

A. Independently each pharmacist assessed patient’s current clinical picture and drug therapy; and documented all potential DDI problems.
B. Independently each pharmacist assessed previous DDI problems. If any previous DDI problem was available and known, it was documented.
C. Independently each pharmacist assessed complete drug therapy in the Mediq® interaction software. Interactions marked red representing highly relevant DDI potential risk with severity degree 3 (according to the software) were always included in the recommendation. Interaction marked orange (middle DDI potential according to the software) and yellow (low DDI potential according to the software) needed additional pharmaceutical expert assessment. Independently each pharmacist did that while considering particularities of single patient. Each pharmacist decided first on his own whether to include the potential DDI in the professional recommendation, or not.
D. Each pharmacist proposed clinically relevant PRs in the team discussion. In case of ambiguity, additional clinical decision support tools were used:

Fachinfo-Service®, Micromedex DRUGDEX®, or additional interaction software: ID Diacos Pharma Check®, Lexicomp®.

E. After discussing individual recommendations and agreeing on a single solution, pharmaceutical team communicated PR to the study ward. Clinically relevant DDIs were treated as DRPs.

The results were presented in two parts: Mediq® software output and pharmaceutical DDI assessment output. It was crucial to distinguish the term "clinically relevant" in the context of the study. Mediq® software had orange-marked potential DDI (middle DDI potential) as clinically relevant but in our study clinically relevant DDI was the one individually assessed for each patient in the pharmaceutical DDI assessment and chose as relevant. Any further notice of clinically relevant DDIs is referred to the outcome of the pharmaceutical DDI assessment, and not to the software output.

3.2.6.3 Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

Principal extension of the MSR was inclusion of the PRO-CTCAE questionnaire. German PRO-CTCAE core item set used in this study includes 31 items about 14 different symptoms. The symptomatic toxicities were clustered as shown in Table 3.10 [147]. Responses were provided on a five-point Likert scale. Recall period for PRO-CTCAE was the past 7 days [143] and in the present study weekly assessment of PRO-CTCAE symptoms was considered.

PRO-CTCAE attributes included **frequency** (e.g. how often did you have nausea), **severity** (e.g. what was the severity of your pain), and **interference** with daily activities (e.g. how much did fatigue interfere with your usual or daily activities) [143]. The inclusion of multiple attributes intended to improve precision of PRO-CTCAE in capturing the latent construct (e.g. pain that is severe but infrequent) [147].

Research pharmacist explained purpose of the questionnaire and directed the PRO-CTCAE questions to patients on admission, after the medication history. Patients had enough time to provide their sincere and subjective answer. Personal contact with the research pharmacist promoted the response rate but not in any way did the research pharmacist influence patients' self-reported answer or interpreted patients' answer. On random occasions, the oncology pharmacist joined the research pharma-

cist during the patient-researcher meeting, monitoring and controlling the process but not actively participating in it. Thereby, the method to minimise missing patient-reported data and real-time monitoring was employed [164]. If the patients' condition was not sufficient, pharmacist referred PRO-CTCAE item questions to the care provider. This was considered as a backup data collection method [164].

The PRO-CTCAE answers were documented in paper form. Further possible administration modes were tablet, computer- or interactive voice response system administration mode. None of them was feasible in this setting. Uncontrolled symptoms were considered in the MSR and when needed, appropriate PRs were given to the medical team on the ward.

Table 3.10: PRO-CTCAE item clusters [147]

Item cluster	Number of items	Item dimensions
Anxiety and sadness	6	Frequency, severity, interference
Nausea and vomiting	4	Frequency, severity
Appetite loss	2	Severity, interference
Fatigue	2	Severity, interference
Pain	3	Frequency, severity, interference
Mucositis and xerostomia	4	Severity, interference
Dyspnoea	2	Severity, interference
Mental concentration	2	Severity, interference
Numbness and tingling	2	Severity, interference
Insomnia	2	Severity, interference
Constipation	1	Severity
Diarrhoea	1	Frequency

Legend: PRO-CTCAE – Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

PRO-CTCAE symptom burden

Responses on PRO-CTCAE items were scored from 0 to 4. There has not yet been defined a standardised scoring rule on how to combine attributes into a single score or how best to analyse PRO-CTCAE data longitudinally [143]. Uncontrolled PRO-CTCAE item clusters that enforced pharmaceutical recommendations and PRO-CTCAE scores for each attribute (frequency, severity, interference) were presented descriptively.

For the purpose of presentation and comparability of symptom burden, the cohort PRO-CTCAE item cluster score was calculated according to the following equations [147] averaging the component items of each of the clusters according to:

$$RS = \frac{I_1 + I_2 + \ldots + I_n}{n}$$

Where $I_{1,2,\ldots,n}$ were item values, *RS* was a raw score and *n* was the number of items.

To ease the interpretation, the PRO-CTCAE item cluster were linearly transformed to a 0 –100 scale so that higher scores indicated worse symptoms, using the formula:

$$Score = \left\{ \frac{RS}{range} \right\} \times 100$$

Range referred to the difference between the maximum possible value and the minimum possible value of answer options (*range = 4 – 0 = 4*) [147].

To compare low and high mean cohort PRO-CTCAE attribute scores, and interdependent main cohort characteristics as low and high, multiple chi-squared tests for binary scales were used. Thereby, the null hypothesis in the testing was the low/high mean cohort PRO-CTCAE attribute score is independent of low/high main cohort characteristics. An alternative hypothesis was that the two are dependent (PRO-CTCAE attribute score is associated with main cohort characteristics). The PRO-CTCAE attributes had potential values from 0 to 4 indicating increasing intensity. Values 0 and 1 was no or very low, and 4 was very high attribute intensity. Thus, the mean cohort PRO-CTCAE attribute scores (frequency, severity interference) was defined as low score 0 - 1 and high score ≥ 2. Independent main cohort characteristics were recoded into binary variables: “number of drugs” low (<8 drugs prescribed) and high (≥8 drugs prescribed); “ECOG performance status” low (0 – 1) and high (2 – 4) impaired performance status [145]; “ADR risk score” low (0 – 4 where ADR is doubt-

ful or possible) and high (5 – 12 ADR probable and definite). Variable "cancer type: solid/haematological tumours" was already binary in the initial data entering. The approach was appropriate because the sampling method was simple random sampling, the variables were categorical, and the expected frequency count was at least 5 in each cell of the contingency table [165]. The results of multiple testing of Pearson's chi square test of independence were presented with two-tailed significance level 0.05.

3.2.6.4 Drug-related problems

The APS-Doc® system was used for measurement and classification of DRPs leading to an intervention. The system was developed for systematic documentation of DRPs within the hospital setting in Germany. All relevant DRP categories from the international classification systems like PI-Doc and PCNE for the hospital setting were included and further DRP categories were added [64].

APS-Doc® consisted of 48 subcategories that describe DRPs (e.g. "missing drug in medication history"). Those subcategories were linked to ten main categories: "drug (Rx)", "dosage form/drug strength (DS)", "dosage (DOS)", "indication (IND)", "contraindication (CI)", "drug-drug interactions (DDI)", "adverse drug reaction (ADR)", "administration/compliance" (AC) nowadays called "adherence", "administration (AP)" and "other (O)" [64]. Two further subcategories were added to the main category "others", "O3: information requirement by patient", "O4: information requirement by physician/nurse" [49].

Variable "DRP day" reflected the day when it was intervened on the particular DRP.

The outcome of PRs provided on DRPs was assessed as:

- "Preventive measures taken" where the pharmaceutical recommendation did not urged for a direct change of the drug therapy, but a particular clinically relevant preventive measure was suggested, e.g. a further diagnostic test because of unclear drug indication/uncontrolled laboratory measurement/patient's complaint, or recommendation could be implemented at a later point because of instability of clinical symptoms which required further observation of the patient state, or where a patient with a particular previous ADR had numerous drugs with the same adverse effect (more solutions were provided and attending physicians made the decision);

- "Implemented" where the pharmaceutical recommendations were explicit and indicated direct change in the drug therapy;
- "Not applicable" when the medical team did not find PR relevant and did not implement the recommendation.

PIs resulting in PRs on the ward were classified using DokuPIK® system for the hospital setting developed by the German Society of Hospital Pharmacists. Eight "DokuPIK" measurements have been used (Table 3.11*)*. For purpose of the present study, three additional categories (M9, M10, M11) were added.

The implementation rate (*IR*) of recommendations on the DRPs was calculated as quotient of the number of implemented PRs (I_{pr}) to the total number of PRs provided (T_{pr}) :

$$IR = \frac{I_{pr}}{T_{pr}}$$

Table 3.11: Doku-PIK®

Measurement number	"DokuPik" categorisation of pharmaceutical recommendations
M1	Instruction on the drug application
M2	Stop/pause the drug
M3	Change of the drug
M4	Suggestion for the prescription of a new drug
M5	Change of the drug dose
M6	Change of the drug form
M7	Information to the attending physician/nurse
M8	Information to the patient
M9*	Symptom surveillance
M10*	Further diagnostic tests
M11*	Change of the drug interval

*Legend: DokuPik – Dokumentation Pharmazeutischer Interventionen im Krankenhaus; * – added for the purpose of this study.*

3.2.7 Drug-related problem prediction model

Since "number of DRPs" was statistically rare event, the frequency distribution represents a Poisson distribution [165]. The Poisson regression model was chosen to determine the influence of 17 different predictors on the number of DRPs, first in a univariable and then in a multivariate analysis. These 17 predictors were following variables: "age", "sex", “body mass index”, “ECOG performance status", ”number of drugs", “number of comorbidities”, “liver disease”, “renal failure”, “heart failure”, “previous ADR”, “ADR risk score”, “cancer type”, “therapy plan”, “CTx cycle”, “current CTx”, “CTx complexity” and “therapy regimen”. Variables were chosen as potential risk factors contributing to the occurrence of DRPs in divers’ patients groups [107, 166] or representing relevant characteristics of oncology patients.

Additionally, adjusted Poisson regression model was used to determine the influence of ADR risk score on the number of DRPs. In the adjusted model, ADR risk score was used as a fixed variable. ADR risk score was a validated and useful method in clinical practice to identify inpatients at risk of an ADR [57]. Thereby, it represented a useful starting point for developing a DRP prediction model (DRP risk score). Variables ”number of drugs", “number of comorbidities”, “liver disease”, “renal failure”, “heart failure”, “previous ADR” that are considered DRP risk factors [107, 114, 116], were already components of ADR risk score. However, ADR represented only a part of all DRPs that may occur. Therefore, further predictors were needed in order to perform the DRP assessment, and as a result to develop the DRP prediction model. Under those circumstances, from previously mentioned 17 variables remaining 16 supporting variables were exploratively examined in the adjusted model.

A univariable Poisson regression model analysis was used as a selection mechanism. Each of 17 potential predicting factors was tested. Variable with p value less or equal of 20 % were selected as candidates for a multivariate analysis.

In the multivariate Poisson regression model, both, forward selection and backward elimination, selection procedures were used to yield the most appropriate regression equation. The prognostic prediction model combined multiple predictors by signing relative weights to each predictor to obtain a risk or probability. In the final model, the significant level was set to 5 %. The results were presented with predicted incidence rates and risks, two-sided p values, coefficient estimates (B) with 95% Wald Confidence Interval (Cl). The prognostic ability of the model was graphically plotted in the

Receiver Operating Characteristic (ROC) curve, true-positive rate (sensitivity or probability of detection) against false-positive rate (fall-out, probability of false alarm, 1 - specificity). Sensitivity and specificity levels of the prognostic models were interpreted. Performance measure was reported with an area under the ROC curve (AUC) of the model included the area under the curve (AUC). An area under the ROC curve (AUC) of 0.5 indicates no discrimination, whereas an AUC of 1.0 indicates perfect discrimination. The estimated AUC was presented with 95 % CI, standard error (SE) and p value.

3.2.8 Bias

Three potential biases were detected. Each bias was considered to limit its impact and certain measures were undertaken, as described below.

Infrastructure bias could arise based on the UKA infrastructure. Standard medical team on the ward consisted of physicians and nurses. Pharmacists were in the hospital pharmacy, doing their routine work in the separate building. Pharmaceutical care, though a legal requirement of pharmacist routine work, had not yet been integrated in routine of any ward in the UKA.

Having an established first research interaction on the study ward (3.1.1 Study background), this study aimed to extend the joint work and come closer to the multiprofessional routine collaboration. To do so, pharmaceutical team in this study presented the project on the ward. The project was implemented in a way routine workflow on the ward was undisturbed and study outcomes were valuable for patients. Pharmaceutical and medical team set structural daily appointments such as discussion of PRs ahead of ward rounds or access to the paper form of patient records on the study ward in between nursing rounds.

Information bias could arise as consequence of UKA infrastructure bias, where pharmaceutical team and medical team worked in different departments and a pharmacist was rarely present in the routine workflow. Professional exchange of patient information within the medical team routinely did not include a pharmacist. To overcome this potential bias, pharmaceutical team (1) had attended ward rounds once a week, (2) had regular afternoon appointment with an attending physician to discuss uncertainties about the patient therapy. (3) Both pharmaceutical team and medical team had an opportunity to communicate via internal phone and E-mail, when necessary. On the other side, separate work routine of two teams contributed to the objectivity of

DRP assessment. In a way, pharmaceutical team was an external objective examiner of DRP existing on the ward.

Detection bias could arise on account of the DRPs detection and pre-selection. As mentioned before in 3.2.5 Intervention/Medication safety review, only DRPs leading to an intervention i.e. where the pharmacist could contribute to their resolution were tracked and discussed with the medical team. Baring in mind the pharmacist had not yet been integrated part of the study ward routine, the pre-selection of the DRPs through a pharmacist is considered as a tool to prevent overflow of the information communicated on the ward. Being aware of the issue, the inclusion of oncology pharmacy in the pharmaceutical team who did the independent assessment approach increased internal validity of the study.

3.3 Results

3.3.1 Participants

Data was collected for four months, from mid August 2016 until mid December 2016 on the study ward. The study consisted of 55 (54.5 %) male and 46 (45.5%) female participants, making the sample of 101 patients.

On average, patients were 65 years old (SD 13.3, median 64, range 26 – 91, IQR 75 – 58) and stayed 10 days on the study ward (SD 7.4, median 7, range 3 – 49, IQR 12 – 4).

Mean BMI was 26.1 kg/m^2 (SD 7.3, median 25.4, range 14.8 – 56.4, IQR 29.1 – 21.3). Seven patients were underweight. Normal weight was observed in 29 (28.7 %) patients. The BMI over 25 kg/m^2 had 38 (36.8 %) patients, 21 (20.8 %) were overweighed and 17 (16.8 %) were obese.

Ten (9.9 %) patients had allergies: food/dust/drug allergy. Only one patient (1 %) had an alcohol abuse problem. Twenty-nine (28.7 %) patients were smokers. Among smokers, 12 (41.4 %) patients had a diagnosis of malignant neoplasm of bronchus or lung.

Oncological characteristics

Cohort had patients with 44 different diagnoses; presented separately in the attachment (Patient Diagnosis in Attachments Model II). Solid and haematological tumour diagnoses were almost evenly distributed (50.5 % vs. 49.5 %). The most frequent solid tumour type was malignant neoplasm of bronchus or lung (24 patients, 23.8 %), and the most frequent haematological tumour diagnosis was diffuse large B-cell lymphoma (16 patients, 15.8 %). The second most frequent haematological diagnosis was multiple myeloma (14 patients, 13.9 %). Other diagnoses had very low relative frequency, from 1 up to 3 %.

Six patients (5.9 %) had normal performance status (ECOG = 0) according to the ECOG grading system. Forty-one patients (40.6 %) were slightly restricted in physically strenuous activity (ECOG = 1) and almost half of the patients, 45 of them (44.6 %), had to certain extend impaired performance status (ECOG = 2 – 4).

Main oncological characteristics are shown in the Tables 3.12 and 3.13 in a gender distribution and in total values. Values where the total number was different from the

sum of women and men were marked with a star (*). For each gender the total number was calculated independently and this disparity was a result of number rounding.

Table 3.12: Main oncological characteristics (part 1)

	Female	Male	Total
ECOG performance status			
0	1 (1.0 %)	5 (5.0 %)	6 (5.9 %)*
1	20 (19.8 %)	21 (20.8 %)	41 (40.6 %)
2	9 (8.9 %)	13 (12.9 %)	22 (21.8 %)
3	9 (8.9 %)	11 (10.9 %)	20 (19.8 %)
4	0 (0 %)	3 (3.0 %)	3 (3.0 %)
Missing values			9 (8.9 %)
Cancer type			
Solid tumours	22 (21.8 %)	29 (28.7 %)	51 (50.5 %)
Haematological tumours	24 (23.8 %)	26 (25.7 %)	50 (49.5 %)
Cancer diagnosis			
Malignant neoplasm of bronchus or lung	12 (11.9 %)	12 (11.9 %)	24 (23.8 %)
Diffuse large B-cell lymphoma	8 (7.9 %)	8 (7.9 %)	16 (15.8 %)
Multiple Myeloma	9 (8.9 %)	5 (5.0 %)	14 (13.9 %)
Others	17 (16.8 %)	30 (29.7 %)	47 (46.5 %)
Therapy regimen			
First line therapy	26 (25.7 %)	31 (30.7 %)	57 (56.4 %)
Second line therapy	11 (10.9 %)	15 (14.9 %)	26 (25.7 %)*
Third line therapy	5 (5.0 %)	7 (6.9 %)	12 (11.9 %)
Fourth line therapy	2 (2.0 %)	2 (2.0 %)	4 (4.0 %)
Unknown	0 (0 %)	2 (2.0 %)	2 (2.0 %)
Therapy plan			
Curative	10 (9.9 %)	9 (8.9 %)	19 (18.8 %)
Palliative	28 (27.7 %)	38 (37.6 %)	66 (65.4 %)
Unclear further diagnostics needed	8 (7.9 %)	8 (7.9 %)	16 (15.8 %)

Table 3.13: Main oncological characteristics (part 2)

	Female	Male	Total
Chemotherapy complexity			
Low	16 (15.8 %)	24 (23.8%)	40 (39.6%)
Moderate	5 (5.0 %)	2 (2.0%)	7 (6.9%)
High	0 (0 %)	3 (3.0%)	3 (3.0%)
Unknown	25 (24.8 %)	26 (25.7%)	51 (50.5%)
Chemotherapy cycle			
First	16 (15.8 %)	20 (19.8 %)	36 (35.6 %)
Second	11 (10.9 %)	13 (12.9 %)	24 (23.8 %)
Third	2 (2.0 %)	5 (5.0 %)	7 (6.9 %)*
Fourth	4 (4.0 %)	2 (2.0 %)	6 (5.9 %)*
Fifth	1 (1.0 %)	1 (1.0 %)	2 (2.0 %)
Sixth	1 (1.0 %)	1 (1.0 %)	2 (2.0 %)
Tenth	1 (1.0 %)	0 (0 %)	1 (1.0 %)
Chemotherapy is planed but it is unknown when does it start	10 (9.9 %)	13 (12.9 %)	23 (22.8 %)
Chemotherapy during the study time			
Yes	26 (25.7 %)	33 (32.7 %)	59 (58.4 %)
No	20 (19.8 %)	22 (21.8 %)	42 (41.6 %)

Solid tumour vs. haematological tumour patients

There were 51 (50.5 %) patients with solid tumour and 50 (49.5 %) patients with haematological tumours. Patients with haematological tumours had a slightly lower median age (64 vs. 65) and slightly shorter stay on the study ward (6.5 vs. 8), but higher median BMI (26 vs. 23), median ADR risk score (7 vs. 6) and incidence rate of DRPs per day on the ward (0.19 vs. 0.17), when compared with patients with solid tumours. In the Tables 3.14 – 3.18 characteristics of those two patient subgroups are presented.

Concerning PRO-CTCAE symptoms that required a PR, there were seven (6.9 %) patients with solid tumours and six (5.9 %) patients with haematological tumours. The PRO-CTCAE symptoms were: shortness of breath (twice), fatigue (twice), insomnia (twice) and concentration (once) by solid tumour patients and nausea (once), de-

creased appetite (once), numbness and tingling (once), fatigue (once), insomnia (once), anxiety (once) by haematological tumour patients.

Table 3.14: Solid tumour patients

Solid tumours (51 patient)				
Characteristic	**mean**	**SD**	**median**	**IQR**
Age	64.9	11.6	65	74 – 58
Days on the study ward	9.3	6.7	8	12 – 5
BMI	24	5.6	23	27 – 20
Number of drugs	12.9	4.4	13	16 – 10
Incidence of DRPs	0.2	0.3	0.2	0.3 – 0
ADR risk score	6.1	1.7	6	7 – 5
Number of clinically relevant DDIs	3.1	5.1	1	5 – 0

Table 3.15: Haematological tumour patients

Haematological tumours (50 patient)				
Characteristic	**mean**	**SD**	**median**	**IQR**
Age	63.7	14.9	64	75.3 – 57.5
Days on the study ward	9.4	8	6.5	14.3 – 4
BMI	27.8	8.1	26.2	31.6 – 22
Number of drugs	13.2	4.6	13	15.3 – 10
Incidence of DRPs	0.3	0.2	0.3	0.3 – 0
ADR risk score	6.6	1.8	7	8 – 5.8
Number of clinically relevant DDIs	3.8	4.8	2	7 – 0

Table 3.16: Solid and haematological tumour patients- counts (part 1)

	Patients with	
	Solid tumours (51)	Haematological tumours (50)
Gender		
Female	22	24
Male	29	26
BMI range		
Underweight	5	2
Normal weight	15	14
Overweight	9	12
Obese	5	12
Missing values	17	10
ECOG performance status		
0	4	2
1	18	23
2	13	9
3	11	9
4	1	2
Missing values	4	5
Therapy regimen		
First line therapy	30	27
Second line therapy	14	12
Third line therapy	4	8
Fourth line therapy	2	2
Unknown	1	1
Therapy plan		
Curative	2	17
Palliative	41	25
Unclear. further diagnostics needed	8	8

Table 3.17: Solid and haematological tumour patients- counts (part 2)

	Patients with	
	Solid tumours (51)	Haematological tumours (50)
Chemotherapy complexity		
Low	21	19
Moderate	4	3
High	2	1
Unknown	24	27
Chemotherapy cycle		
First	16	20
Second	12	12
Third	6	1
Fourth	1	5
Fifth	1	1
Sixth	1	1
Tenth	0	1
Chemotherapy start unknown	14	9
Chemotherapy during the study time		
Yes	28	31
No	23	19
Number of comorbidities		
Less than 4	13	12
4 or more	38	38
Previous ADRs		
Yes	37	37
No	14	13
Allergies		
Yes	3	7
No	48	43

Table 3.18: Solid and haematological tumour patients- counts (part 3)

	Patients with	
	Solid tumours (51)	Haematological tumours (50)
Alcohol consume		
Yes	0	1
No	51	49
Smoking		
Yes	23	6
No	28	44
Diagnosed renal failure		
Yes	5	13
No	46	37
Diagnosed liver disease		
Yes	3	2
No	48	48
Diagnosed heart failure		
Yes	10	19
No	41	31

Organ-specific function

Liver function

Five (5 %) patients had diagnosed liver disease, documented in patients' records. The mean total bilirubin was 0.4 µmol/L (SD 0.4, median 0.3, IQR 0.53 – 0.19), the mean serum albumin 3.1 g/dL (SD 0.7, median 3.2, IQR 3.8 – 2.5) and the mean INR 1.1 (SD 0.3, median 1, IQR = 1.16 – 0.98). For 67 (66.3 %) patients at least one parameter was missing and Child-Pugh score could not be calculated (Table 3.19). From the remaining patients, 22 (21.8 %) patients had Child-Pugh class A and 12 (11.9 %) patients had Child-Pugh class B.

Table 3.19: Child Pugh score

Child-Pugh score	Frequency	Percent (%)
5	9	8.9
6	13	12.9
7	9	8.9
9	3	3.0
Missing data	67	66.3
Total	101	100

Renal function

Eighty-three (82.2 %) patients had normal renal function. According to patient records, impaired renal function was diagnosed in 18 (17.8 %) patients. Mean Scr was 1.1 (SD 0.8, median 0.90, IQR 1.2 – 0.6). Estimated GFR using the CKD-EPI formula had the mean of 76.3 ml/min (SD 29.4, median 83, IQR 99 – 55.5). Estimated CrCl using Cockcroft-Gault (CG) formula was possible to calculate for 69 (68.3 %) patients. It had the mean of 89.9 ml/min (SD 51.9, median 81.1, IQR 113 – 54.7). GFR values were interpreted according to the stages of CKD and patient distribution is shown in the Table 3.20.

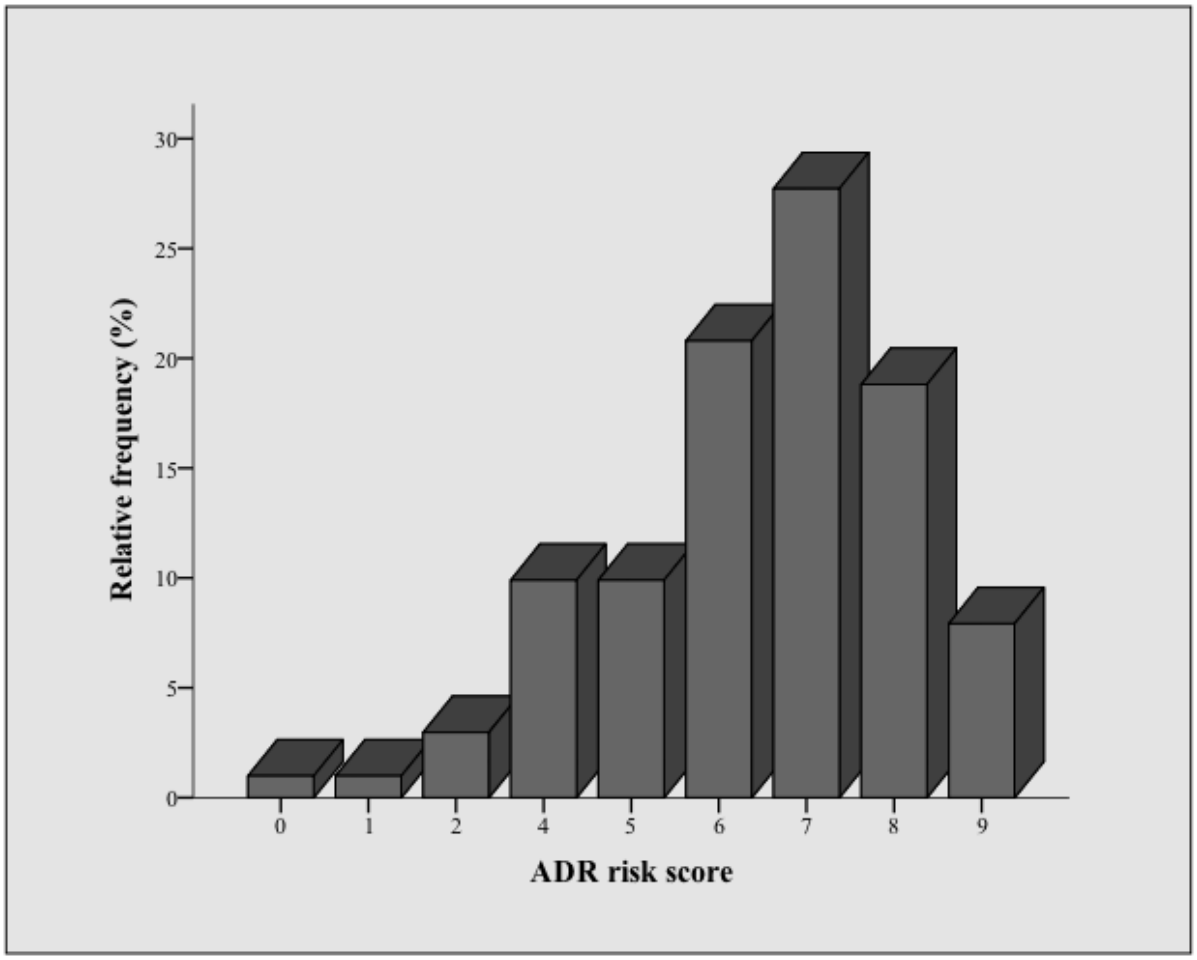
Table 3.20: Interpretation of GFR value

Stages of Chronic Kidney Disease	CKD-EPI formula	CG formula
1: Normal kidney function	39 (38.6 %)	22 (22.8 %)
2: Mildly reduced kidney function	32 (31.7 %)	22 (21.8 %)
3: Moderately reduced kidney function	25 (24.8 %)	19 (18.8 %)
4: Severely reduced kidney function	2 (2 %)	4 (4 %)
5: Very severe kidney failure	3 (3 %)	1 (1%)
Missing values	0	32 (31.7 %)
Total	101 (100 %)	32

3.3.2 Adverse drug reaction risk score

The cohort had ADR risk score from 0 to 9 (Figure 3.1). None of patients had a maximum of 10 points. The mean ADR risk score was 6.4 (SD 1.8, median 7, IQR 8 – 5.5). Following the score interpretation, occurrence of the ADR was **doubtful** in 1 (1 %) patient and **possible** in 14 (13.9 %) patients. In majority of patients, 78 (77.2 %), ADR occurrence was **probable**. In eight (7.9 %) patients ADR was predicted as **definite**.

Figure 3.1: ADR risk score



Each individual discrete variable producing the score was analysed. One patient (1 %) had less than five prescribed drugs, 11 (10.9 %) patents had 5 – 7 prescribed drugs and 89 (88.1 %) of patients had more than eight drugs prescribed. Twenty-five (24.8 %) patients had less than four comorbidities and remaining 76 (75.2 %) had four or more comorbidities. Eighteen (17.8 %) patients had renal failure and five (5 %) had liver disease. Heart failure was diagnosed in 29 (28.7 %) patients. Previous ADR experienced 74 (73.3 %) patients.

3.3.3 Drug-drug interactions

DDIs assessment was performed by the software and by the pharmaceutical team.

For each patient, DDIs were reviewed with the Mediq® software that provided DDI assessment in three different severity levels:

1. Yellow – low DDI potential, relevant in exception cases
2. Orange – middle DDI potential, clinically relevant
3. Red – highly relevant DDI potential risk
4. Summary – all potential DDIs (pDDI)

As reported by the software, there were 24 DDI/patient. The pharmaceutical team assessed 14.5 % of DDIs clinically relevant (cr), 3 crDDI/patient. The results of the Mediq® software output and pharmaceutical DDI assessment are presented in the Table 3.21.

Table 3.21: Mediq® output and clinically relevant DDIs

№	Drugs	pDDI	DDI_1	DDI_2	DDI_3	crDDI	crDDI with CTx
Median (IQR)	13 (16-10)	19 (30-10)	16 (24-8)	3 (7-1)	0 (0-0)	1 (6-0)	0 (0-0)
Sum	1315	2393	1900	477	16	347	45
Min	4	0	0	0	0	0	0
Max	26	115	95	20	2	25	7

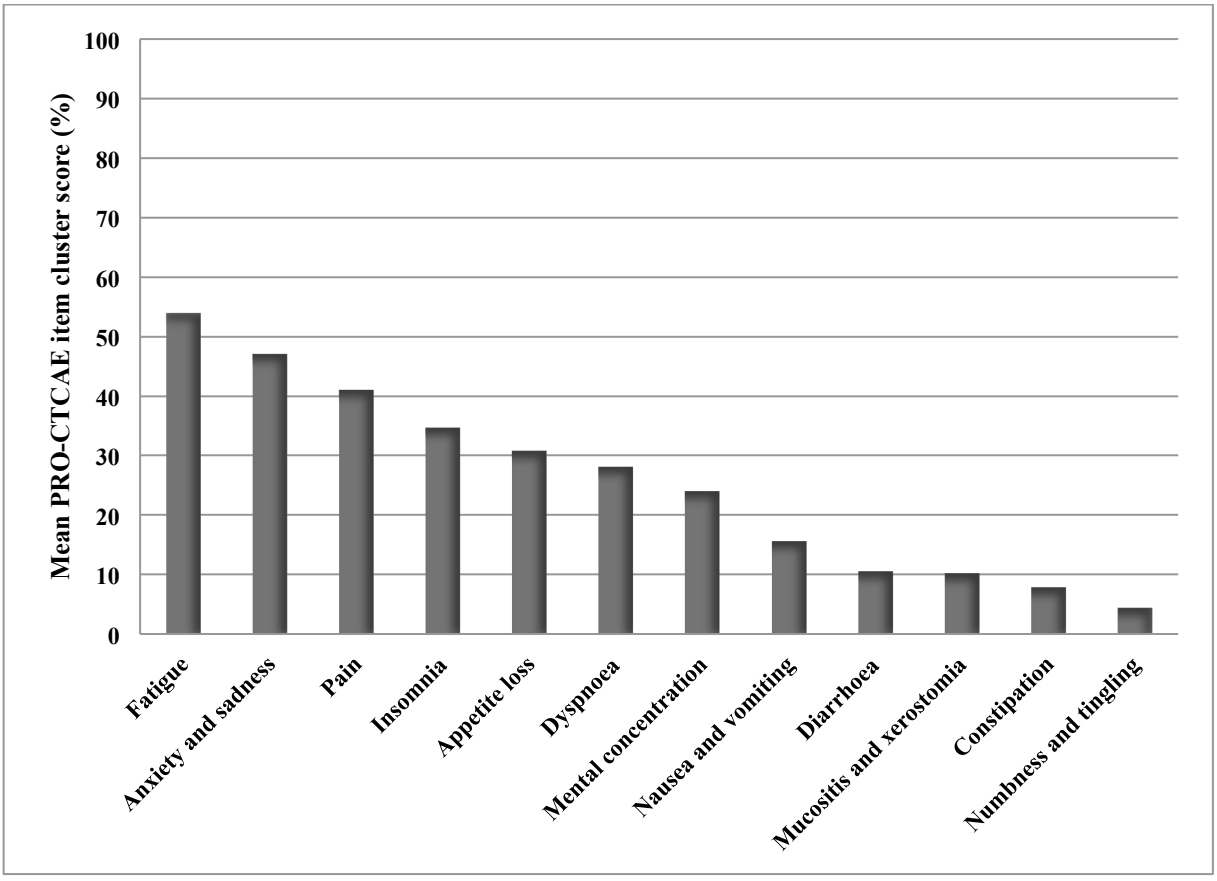
Legend: pDDI – potential DDIs reported by the Mediq® software; crDDI – clinically relevant DDI by the pharmaceutical DDI assessment; CTx – chemotherapeutics

3.3.4 Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

The German PRO-CTCAE core set item questionnaire was successfully applied once a week to 101 patients in the study. From the 100 % response rate, in 23 cases (22.77 %) patient's care-providers helped (backup method) to complete the questionnaire.

Symptom burden calculated as a mean cohort PRO-CTCAE item cluster scores is presented in the Figure 3.2. The greatest symptom burden to the patients imposed fatigue (53.9 %), anxiety and sadness (47 %), pain (41.08 %) and insomnia (34.69 %). Appetite loss (30.78 %), dyspnoea (28.11 %), mental concentration (24 %), nausea and vomiting (15.64 %) showed intermediate burden. Lighter burden indicated diarrhoea (10.59 %), mucositis and xerostomia (10.29 %), constipation (7.85 %) and the lowest numbness and tingling (4.46 %). Mean cohort attribute: frequency, severity and interference scores are shown in the attachment (Mean cohort attribute scores in Attachments Model II).

Figure 3.2: PRO-CTCAE symptom burden



If either one of the attributes: frequency, severity, interference was uncontrolled in any of the item clusters and the therapy was not appropriately adjusted, PR was provided to the medical team. That was the case in 13 patients (12.90 %) representing 6.67 % of all PRs provided. The items cluster included in recommendations were: anxiety and sadness (once), nausea and vomiting (once), appetite loss (once), mental concentration (once), numbness and tingling (once), dyspnoea (twice), insomnia (three times), fatigue (three times).

Pearson's multiple chi square testing

The results of Pearson's chi square test of independence between low (value 0 – 1)/ high (value 2 – 4) mean cohort PRO-CTCAE attribute score and low/high mean cohort characteristics are presented here. Supporting material for the PRO-CTCAE attributes score relations with cohort characteristics is in the attachment (Pearson's chi square test of independence – Crosstabs Table in Attachments Model II). In explorative Pearson's multiple chi square testing, there was a high probability that maximum two results are false positive (type I error).

Mean cohort PRO-CTCAE **frequency** score showed a relationship with ECOG performance status ($p = 0.035$). Patients with 0 and 1 ECOG performance status had mostly mean frequency score up to 2. Patients with impaired performance status (ECOG 2 – 4) had mostly mean frequency score higher than 2. Mean frequency score was independent in relation to number of drugs, number of DRPs, ADR risk score and cancer type.

Mean cohort PRO-CTCAE **severity** score showed a relationship with number of DRPs ($p = 0.025$) and it was independent in relation to ECOG performance status, cancer type, number of drugs and ADR risk score. Though all patient with severe mean cohort PRO-CTCAE score had more than eight drugs prescribed (high number of medication) and more than five ADR risk score (high ADR risk score), no significance has been observed.

Mean cohort PRO-CTCAE **interference** score showed a relationship with ECOG performance status ($p = 0.013$) and number of drugs ($p = 0.038$). Majority of patients with 0 and 1 ECOG performance status had mean interference score up to 2. Mean interference score higher than 2 had significantly more patients with impaired performance status (ECOG 2 – 4) and more than eight drugs prescribed. Mean cohort PRO-CTCAE interference score was in relation with cancer type ($p = 0.012$) too, show-

ing that more solid tumour patients had mean interference score higher than 2. Mean interference score was independent in relation to the number of DRPs and ADR risk score.

PRO-CTCAE score over time

Given the application of PRO-CTCAE item questionnaire was performed weekly, each patient had a different number of repeated questionnaires based on their different length of stay on ward. Some patients had 2, 3, 5 or even 7 repetitions of the questionnaire (see Figures 3.3 – 3.8). That caused inability to show unified mean cohort PRO-CTCAE score over time. Individual cases of three patients are presented here. Mean patient PRO-CTCAE attribute score decreased over time on the study ward, having the lowest value at the last time point. The same pattern could be seen in majority of mean patient PRO-CTCAE item cluster scores.

Patient A with two PRO-CTCAE item questionnaires (PRO-CTCAE Output)

Figure 3.3: Mean patient PRO-CTCAE item cluster score over time (patient A)

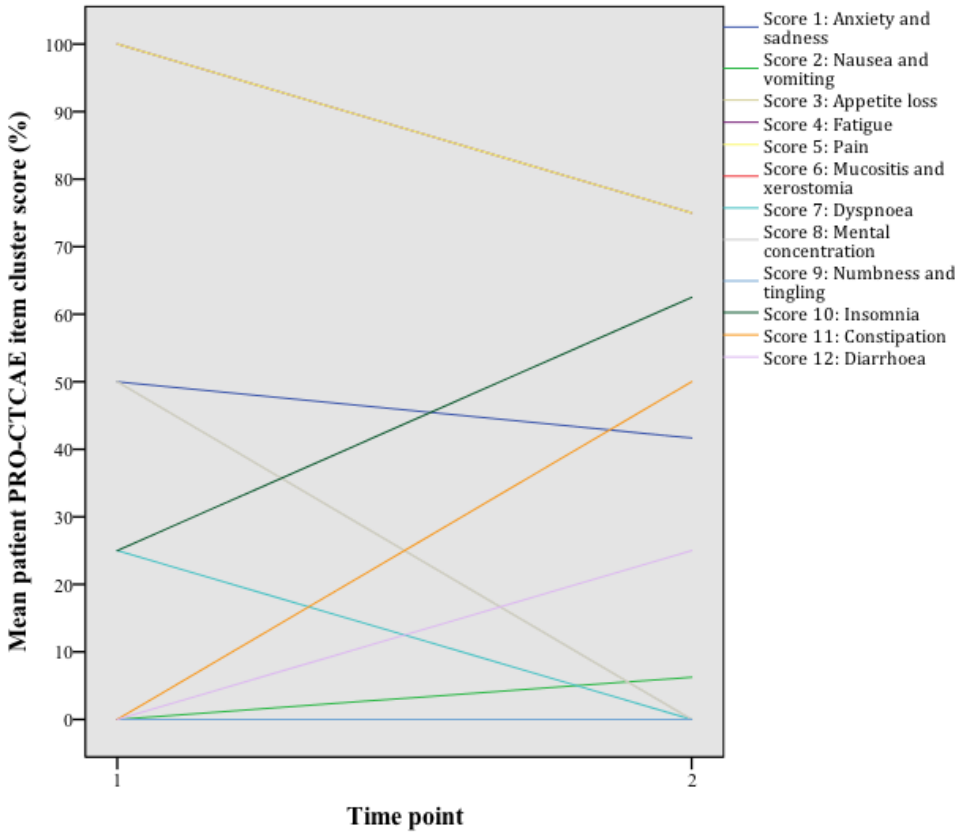
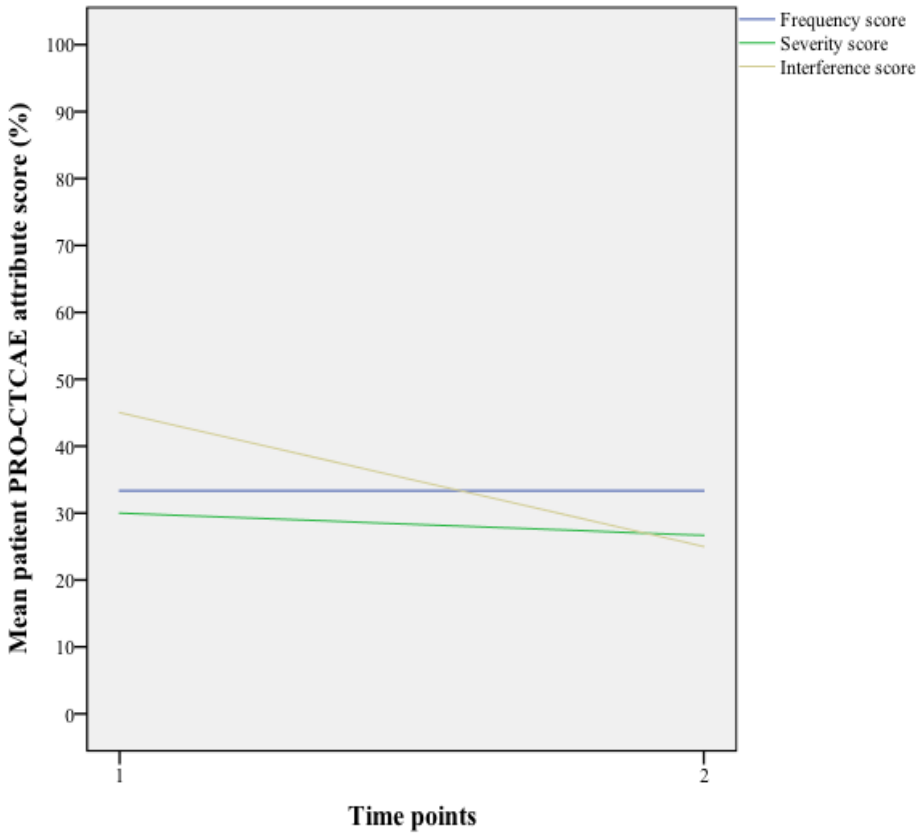


Figure 3.4: Mean patient PRO-CTCAE attribute score over time (patient A)



Patient B with five PRO-CTCAE item questionnaires

Figure 3.5: Mean patient PRO-CTCAE item cluster score over time (patient B)

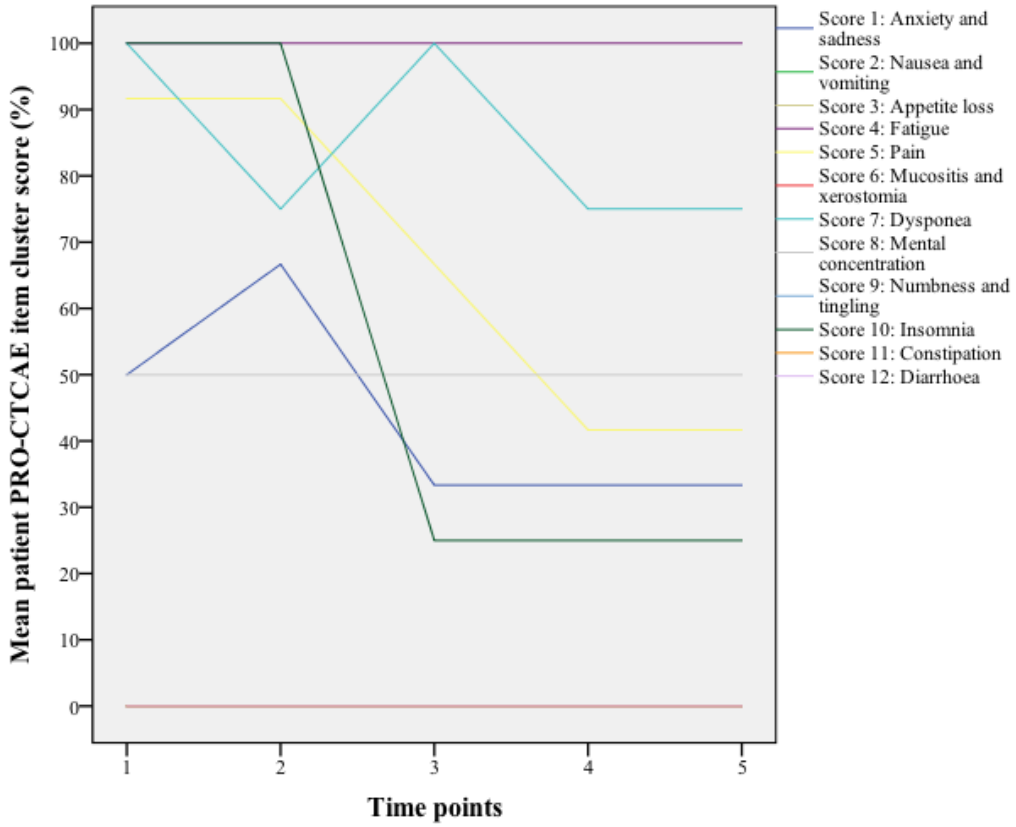
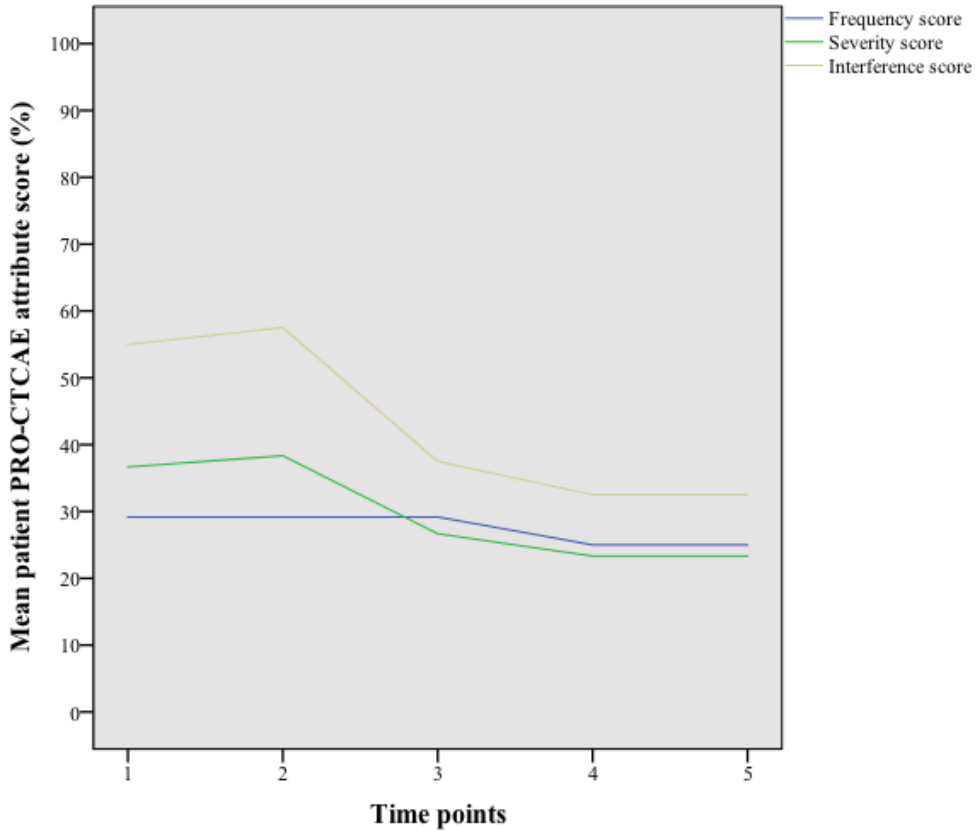


Figure 3.6: Mean patient PRO-CTCAE attribute score over time (patient B)



Patient C with seven PRO-CTCAE item questionnaires

Figure 3.7: Mean patient PRO-CTCAE item cluster score over time (patient C)

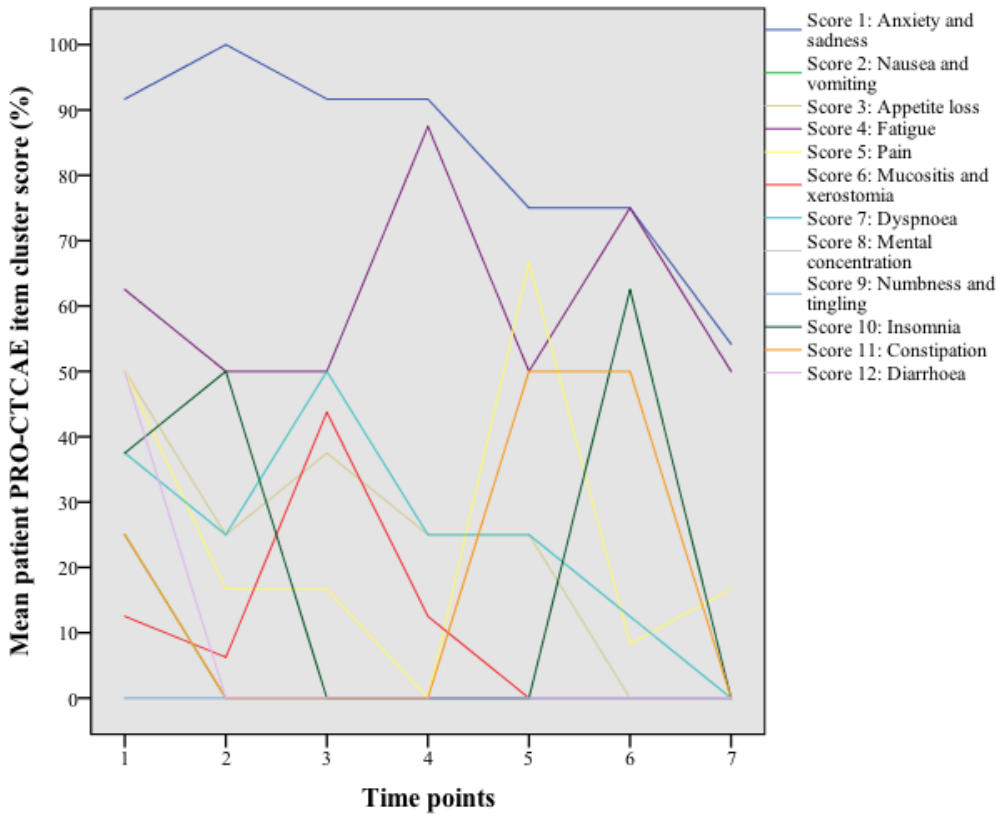
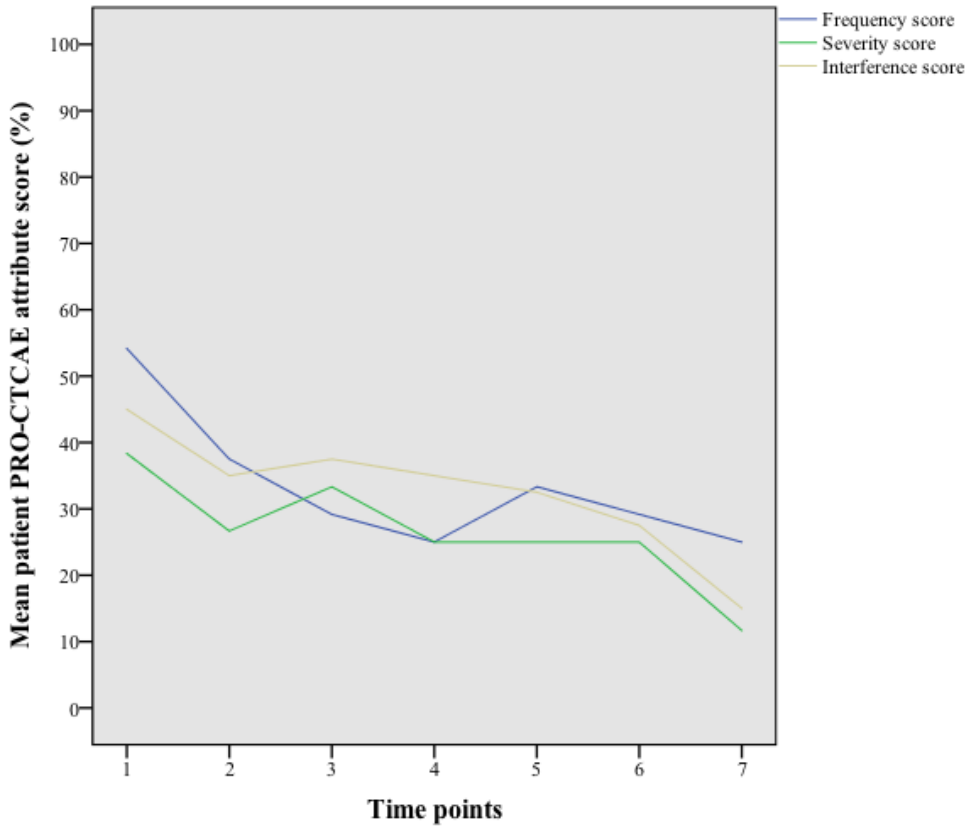


Figure 3.8: Mean patient PRO-CTCAE attribute score over time (patient C)



3.3.5 Drug-related problems

Type, frequency and occurrence

Patients had on average 13 drugs prescribed (SD 4.5, median 13, IQR 16 – 10, min 4 max 26) when the first MSR was performed. During the study time 191 DRPs led to PI. On average every patient had 1.9 DRPs (SD 2.1, median 1, IQR 3 – 0, min 0 max 13). Mean DRP incidence rate was 0.26 (SD 0.3, median 0.17, IQR 0.33 – 0).

In the Figure 3.9 is shown the distribution of DRPs in APS-Doc® classification categories. In 21 cases (10.9 %) DRPs included anti-cancer drugs. The other DRPs were with supportive or concomitant therapy. Type and frequency of DRPs according to the APS-Doc® system are showed in the Table 3.22.

Figure 3.9: APS-Doc® categories of DRPs

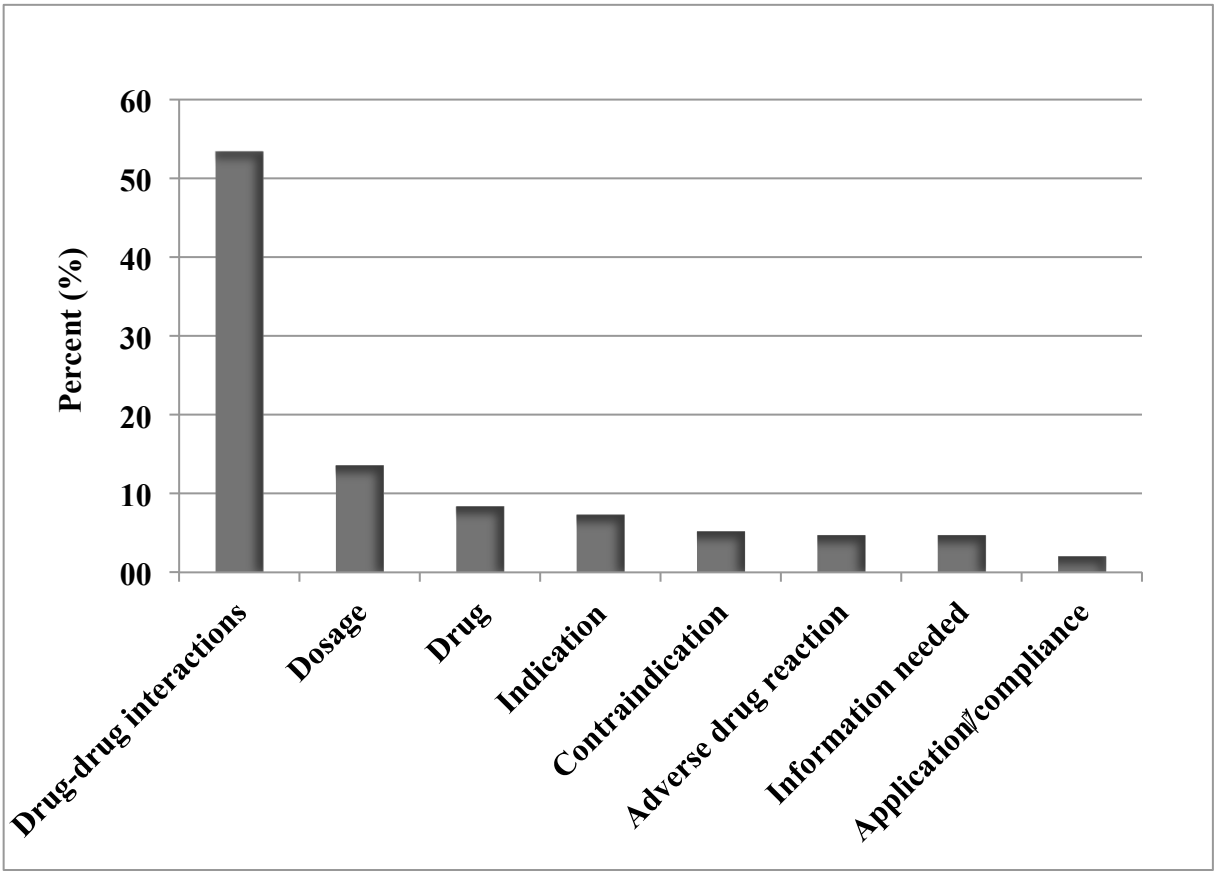


Table 3.22: APS-Doc® classification of DRPs

APS-Doc® category	APS-Doc® subcategory	Frequency	Percent (%)
Administration/ compliance	AC 1	1	0.5
	AC 2	1	0.5
	AC 3	1	0.5
	AC 4	1	0.5
Drug	Rx 6	1	0.5
	Rx 8	10	5.2
	Rx 10	1	0.5
	Rx 11	4	2.1
Dosage	DOS 2	1	0.5
	DOS 3	7	3.7
	DOS 4	5	2.6
	DOS 5	5	2.6
	DOS 6	8	4.2
Dosage form/ drug strength	DS 1	1	0.5
Indication	IND 1	2	1.1
	IND 2	9	4.7
	IND 3	3	1.6
Contraindication	CI 1	10	5.2
Adverse drug reaction	ADR 1	8	4.2
	ADR 2	1	0.5
Drug-drug interactions	DDI 1	98	51.3
	DDI 2	4	2.1
Other: Information needed	O 3	2	1.1
	O 4	7	3.7
Total		191	100

Legend: AC 1 – Lack of patient's knowledge about correct administration; AC 2 – Patient does not take the drug; AC 3 – Patient alteration of the recommended dosage (without consultation with pharmacist or physician); AC 4 – Inappropriate duration (too short/too long); Rx 6 – Discontinuation of ambulatory medication (complete drug history is available. but not each drug is prescribed);

Rx 8 – Transcription error/unintended discontinuation of drug therapy (during the hospital stay); Rx 10 – Unintended prescribing of a product from the same class of drugs; Rx 11 – No/inadequate drug monitoring; DOS 2 – Prescription of an incorrect dosage or no dosage prescribed; DOS 3 – Dose to low; DOS 4 – Dose to high; DOS 5 – Inappropriate administration interval; DOS 6 – No dosage adjustment in case of renal failure; DS 1 – Wrong dosage form prescribed; IND 1 – Medication inappropriate (better option available); IND 2 – No indication; IND 3 – Drugs missing (no drug prescribed in patients with an existing indication) or suboptimal dosage; CI 1 – Contraindication not accounted for; ADR 1 – Symptoms of an adverse drug reaction; ADR 2 – Patient's fear of an adverse drug reaction; DDI 1 – Drug–drug interaction as indicated by literature (clinical relevance not proven); DDI 2 – Symptoms of a drug-drug interaction; O 3 – Information requirement by patient; O 4 – Information requirement by physician/nurse

Pharmaceutical intervention and implementation

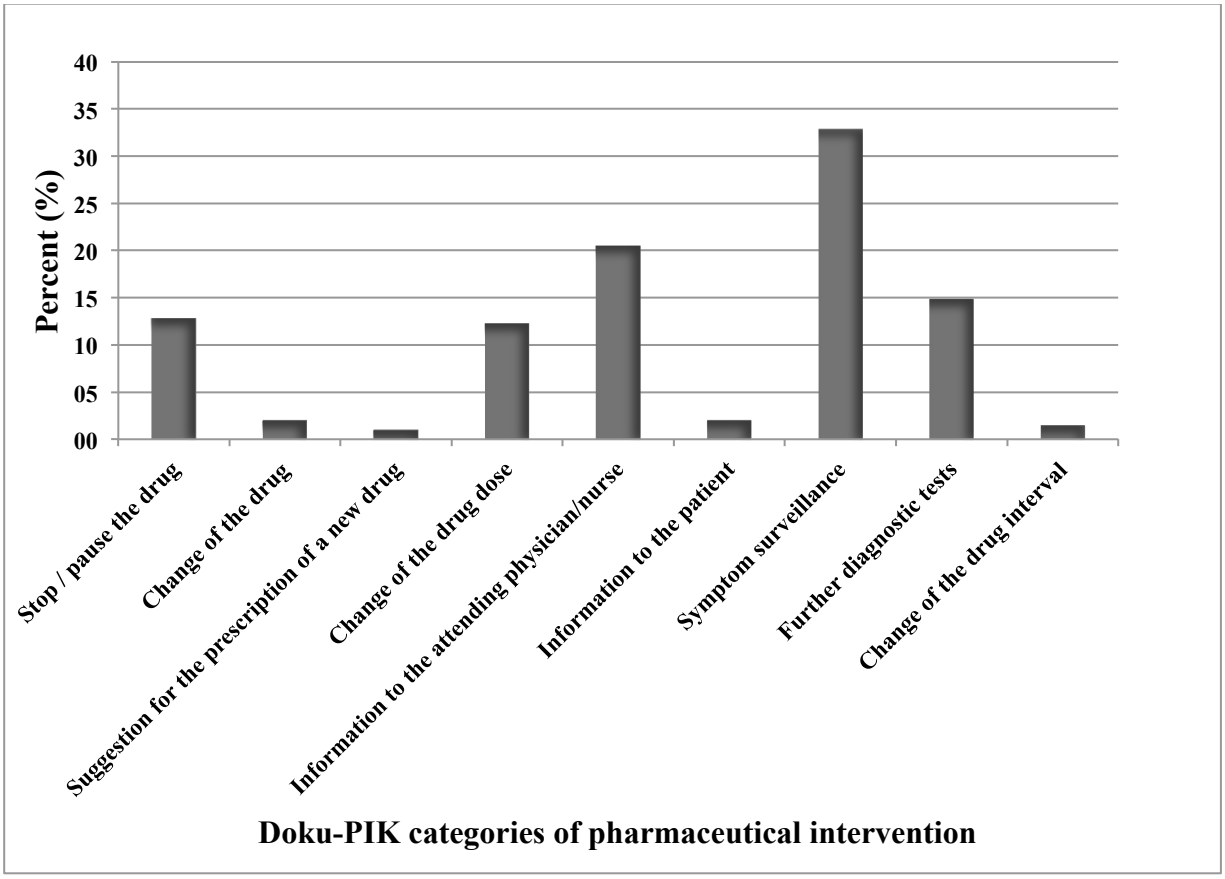
For each DRP pharmaceutical team provided adequate PR (intervention) to the medical team on the ward. The PRs were delivered in paper form and directly discussed on the ward. In some cases one DRP needed more than one PR. For 191 DRPs pharmaceutical team delivered 195 PRs. The recommendations were categorised according to the DokuPIK system into nine different categories of PIs. PIs and their relative frequency were expressed in percentage and shown in the Figure 3.10. **Implementation rate** of the pharmaceutical recommendation was 93.3 %.

In 78 (40 %) recommendations, preventive measure were suggested to the medical team on the ward and considered timely. One-hundred and four (53.3 %) recommendations were directly implemented. In 13 (6.7 %) cases pharmaceutical recommendation were not implemented.

Expenditure of time

The time invested in patient recruitment and documentation, and the time invested in the complete pharmaceutical care was tracked in hours. The time invested on each patient case was on average 10 hours. Patient recruitment and documentation per se took 2 hours/patient. Expenditure of time for pharmaceutical care provided during the entire patient's hospital stay was on average 8 hours/patient. From that, 6.4 h on average was individual work of the research pharmacist. The rest of 1.6 hours/patient on average were teamwork: within pharmaceutical team itself and interactions with the ward based team.

Figure 3.10: Doku-PIK categories of pharmaceutical intervention

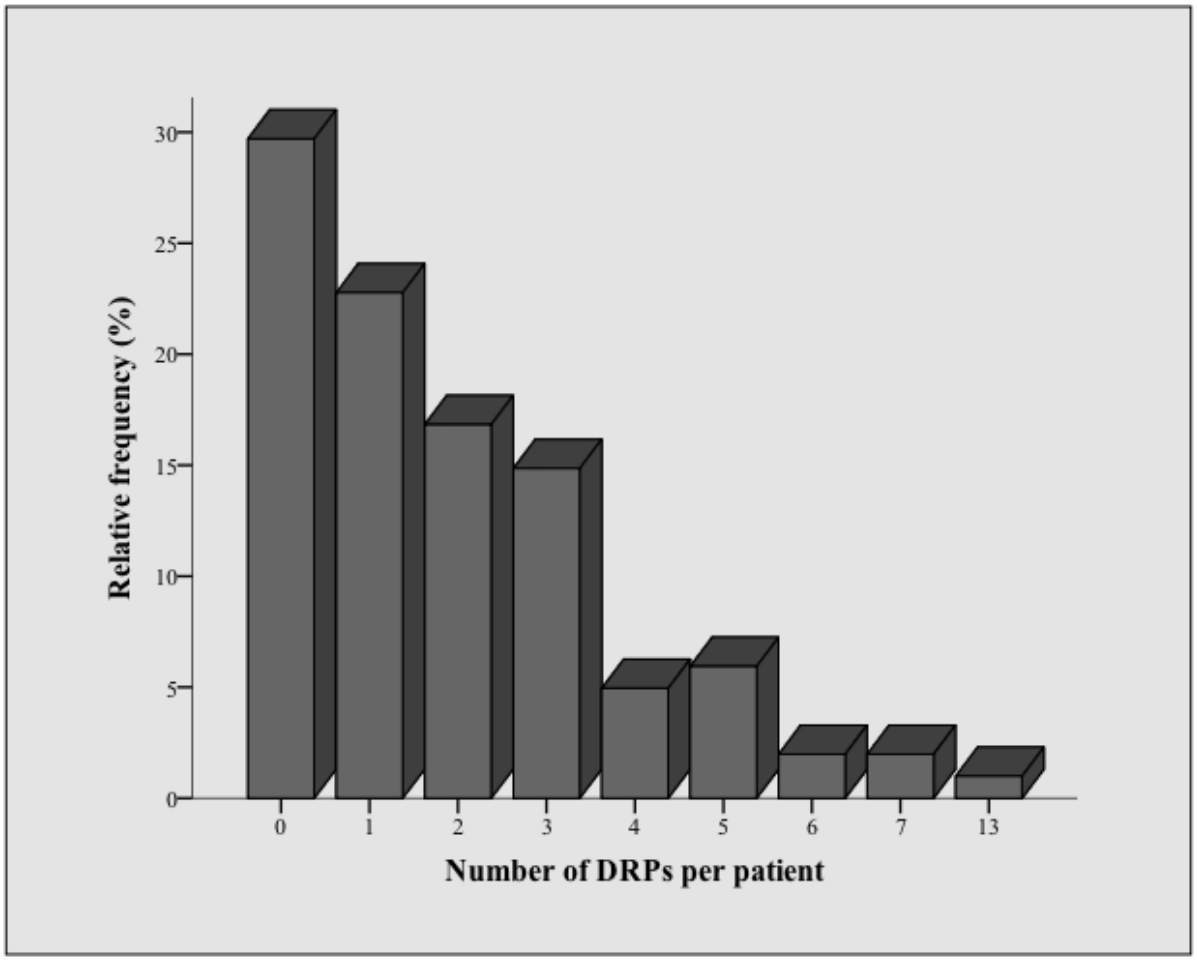


3.3.6 Drug-related problem prediction model

Model development

Variable "number of DRPs" had count data, nonnegative integer numbers. Few DRPs leading to PI occur in many patients as it can be seen in the Figure 3.11. Representing rare events, it was assumed that the **Poisson distribution** was a natural candidate for modelling such data.

Figure 3.11: Relative frequency of DRPs per patient



Poisson distribution calculated the probability of a DRP occurring over the time interval - stay on the study ward. Discrete random variable "number of DRPs" was a Poisson random variable with parameter μ as mean of expected DRPs, n as number of DRPs (n = 0.1.2.3…), λ incidence rate per time unit (day on the study ward) and probability *P*:

$$P_\lambda\,(n|\,total\ time\ T)\ =\ \frac{\mu^n}{n!}\ *\ e^{-\mu}$$

e was a mathematical constant approximately equal to 2.718, *!* referred to the factorial.

Mean of expected DRPs was defined as:

$$\mu = \lambda * T$$

where *T* was an offset. Each patient had a different stay on the study ward i.e. individuals did not follow the same time. The "offset" variable was calculated as natural logarithm of the days on the study ward.

The Poisson regression model function to estimate DRP incidence rate was:

$$\lambda = \lambda_0 * {R_1}^{X_1} * {R_2}^{X_2} * \ldots * {R_n}^{X_n}$$

where λ_o was baseline incidence rate, *R* relative risks, *X* influential factors. [165]

For the outcome representing Poisson distribution, the **Poisson regression model** was the most appropriate choice.

Model specification and performance

The Poisson model assumed that the risk, in our case of DRP, was the same each day of the hospital stay. Based on the intervention provided in this study that was not the case. Two different time periods were distinguished: (A) **initial** and (B) **follow-up**. Initial time period (A) was at the beginning of the hospital stay on the ward, up to the 5th day in the hospital. Within this time the patient was recruited and pharmaceutical team performed – extended patient medication history, medication reconciliation and MSR. If any DRP was detected, first pharmaceutical intervention was provided as described in the chapter 3.2.5 Intervention. Follow-up time period (B) in the hospital stay was considered from the 5th up to the 10th day – in other words comparable time span of 5 days as in the initial time period.

The Poisson regression was run (I) to predict the number of DRPs based on 17 potential risk factors. Further, the adjusted model (ADR risk score as fixed variable) was run (II) to predict the number of DRPs based on ADR risk score. The results of univariable and multivariate regression models are presented below.

Univariable analysis

(I) In the Univariable Poisson regression model, 17 different predictors were exploratively assessed. Components of ADR risk score: "number of drugs", "number of comorbidities", "renal failure", "heart failure", "liver disease", "previous ADR", the score itself and oncological characteristics "ECOG performance status", "therapy plan", and "therapy regimen" had significance level $p \leq 0.2$. They were selected as

potential predicting factors of the number of DRPs in the multivariate regression. The number of participants without missing values for each selected predictor and the corresponding number of DRPs in those participants is presented in the Table 3.23.

Table 3.23: Participants characteristics in development data set

Predictors	Number of participants (n=101)	Number of DRP (n=191)
ADR risk score, n (%)		
ADR doubtful, score 0	1 (0.9)	0 (0)
ADR possible 1 – 4	14 (14)	12 (6.3)
ADR probable 5 – 8	78 (77.2)	159 (83.2)
ADR definite 9 – 10	8 (7.9)	20 (10.5)
ECOG, n (%)		
0-1	47 (46.5)	57 (29.8)
2	22 (21.8)	55 (28.8)
3-4	23 (22.8)	64 (33.5)
Missing values	9 (8.9)	15 (7.9)
Therapy regimen, n (%)		
First line therapy	57 (56.4)	112 (58.6)
Second line therapy	26 (25.7)	47 (24.6)
Third line therapy	12 (11.9)	25 (13.1)
Fourth line therapy	4 (4.0)	2 (1.1)
Unknown	2 (2.0)	5 (2.6)
Therapy plan, n (%)		
Curative	19 (18.8)	30 (15.7)
Palliative	66 (65.4)	136 (71.2)
Unclear further diagnostics needed	16 (15.8)	25 (13.1)

(II) It was assumed that the ADR risk score fit to our data. As a result, logistic linear influence was expected. ADR risk score with B 0.219 (95% CI 0.119 to 0.319), had

statistical significance of p < 0.001 in the univariable Poisson regression model. The predicted daily incidence rates (*IR*) of DRPs based on the ADR risk score were:

$$IR = e^{\{-3.081+RS\times 0.219\}}$$

where *RS* was ADR risk score with values from 0 to 10.

The related *Risk* during the *Time* of 5 days (A) in the hospital was expressed as:

$$Risk = IR \times Time$$

The results are shown in the Table 3.24. The table shows that among 100 patients who based on the ADR risk score were interpreted as doubtful of experiencing an ADR, almost 25 % of them had experienced at least one DRP during five days in hospital. On the other hand, among 100 patients who were probable to experience an ADR, the risk of DRP was three to five times higher. A patient with a definite ADR risk was predicted to experience 2.1 DRPs up to day five on the study ward or in other words, a group of 10 patients with a definite ADR risk was predicted to experience 21 DRPs.

Table 3.24: Univariable Poisson regression model

ADR risk score	Score interpretation	Five days incidence rates of DRPs
0 point	Doubtful	0.23
1 – 4 points	Possible	0.3 – 0.6
5 – 8 points	Probable	0.7 – 1.3
9 – 10 points	Definite	1.7 – 2.1

Multivariate analysis

(I) In the multivariate analysis the data was modelled considering two time periods. Consequently two different models were presented. Model (A) shows initial DRP risk and model (B) follow-up DRP risk. Both selection procedures: forward selection and backward elimination, are jointly presented below as they showed similar results.

(A) Initial DRP risk model

Initial DRP risk model assessed risk of DRP up to 5th day in hospital, on the study ward. Significant risk factors are **ECOG** performance score (p = 0.003), presence of **heart failure** diagnosis (p < 0.001) and **ADR risk score** (p < 0.001). Parameter estimates are presented in the Table 3.25.

Table 3.25: Parameter Estimates – Model A

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test			Exp(B)	95% Wald Confidence Interval for Exp(B)	
			Lower	Upper	Wald Chi-Square	df	Sig.		Lower	Upper
Intercept	-3.990	.5345	-5.038	-2.942	55.727	1	.000	.018	.006	.053
ECOG = 3,4	.680	.2115	.265	1.094	10.329	1	.001	1.973	1.304	2.986
ECOG = 2	.542	.2095	.131	.952	6.686	1	.010	1.719	1.140	2.591
ECOG = 0,1	0[a]	.	.	.	.	.	.	1	.	.
HF = present	-1.001	.2305	-1.453	-.549	18.865	1	.000	.368	.234	.577
HF = not present	0[a]	.	.	.	.	.	.	1	.	.
ADR Risk Score	.442	.0770	.291	.593	33.022	1	.000	1.556	1.338	1.810
(Scale)	1[b]									

Legend: B – coefficient estimate, Sig. – significance probability (p – value), ECOG – performance score values from 0 up to 4, HF – heart failure diagnosis;
Dependent Variable: event_t5_sum, Model: (Intercept), ECOG, HF, ADR RS, offset = offset_t5,
a. Set to zero because this parameter was redundant, b. Fixed at the displayed value.

Validation of the initial DRP risk model estimated AUC of 0.777 (95 % CI 0.686 – 0.868, SE 0.046, $p < 0.001$). True-positive rate (sensitivity or probability of detection) against false-positive rate (fall-out, probability of false alarm, 1 – specificity) is plotted in Figure 3.12. Considering equal importance of sensitivity and specificity, maximized sensitivity and specificity values were 0.738 and 0.722, respectively. That is the point on the ROC curve where sensitivity is the highest and 1 – sensitivity the lowest.

The Table 3.26 shows the probability of no event (patients without DRP) during the first five days on the study ward. Column “Valid” represents the calculated probabilities of no events. Column “Frequency” shows number of patients with particular probability. “Valid Percent” shows the percent of patients with particular probability. From the column “Cumulative Percent” it can be derived that half of the study patients had a no-event probability below 0.2 or a high probability (0.8) of experiencing DRP. Further, 25 % of patients had no-event probability of above 0.5 or in other words, a quarter of patients had a probability of 0.5 and less to experience a DRP

Figure 3.12: ROC curve – Model A

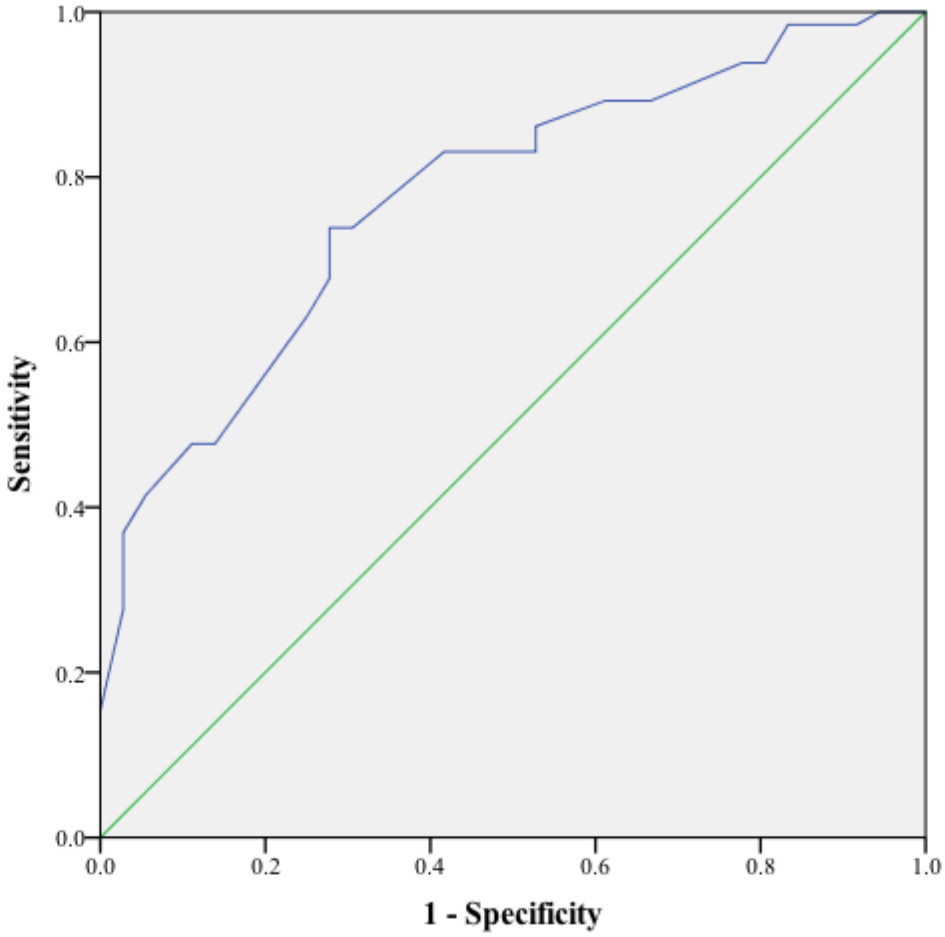


Table 3.26: Probability of no event (up to 5th day)

Valid	Frequency	Valid Percent	Cumulative Percent
.01	3	3.0	3.0
...			
.13	4	4.0	28.7
.16	7	6.9	35.6
.20	18	17.9	53.5
...			
.51	5	5.0	79.2
.52	1	1.0	80.2
.55	1	1.0	81.2
...			
.89	1	1.0	100.0
Total	101	100.0	

(II) Additionally, the analysis was run to predict the number of DRPs based on ADR risk score, as fixed variable. It was assessed whether the single ADR risk score fit to our data to predict DRPs. ADR risk score had $p < 0.001$, B 0.442, 95% CI 0.291 – 593 in the multivariate analysis of the initial risk. Next, results suggested including two corrections: consideration of ECOG performance status and change of individual component's weight, heart failure, in ADR risk score. The corrections were based on the significant probability and presented below in transformed form to ease the use of the model in the practice. Other variable did not significantly influence the initial model.

First correction in the score was ECOG performance status. ECOG was an informative variable with $p = 0.003$ (B 0.542, 95% CI 0.131 – 0.954). As shown in the Table 3.27 to implement ADR risk score in our population of oncology patients and predict initial risk of DRPs, it was necessary to consider ECOG. For the patient with no or low degree of functional impairment (ECOG performance status ≤ 2) there was no change in the risk of DRP compared to the one predicted solely on ADR risk score. But the patients with impaired performance status (ECOG score 2 – 4) should be interpreted for a class higher. That means, for instance, a patient with ADR risk score 4 and ECOG performance score ≥ 2 were not possible than probable to experience an ADR. The risk went up for one interpretation class.

Table 3.27: Multivariate analysis – Incidence rates of DRPs based on ADR risk score and ECOG performance status

ADR risk score	Score interpretation	ECOG performance score < 2	ECOG performance score ≥ 2
0 point	Doubtful	0.02	0.05
1 – 4 points	Possible	0.03 – 0.1	0.09 – 0.3
5 – 8 points	Probable	0.2 – 0.6	0.5 – 1.9
9 – 12 points	Definite	1 – 1.5	2.9 – 4.5

Second correction was change of weight of individual component of ADR risk score, particularly heart failure. Other components should not be weighted differently, as they showed no statistical significance in the initial DRP risk model. Presence of heart failure diagnose was statistically significant with $p < 0.001$, B –1.001, 95% CI 0.2305 – 1.453 and thereby needed lower critical interpretation. As the coefficient estimate of

heart failure was two times higher and had a negative value (Table 3.28), interpretation in the new score should be that the presence of heart failure lowers the risk two times. ADR risk score as predicting factor was hard on patients with heart failure. In other words, heart failure was overestimated in our study population as a component of the ADR risk score. Patients with heart failure were half risky.

Table 3.28: Coefficient estimates interpretation

Parameter	Coefficient estimate	Interpretation
ADR risk score (fixed variable)	0.44	Measure taken to interpret other coefficients
Heart failure	– 1	Risk lowers two times

Finally, when these two corrections were considered, a new prognostic model **Initial DRP risk score** for oncology inpatients (Table 3.29) was proposed on the basis of ADR risk score. Two corrections brought two new parameter weights. ECOG performance status was a new included parameter, where one point went to patients with ECOG performance status ≥ 2. Presence of heart failure diagnosis was instead of +1, weighted –1, as explained earlier. Total number of points in Initial DRP risk score stayed the same as in the ADR risk score, 10 points. The cut off point of 4 remained the same and it was confirmed in validation analysis of coordinates of the ROC curve of the Initial DRP risk score (AUC of 0.790 (95 % CI 0.697 – 0.883, SE 0.048, $p < 0.001$), showing the sensitivity of 0.83 and specificity of 0.56. The prognostic ability of the model is shown in Figure 3.13. As a result, the interpretation of the Initial DRP risk score should not differ from the validated ADR risk score. In the ADR risk score, patients who had a higher score than 5 were considered together as being more prone to ADRs then the patients with lower ADR risk score 0 – 4 [57, 167]. Consequently, for the interpretation of the prognostic model, it was proposed to combine “probable (5 – 8 points)” and “definite (9-10 points)” naive interpretation class into “highly probable (5 – 10 points)” to experience DRP during the stay on the oncology ward (Table 3.30).

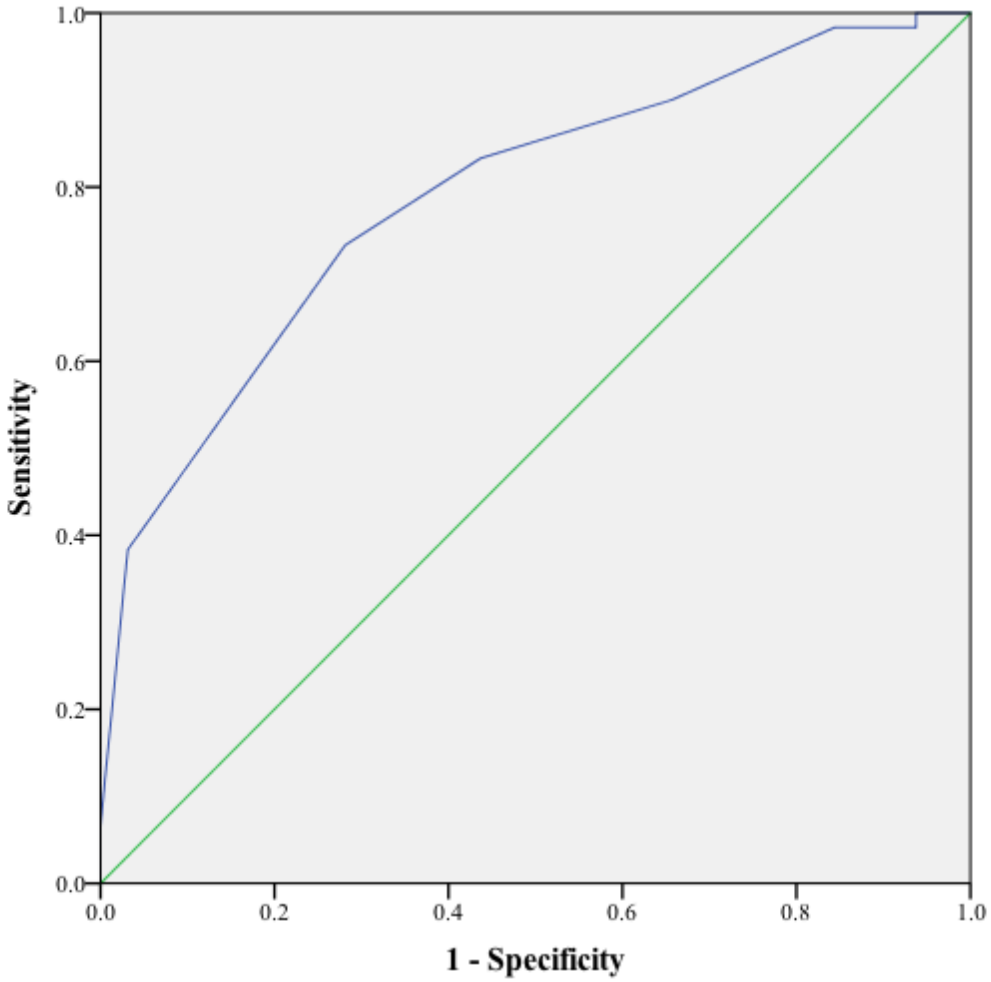
Table 3.29: New prognostic model "Initial DRP risk score" (new weights of parameters)*

Parameter	Weight of parameters: **ADR risk score** (points)	New weight of parameters: **Initial DRP risk score** (points)
Number of drugs	≤ 5 drugs 0 6 or 7 drugs +1 ≥ 8 drugs +4	≤ 5 drugs 0 6 or 7 drugs +1 ≥ 8 drugs +4
Previous ADR	No 0. Yes +2	No 0. Yes +2
Comorbidities	No 0. Yes +1	No 0. Yes +1
Heart failure	No 0. Yes +1	No 0. Yes -1 *
Renal failure	No 0. Yes +1	No 0. Yes +1
Liver disease	No 0. Yes +1	No 0. Yes +1
ECOG performance score	/	ECOG 0.1 0 * ECOG ≥ 2 +1
Total (maximum)	10 points	10 points

Table 3.30: Proposal of "Initial DRP risk score" interpretation

DRP risk score	DRP occurrence
0 point	Doubtful
1 – 4 points	Possible
5 – 10 points	Highly Probable

Figure 3.13: ROC curve – Score



(B) Follow-up DRP risk score

Follow-up DRP risk model assessed the risk of DRP from 5th day up to 10th day in hospital on the study ward. Significant risk factors were **ECOG** performance status (p = 0.039) and presence of **renal failure** diagnosis (p = 0.016). Parameter estimates are presented in the Table 3.31.

Table 3.31: Parameter Estimates – Model B

			95% Wald Confidence Interval		Hypothesis Test				95% Wald Confidence Interval for Exp(B)	
Parameter	B	Std. Error	Lower	Upper	Wald Chi-Square	df	Sig.	Exp(B)	Lower	Upper
Intercept	-2.627	.3811	-3.374	-1.880	47.492	1	.000	.072	.034	.153
ECOG = 3,4	.893	.4381	.034	1.751	4.155	1	.042	2.442	1.035	5.763
ECOG = 2	.842	.5181	-.173	1.858	2.642	1	.104	2.321	.841	6.409
ECOG = 0,1	0[a]	.	.	.	.	.	.	1	.	.
RF = present	.931	.3877	.172	1.691	5.771	1	.016	2.538	1.187	5.427
RF = not present	0[a]	.	.	.	.	.	.	1	.	.
(Scale)	1[b]									

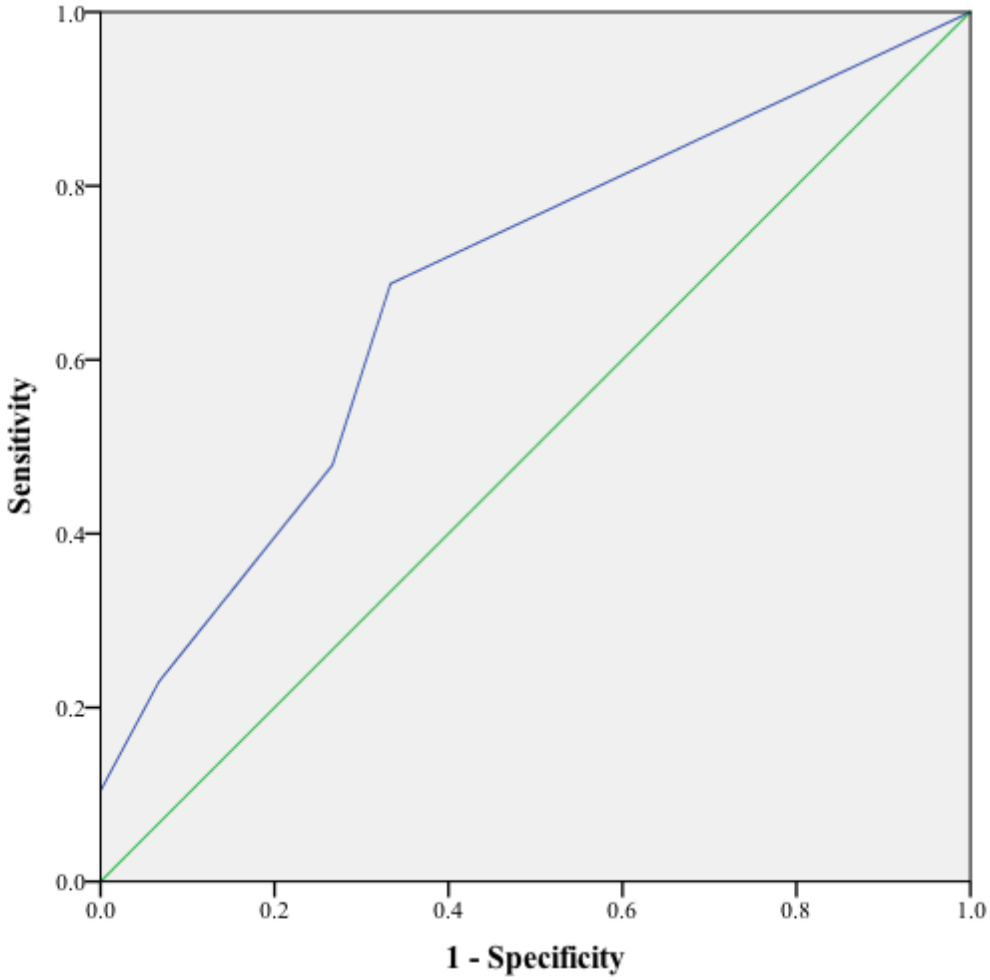
Legend: B – coefficient estimate, Sig. – significance probability (p – value), ECOG – performance score values from 0 up to 4, RF – renal failure diagnosis;
Dependent Variable: event5_t10_sum, Model: (Intercept), ECOG, RF, offset = offset_t5_10,
a. Set to zero because this parameter was redundant, b. Fixed at the displayed value.

Validation of the follow-up DRP risk model estimated AUC of 0.683 (95 % CI 0.532 – 0.835, SE 0.077, p = 0.033). True-positive rate (sensitivity or probability of detection) against false-positive rate (fall-out, probability of false alarm, 1 – specificity) is plotted in Figure 3.14. Considering equal importance of sensitivity and specificity, maximized sensitivity and specificity values were 0.688 and 0.667, respectively. That is the point on the ROC curve where sensitivity is the highest and 1 – sensitivity the lowest.

Table 3.32 shows the probability of no event (patients without DRP) from the 5th day until the 10th day on the study ward. Column "Valid" represents the calculated probabilities of no events. Column "Frequency" shows number of patients with particular probability, "Percent" shows the percent of patients with particular probability. "Valid

percent" is the percent of patients, when those discharged from the study ward before the 5th day are excluded. 60 % of patients stayed longer than 5 five days on the study ward. From the column "Cumulative Percent" it can be derived that less than 10 % of the study patients had a no-event probability below 0.2 between 5th and 10th day, or high probability (0.8) of experiencing DRP in that time. Further, 40 % of patients had no-event probability below 0.5. No patient had a no-event probability higher than 0.75 after the 5th day on the study ward.

Figure 3.14: ROC curve – Model B



Probability of no event for the entire time period (Initial and Follow-up) up to 10th day in hospital is presented in Table 3.33. It can be seen that over 10 days on the ward 50 % of patients had a no-event probability of 0.13 or below, in other words high probability of experiencing DRP. Furthermore, over 10 days on the study ward 92 % of patients had a no-event probability below 0.5 in other words – more than 90 % of patients had a probability of experiencing DRP 0.5 or higher during 10 days on the study ward.

Table 3.32: Probability of no event (from the 5th day up to 10th day)

Valid		Frequency	Percent	Valid Percent	Cumulative Percent
	.17	4	4.0	6.3	6.3
	.18	1	1.0	1.6	7.9
	.48	7	6.9	11.1	19.0
	.49	15	14.9	23.8	42.9
	.51	11	10.9	17.5	60.3
	.75	25	24.8	39.7	100.0
	Total	63	62.4	100.0	
Missing		38	37.6		
Total		101	100.0		

Table 3.33: Probability of no event (up to 10th day on the study ward)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	.00	2	2.0	3.2	3.2
	.01	3	3.0	4.8	7.9
	...				
	.10	3	3.0	4.8	42.9
	.11	3	3.0	4.8	47.6
	.13	1	1.0	1.6	49.2
	.15	7	6.9	11.1	60.3
	...				
	.29	2	2.0	3.2	82.5
	.38	2	2.0	3.2	85.7
	.43	1	1.0	1.6	87.3
	.49	3	3.0	4.8	92.1
	.51	2	2.0	3.2	95.2
	.58	1	1.0	1.6	96.8
	.63	2	2.0	3.2	100.0
	Total	63	62.4	100.0	
Missing		38	37.6		
Total		101	100		

3.4 Discussion

In order to ensure safe and effective drug therapy for cancer patients, a structured approach in multi-professional collaboration is essential [21, 22, 118, 119, 168]. This feasibility study represents first steps toward an effective multi-professional teamwork on the oncology ward in the hospital setting and may be the basis for the model evaluation on a big scale.

Within the scope of this feasibility study the developed model was assessed for strengthening the drug management in cancer patients. The results showed that integrating the pharmaceutical care service and applying the patient-related outcome questionnaire had contributed to the multi-professional collaboration and had a potential to improve patient safety. DRP prediction model offers further optimisation of the pharmaceutical care service in oncology.

Results with their strengths and limitations, as well as interpretation and generalisability of the study are discussed below.

3.4.1 Participants

The inclusion and supervision of study patients was carried out consistently. All patients who fulfilled the inclusion criteria during the study period were included. However, it has to be mentioned that the inclusion criteria had to be solved individually on the ward. Based solely on electronically available patient documentation, eligible patients could not be identified. Notably greater time was needed than initially planned to identify patients with appropriate inclusion criteria. The documentation gaps in the hospital information system might have caused the exclusion of some patients in the study. However, this proportion of patients is estimated to be rather low.

In this feasibility study 101 patients were included with fairly equal gender distribution (55 men and 46 women) and the average age was 65 (min 26, max 91). Previous feasibility study of our research group had comparable population – 306 patients (ca. 100 on every ward), equal gender balance (166 men and 140 women) and average age 66 (min 18, max 97) [49]. Lenssen with colleagues conducted the study on three other UKA wards: urology, neurology gastroenterology, and had the same inclusion criteria when non-disease specific parts are concerned – minimum of three days on the ward and medication plan at the hospital admission. Each investigated ward defined the disease-specific characteristics of inclusion criteria. An average age of cancer patients on the national level is 69 years [70]. Present study has on average slightly younger patient population.

Patients with solid and haematological tumour diagnosis were evenly distributed. The most frequent solid tumour type was malignant neoplasm of bronchus or lung with 23.8 % and most frequent haematological tumour diagnoses were diffuse large B-cell lymphoma with 15.8 % and multiple myeloma with 13.9 %. The study ward had two focuses: haematology-haemostasis and oncology. The expertise of the study ward was in leukaemia, lymphoma, multiple myeloma among haematology-haemostasis diseases, and the area of the bronchial carcinoma, the head and neck tumours among oncological diseases. Given these points, it could be said the diagnosis distribution of the study met the expectations. However, this did not coincide with general distribution of cancer diagnosis in Germany, where beside the lung cancer - prostate, the breast and intestinal cancer were the most frequent cancer diagnosis as stated in last report “Cancer in Germany 2011/2012” by the Robert Koch Institute and Association of Population-based Cancer Registries in Germany (GEKID) [70].

3.4.2 Pharmaceutical care

Provided pharmaceutical care service was based on the premise to maintain the current state of good, evidence-based pharmaceutical recommendation [169]. Pharmaceutical team had access to the medical-scientific databases and interaction software available at the UKA. The service was tested in previous projects of our research group and was defined as SOP for the succeeding studies, corresponding to the recommendations on design and evaluation of complex interventions to improve health care service [170]. The equality of observation was thereby ensured for all patients throughout the study period. As stated in previous works of the clinical pharmacy research group in Bonn [171, 172], it is important for a scientific evaluation of a new service that the pharmaceutical care (intervention) as well as the collection of the data (observation, documentation) is consistently conducted throughout the entire study period to all participants. The research pharmacist, the author of the present work, conducted each phase of the service. The collection and documentation of the data was therefore uniform which is an optimal prerequisite for the comparability of the results. For the first time the comprehensive pharmaceutical care was applied on the oncology ward. However, it was tested before on different UKA wards and study populations [51]. This provides a possibility to optimally compare the study results and thereby the needs of pharmaceutical care on various wards and patient populations.

Expenditure of time for pharmaceutical care provided during the entire patient's hospital stay was on average 8 h/patient. Therefrom, 6.4 hours on average were individual work of the research pharmacist. The rest of 1.6 hours/patient on average was teamwork: within pharmaceutical team itself and interactions with the ward based team. Time for data insertion, evaluation and analysis was not included. Previous studies on different ward of UKA [51] determined an overall time requirement of about 6 h/patient for inpatient pharmaceutical care. Lenssen and the team had a single clinical pharmacist supervising the patients, therefore no time expenditure for pharmaceutical team discussions as in present study. Taking that into the consideration, the expenditure of time of the two studies is quite similar.

An eight-hour care per patient with an average patient stay on the ward of ten days means a daily expenditure of about 50 minutes. For instance, on a ward with 30 beds, this represents a considerable need for additional medical stuff. Potential solution can be the involvement of a trained pharmacist [51] or trained pharmaceutical team

providing pharmaceutical care on the ward, as showed in this study. However, in order to achieve measurable benefit through pharmaceutical care an appropriate prior knowledge and training is needed. Further, it opens a discussion about task allocation. Different occupational groups involved in the medication process may potentially provide individual elements. Recent Cochrane Review showed several studies on inpatient medication management in which pharmacists and/or physicians performed the intervention. It was not possible to determine which professional group and/or which team constellation shows as the best option [45]. Taken an example of UKA hospital, integrating comprehensive medication safety review within the framework of physicians is simply not feasible in the determined physician's working hours. Thus, further resources are necessary to enable complete medication management. Finally, a multiprofessional team with clearly defined roles and responsibilities, with integrated clinical pharmacist within it, offers a solution for safer medication therapy and consequently enhanced patient safety.

Multi-professional team

Good cooperation among all parties involved: patient, physicians, nurses and pharmacists underpin the successful study implementation. For the first time, such team constellation was introduced on the UKA oncology ward. As described in 3.2 Methods the exciting team rolls of nurses, physicians and patients were maintained. Presence and structured activity of the pharmacist in the team as well as additional shift of focus on more active patient's role caused the described adjustment. In this feasibility study, the main focus was to measure contribution of a new member – pharmacist, and structurally evaluate direct patient-provided outcome. Thereby, a solid foundation for further optimisation of the multi-professional medication management process was formed. Following the recommendations [173-175], our goals were achieved on account of evidence-based decision-making and improved communication between the participants, placing the patient at the centre of medical care attention.

Throughout the whole study, the positive acceptance of the pharmacist in the team was present. Each cooperating party showed strong motivation and competent support in participation and contribution to the overall goal of safe patient and medication therapy. The high implementation rate of PR of 93 % has confirmed it. Previous studies of Lenssen et al. on other UKA wards obtained the acceptance rate ranging from 68 up to 80 % [51]. Given these points, it is clear the pharmacist was welcomed and highly accepted in the multi-professional oncology-ward based team.

However, the acceptance of pharmacist on the ward varies among different German hospitals. Comparably high implementation rate of pharmaceutical intervention of 93 % was shown in the departments of stem cell transplantation and intensive care medicine in the University hospital in Hamburg [176]. Optimising the medication management of neurological patients had 89 % [47] and of cardiological patients 63 % [46] successfully implemented interventions. A multi-centric study exploring the potential of a hospital pharmacist on the ward addressed acceptance rate from 11% up to 63 % [177].

In light of international studies, for example in Norway, an acceptance rate of recommendations on DRPs in discussion with the physicians was 50 % concerning the DRPs with low clinical relevance and up to 80 % with very important and clinically relevant DRPs [178]. A study from Switzerland determined an acceptance rate of 83 % [179]. An old review from 1990 showed an average acceptance rate of 85 % based on 23 studies [180]. Recent Cochrane review about inpatient care for elderly patients reported implementation rates of 18-94 % [45]. Giving emphasis to the haemato-oncology ward, the implementation rate of pharmaceutical interventions ranged from 60 % in Swedish hospital up to 96 % in French hospital [98, 181].

Putting in perspective, the present study is in the upper third of national and international available literature data.

Bias

Concerns about infrastructure and information bias were raised during the methodology development. Integrating pharmacist in the routine work of the ward-based team was highly accepted and welcomed on the study ward. Döhler et al. have shown the benefit of the integrated pharmacist, thereby supporting our approach. They compared two types of pharmaceutical care service for breast cancer patients. A pharmacist on-demand provided first type of the service in multiple study centers, considered as control group, and a pharmacist integrated in the cancer care team in one study center provided the second service type, considered as intervention group. Significantly more DRPs (2.5 times) were identified in the intervention group with an integrated pharmacist than in the control group with on-demand pharmacist. Although the total number of interventions did not significantly differ, several specific interventions indicated the advantage of more team- and medication-related role of the integrated pharmacist. Both pharmacist types were highly recognized and considered as valued source of information for the cancer patients though, at the end of that study the integrated

pharmacist received significantly higher scores [182]. However, recent Cochrane systematic review of complex interventions using medication reviews in the hospital setting indicated different professional groups performing the medication review. Focusing on patient-related outcomes, it is irrelevant who performs the medication review as long as the team performing medication review includes members that are competent to change patient medications [45]. This leads us to suggestion for further evaluation study. The present study did not assess if the infrastructure and information biases could be avoided. For that purpose in the following study the team could organize the focus group to discuss the current status quo of the multi-professional team. Each profession should have a chance to address benefits and shortcomings of the current infrastructure and task allocation of the team. Further, each profession should suggest ways how to enhance communication and teamwork from the patient's point of view.

Setting up the pharmaceutical team of two pharmacists was the best solution in the given circumstances at the UKA. DRPs detection, pre-selection and respective PR to it, showed great acceptance (implementation rate 93 %). However, the pre-selection of DRPs left many other potential DRPs, which the present pharmaceutical team did not considered. In order to evaluate the work of the pharmaceutical team, the following evaluation should consider documenting both: (1) all potential DRPs and (2) selected, relevant DRPs leading to the pharmaceutical intervention (as in the present study). In order to assess the value of the pre-selection, an external and blinded outcome assessment committee may be involved in the study team. As a result, the detection bias would be more effectively controlled.

3.4.3 Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

Paper-based administration of PRO-CTCAE questionnaire was the most suitable in this setting. On behalf of the NCI PRO-CTCAE Study Group, Bennet et al. indicated the mode equivalence of tablet computer-, interactive voice response system- and paper-based administration of PRO-CTCAE, observing very small mean differences between modes intraclass correlation coefficients (median 0.80). This evidence supports study designs that are responsive to patient or investigator preference for mode

of administration, and justifies comparison of results and pooled analyses across studies that employ different PRO-CTCAE modes of administration [183].

The recall period in the study was the past seven days as suggested by NCI. The change of the PRO-CTCAE score over time was more of case reports, presented only descriptively and for particular patients. A recent trial from Mendoza et al. evaluated the differences between one-, two-, three-, and four-week recall periods, using daily reporting as the reference. The trail reported that a one-week recall corresponded well to daily reporting. Small but progressively larger differences between daily and longer recall period were observed, although correlations remained stable over time. Therefore, the preferred recall period was the past seven days. When longer recall periods have to be selected as dictated by logistics, it is recommended to consider some loss of information [184].

The German core set PRO-CTCAE was used in the present study merely descriptively. Further inspiration on how to measure the effect of multi-professional medication management by the German core set PRO-CTCAE can be gained from the recently published PhD thesis of the clinical pharmacy research group in Bonn. They developed and evaluated the best practice model to increase the medication safety in outpatient cancer care. The model included a basic module for medication analysis and modules for the symptoms such as nausea and vomiting, mucositis, fatigue and pain. In a randomised two-arm intervention study, multi-professional medication management was evaluated by the onset time of four selected symptoms, or PRO-CTCAE score 3 or 4, measured over five cycles of therapy. The results showed that the median onset time of symptoms of PRO-CTCAE scores 3 or 4 could be extended from two cycles in the control group to three cycles in the intervention group. The results were not statistically significant. Nevertheless, a trend towards the later onset of serious symptoms could be observed for all four studied symptoms [174].

Symptoms burden and attributes

Fatigue occurred in over 50 % of all patients interviewed. Comparatively, a systematic review of 21 studies with a total of 4,067 patients from Reilly et al. revealed a pooled prevalence of fatigue of 60 % in patients under cancer therapy, chemotherapy and/or radiotherapy [185]. In a cross-sectional study with a total of 1,569 patients included, fatigue occurred in 80 % of patients receiving cancer therapy [186]. The other studies indicated fatigue as the most frequent symptom as well, with prevalence range from 4 % to 92 % [174, 187].

The second most common symptom was anxiety and sadness present with almost every second patient (47 %). Similarly, the cross-sectional study reported prevalence of anxiety of 46 % [186]. In the review by Reilly et al. depression and sadness were moderately present with a pooled value of 34 % [185].

Pain was present with 41 %. This value was confirmed by other investigations [174, 185, 186]. Sleep problems occurred in 35 % of patients, where other studies reported slightly higher prevalence range from 45 to 74 % [174, 185, 186]. Appetite loss with 31 %, dyspnoea with 28 % and mental concentration with 24 % were to some degree less frequently present as the pooled values indicated the prevalence of each symptom of about 45 % [185]. Mucositis and xerostomia occurred in 10 % of patients. In the literature different values were reported. The review outlined pooled prevalence of oral lesions of 5 % [185] but in other literature sources the occurrence of mucositis and xerostomia was 25 % [174, 186]. Rather minor symptoms were: nausea and vomiting with 16 %, diarrhoea with 11 %, constipation 8 %, numbness and tingling with 5 %. Although the pooled prevalence of diarrhoea was quite similar with 15 % [185], a prevalence of about 40 % was described in the literature for these four symptoms.

Eight different symptoms in 13 patients were not adequately controlled by patient self-report and therefore needed a pharmaceutical recommendation. The two most common symptoms, fatigue and insomnia, were the most frequently included in the recommendations, which was three times. Dyspnoea was included twice. In 87 % of patients the symptoms, although present, had been appropriately controlled by the standard medical team on the ward. This represents good, close and trustful collaboration between physicians, nurses and patients already existing on the study ward.

The research pharmacist conducting the interview and directing PRO-CTCAE item questions to the patients was a new member in the well-coordinated standard ward team. The full response rate was indisputable. The research team considered the recommendations for incorporating PRO in the clinical trials such as limited time for data collection and real-time monitoring of adherence with backup data collection [164]. However, the approach can potentially raise a concern of response bias. A strategy called “self-administered questionnaires” involves isolating the participant before they begin answering the questionnaire to hopefully remove any social cues the researcher may present to the participant [188]. This may be a solution for the following trials. Important to mention here is that the potential response bias may be an answer why majority of symptoms are less frequently presented in this study than in the others.

When concerned with PRO-CTCAE attributes, it was shown that patients with impaired performance status encountered more frequently adverse events and had self-reported more adverse events that interfered with their usual or daily activities. Further, patients with more than eight drugs prescribed faced more self-reported adverse events that interfered with their usual or daily activities than patients with less drugs prescribed, as well as the patients with solid tumour diagnosis. On the other hand, major part of patients, who had experience of severe self-reported adverse events, had at least one DRP.

3.4.4 Drug-related problems

Documentation and classification

The research pharmacist, author of this work, documented DRPs during the entire pharmaceutical care process. This has ensured that the DRPs were documented promptly up on the detection and intervention, avoiding distortions in the documentation process.

Paper-based system APS-Doc® for classification of DRPs in the hospital setting in Germany was used [64]. The system existed as a table where the user was required to design a corresponding data digitalisation for data evaluation. Given that UKA at the time had a purely paper-based documentation of the drug regulation and application on the wards, the data collection was paper-based. The exception on the study ward was that the cancer drugs were electronically prescribed making the cancer drug list of each patient electronically available. Although, the APS-Doc® system was the most suitable based on the previous work in UKA [51], it should be noted that the classification into such system is always dependent on the observer's assessment of the respective case. When Hohmann and the team developed the APS-Doc® system they reported kappa correlation coefficient of 0.71 [64]. However, an analysis of the Dresden University hospital showed a kappa coefficient of 0.52 for the same system [189]. This shows the assessment of DRPs with APS-Doc® system leaves a certain room for individual interpretation. To minimise that, in the present study the classification of the data was performed by a single person, the research pharmacist - the same person who knew the patient's case, who was present at the study ward and who had collected the DRPs. In addition, all classifications were checked for consistency within the pharmaceutical team, the research pharmacist and the oncology pharmacist.

Types of DRPs and resulting interventions

DRPs leading to a pharmaceutical intervention were collected for the first time from the oncology ward and classified into ten main DRPs categories defined by the APS-Doc® classification system. Each DRP category had one or more subcategories, making together 48 different DRP subcategories [64].

The predominant category of DRPs leading to pharmaceutical intervention was DDI with 53 %. Unsurprisingly, as the median of prescribed drugs was 13. The large number of prescribed drugs administered to cancer patients leads to a high potential for DDIs [72]. In addition to antineoplastic agents and drugs to treat comorbid conditions, cancer patients usually receive medications to treat both therapy-induced toxicity and cancer-related syndromes, such as pain, seizures, and venous thrombosis. The risk of drug interactions is further heightened because the cancer patient's pharmacokinetic parameters may be altered. The change in pharmacokinetic parameters may be due to a number of factors: impaired drug absorption due to mucositis and malnutrition, variation in a drug's volume of distribution because of reduced levels of serum-binding proteins and generalised oedema, or, in patients with renal and/or hepatic dysfunction, altered drug excretion [91, 92]. Prevalence of DDIs among cancer patients has been reported from 18 % up to 83 % [91, 190]. For instance patient X in the present study had chemotherapy-induced myelosuppression. Although predictable side effect of doxorubicine, in this case was intensified due to concomitant use of ondansetron, citalopram and melperone. Another example, patient Y, had strong comorbid DDI. Amlodipine, carvedilol, mirtazapine and phenoxubenzamine in a concomitant therapy caused serious oedema. Those are examples that not all DDIs can be predicted, and those that are predictable are not always avoidable. However, increased awareness of the potential for these interactions allows healthcare providers to minimize the risk by choosing appropriate drugs and also by monitoring for signs of interaction [90]. The appropriate DDI evaluation is, thereby, highly beneficial. As described in 3.2.6.2 DDI Assessment, the pharmaceutical team directed special attention to the assessment of DDIs. That contributed to the continuous monitoring of all potential DDIs and adequate intervention when needed. Furthermore, the software detection of drug interaction supplied the supporting information in order not to miss any interaction. Although usual heavy information load provided by the software was particularly time consuming, it provided reassurance mechanism of full commitment to the details in the process of medication therapy management.

In the previous work on other UKA wards, DDI was the most common DRP category leading to PI on the neurology ward. Comparable value of 55 % of DDIs could be explained with a high interaction potential neurological drugs have. On the urology ward 26 % of DRPs were related to DDIs that led to PI and notably lower 15 % on the gastroenterology ward [49].

Second most common category of DRPs leading to PI on the oncology ward was "Dosage" with 14 %. The subcategories: "Dose to low/high", "Inappropriate administration interval" and "No dosage adjustment in case of renal failure" were the most prominent. The proportion on the urology ward and the gastroenterology ward of UKA was similar with 13 % and 15 %, respectively [49]. These DRPs can be identified and solved within the comprehensive MSR underling thereby its importance.

Third, in the descending order of DRP frequencies, was a category "Drug" 8 %, where in the present study the subcategories "Transcription error/unintended discontinuation of drug therapy (during the hospital stay)" and "No/inadequate drug monitoring" dominate. Transcription error happened mostly at the transition of care from the emergency department to the oncology ward. On the other side, at the urology ward 30 % of the DRPs were found in the category "Drug" (e.g. "incomplete drug history" or "unintended discontinuation of drug therapy" and "inadequate generic substitution"), 21 % on gastroenterology ward and 14 % on neurology ward [49]. Extended medication history and following medication reconciliation offer a solution to reduce those issues. Implementing the proposed pharmaceutical activities in the routine ward-based work could prevent them from happening. The following substantial DRP category was "Indication", e.g. no indication for certain medication, or inappropriate medication for the given indication, no medication prescribed/suboptimal dosage with an existing indication. Recognised more as a setback (higher percentage of DRPs) at the internal wards where patients have extensive medication therapies: the study ward had 13 average medications prescribed and at the gastroenterology ward, where Lenssen with her team worked, there were 16 average medications prescribed [49]. The standard national medication record as part of the Action Plan for the improvement of medication safety in Germany, as mentioned before, was introduced at the end of 2016. The present study was not influenced by it. However, that step represents one of the strategies to uniformly transfer patient's medication therapy record between the interfaces such as ambulatory care - hospital care, and to a certain extend to avoid above given problems.

DRPs led to various pharmaceutical interventions. To a large extent, the pharmaceutical team suggested to stop/pause the drug, advised to change the drug dose or initiated further diagnostic tests. Further, during the intensive discussions, the pharmaceutical team provided additional information to the attending physicians and nurses regarding the drugs and also, different solutions on variety of potential scenarios were suggested. Thereby, the most appropriate drug choice in terms of efficacy, dosage, adverse events, and interactions was specified. The close collaboration with the medical team resulted in measurable and valuable contribution to the optimisation of the pharmacotherapy.

Taking into consideration comparable literature on the national level on the oncology ward, it is relevant to refer to the evaluation of ward-based clinical pharmacists interventions at the university hospital in Hamburg. Among 10 different wards where the intervention was provided, haematology/oncology and stem cell transplantation ward outnumbered the others wards. DRPs leading to clinical pharmacist intervention were, above all, wrong dose or no dose adjustment, inappropriate drug or no clear indication for the drug and advice to the medical team/selection of drug. The most frequent interventions on those DRPs were recommendations for addition, withdrawal or replacement of a certain drug and recommendations for changes of dosage, dosing intervals or dose adjustment according to the level of renal or liver impairment [176]. Further, in the recent PhD thesis from the clinical pharmacy research group in Bonn, two pharmaceutical care services for breast cancer patients were compared. Pharmacist on-demand in the control group recorded on average 2.7 DRPs (median 2, IQR 1 – 4, range 0 – 9), where the pharmacist integrated in the team documented 6.7 DRPs (median 6, IQR 4 – 8, range 1 – 33). The observed difference of 4 DRPs/patient was statistically significant ($p < 0.001$, Mann-Whitney U-test). ADR was the most recurrent DRP, making 76 % of all DRPs. The most repeated intervention was interviewing and counselling the patients, 25 % of all interventions. Other frequent interventions were recommendation of a drug/treatment (15 %) and documentation of symptoms of an ADR (14 %) [182].

In the context of international literature, there are several studies on outpatient cancer care, DRPs and therapy optimisation. Prospective studies showed that pharmacy-directed seamless care could identify from 1 up to 3 DRPs per patient and had high acceptance rate of the intervention of 93 % [191-194]. It is important here to mention, that the studies that have identified 3 DRPs per patient, reported all DRPs a pharma-

cist could detect [192, 194]. Given that in the present study only DRPs leading to PI were evaluated (2 DRPs per patient) and not all DRPs pharmaceutical team that could have potentially be detected, there is a limited use of such a comparison. On the other hand, the studies in inpatient setting, reported from 1.1 DRP/patient up to 2 DRPs/patient leading to PI, presenting thereby similar results. Further, those studies had resemblance in character of DRPs when compared to the present study. The most common DRPs were untreated/not enough treated indications, inappropriate medications and DDIs [98, 181, 195]. Although one can observe the similarity of the DRP characteristics, it has to be considered that every study uses different DRP classification system and thereby partially limits the comparison effect.

3.4.5 Drug-related problem prediction model

To provide more in-depth understanding of DRP risk pattern the Poisson regression model was performed. As throughout this study, DRP referred to those DRPs leading to PI in oncology patients. With the Poisson regression model multiple predictors were investigated. The significant multiple predictors were combined in a tool by assigning relative weights to each predictor. The tool, also commonly called “prediction model” or “prognostic model” or “risk score” was transformed to ease its use in practice. The developed prediction model can be used to aid health care provider in estimating the risk that the DRP will occur during the stay on the oncology ward and to inform their decision-making.

The Poisson regression model assumed the risk of experiencing a DRP was the same each day of the hospital stay. However, nature of the provided intervention did not assure it. Instead, the two time periods could be distinguished during which the provided intervention assured the same risk of DRP. That was the initial and the follow-up time on the study ward. The initial time period was related to the beginning of the stay on ward, up to the 5th day in hospital. In that time, the patient was recruited in the study (within first three days of the hospital stay) and pharmaceutical team performed extended patient medication history, medication reconciliation and MSR. If any DRP had been detected, first pharmaceutical intervention was provided up to the 5th day (the latest). Follow-up time period was related to the time after the initial time. On average patient stayed on the ward for 10 days. Hence, the time span of five days was considered, from the 5th day up to 10th day of the hospital stay. This proved compara-

ble number of days with the initial time period. Under those circumstances, two DRP risk models were presented: Initial and Follow-up. Initial DRP risk model referred to the initial time period that is up to the 5th day and Follow-up DRP risk model from the 5th up to the 10th day on the study ward.

When the two models were compared, the initial model showed more significant risk factors predicting what patients were more likely to experience DRPs than the follow-up model. This could be explained by the fact that all patients were treated equally at the beginning of the hospital stay. Pharmaceutical team with no exception implemented step-by-step intervention (3.2.5 Intervention). Particularly at the hospital beginning, the intervention took a considerable amount of time. Once the initial time period was over, every further step of the pharmaceutical care was adjusted to each patient. That means that the pharmaceutical care was at that stage (follow-up period) narrowed and adjusted entirely to the patients' needs. Certain parameters were more important to one patient and different ones for the other patient. Consequently, the Follow-up DRP risk model was as expected less informative. Only two risk factors were shown as potential predictor of DRPs leading to pharmaceutical intervention. In the follow-up time period it was more difficult to foresee which oncology patient subgroup was more prone to DRPs leading to pharmaceutical intervention. Further, pharmaceutical care approach was at that time rather individualised then generalised.

Initial DRP risk prognostic model showed as significant risk factors ADR risk score and ECOG performance score. ADR risk score itself [57, 167] contains six risk factors: presence of renal failure/heart disease/liver disease/four or more comorbidities, history of ADRs and polypharmacy. These risk factors were prominent in the literature for DRPs concerning the general inpatient population as well [107, 114, 116, 166]. The ECOG performance status represented one of the recommendations for researchers planning oncological clinical trials [163]. It was a significant factor in both (Initial and Follow-up) models, indicating relevant parameter for following oncology studies in our research group. In the Follow-up model, impaired renal function was the significant risk factor. Thus, the patients with instable renal function were more likely to experience a DRP leading to a pharmaceutical intervention during the longer stay on the study ward.

Further, DRP risk models were presented in light of the probability of no event. No-event probability up to 10 days on the study ward was in more than 90% of patients equal or below 0.5. When observing only the follow-up time period, from the day 5 up

to day 10 on the study ward, it could be seen that only 40% of patients have no-event probability equal or below 0.5. On the other hand, in the initial time period, up to day 5 on the study ward, 75% of patients had no-event probability equal or below 0.5. On that account, in the study sample patients had a higher probability of experiencing DRP leading to pharmaceutical intervention in the initial time period (up to 5th day) on the ward. This could be explained by fact that in the initial time period DRPs existing prior to hospitalization were recognized and resolved, too.

Additionally, the initial DRP prediction model was transformed to ease its use in the routine work and the scoring system was proposed. The prognostic ability of the model was graphically plotted in the ROC curve and the AUC was 0.790 (95% CI 0.697 – 0.883). As an AUC of the ROC curve of 0.5 indicates no discrimination and an AUC of 1.0 indicates perfect discrimination, the AUC of the DRP prediction model indicates a fair, not terminally reliable or accurate model. The DRP score for general inpatient from Urbina et al. had comparable AUC of 0.776 (95% CI 0.759 – 0.792) in the validation set cohort [116]. As the DRP model was based on ADR risk score fixed variable, the interpretation in the new score was proposed on the same basis. Cut off was at five points i.e. patients with five and more points were prone to DRP. The cut off point was confirmed in the analysis of coordinates showing good sensitivity (0.83) and slightly lower specificity (0.56). The tools available in the literature were either self-assessment tools or screening tools for clinical pharmacists. Either of them showed comparable sensitivity ranging from 0.81 to 0.95 and specificity from 0.58 up to 0.61 [113-115].

Strengths and limitations of the DRP prediction model

Based on the current results, the Initial DRP risk score has a modest role in predicting DRPs up to day five on the oncology ward. The score strengths are that it is based on a statistical analysis of variables and supplemented with data from the literature. Knowledge of the variables associated with DRP can assist in early prediction of oncology at-risk patients. Despite the thorough statistical approach, the critical score limitation is the prediction model development on a small cohort. Study sample of 101 patients was restricted to produce valid and relevant tool. Only the prediction ability of the model could be shown and no internal or external validation.

Quantifying the predictive ability of a model on the same data from which the model was developed tend to give an optimistic estimate of performance, owing to overfitting (too few outcome events relative to the number of candidate predictors) and the

use of predictor selection strategies [196]. Therefore, it is suggested that studies developing new prediction models include some form of internal validation to quantify any optimism in the predictive performance (for example, calibration and discrimination) of the developed model [106]. Internal validation techniques use the original study sample and include such methods as bootstrapping or cross-validation. However, in the present pilot study the small cohort disabled to produce a cross-validation as internal validation. Consequently, the proposed model was not further investigated on a new independent patient sample and no external validation was provided.

After developing a prediction model, it is strongly recommended to evaluate the performance of the model in other participant data than was used for the model development. Such external validation may use participant data collected by the same investigators, typically using the same predictor and outcome definitions and measurements, but sampled from a later period (temporal or narrow validation); by other investigators in another hospital, sometimes using different definitions and measurements (geographic or broad validation); in similar participants but from an intentionally different setting (for example, model developed in secondary care and assessed in similar participants but selected from primary care); or even in other types of participants. [106]

Implication for the future research is therefore development of the model in a bigger cohort, with adequately planned internal and external validation strategies.

3.4.6 Interpretation and generalisability

The study outcomes could be interpreted in terms of internal and external generalisability.

The pharmaceutical team composed of the research pharmacist and the oncology pharmacist specialist was consistent during the study time applying the predefined study intervention. The oncology pharmacist supervised the pharmaceutical work of the research pharmacist. On the other hand, the attending physicians and nurses on the ward were not. The study ward has more than 20 attending physicians supervising 46 beds on the study ward. Having such a high acceptance rate of pharmaceutical recommendations in those circumstances indicate the inherent repeatability of findings or more precisely ensures the reliability of the study outcomes. Having two phar-

macists in the pharmaceutical team protected internal validity, or that the intervention used in the present study measured what it was supposed to measure.

The comparability of the results of the present study with results of the work from Lenssen and the team has been discussed above. Each sector in the UKA has shown variety in DRP pattern and occurrence. That underlines the need of assessment and evaluation of each sector independently [51]. Pharmaceutical contribution to the ward-based teamwork offered a uniform approach (in terms of SOP) to identify and solve DRPs. Comparable number of DRPs per patient within the UKA and in external settings, and high acceptance rate of pharmaceutical intervention within the ward-based team, confirmed the success of the intervention. In the present study, the intervention was continuously reflecting on the routine workflow showing thereby beneficial outcome. This corresponds to the sense of health service research [37]. Furthermore, the approach provided the basis for further development of the most optimised patient-oriented, quality-driven, outcome-based ward teamwork [22]. To emphasize the strength of this phenomenon and to quantify the effect size, a larger study with bigger patient samples and comparison groups is needed.

Interpretation of the Initial DRP risk score should be provisional. The prognostic ability of the score might provide optimistic estimates but the implementation of the model as a tool to estimate the probability that the DRP will occur during the stay on the oncology ward is currently limited. To start, it may help pharmacists to prioritise their medication reviews and to optimise their workload in the local setting. However, due to a development on a small cohort and lack of internal validity, further development and validation studies for such a prognostic model are required. Only then, the predictive model may serve as a valid tool applicable in various oncological populations and settings. This pilot study should therefore present the potential solution how the predictive model could be developed and pave the way for further oncology DRP prognostic model development. Additionally, qualitative research approach would be useful. It could address variety of contributing factors to the DRP occurrence underpinned by communication failures (between patients and healthcare professionals and different groups of healthcare professionals) and knowledge gaps (about drugs and patients' medical and medication histories) [117]. Development and implementation of a DRP risk assessment tool should not be isolated, but rather followed by the team optimisation, as introduced in the present study.

In terms of external generalisability, results of such examination cannot be easily transferred to other health systems, as it was noticed in the previous works [51, 53, 197]. The intervention in the present study represents only the development phase of the ward-based complex intervention team. Number of interacting components within the ward-base team, difficulty of behaviour required by those delivering or receiving the intervention, and number and variability of outcomes make the intervention complex [37]. The present study did not take into account only one measure, such as patient training, but a complex supplement in the therapeutic team. It provided a realistic care and evaluated the benefits in daily routine. The first step is taken, but successful and effective teamwork based on its complexity is a long-term goal. The extension of the intervention is necessary in terms of additional patient training, continuous review and enhancement of the intervention, particularly from the patient's point of view and improvement of workflows in terms of communication and consultation within the team [123]. For the stepwise improvement, the regular measurement of endpoints should determine the success of each step [119]. Besides focusing on quantitative endpoints, as in the present study, future research and ward-based team improvement should shift the focus and include qualitative methods, too. Qualitative methods provide better understanding of complex pathways capturing emerging changes in implementation and experiences of the intervention. Further, it could help identify unexpected mechanisms and generate new theory [39], and understand strong points and flaws of team communication and collaboration. In present work, economic aspect has not been considered. Having almost 200 DRPs in a group of 100 patients during the four months, proclaim a need for optimisation of the health care structure in pharmacotherapy. The intervention tested here represents a measurable benefit for the patients. In order to further verify current supposition, the study results represent a starting point and motivation to carry out further studies using the methodology that was developed here.

4 Conclusion and outlook

The present work described two models to optimise medication safety in the hospital setting.

The first model was developed as optimised multi-professional model to reduce time to drug-related hospital readmissions of care-dependent elderly. The primary endpoint – time-dependent occurrence of drug-related rehospitalisation is to be measured during a 12-month follow-up period. In comparison with other RCTs included in a recent Cochrane review [45], the follow-up period is relatively long. Care-dependent elderly represent high-risk population. Thus, the present model follows review's recommendations what novel studies concerned with medication safety review need. Previous work on this model [49, 51] suggests that the primary endpoint is a good reflection of real care. Further in the pilot study [51] multi-professional teamwork indicated a tendency to prolong time to DRR, especially early DRRs up to tenth week after hospital discharge. The model exhibited thereby lasting measurable effect and patients' health-related quality of life was improved. The clear sign was that ADRs were of notable relevance in the daily care, particularly those preventable or ameliorable leading to DRRs. Integrating surgical, internal and neurological wards in the model, a cross-section between different disciplines was formed.

By combining quantitative and qualitative methodologies, the model corresponds to the recommendations of the health service research [37-39]. Beside quantification of the model's intervention effectiveness, qualitative assessment of the team's individuals in their natural setting should assist to characterise and explain certain multi-professional team behavioural phenomena. The evaluation of the model using mixed-methods approach should provide a useful example for further improvements of multi-professional complex intervention models and medication safety in Germany. The benefits and building blocks of model's evaluation will offer interesting questions for studies to follow.

The second model was developed and applied as optimised pharmaceutical care model contributing to the oncology ward-based team in medication management. The model was focused on a core multi-professional ward-based team, which consisted of patients, physicians, nurses and pharmacists. Further development of the model should

include additional professional groups, such as psycho-oncologists, dieticians or physiotherapists. Thereby, a potential follow-up project may develop and evaluate comprehensive multi-professional cancer care.

The pharmaceutical team providing pharmaceutical care service in this pilot study was introduced to the oncology ward for the first time. The pilot study showed that cancer patients exhibit many DRPs requiring a pharmaceutical intervention. The high acceptance of the intervention indicates the need of a pharmacist as integrated part of the oncology ward-based team. The initial DRP risk score may assist pharmacist to prioritise their service and to optimise their workload. But small study sample limits score interpretation and validation. Considering current results provisional, there is a call for the score development and validation on a larger cohort. The approach, however, provides the methodology for further research of the most optimised oncology ward teamwork and prognostic model development, and the foundation for cancer medication safety improvements.

Validity and reliability of the German PRO-CTCAE core item set was demonstrated in the previous work of the clinical pharmacy research group from the University of Bonn [147]. As illustrated in the present pilot study, the German PRO-CTCAE core item set may support pharmaceutical care on the oncology ward. Thus, the questionnaire is useful in the following cancer patient studies and represents a valuable tool for assessing benefits and safety of an intervention from the patient's point of view, in addition to the medical assessment. Further, the validated PRO-CTCAE core questionnaire was used in the best-practice model for outpatient care developed by the clinical pharmacy research group in Bonn. For the analysis of the primary and secondary endpoints of the best-practice model, they considered the highest value of all items belonging to a symptom scale. They evaluated multi-professional cancer medication management by the onset time of the four selected symptoms, or PRO-CTCAE score 3 or 4, measured over five cycles of therapy. A trend towards later onset of serious symptoms could be observed for all four symptoms studied [174]. Succeeding evaluation of the endpoints is in a follow-up project in cooperation with the Center for Integrated Oncology in Bonn [175]. However, the NCI who has developed the PRO-CTCAE provided no exact recommendations for the evaluation of the individual items and symptom scales. In the future, a scoring manual should be developed in collaboration with the NCI to simplify and standardise the interpretation of PRO-CTCAE items.

Despite some limitations, both models present first indication of a positive effect of multi-professional medication safety management and may serve as a basis for hypothesis generation and planning of the following study samples and study designs. If possible, future studies should be multi-centred, in order to allow cluster randomisation and supplementary increase validity of the results. Finally, in view of sustainability, upcoming studies should promote further implementation of the models in the routine care.

5 Summary

Medication therapy is recognised as a high-risk process. German Federal Ministry of Health has proposed certain measures to ensure an optimal medication process with the aim of reducing medication errors and thereby avoidable risks for the patient in drug therapy. The concept is called medication safety. Its centre of attention is fostering awareness of medication safety among patients, physicians, pharmacists and caregivers, to improve information on medicines and intersectional communication about drug therapy as well as facilitation of medication safety research. A central point represents the need for greater involvement and information of the patient with regard to his medication therapy.

The focus of this thesis is to propose models to optimise medication safety in the hospital setting.

The first part of the thesis presents a study protocol for multi-professional model to reduce drug-related readmissions in care-dependent elderly. The protocol is based on the foundation of Spirit 2013 statement, which defines standard protocol items for clinical trials. The model recognises the need for safer medication use through the concerted efforts of all caregivers. It has been developed and recently tested in a pilot study. First results showed the model's tendency toward active collaboration among the ward-based caregivers and outlined a positive impact on medication safety. However, its effectiveness has still to be assessed in a full-scale evaluation with an adequate sample size.

The planed evaluation study is an open randomised controlled trial supplemented by a qualitative evaluation of the intervention. During the hospital stay, patients are randomly allocated to either a control or an intervention group. Control group represent current medical standard of care where the intervention represents multi-professional care according to the defined Standard Operating Procedure for this purpose. After the hospital stay, both patient groups are followed up in the same manner for 12 months to assess the long-term efficacy of the model with a patient-relevant outcome – drug-related hospital readmissions. Qualitative assessment in this evaluation study consists of patient interviews at the end of the hospital stay and focus group for care providers after the study intervention time. Integrating qualitative methodologies implies studying individuals in their natural setting to characterise and provide potential explana-

tions for particular events and behaviours. Evaluation of the model using mixed-methods approach should provide a useful example for further improvements of multi-professional complex intervention models and medication safety in Germany.

The second part of this thesis presents the model of optimised pharmaceutical care service on the oncology ward and development of a prediction model. It is a pilot study outlined by STROBE and TRIPOD statement. Pharmaceutical care service was assessed in terms of management of drug-related problems (DRPs). The aim was to develop DRP prognostic model. The pharmaceutical care model was further assessed in terms of number, type and risk factors of DRPs leading to intervention, type of intervention provided, and PRO-CTCAE symptom burden and impact on pharmaceutical intervention. The most important measurements were: German PRO-CTCAE core item set (weekly assessment, recall period 7 days, 12 symptom item clusters, three dimensions: frequency, severity, interference), adverse drug reaction risk score on admission, APS-Doc® classification system for drug-related problems and Doku-PIK documentation system for pharmaceutical intervention, both developed for the hospital setting.

In the study sample of 101 patients, 46 were women. Average age was 65 years and average stay on the ward was 10 days. The most frequent diagnoses were malignant neoplasm of bronchus or lung, diffuse large B-cell lymphoma and multiple myeloma. On average each patient had two DRPs leading to pharmaceutical intervention. The most common drug-related problems were drug-drug interactions, drug dosage, drug prescription/monitoring, indication and contraindication. The most frequent pharmaceutical interventions were symptom surveillance, information to physicians and nurses, initiated diagnostic tests, stop/pause the drug and change of the drug dose. The most frequently reported PRO-CTCAE symptoms were fatigue, anxiety and sadness, and pain. For 13 patients pharmaceutical recommendations were based on the PRO-CTCAE items. The implementation rate of pharmaceutical recommendations by the ward-based team was 93 %. Poisson regression model was performed to assess risk factors predicting pattern of DRPs leading to pharmaceutical intervention on the oncology ward. In the second step, the regression was used to combine multiple predictors by assigning relative weights to each predictor to obtain a probability of DRP during the stay on the oncology ward. There are two models to be distinguished: the initial or up to 5th day on the study ward, and follow-up model from the 5th day up to 10th day on the study ward. Significant risk factors in the initial model were ECOG

performance score, adverse drug reaction risk score and presence of heart failure; in the follow-up model ECOG performance score and presence of renal failure. Prognostic ability of both regression models was assessed with ROC curve showing AUC of 0.777 (95 % CI 0.686 – 0.868, SE 0.046, $p < 0.001$) and AUC of 0.683 (95 % CI 0.532 – 0.835, SE 0.077, $p = 0.033$), respectively. Based on the initial regression model, DRP prognostic model has been proposed (AUC of 0.790 (95 % CI 0.697 – 0.883, SE 0.048, $p < 0.001$), with a scoring system from 0 to 10 and cut off at 5. That means patients with 5 or more points are according to the Initial DRP prognostic model highly probable to experience DRP leading to a pharmaceutical intervention during the five-day stay on oncology ward.

The pilot study has showed that cancer patients exhibit many DRPs requiring a pharmaceutical intervention. PRO-CTCAE may support pharmaceutical care on the oncology ward. The high acceptance of the intervention indicates the need of a pharmacist as integrated part of the oncology ward-based team. The initial DRP prognostic model may assist pharmacist to prioritise their service and to optimise their workload. But small study sample and lack of internal validation limits score interpretation, considering current results provisional and calling for the score development and validation in a study with bigger sample size. The approach, however, provides the methodology for further research of the most optimised patient-oriented, quality-driven, outcome-based oncology ward teamwork.

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7 Attachments

Attachments Model I

SOP Medication safety with CRF
Informed consent
Patient information

5.4.6 AA1-1

Prüfung der Arzneimitteltherapiesicherheit

1. Ziel und Zweck

Ziel der SOP ist die Festlegung von Prozessen im Rahmen der Studie „AMTS älterer Patienten in der stationären Versorgung unter besonderer Berücksichtigung der Schnittstellen Heim – Klinik und Klinik – Heim und in der ambulanten Versorgung“. Der Ablauf der Datenerhebung, der Umfang der multiprofessionellen Betreuung durch Apotheker, Arzt und Pflege im Rahmen der Studie sowie die zur Dokumentation zu verwendenden Vorlagen werden hier aufgeführt.

2. Anwendungsbereich

Diese SOP gilt für die entsprechende Studiendauer für Apotheker, Ärzte und Pflege, die im Rahmen der Studie „„AMTS älterer Patienten in der stationären Versorgung unter besonderer Berücksichtigung der Schnittstellen Heim – Klinik und Klinik – Heim und in der ambulanten Versorgung“ tätig sind. Eine spätere Implementierung des Prozesses in den allgemeinen Arbeitsablauf des UKA nach Studienende ist angedacht.

3. Begriffe, Abkürzungen

Arzneimittelbezogene Probleme	ABP
Arzneimitteltherapiesicherheit	AMTS
Forschergruppe	FG
Standardisierte Prozessbeschreibung (engl. Standard Operating Procedure)	SOP
Studienapotheker	SA
Studienleiter	SL
Universitätsklinikum Aachen	UKA

4. Verantwortlichkeiten

Die Aufgaben und Verantwortlichkeiten des Studienapothekers sowie die Aufgaben, die Ärzte und Pflege zusätzlich zu ihren Standardaufgaben übernehmen werden hier im Weiteren beschrieben. Bei den in dieser SOP erwähnten Patienten, handelt es sich ausschließlich um Patienten die der Intensivbetreuungsgruppe zugewiesen wurden.

5. Prozessbeschreibung, SOP

Beschreibung	verantwortlich
Information der Station	
- Information der studienbeteiligten Stationen über die Weiterführung der multiprofessionellen Studie	SL
Training vor dem Studienbeginn	
Schulung - Schulung von Ärzten und Pflege auf den studienbeteiligten Stationen bezüglich des Berichtens aller den Patienten betreffenden studienrelevanten Ereignisse - Schulung des Studienapothekers bezüglich seiner Aufgaben im Studienprotokoll sowie in der Verwendung der Dokumentationsbögen	SL/FG
Tag 1 nach Aufnahme des Patienten	
1. Pflege - SA Gespräch - Bericht der Pflege über Besonderheiten und aufgetretene Symptome des Patienten - Dokumentation durch den SA im Dokubogen 0.1 (Anlage1).	Pflege und SA
2. Arzneimittelanamnese - Gespräch zwischen SA und Patient über die derzeitige Arzneimitteltherapie - Arzneimittelanamnese durch den SA unter Verwendung der Patientenakte, der vom Patienten mitgeführten Dokumente, der mündlichen Auskunft des Patienten und sonstiger Informationsquellen; die Dokumentation erfolgt im Dokumentationsbogen 1.1 (Anlage2).	SA
3. Vergleich stationäre Medikation und Hausmedikation - Vergleich der Arzneimittel aus der Arzneimittelanamnese (Hausmedikation; Anlage 2) mit stationären Anordnungen und/oder der Dokumentation der ärztlichen Anamnese. Die Dokumentation erfolgt im Dokumentationsbogen 1.1 (Anlage2). Im Feld „Bemerkungen“ werden die Abweichungen aufgeführt.	SA
4. AMTS-Prüfung und pharmazeutische Empfehlungen - AMTS-Prüfung der Arzneimitteltherapie nach der Checkliste AMTS-Prüfung (Anlagen 5). - Dokumentation identifizierter ABPs im Dokumentationsbogen 1.5 (Anlage 4). Relevante Informationen aus der AMTS-Prüfung werden im Bemerkungsfeld des Dokumentationsbogens 1.1 festgehalten. (z.B. Hinweise auf Überdosierung, vorangegangene/abgebrochene Arzneimitteltherapien, Arzneimittelinteraktionen, wichtige Informationen aus Gesprächen mit anderen Mitgliedern des multiprofessionellen Teams (Patienten, Pflege, Ärzte, etc.)). Weitergabe der Empfehlungen des SA zur Medikation basierend auf den ABPs der AMTS-Prüfung an alle Mitglieder des multiprofessionellen Teams (vgl. Punkt 5, 6 und 7).	SA
5. Arzt - SA Gespräch - Besprechung der Empfehlungen aus der AMTS-Prüfung mit dem Behandelnden Arzt und Klärung eventueller Rückfragen	Arzt und SA

6. Pflege - SA Gespräch (ggf.) - Besprechung der Empfehlungen aus der AMTS-Prüfung mit der betreuenden Pflegekraft und Klärung eventueller Rückfragen
7. Patient - SA Gespräch (ggf.) - Informationen zu neuen Therapien - Einführung in die richtige Anwendung neuer Darreichungsformen - Klärung eventueller Rückfragen
8. Umsetzung der pharmazeutischen Empfehlungen - Überprüfung der Umsetzung von Empfehlungen zu ABPs. Dokumentation im Dokumentationsbogen 1.5 (Anlage 4).
Während des stationären Aufenthalts (täglich an Werktagen)
9. Follow Up des Zustands des Patienten: - Einsicht des SA in die elektronische Dokumentation auf Station: Laborwerte, Vitalparameter, Untersuchungsergebnisse, Verlaufsdokumentationen (schriftliche Dokumentation von Besonderheiten durch Arzt und Pflege) - Visite des Patienten auf Station, wobei der Patient über Veränderungen seines Gesundheitszustandes berichten kann
10. Pflege - SA Gespräch - Bericht der Pflege über Besonderheiten und neue Symptome des Patienten - Dokumentation durch den SA im Dokumentationsbogen 0.1 (Anlage1).
11. Veränderungen der Arzneimitteltherapie - Bei Veränderungen der Arzneimitteltherapie wird eine erneute AMTS-Prüfung durch den SA nach der Checkliste AMTS-Prüfung (Anlage 5) durchgeführt (Siehe Punkt 4). - Erneute Durchführung Schritte 5-9
Bei Entlassung
12. Pflege - SA Gespräch - Bericht der Pflege über Besonderheiten und neu aufgetretene Symptome des Patienten - Dokumentation durch den SA im Dokumentationsbogen 0.1 (Anlage1).
13. Entlassgespräch - Bei Entlassung findet zusätzlich zu den Informationen durch den Arzt ein Entlassgespräch mit dem Patienten durch den SA bezogen auf Veränderungen in der Arzneimitteltherapie statt.
14. Entlassungsbrief - Zusammenfassung der pharmazeutischen Empfehlungen für den behandelnden Arzt in Textform. Der Arzt entscheidet ob die Empfehlungen Teil des Entlassungsbriefs werden. - Ausgabe des Entlassungsbrief an den Patienten
15. Zeitaufwand - Zeiterfassung der pharmazeutischen Tätigkeiten des SA im Dokumentationsbogen 3.1 (Anlage 6).

7. Anlagen

Anlage 1 Dokumentationsbogen 0.1 Multiprofessionelles Team Gespräch
Anlage 2 Dokumentationsbogen 0.2 Vulnerable Elders Survey (VES-13)
Anlage 3 Dokumentationsbogen 0.3 The GerontoNet ADR Risk Score
Anlage 4 Dokumentationsbogen 1.1 Arzneimittelanamnese
Anlage 5 Dokumentationsbogen 1.4 Stationäre Medikation
Anlage 6 Dokumentationsbogen 1.5 Datenerfassung ABP
Anlage 7 Checkliste AMTS-Prüfung
Anlage 8 Dokumentationsbogen 3.1 Dokumentation Interventionsapotheker

8. Änderungshistorie

Bei der vorliegenden SOP handelt es sich um die erste Version. Änderungen liegen daher nicht vor.

	Erstellung	Prüfung	Freigabe
Name	Sarcevic	Eisert	01.07.16
Datum			
Unterschrift			
Dokumentenablage			

Gelesen und verstanden:

Kürzel Mitarbeiter									
Unterschrift									

0.1 Multiprofessionelles Team Gespräche

Patientennummer _____

Studienstation _____

Datum_____

Gespächsnummer_____

Zeitpunkt ☐ bei der Aufnahme

☐ während des stationären Aufenthalts

☐ bei der Entlassung

Gespräch Pflege – Studienapotheker

Ein Gespräch hat stattgefunden: ja ☐ nein ☐ wenn nein bitte Grunde angeben

_____

☐ keine Anmerkung durch die Pflege

Noti-
zen_____
_____
_____
_____

Gespräch Arzt – Studienapotheker

Ein Gespräch hat stattgefunden: ja ☐ nein ☐ wenn nein bitte Grunde angeben

_____

☐ keine Anmerkung durch den Arzt

Notizen

_____
_____
_____

0.2 Vulnerable Elders Survey (VES-13)

Kennzeichen_____

Geschlecht**:** ☐ weiblich ☐ männlich

Datum_____

F1. Alter _____

PUNKTZAHL: *1 PUNKT FÜR JAHRE 75-84*
3 PUNKTE FÜR JAHRE ≥ 85

Punktzahl ☐

F2. Im Vergleich zu anderen Menschen in Ihrem Alter, wie würden Sie generell Ihren Gesundheitszustand, einschätzen:

☐ schlecht,* *(1 PUNKT)*
☐ mäßig,* *(1 PUNKT)*
☐ gut,
☐ sehr gut, oder
☐ ausgezeichnet

PUNKTZAHL: *1 PUNKT FÜR SCHLECHT ODER MAßIG*

Punktzahl ☐

F3. Wie viele Schwierigkeiten haben Sie, üblicherweise, mit den folgenden körperlichen Aktivitäten:

	keine Schwierigkeiten	wenig Schwierigkeiten	einige Schwierigkeiten	viele Schwierigkeiten	nicht dazu in der Lage
a) Bücken, Hocken oder Knien?	☐	☐	☐	☐*	☐*

	keine Schwierigkeiten	wenig Schwierigkeiten	einige Schwierigkeiten	viele Schwierigkeiten	nicht dazu in der Lage
b) Heben oder Tragen von Gegenständen mit einem Gewicht von 5kg…….....☐	☐	☐	☐*	☐*	
c) Etwas erreichen oder Ausstrecken der Arme über Schulterhöh.....☐	☐	☐	☐*	☐*	
d) Schreiben oder Anfassen und Greifen kleiner Gegenstände..☐	☐	☐	☐*	☐*	
e) einen 500m gehen..☐	☐	☐	☐*	☐*	
f) schwere Hausarbeit wie Boden wischen oder Fenster putzen.....☐	☐	☐	☐*	☐*	

PUNKTZAHL: *1 PUNKT FÜR JEDE * ANTWORT IN F3 VON a BIS f*
MAXIMAL 2 PUNKTE

Punktzahl ☐

F4. Haben Sie aufgrund Ihres Gesundheitszustandes oder körperlichen Zustandes irgendwelche Schwierigkeiten bei:

a) Einkaufen persönlicher Gegenstände (wie Hygieneartikel oder Medikamente)?

☐ JA → Erhalten Sie Hilfe beim Einkaufen? ☐ JA* ☐ NEIN

☐ NEIN

☐ MACHE ICH NICHT → Aufgrund Ihres Gesundheitszustandes? ☐ JA* ☐ NEIN

b) Finanzielle Angelegenheiten (wie das Auflisten von Ausgaben oder Zahlung von Rechnungen)?

☐ JA → Erhalten Sie Hilfe bei finanziellen Angelegenheiten? ☐ JA* ☐ NEIN

☐ NEIN

☐ MACHE ICH NICHT → Aufgrund Ihres Gesundheitszustandes? ☐ JA* ☐ NEIN

c) durch den Raum gehen (Verwendung von Spazierstock oder Rollator ist ok)?

☐ JA → Erhalten Sie Hilfe beim Gehen? ☐ JA* ☐ NEIN

☐ NEIN

☐ MACHE ICH NICHT → Aufgrund Ihres Gesundheitszustandes? ☐ JA* ☐ NEIN

d) Erledigen leichter Hausarbeit (wie Geschirrspülen, Aufräumen oder leichte Reinigungen) ?

☐ JA → Erhalten Sie Hilfe bei leichter Hausarbeit? ☐ JA* ☐ NEIN

☐ NEIN

☐ MACHE ICH NICHT → Aufgrund Ihres Gesundheitszustandes? ☐ JA* ☐ NEIN

e) Baden oder Duschen?

☐ JA → Erhalten Sie Hilfe beim Baden oder Duschen? ☐ JA* ☐ NEIN

☐ NEIN

☐ MACHE ICH NICHT → Aufgrund Ihres Gesundheitszustandes? ☐ JA* ☐ NEIN

PUNKTZAHL: ***4 PUNKTE*** *FÜR EIN ODER MEHR * ANTWORT IN F4 VON a BIS e*

Punktzahl ☐

Gesamtpunktzahl ☐

Quelle: Saliba D et al. *The Vulnerable Elders Survey: A Tool for Identifying Vulnerable Older People in the Community,* The American Geriatrics Society JAGS 49:1691–1699, 2001

0.3 The GerontoNet ADR Risk Score

Kennzeichen: _____

Alter:_____

Geschlecht: ☐ weiblich ☐ männlich

Datum: _____

Risikofaktor	**Punkt**	**Punktzahl**
4 oder mehr Komorbiditäten	**1**	
Herzinsuffizienz	**1**	
Lebererkrankungen[a]	**1**	
Anzahl der Medikamente		
<5	**0**	
5-7	**1**	
≥ 8	**4**	
Früher ADR	**2**	
Nierenversagen[b]	**1**	
a Definiert als die Leberfunktionswerte >2x oberen Grenzwert b Definiert als berechnete glomeruläre Filtrationsrate <60mL/min/ 1,73 m2 ADR= adverse drug reaction		**Gesamtpunktzahl**

Quelle:

Onder G, Petrovic M, Tangiisuran B, et al. *Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: the GerontoNet ADR Risk Score*. Arch Intern Med 2010; 170:1142-8

1.1 Arzneimittelanamnese

Klinik:	Station:	Arzt:

Patientennummer: Größe: Gewicht:	Allergien: Alkohol: Rauchen:	Kreatinin [mg/dl]: GFR [ml/min]: Sonstiges:

Medikation bei Aufnahme				**Ersatz Medikation auf Station**					
Name	**Stärke**	**Arznei-form**	**Dosierung**	**Name**	**Stärke**	**Arznei-form**	**Dosierung**	**E**	**S**

E = Ersatzmedikament gleicher Wirkstoff S= Substitution gleiche Wirkstoffgruppe

Bemerkung:

Erledigt am:
Erledigt durch:

1.4 Stationäre Medikation:

Kennzeichen: ________________

Verord-nungs-datum	Name	Stärke	Arznei-form	Dosie-rung	(vermutete) Indikation	Bemerkung/ ATC-code

1.5 Datenerfassung Azneimittelbezogene Probleme (ABPs):

Patientennummer: _____

Arzneimittel:

_____

Beschreibung des Problems:

_____

_____

_____

_____

Intervention:

_____

_____

_____

_____

Klassifikation nach APS-Doc: _____

Problem entstand: ☐ vor Aufnahme ☐ Schnittstelle ☐ während stat. Aufenthalt

Problem wurde: ☐ gelöst ☐ teilweise gelöst ☐ nicht gelöst

Bemerkung:

_____

_____

_____

_____

_____

_____

_____

_____

Checklist AMTS-Prüfung [198]
Studie: „AMTS älterer Patienten in der stationären Versorgung unter besonderer Berücksichtigung der Schnittstellen Heim – Klinik und Klinik – Heim und in der ambulanten Versorgung“

Begriffe	**Abkürzungen**
Arzneimittel	AM
Azneimittelbezogene Probleme	ABP
Arzneimitteltherapiesicherheit	AMTS
C-reaktives Protein	CRP
Dosisanpassung bei Leberinsuffizienz	DALI
Dosisanpassung bei Niereninsuffizienz	DANI
Glomeruläre Filtrationsrate	GFR
Therapeutisches Drug Monitoring	TDM

	erfolgt	nicht erfolgt	nicht zutreffend
1. Abgleich der Anamnese mit der stationären Medikation Gibt es gewollte/ungewollte Abweichungen (Arzneimittelname, Stärke, Dosierung, Darreichungsform) zwischen Hausmedikation oder vorangegangener Medikation und der stationären Anordnung?	☐	☐	☐
2. Plausibilität der Medikation (Abgleich Diagnosen – Arzneimittel) Gibt es AM zu denen keine Diagnose dokumentiert ist? Gibt es Diagnosen, bei denen keine AM-Therapie besteht?	☐	☐	☐
3. Prüfung auf Allergien Rückfrage im Anamnesegespräch, Abgleich mit Dokumentationen in Akte und elektronisch	☐	☐	☐
4. Überprüfung der Nierenfunktion, Prüfung der Arzneimitteltherapie auf DANI Prüfung der Nierenfunktion (GFR Berechnung nach Cockroft-Gault), bei GFR<60ml/min AM auf DANI prüfen, ggf. Dosisanpassung oder Alternativmedikation vorschlagen	☐	☐	☐
5. Überprüfung der Leberfunktion, Prüfung der Arzneimitteltherapie auf DALI Prüfung ob Leberfunktionsstörung in Anamnese/Diagnosen; Berechnung der Leberfunktion (Bestimmun Child Pugh), bei Child A,B,C: AM auf DALI prüfen, ggf. Dosisanpassung oder Alternativmedikation vorschlagen	☐	☐	☐

	erfolgt	nicht erfolgt	nicht zutreffend
6. Prüfung relevanter Laborwerte (Kalium, CRP usw.) Welche Laborwerte weichen von Normwert ab? Gibt es einen Zusammenhang zur Arzneimitteltherapie?	☐	☐	☐
7. Prüfung auf Kontraindikationen Sind AM-Kombinationen kontraindiziert? Sind AM aufgrund von bestehenden Vorerkrankungen kontraindiziert?	☐	☐	☐
8. Medikationsplan: *Dosierung*: gibt es Unterdosierungen und/oder Überdosierungen bei den AM? *Interaktionen:* welche Interaktionen und mit welchem Schweregrad? *Leitliniengerechte Therapie*: entspricht die Medikation einer bestehenden Leitlinien-Stufe? Fehlen AM? Ist die Kombination bestimmter AM sinnvoll und wurde diese berücksichtigt? *Altersspezifiesche Medikation (PRISCUS):* sind an der PRISCUS-List im Medikationsplan enthalten? Gibt es bestimmte Monitoring-Empfehlungen oder eine Alternativmedikation, auf die umgestellt werden sollte?	☐	☐	☐
9. Patient prä-OP? (Evaluation der Medikation) Gibt es AM, die prä-OP pausiert werden müssen (wenn ja wie lange vor OP?), Vermerk der pausierten Medikation in der Anordnung; ggf. Rucksprache mit anderen Fachabteilungen (z.B. Anästhesie), wenn offene Fragen	☐	☐	☐
10. Patient vor einer Untersuchung? (z.B. Endoskopie) Gibt es AM, die vor der Untersuchung abgesetzt/ pausiert werden müssen (wenn ja, wie lange vor der Untersuchung?), Vermerk der pausierten Medikation in der Anordnung	☐	☐	☐
11. Therapiedauer Evaluation von Therapiedauern, z.B. Antibiotikatherapie – wie lange wird das Antibiotikum schon gegeben? Wie sieht die klinische Entwicklung der Situation aus? Infektionsparameter rückläufig? Antibiose weiter?	☐	☐	☐
12. Neue Arzneimitteltherapien Bei neu angesetzten AM wird seitens der Apotheke eine Patientenberatung/-schulung zu dem neuen AM angeboten	☐	☐	☐
13. TDM Bei critical dose drugs (z.B.Aminoglykoside) Empfehlung einer Blutspiegelbestimmung und Unterstützung der Ärzte bei Dosisanpassung	☐	☐	☐

Warum erfolgt nicht die Bearbeitung eigenen Punkten:

_____

_____

_____

_____

_____

_____

_____

_____

_____

Bemerkungen

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

3.1 Zeiterfassungen für die Intervention

Datum	Patientennummer	Tätigkeit	Apotheker	Uhrzeit	Handzeichen

Apotheke des Universitätsklinikums Aachen
Dr. Albrecht Eisert
Steinbergweg 20
52074 Aachen
Tel.: 0241-8080063
Fax: 0241-8082402

Einwilligungserklärung zur Teilnahme an dem Forschungsvorhaben: „ Multiprofessionelles Arznemitteltherapiesicherheitsmodell zur Senkung der arzneimittelbezogenen Krankenhauswiedereinweisungen älterer Patienten “

Name des Patienten:_____

Ggf. Name des gesetzlichen Betreuers: _____

Name des Aufklärenden _____

Ich bestätige hiermit, dass ich durch Frau/Herr..... mündlich über Wesen, Bedeutung, Risiken und Tragweite der beabsichtigten Studie aufgeklärt wurde und für meine Entscheidung genügend Bedenkzeit hatte.

Ich habe die Patienteninformation gelesen. Ich fühle mich ausreichend informiert und habe verstanden, worum es geht. Es wurde mir ausreichend Gelegenheit gegeben, Fragen zu stellen, die alle für mich ausreichend beantwortet wurden. Ich hatte genügend Zeit mich zu entscheiden.

Mir wurde mitgeteilt, dass für den Fall einer Gesundheitsschädigung infolge meiner Teilnahme an diesem Forschungsvorhaben eine Versicherung bei der nachfolgend genannten Versicherungsgesellschaft zu meinen Gunsten besteht.

Es besteht eine Haftpflichtversicherung für die Zeit des stationären Aufenthaltes, wenn der Versicherungsfall auf das Verschulden des Hauses oder eines seiner Angestellten zurückzuführen ist. Die Haftpflichtversicherung des UK Aachen besteht bei der Zürich Versicherungs-AG, Versicherungsschein-Nr. 813.380.000.270.

Meine Einwilligung, an dieser Studie als Patient teilzunehmen, erfolgt ganz und gar freiwillig. Ich wurde darauf hingewiesen, dass ich meine Einwilligung jederzeit ohne Angaben von Gründen widerrufen kann, ohne dass mir dadurch irgendwelche Nachteile für meine weitere ärztliche Behandlung und medizinische Versorgung entstehen.

Ich bin mit einer Kontaktaufnahme nach dem stationären Aufenthalt und den beschriebenen Datenerhebungen durch das Studienteam einverstanden. Ich erteile zudem dem Studienteam die Erlaubnis, auch nach dem stationären Aufenthalt Einblick in meine aktuelle Medikations- und Patientendaten zu nehmen und ggf. den behandelnden Arzt zur aktuellen Medikation zu kontaktieren.

Ich habe eine Kopie der Patienteninformation und dieser unterschriebenen Einwilligungserklärung erhalten.

Ich habe verstanden, dass bei wissenschaftlichen Studien persönliche Daten und medizinische Befunde erhoben werden. Die Weitergabe, Speicherung und Auswertung dieser studienbezogenen Daten erfolgt nach gesetzlichen Bestimmungen und setzt vor Teilnahme an der Studie meine freiwillige Einwilligung voraus:

Ich erkläre mich damit einverstanden, dass im Rahmen der Studie erhobene Daten/Krankheitsdaten auf Fragebögen und elektronischen Datenträgern aufgezeichnet und ohne Namensnennung weitergegeben werden an.

a. **die Mitglieder des Studienteams aus dem Universitätsklinikum Aachen und dem Pharmazeutischen Institut der Universität Bonn. Dies kann auch die Veröffentlichung der Daten für wissenschaftliche Darstellungen und Veröffentlichungen in anonymisierter Form einschließen**.
b. **die zuständige Überwachungsbehörde (Landesamt oder Bezirksregierung) oder Bundesoberbehörde (Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn) zur Überprüfung der ordnungsgemäßen Durchführung der Studie.**

Ich willige hiermit ein, als Patient an der Studie „Arzneimitteltherapiesicherheit älterer Patienten in der stationären Versorgung unter besonderer Berücksichtigung der Schnittstellen bei Aufnahme und Entlassung“ teilzunehmen.

Aachen, den _____ _____

(Datum) (Name und Unterschrift des Patienten/gesetzl. Betreuer)

Ich habe den Patienten mündlich über Wesen, Bedeutung, Reichweite und Risiken der Studie aufgeklärt.

Aachen, den_____ _____

(Datum) (Name und Unterschrift des/der Aufklärenden)

Patienteninformation

zur Vorbereitung der mündlichen Aufklärung zur Studie

„ Multiprofessionelles Arznemitteltherapiesicherheitsmodell zur Senkung der arzneimittelbezogenen Krankenhauswiedereinweisungen älterer Patienten “

Verantwortliche Leiter

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Pharmazeutisches Institut der Universität Bonn, Klinische Pharmazie

An der Immenburg 4

53121 Bonn

Tel.: 0228 73 5252

Patienteninformation für: _____

Sehr geehrte Patientin, sehr geehrter Patient,

Sie sind im Universitätsklinikum Aachen (UKA) stationär aufgenommen worden.
Während Ihres stationären Aufenthaltes werden Sie rund um die Uhr von einem multiprofessionellen Team aus Ärzten, Pflegenden und vielen anderen Personen betreut.

Zusammen mit der Universität Bonn führen wir zurzeit am UKA eine Studie durch. Ziel unserer Studie ist es, herauszufinden, welche Risiken in der Arzneimitteltherapie zum einen im Krankenhaus und zum anderen in der sich anschließenden Weiterbehandlung außerhalb des Krankenhauses bestehen können. Insbesondere interessiert uns dabei die Fragestellung, wie die Arzneimitteltherapie bei älteren Patienten sicherer gestaltet werden kann und ob die Unterstützung des multiprofessionellen Teams durch einen Apotheker für Sie als Patienten einen Nutzen zeigt.

Dafür benötigen wir Ihre Mithilfe.

Auf den folgenden Seiten haben wir für Sie alle wichtigen Informationen zur Studie zusammengestellt.
Sollten Sie Fragen haben, stehen wir Ihnen selbstverständlich jederzeit gerne zur Verfügung.

Vielen Dank für Ihr Interesse und Ihre Unterstützung!

Dr. rer. nat Albrecht Eisert

(leitender Studienapotheker)

Inhalt

I. Darstellung der Studie

Um die Qualität der Gesundheitsversorgung zu verbessern, ist es erforderlich, eine aktive und effektive Zusammenarbeit zwischen Fachkräften des Gesundheitswesens zu schaffen. Wenn sich ein Team aus Ärzten, Pflegern und Apothekern um die Versorgung der Patienten kümmert, wird dies als „multiprofessionelle Zusammenarbeit“ bezeichnet.

Weltweit gibt es viele Bemühungen, die Sicherheit des Patienten zu verbessern. Ein besonderes Interesse liegt dabei oft auf der Arzneimitteltherapie. Hierfür wurde der Begriff „Arzneimitteltherapiesicherheit“ etabliert. Die Arzneimitteltherapiesicherheit stellt so gut wie möglich sicher, dass Patienten ihre Arzneimittel richtig anwenden. Insbesondere sollen unerwünschte Arzneimittelereignisse durch Medikationsfehler vermieden werden. Damit werden die Risiken einer Arzneimitteltherapie minimiert.

Im Rahmen der sowohl bundes- als auch weltweiten Initiativen zur Untersuchung der Arzneimitteltherapiesicherheit sollen in dieser Studie vor allem die Übergänge im Behandlungsprozess näher betrachtet werden:
Insbesondere bei der Einweisung ins Krankenhaus und bei Entlassung aus dem Krankenhaus können sich viele Veränderungen in der medikamentösen Versorgung ergeben. Dies bedeutet, dass Arzneimittel, die vor dem Krankenhausaufenthalt regelmäßig eingenommen wurden, nach der Entlassung nicht mehr nötig sind oder das neue Arzneimittel hinzukommen. Eventuell ändert sich auch nur der Zeitpunkt, zu dem ein Arzneimittel eingenommen werden muss oder dessen Stärke. Da bei Aufnahme und Entlassung in ein Krankenhaus Informationen zu diesen Änderungen verloren gehen können, steigt das Risiko für Medikationsfehler.
Die geplante Studie soll dazu beitragen, diese Risiken so gering wie möglich zu halten und auf diese Weise die Arzneimitteltherapiesicherheit zu verbessern.

II. Hintergrund

Bei der Anwendung von Arzneimitteln können neben den gewünschten positiven Effekten auch Risiken auftreten – sowohl bei unsachgemäßer Anwendung (z.B. Überdosierung, falsche Einnahme), als auch bei bestimmungsgemäßem Gebrauch (z.B. durch gegenseitige Beeinflussung der Medikamente in der Wirkung oder durch Auftreten von Nebenwirkungen).
Je mehr Arzneimittel Sie einnehmen, desto höher ist das Risiko für Probleme in der Arzneimitteltherapie. Viele Risiken können frühzeitig aufgedeckt werden, vor allem, wenn Sie gut über Ihre Arzneimittel informiert sind und die aktuell eingenommenen Arzneimittel gut dokumentiert sind. Zusätzlich kann bei Veränderungen in Ihrer Versorgungssituation, z.B. bei Einwei-

sung in ein Krankenhaus oder bei Verlegung in eine andere Klinik, ein Informationsverlust entstehen.

Um die Abläufe und mögliche Risiken/Probleme in der Arzneimitteltherapie an den unterschiedlichen Orten, an denen Sie mit Arzneimitteln versorgt werden, zu untersuchen, haben wir diese Studie entworfen. Mit Hilfe der Ergebnisse sollen Strukturen und Abläufe entwickelt werden, die der Sicherheit der Arzneimitteltherapie dienen.

III. Ziel der Studie

Ziel der Studie ist die Untersuchung von Arzneimittelrisiken im Krankenhaus und des Nutzens einer intensiveren multiprofessionellen Zusammenarbeit unter stärkerer Einbeziehung des Apothekers zur Verbesserung der Arzneimitteltherapiesicherheit.

IV. Erläuterung des Forschungsplans (Studiendesign)

In die Studie werden insgesamt 138 Patienten aufgenommen und in zwei Gruppen eingeteilt. Nach Einwilligung in die Studienteilnahme werden Sie nach dem Zufallsprinzip entweder der Kontrollgruppe oder der Intensivbetreuungsgruppe zugeteilt. Der Ablauf ist in Abbildung 1 schematisch dargestellt.

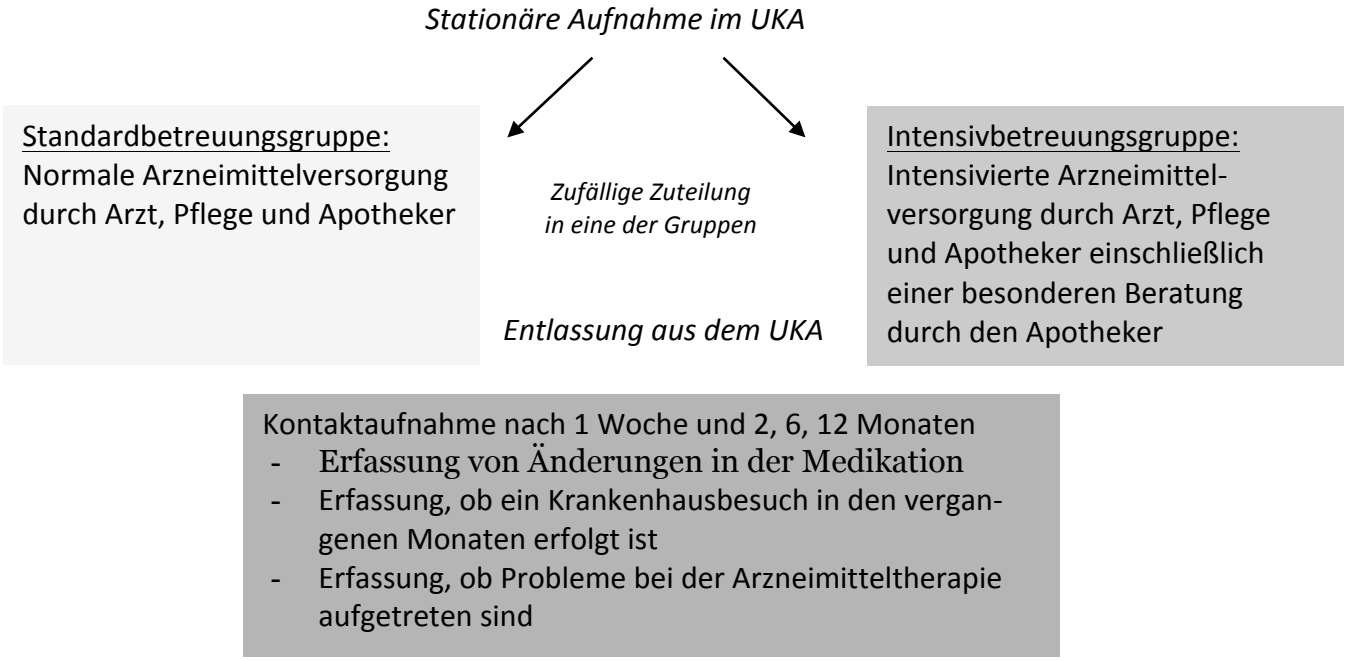

Abbildung 1: Schematische Darstellung des Studienablaufs

Alle Patienten erhalten eine Therapie nach aktuellem Standard. Sie werden weiterhin in gewohntem Umfang durch Ihren Arzt und durch die anderen Mitglieder des therapeutischen Teams betreut.

Eine der beiden Gruppen wird als Standardbetreuungsgruppe (**Kontrollgruppe**) geführt. Hier wird die Arzneimitteltherapie in der **gewohnten Weise** durch Ärzte, Pflegekräfte und Apotheker durchgeführt.

In der anderen Gruppe (**Intensivbetreuungsgruppe**) arbeiten die verschiedenen Berufsgruppen intensiver zusammen. Vor allem der **Apotheker** tritt wesentlich stärker in Erscheinung als in der Kontrollgruppe. Der Apotheker berät Sie, sowie die Ärzte und die Pflege intensiver zu den einzelnen Arzneimitteln. Ob eine Therapie verändert wird, entscheidet jedoch weiterhin der Arzt. Am Ende des stationären Aufenthalts bitten wir Sie an einer Befragung teilzunehmen. Hierbei werden Ihnen Fragen zu Ihrer Zufriedenheit mit der Betreuung durch Arzt, Pflege und Apotheker gestellt.

Welche Daten werden erhoben?

Am Anfang des stationären Aufenthaltes werden Daten über ihren Gesundheitszustand und ihre körperlichen und kognitiven Fähigkeiten erhoben. Während des stationären Aufenthaltes werden Daten zu Ihrer Hausmedikation und zu Ihrer aktuellen Arzneimitteltherapie erfasst. Die Erhebung der Daten erfolgt anhand der Angaben in der Patientenakte.

Diese Dokumentation ist für alle Patienten der Studie gleich!

Nach der Krankenhausentlassung werden zu vier Zeitpunkten (1 Woche nach Entlassung und 2, 6 und 12 Monate nach Entlassung) Ihre aktuellen Medikamente und Ihre aktuellen Diagnosen erhoben.

Diese Erfassung wird durch ein telefonisches Gespräch oder ein persönliches Gespräch mit Ihnen oder einem Ihrer Betreuer oder Angehörigen erfolgen.

Wichtig:

Nach der Entlassung werden alle Patienten gleich behandelt, egal in welche Gruppe sie zugeteilt wurden. Die Kontaktaufnahme nach der Entlassung durch ein Mitglied des Studienteams aus dem Uniklinikum Aachen dient der Dokumentation.

Wenn unerwünschte Arzneimittelwirkungen bei der Dokumentation auffallen, wird der Arzt aus Gründen der Sicherheit hierzu informiert, gleich welcher Betreuungsgruppe Sie zugehören.

IV. Zeitplan / Ablauf der Studie

Zu Beginn des Aufenthaltes im Universitätsklinikum Aachen erhalten Sie Informationen zu dieser Studie und werden zur Teilnahme eingeladen (Aufklärungsgespräch).
Nach Ihrer Zustimmung zur Studienteilnahme werden Sie nach dem Zufallsprinzip in eine der beiden Behandlungsgruppen (Kontrollgruppe oder Intensivbetreuungsgruppe) zugeteilt.

Wie ist der Ablauf, wenn ich in die Kontrollgruppe zugeordnet werde?

Bei Zuteilung in die Kontrollgruppe werden Sie nach dem derzeitigen Standard durch Arzt und Pflegekräfte stationär betreut. Ein Apotheker wird Sie während des stationären Aufenthaltes nur in Einzelfällen kontaktieren.
Um den Langzeit-Effekt zu erfassen, werden wir Sie nach Entlassung aus dem Krankenhaus nach 1 Woche und nach 2, 6 und 12 Monaten nochmals kontaktieren und Sie zu Ihren aktuellen Medikamenten, unerwünschten Ereignissen im Zusammenhang mit Arzneimitteln und zu weiteren Krankenhausaufenthalten befragen.

Die Kontaktaufnahme wird telefonisch/schriftlich oder persönlich erfolgen. Ein persönlicher Kontakt wird vor allem dann erfolgen, wenn Sie in einer betreuten Einrichtung wohnen. Pro Kontaktaufnahme werden etwa 30 Minuten veranschlagt.

Wie ist der Ablauf, wenn ich in die Intensivbetreuungsgruppe eingeteilt werde?

Im Falle der Zuteilung in die Intensivbetreuungsgruppe erfolgt ein Arzneimittel-Anamnesegespräch durch einen Apotheker. Im Verlaufe des stationären Aufenthaltes wird durch den Apotheker Ihre Medikation regelmäßig auf mögliche Probleme untersucht. Bei Fragen zu Arzneimitteln steht Ihnen der Apotheker gerne zur Verfügung.
Zum Ende des stationären Aufenthaltes besteht für Sie auf Wunsch die Möglichkeit eines weiteren Gesprächs, vor allem, wenn sich während des Aufenthaltes im UKA Änderungen in Ihrer Arzneimitteltherapie ergeben haben (Arzneimittel-Entlassgespräch). Die Informationen können auch in schriftlicher Form zur Verfügung gestellt werden.

a) Aufklärungsgespräch und Folgegespräch

Im ersten Gespräch werden Sie über die Ziele und Hintergründe der geplanten Studie informiert. In diesem Gespräch wird Ihnen vermittelt, was Sie von der Teilnahme an dieser Studie erwarten können und was als Patient/-in auf Sie zukommt. Sie erhalten die Patienteninformation, die Sie gerade lesen, sowie eine Einverständniserklärung zur Teilnahme

an der Studie und eine Datenschutzerklärung. Im Verlauf dieses Gespräches haben Sie die Gelegenheit, Fragen zu stellen und sich Dinge erläutern zu lassen, die Ihnen unklar erscheinen.

Im **folgenden Gespräch** können Sie Ihre Entscheidung mitteilen, ob Sie bereit sind, an der Studie teilzunehmen oder lieber davon absehen möchten. Zuvor besteht die Möglichkeit, weitere Fragen zu klären. Falls Sie an der Studie teilnehmen möchten, werden Sie gebeten, Ihre Einwilligung zur Teilnahme und zur Speicherung Ihrer persönlichen Daten schriftlich zu bestätigen. Diese Daten werden ausschließlich für Zwecke der Studie verwendet.

b) Arzneimittel-Anamnesegespräch durch den Apotheker

Im Arzneimittel-Anamnesegespräch wird der betreuende Apotheker sich mit Ihnen über Ihre aktuellen Medikamente unterhalten. Hierbei werden alle von Ihnen bisher eingenommenen Medikamente nochmals erfasst, neben weiteren persönlichen Daten.
Im Gespräch haben Sie außerdem die Möglichkeit, Fragen zu klären.

c) Weitere Gespräche mit dem Apotheker

Weitere Gespräche mit dem Apotheker erfolgen auf Wunsch des Patienten oder der Ärzte.

d) Arzneimittel-Entlassgespräch

Auf Wunsch kann zum Ende des Krankenhausaufenthaltes ein Arzneimittel-Entlassgespräch erfolgen, in dem eventuell vorliegende Änderungen im Medikamentenplan besprochen werden können. Die Informationen können auch in schriftlicher Form zur Verfügung gestellt werden.

e) Zufriedenheitsbefragung

Ihre Meinung ist uns wichtig. Daher werden Sie gebeten am Ende des stationären Aufenthalts einen Fragebogen mit offenen und geschlossenen Fragen zu beantworten. Dabei geht es um Ihre Erfahrung und Zufriedenheit zu der Kommunikation mit dem multiprofessionellen Team unter Einbeziehung des Apothekers.

Um den Langzeit-Effekt zu erfassen, werden wir Sie nach Entlassung aus dem Krankenhaus nach 1 Woche und nach 2, 6 und 12 Monaten nochmals kontaktieren und Sie zu Ihren aktuel-

len Medikamenten, unerwünschten Ereignissen im Zusammenhang mit Arzneimitteln und zu weiteren Krankenhausaufenthalten befragen.

Die Kontaktaufnahme wird telefonisch/schriftlich oder persönlich erfolgen. Ein persönlicher Kontakt wird vor allem dann erfolgen, wenn Sie in einer betreuten Einrichtung wohnen. Pro Kontaktaufnahme werden etwa 30 Minuten veranschlagt.

V. Risiko/Nutzen-Relation:

Bei der Teilnahme an der Studie bestehen für Sie keinerlei medizinische Risiken.
Falls einem Apotheker während der Dokumentation eine schwerwiegende, unerwünschte Wirkung auffällt, welches durch ein Arzneimittel eingetreten sein könnte, wird unverzüglich Ihr behandelnder Arzt informiert - egal in welche der beiden Behandlungsgruppen Sie zugeteilt worden sind!
Über die weiteren Maßnahmen entscheidet Ihr behandelnder Arzt.
Bei **Zuteilung in die Kontrollgruppe** erfahren Sie weiterhin die gewohnte Betreuung durch erfahrene Ärzte und Pflegepersonal.
Ihr zusätzlicher Aufwand durch die Teilnahme an der Studie besteht, neben dem Lesen der Patienteninformation und dem Aufklärungsgespräch, aus einer Zusammenarbeit mit dem Forschungsteam und einer Kontaktaufnahme nach dem Krankenhausaufenthalt.
Nach Entlassung aus dem Krankenhaus wird ein Mitglied des Studienteams Sie zu vier Zeitpunkten kontaktieren. Die Gespräche werden etwa 30 Minuten dauern. Diese Gespräche können auch von Ihnen beauftragte Angehörige oder andere betreuende Personen übernehmen.
Bei der **Zuteilung in die Intensivbetreuungsgruppe** kann sich durch die intensivere pharmazeutische Beratung in dem multiprofessionellen Team ein positiver Nutzen für Sie als Patient ergeben. Möglicherweise lässt sich Ihre Arzneimitteltherapie durch einen Apotheker noch weiter verbessern. Der Apotheker steht Ihnen für alle aufkommenden arzneimittelbezogenen Fragen zur Verfügung.
Der Apotheker hat, entsprechend den gesetzlichen Bestimmungen, nur eine beratende Funktion gegenüber Ihnen und Ihrem Arzt. Weiterhin entscheidet ausschließlich der behandelnde Arzt über Ihre Medikamente und Ihre Therapie.
Ihr zusätzlicher Aufwand durch die Teilnahme an der Studie besteht in dem Aufklärungsgespräch, aus einer Zusammenarbeit mit dem Forschungsteam, dem multiprofessionellem Team mit einbezogenem Apotheker und einer Kontaktaufnahme nach dem Krankenhausaufenthalt.

Während des stationären Aufenthaltes ergeben sich für Sie oder Ihre Angehörigen etwa 15 minütige Betreuungsgespräche mit dem Apotheker.
Nach Entlassung aus dem Krankenhaus wird ein Mitglied des Studienteams Sie zu vier Zeitpunkten kontaktieren. Die Gespräche werden etwa 30 Minuten dauern. Diese Gespräche können auch von Ihnen beauftragte Angehörige oder andere betreuende Personen übernehmen.

Es besteht eine Haftpflichtversicherung, wenn der Versicherungsfall auf das Verschulden des Hauses oder eines seiner Angestellten zurückzuführen ist. Die Haftpflichtversicherung des UK Aachen besteht bei der Zürich Versicherungs-AG, Versicherungsschein-Nr. 813.380.000.270.

VI. Datenschutz und Patienteneinwilligung

Die Teilnahme an der Studie birgt für Sie keine zusätzlichen Risiken.
Sie haben das Recht, jederzeit und ohne Angaben von Gründen von der Teilnahme an der Studie zurückzutreten. Ihre personenbezogenen Daten werden nach Widerruf/Rücktritt unverzüglich gelöscht bzw. anonymisiert. Es entstehen Ihnen dadurch keine Nachteile in Ihrer Behandlung.
Wie oben erläutert, werden wir erst nach Ihrem Einverständnis zur Teilnahme an der Studie personenbezogene Daten erheben. Zum einen sind bestimmte Daten zur Beratung notwendig, zum anderen sollen Informationen, die sich im Gespräch ergeben, gespeichert werden. Außerdem sollen Daten gespeichert werden, die speziell für die Auswertung der Studie wichtig sind und auch nach der Entlassung eine Kontaktaufnahme zu Ihnen ermöglichen.
Die gesammelten Informationen sollen in einer Datenbank gespeichert werden, die nur den Studienbeteiligten zugänglich ist (Kennwortschutz). Die Daten dienen ausschließlich dem Zweck der Durchführung der Studie und werden in diesem Zusammenhang entsprechend ausgewertet. Für die Auswertung werden die Daten ausschließlich in pseudonymidierter, d.h. verschlüsselter Form verwendet.

Die Ergebnisse werden ausschließlich anonymisiert veröffentlicht und stehen Ihnen dann auf Anfrage zur Verfügung.
Wir arbeiten ausschließlich mit klinikeigener Hard- und Software des Universitätsklinikums Aachen. Diese entspricht den aktuellen Datensicherheits- und Datenschutzanforderungen. Nach Ablauf der Studie bzw. uns bindender spezieller Aufbewahrungsvorschriften werden Ihre personenbezogenen Daten gelöscht bzw. anonymisiert.

Die erhobenen Daten unterliegen den gesetzlichen Bestimmungen des Datenschutzes und setzen Ihre schriftliche Einwilligung zur Weitergabe, Speicherung und Auswertung im Rahmen der Studie voraus (Datenschutzerklärung, Einverständniserklärung).

Wenn Sie die Informationen in diesem Informationsblatt gelesen haben und noch Fragen offen geblieben sind, so können Sie diese gerne mit uns im persönlichen Gespräch klären.
Sie können frei über die Teilnahme an der Studie entscheiden.
Wir würden uns freuen, wenn Sie Interesse haben, an der Studie teilzunehmen.
Ihr Einverständnis und Ihre Teilnahme bestätigen Sie schriftlich mit einer so genannten Patienten-Einwilligungserklärung und einer Datenschutzerklärung, die Sie auf einem separaten Bogen erhalten.

Für Ihre Bemühungen und Ihre Mitarbeit danken wir Ihnen recht herzlich!!!

Hinweis:

Aus Gründen der besseren Lesbarkeit wurde auf die Verwendung weiblicher Schreibformen verzichtet. Alle entsprechend verwendeten Bezeichnungen beinhalten auch die weibliche Form

Attachments Model II

Oncology CRFs
Approval from the study ward
Ethic Committee Opinion
Patient diagnosis
Mean cohort attribute scores
Person's chi square test of independence- Crosstabs table

0 Patientennummer

Patientennummer_____
Name_____
Geschlecht_____
Alter_____
Aufnahmedatum_____
Entlassdatum_____

0.1 The GerontoNet ADR Risk Score

Kennzeichen: _____

Alter:_____

Geschlecht: ☐ weiblich ☐ männlich

Datum: _____

Risikofaktor	**Punkt**	**Punktzahl**
4 oder mehr Komorbiditäten	**1**	
Herzinsuffizienz	**1**	
Lebererkrankungen[a]	**1**	
Anzahl der Medikamente		
<5	**0**	
5-7	**1**	
≥ 8	**4**	
Früher ADR	**2**	
Nierenversagen[b]	**1**	
a Definiert als die Leberfunktionswerte >2x oberen Grenzwert b Definiert als berechnete glomeruläre Filtrationsrate <60mL/min/ 1,73 m2 ADR= adverse drug reaction		**Gesamtpunktzahl**

Quelle:
Onder G, Petrovic M, Tangiisuran B, et al. *Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: the GerontoNet ADR Risk Score.* Arch Intern Med 2010; 170:1142-8

UNIKLINIK RWTH AACHEN

Klinische Pharmazie

universitätbonn

0.2 PRO-CTCAE: Fragebogen zu Symptomen bei Krebspatienten unter medikamentöser Tumortherapie

Bitte beantworten Sie die folgenden Fragen zu häufig vorkommenden Symptomen während einer Krebstherapie selbst, indem Sie die Antwort ankreuzen, die für Sie am besten zutrifft. Bitte beziehen Sie sich bei der Antwort immer auf **die schwerste Ausprägung** des jeweiligen Symptoms **in den letzten 7 Tagen** (gemeint ist nicht der Durchschnittswert).

---

1. Während der letzten 7 Tage: wie HÄUFIG hatten Sie **Übelkeit**?

Nie	Selten	Gelegentlich	Häufig	Fast immer
☐	☐	☐	☐	☐

2. Während der letzten 7 Tage: wie STARK war Ihre **Übelkeit** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

3. Während der letzten 7 Tage: wie HÄUFIG mussten Sie **erbrechen**?

Nie	Selten	Gelegentlich	Häufig	Fast immer
☐	☐	☐	☐	☐

4. Während der letzten 7 Tage: wie STARK war Ihr **Erbrechen** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

---

5. Während der letzten 7 Tage: wie HÄUFIG hatten Sie **Schmerzen**?

Nie	Selten	Gelegentlich	Häufig	Fast immer
☐	☐	☐	☐	☐

6. Während der letzten 7 Tage: wie STARK waren Ihre **Schmerzen** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

7. Während der letzten 7 Tage: wie SEHR haben **Schmerzen** Sie in Ihren täglichen Aktivitäten GESTÖRT?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

8. Während der letzten 7 Tage: wie STARK war Ihre **Verstopfung** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

9. Während der letzten 7 Tage: wie HÄUFIG hatten Sie **Durchfall**?

Nie	Selten	Gelegentlich	Häufig	Fast immer
☐	☐	☐	☐	☐

10. Während der letzten 7 Tage: wie STARK war Ihr **Appetitmangel** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

11. Während der letzten 7 Tage: wie SEHR hat Ihr **Appetitmangel** Sie in Ihren täglichen Aktivitäten GESTÖRT?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

12. Während der letzten 7 Tage: wie STARK waren Ihre **Schwierigkeiten beim Schlucken** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

13. Während der letzten 7 Tage: wie STARK war Ihre **Mundtrockenheit** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

14. Während der letzten 7 Tage: wie STARK hatten Sie **wunde oder offene Stellen in Mund oder Hals** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

15. Während der letzten 7 Tage: wie SEHR haben **wunde oder offene Stellen in Mund oder Hals** Sie in ihren täglichen Aktivitäten GESTÖRT?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

16. Während der letzten 7 Tage: wie STARK waren **Taubheit oder Kribbeln in Händen oder Füßen** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

17. Während der letzten 7 Tage: wie SEHR hat Sie **Taubheit oder Kribbeln in Händen oder Füßen** in Ihren täglichen Aktivitäten GESTÖRT?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

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18. Während der letzten 7 Tage: wie STARK war Ihre **Kurzatmigkeit** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

19. Während der letzten 7 Tage: wie SEHR hat **Kurzatmigkeit** Sie in Ihren täglichen Aktivitäten GESTÖRT?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

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20. Während der letzten 7 Tage: wie STARK war Ihre **Müdigkeit, Erschöpfung oder fehlende Energie** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

21. Während der letzten 7 Tage: wie SEHR haben **Müdigkeit, Erschöpfung oder fehlende Energie** Sie in Ihren täglichen Aktivitäten GESTÖRT?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

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22. Während der letzten 7 Tage: wie STARK waren Ihre **Probleme sich zu konzentrieren** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

23. Während der letzten 7 Tage: wie SEHR haben Ihre **Probleme sich zu konzentrieren** Sie in Ihren täglichen Aktivitäten GESTÖRT?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

---

24. Während der letzten 7 Tage: wie STARK waren Ihre **Probleme beim Schlafen** (wie z.B. Schwierigkeiten beim Einschlafen, Durchschlafen oder zu frühes Aufwachen) im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

25. Während der letzten 7 Tage: wie SEHR haben **Probleme beim Schlafen** (wie z.B. Schwierigkeiten beim Einschlafen, Durchschlafen oder zu frühes Aufwachen) Sie in Ihren täglichen Aktivitäten GESTÖRT?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

---

26. Während der letzten 7 Tage: wie HÄUFIG hatten Sie **Angst**?

Nie	Selten	Gelegentlich	Häufig	Fast immer
☐	☐	☐	☐	☐

27. Während der letzten 7 Tage: wie STARK war Ihre **Angst** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

28. Während der letzten 7 Tage: wie SEHR hat **Angst** Sie in Ihren täglichen Aktivitäten GESTÖRT?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

---

29. Während der letzten 7 Tage: wie HÄUFIG waren Sie **traurig**?

Nie	Selten	Gelegentlich	Häufig	Fast immer
☐	☐	☐	☐	☐

30. Während der letzten 7 Tage: wie STARK war Ihre **Traurigkeit** im schlimmsten Fall?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

31. Während der letzten 7 Tage: wie sehr hat Ihre **Traurigkeit** Sie in Ihren täglichen Aktivitäten GESTÖRT?

Gar nicht	Ein wenig	Mäßig	Ziemlich	Sehr
☐	☐	☐	☐	☐

1 Arzneimittelanamnese

Patientennummer: Größe: Gewicht:	Allergien: Alkohol: Rauchen:	Kreatinin [mg/dl]: GFR [ml/min]: Sonstiges:

Medikation bei Aufnahme				Ersatzmedikation auf Station					
Name	**Stärke**	**Arznei-form**	**Dosierung**	**Name**	**Stärke**	**Arznei-form**	**Dosierung**	**E**	**S**

E = Ersatzmedikament gleicher Wirkstoff gruppe S= Substitution gleiche Wirkstoff-

Bemerkung:

Erledigt am:
Erledigt durch:

2 Stationäre Medikation:

Patientennummer: _____

Verord-nungs-datum	Name	Stärke	Arznei-form	Dosie-rung	(vermutete) Indikation	Bemerkung/ ATC-code

3 Datenerfassung Azneimittelbezogene Probleme (ABPs):

Patientennummer: _____

Arzneimittel: _____

Beschreibung des Problems:

_____

_____

_____

_____

Intervention:

_____

_____

_____

_____

Klassifikation nach APS-Doc: _____

Problem entstand: ☐ vor Aufnahme ☐ Schnittstelle ☐ während stat. Aufenthalt

Problem wurde: ☐ gelöst ☐ teilweise gelöst ☐ nicht gelöst

Bemerkung: _____

_____

_____

_____

_____

_____

_____

4 Zeiterfassungen für die Intervention

Datum	Patientennummer	Tätigkeit	Apotheker	Uhrzeit (von-bis)	Handzeichen

Empfehlungen aus dem Medikationscheck

Folgende Angaben betreffen die Arzneimitteltherapie Ihres Patienten

Herr/Frau _____

Unterschrift des Apothekers: _____

Empfehlungen wurden mit _____ besprochen.

Datum_____

ONKO Pilotstudie, Apotheke der Uniklinik RWTH Aachen, A. Šarčević, Tel.: 0241 8085046
K. Schmitz 2014©, Update A. Šarčević 2016

Research Study Proposal

7. Approval from the study ward

Hereby is the approval from the department director for the project implementation and permission for data collection in the pilot project "Medication safety in the oncological department".

The Department of haematology, haemostasis and stem cell transplantation (Internal medicine IV)

Univ.-Prof. Dr. med. Tim H. Brümmendorf

8. Signature of the study director and study manager

Study director

Dr. rer. nat Albrecht Eisert

Study manager

Ana Šarčević

ETHIK-KOMMISSION AN DER MEDIZINISCHEN FAKULTÄT
DER RHEINISCH-WESTFÄLISCHEN TECHNISCHEN HOCHSCHULE AACHEN
Pauwelsstr. 30, 52074 Aachen - Tel. 0241-80 89 963 – FAX 0241-80 82 012
E-Mail: ekaachen@ukaachen.de

Ethik-Kommission an der Medizinischen Fakultät
der RWTH Aachen – Pauwelsstr. 30 – D - 52074 Aachen

Aachen, den 14.6.16

Herrn
Dr. rer. nat. Albrecht Eisert
Apothekencenter
Im Hause
aeisert@ukaachen.de

Schmal/pre

Betrifft:

EudraCT-Nr.:	-
Protokoll-Nr:	-
Titel:	AMTS auf der Onkologischen Station.
Sponsor:	-
Eingereicht von:	Dr. rer. nat. Albrecht Eisert, Apothekencenter, Uniklinik RWTH Aachen, Pauwelsstr. 30, 52074 Aachen
Antragsteller:	Dr. rer. nat. Albrecht Eisert, s.o.
LKP:	-
Lokaler Hauptprüfer:	Dr. rer. nat. Albrecht Eisert, s.o.
Internes Aktenzeichen:	EK 142/16

Hier: Stellungnahme

Sehr geehrter Herr Dr. Eisert,

Vielen Dank für Ihr Schreiben vom 29.4.16 und vom 30.05.16 – Eingang in der Geschäftsstelle der Ethik-Kommission am 12.5.16 und am 30.05.16 – mit dem Sie um Stellungnahme zu der von Ihnen geplanten Studie bzgl. Beratung zur Arzneimitteltherapie stationärer Patienten durch den approbierten Apotheker des Klinikums zur Evaluierung des Klinikstandards bitten. Die Datensammlung und Auswertung erfolgt ausschließlich anonymisiert. Entsprechend § 6 (2) GDSG NRW ist eine Antragstellung zu dem von Ihnen geplanten Versuchsvorhaben nicht notwendig.

Es bestehen keine Bedenken aus ethischer und berufsrechtlicher Sicht hinsichtlich des Forschungsvorhabens.

Die eingereichten Unterlagen wurden nicht im Rahmen einer Sitzung, sondern im Auftrag der Ethik-Kommission satzungsgemäß im vereinfachten Verfahren durch den Vorsitzenden und den stellv. Vorsitzenden der Ethik-Kommission bewertet.

Viel Erfolg bei Ihrem Forschungsvorhaben.

Mit freundlichen Grüßen

Prof. Dr. med. G. Schmalzing
Vorsitzender

Prof. Dr. med. U. Büll
Stellv. Vorsitzender

Tel.: Prof. Dr. G. Schmalzing, Vorsitzender: +49 241 80 89 087; Dr. P. Prével, Geschäftsführerin: +49 241 80 89 963,
Fax +49 241 80 82 012; E-mail:ekaachen@ukaachen.de, Homepage: www.medizin.rwth-aachen.de/EK

Ethik-Kommission an der Medizinischen Fakultät der RWTH Aachen
EudraCT - EK 142/16

Die Ethik-Kommission ist nach Landesrecht konstituiert und bei den zuständigen Landesbehörden, beim Bundesamt für Arzneimittel (BfArM) sowie beim Bundesamt für Strahlenschutz (BfS) registriert. Sie berät unabhängig nach den Regeln des Weltärztebundes in der Deklaration von Helsinki über Forschung am Menschen in der Fassung von 1996 in Somerset West, nach nationalen Gesetzen, Vorschriften und der ICH-GCP-Leitlinie in der jeweils gültigen Fassung (siehe Homepage der Ethik-Kommission unter www.medizin.rwth-aachen.de/EK).

ETHIK-KOMMISSION AN DER MEDIZINISCHEN FAKULTÄT
DER RHEINISCH-WESTFÄLISCHEN TECHNISCHEN HOCHSCHULE AACHEN
Pauwelsstr. 30, 52074 Aachen - Tel. 0241-80 89 963 – FAX 0241-80 82 012
E-Mail: ekaachen@ukaachen.de

Ethik-Kommission an der Medizinischen Fakultät
der RWTH Aachen – Pauwelsstr. 30 – D - 52074 Aachen

Aachen, den 09.08.16

Herrn
Dr. rer. nat. Albrecht Eisert
Apothekencenter
Im Hause
aeisert@ukaachen.de

Schmal/ah

Betrifft:

EudraCT-Nr.:	-
Protokoll-Nr:	-
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LKP:	-
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Internes Aktenzeichen:	EK 142/16

Hier: Stellungnahme

Sehr geehrter Herr Dr. Eisert,

Vielen Dank für Ihre Schreiben vom 29.04.16, 30.05.16 und vom 13.07.16 – Eingang in der Geschäftsstelle der Ethik-Kommission am 12.05.16, 30.05.16 und am 14.07.16 – mit denen Sie um Stellungnahme zu der von Ihnen geplanten Auswertung der Beratung zur Arzneimitteltherapie stationärer Patienten durch den approbierten Apotheker des Klinikums bitten. Sie legen dar, dass nach §20 der Apothekenbetriebsordnung (ApBetrO), welche nach §1 ApBetrO auch für Krankenhausapotheken anzuwenden ist, Apotheker zur Informationen und Beratung verpflichtet sind.

Bei unserem Gespräch am 09.08.2016 mit Ihnen und Frau Apothekerin Ana Sarcevic in der Geschäftsstelle der Ethik-Kommission wurde klar, dass die Datensammlung zwar pseudonymisiert erfolgt, dass aber vor der Auswertung der Daten jeglicher Personenbezug gelöscht wird. Die Datenauswertung erfolgt ausschließlich anonymisiert und stellt eine Qualitätssicherung dar. Entsprechend § 6 (2) und § 11 (2) GDSG NRW ist die von Ihnen geplante wissenschaftliche Verwendung der Patientendaten auch ohne Zustimmung der Patienten zulässig.

Es bestehen keine ethischen oder berufsrechtlichen Bedenken gegen das Forschungsvorhaben.

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Ethik-Kommission an der Medizinischen Fakultät der RWTH Aachen
EK 142/16

Bitte beachten Sie, dass diese Stellungnahme unsere Stellungnahme vom 14.06.2016 ersetzt.

Die eingereichten Unterlagen wurden nicht im Rahmen einer Sitzung, sondern im Auftrag der Ethik-Kommission satzungsgemäß im vereinfachten Verfahren durch den Vorsitzenden und den stellv. Vorsitzenden der Ethik-Kommission bewertet.

Viel Erfolg bei Ihrem Forschungsvorhaben.

Mit freundlichen Grüßen

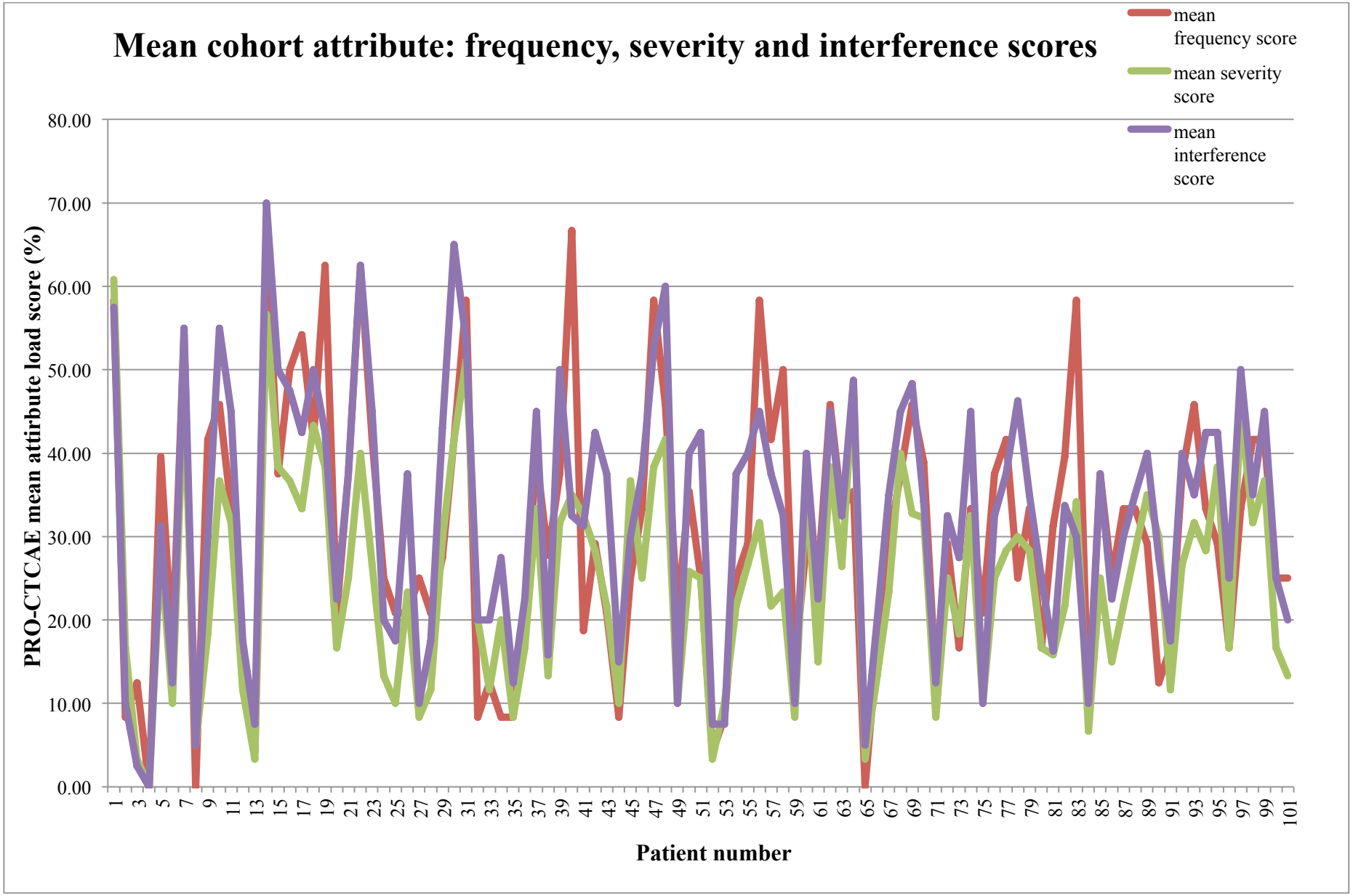
Prof. Dr. med. G. Schmalzing	Prof. Dr. med. U. Büll
Vorsitzender	Stellv. Vorsitzender

Die Ethik-Kommission ist nach Landesrecht konstituiert und bei den zuständigen Landesbehörden, beim Bundesamt für Arzneimittel (BfArM) sowie beim Bundesamt für Strahlenschutz (BfS) registriert. Sie berät unabhängig nach den Regeln des Weltärztebundes in der Deklaration von Helsinki über Forschung am Menschen in der Fassung von 1996 in Somerset West, nach nationalen Gesetzen, Vorschriften und der ICH-GCP-Leitlinie in der jeweils gültigen Fassung (siehe Homepage der Ethik-Kommission unter www.medizin.rwth-aachen.de/EK).

Patient diagnosis

Cancer type ICD-10			Frequency	Per-cent
Valid	C04.1	Malignant neoplasm of lateral floor of mouth	1	1.0
	C07	Malignant neoplasm of parotid gland	1	1.0
	C10.8	Malignant neoplasm of overlapping sites of oropharynx	1	1.0
	C15.9	Malignant neoplasm of esophagus, unspecified	1	1.0
	C22.0	Liver cell carcinoma	1	1.0
	C25.1	Malignant neoplasm of body of pancreas	1	1.0
	C32.8	Malignant neoplasm of overlapping sites of larynx	1	1.0
	C34.0	Malignant neoplasm of main bronchus	5	5.0
	C34.1	Malignant neoplasm of upper lobe, bronchus or lung	13	12.9
	C34.2	Malignant neoplasm of middle lobe, bronchus or lung	2	2.0
	C34.3	Malignant neoplasm of lower lobe, bronchus or lung	4	4.0
	C43.5	Malignant melanoma of lower limb, including hip	1	1.0
	C43.7	Malignant melanoma of trunk	1	1.0
	C45.0	Mesothelioma of pleura	1	1.0
	C50.4	Malignant neoplasm of upper-outer quadrant of breast	1	1.0
	C50.9	Malignant neoplasm of breast of unspecified site	1	1.0
	C53.8	Malignant neoplasm of overlapping sites of cervix uteri	1	1.0
	C56	Malignant neoplasm of ovary.	3	3.0
	C57.0	Malignant neoplasm of fallopian tube	1	1.0
	C61	Malignant neoplasm of prostate	3	3.0
	C62.0	Malignant neoplasm of undescended testis (C62.1 the same)	1	1.0
	C62.1	Malignant neoplasm of overlapping sites of bladder	1	1.0
	C67.8	Secondary malignant neoplasm of retroperitoneum and peritoneum	2	2.0
	C78.6	Secondary malignant neoplasm of bone and bone marrow	1	1.0
	C80.0	Disseminated malignant neoplasm, unspecified	2	2.0
	C81.1	Hodgkin-lymphom	1	1.0
	C81.7	Other Hodgkin lymphoma	1	1.0
	C82.0	Follicular lymphoma grade I	1	1.0
	C82.1	Follicular lymphoma grade II	1	1.0
	C83.1	Mantle cell lymphoma	3	3.0
	C83.3	Diffuse large B-cell lymphoma (DLBCL or DLBL)	16	15.8
	C84.4	Peripheral T-cell lymphoma, not classified	1	1.0
	C86.5	Angioimmunoblastic T-cell lymphoma	1	1.0
	C88.0	Waldenström macroglobulinemia	1	1.0
	C90.0	Multiple Myeloma not having achieved remission	14	13.9
	C90.10	Plasma cell leukemia not having achieved remission	1	1.0
	C91.1	Chronic lymphocytic leukemia of B-cell type	1	1.0

	C91.6	Prolymphocytic leukemia of T-cell type	1	1.0
	C91.8	Burkitt acute lymphoblastic leukaemia	1	1.0
	C92.0	Acute myeloblastic leukemia	2	2.0
	C92.1	Chronic myeloid leukemia	1	1.0
	C92.4	Acute promyelocytic leukemia (AML M3)	1	1.0
	C92.5	Acute myelomonocytic leukemia (AML M4)	1	1.0
	C96.5	Multifocal and unisystematic Langerhans-cell histiocytosis	1	1.0
	Total		101	100.0


Mean cohort attribute: frequency, severity and interference scores
mean frequency score
mean severity score
mean interference score
PRO-CTCAE mean attirbute load score (%)
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63 65 67 69 71 73 75 77 79 81 83 85 87 89 91 93 95 97 99 101
Patient number

Pearson's chi square test of independence – Crosstabs Table										
Mean cohort PRO-CTCAE attribute score **p < 0.05**	Number of medication		Number of drug-related problems		Adverse drug reaction risk score		Cancer type		ECOG performance score	
	LOW (≤ 7)	HIGH (> 8)	LOW (= 0)	HIGH (> 1)	LOW (≤ 4)	HIGH (> 5)	Solid	Haematological	LOW (0-1)	HIGH (2-4)
Frequency (0-1) LOW	8	56	22	42	11	53	31	33	35	24
(2-4) HIGH	4	33	8	29	4	33	20	17	12	21
Severity (0-1) LOW	12	73	29	56	15	70	41	44	40	37
(2-4) HIGH	0	16	1	15	0	16	10	6	7	8
Interference (0-1) LOW	10	46	19	37	10	46	22	34	32	19
(2-4) HIGH	2	43	11	34	5	40	29	16	15	26

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Dean's Office
Medical Faculty

Confirmation of congruency between printed and electronic version of the doctoral thesis

Šarčević, Ana

Surname, first name

Street

Zip code, town

Country

I hereby declare that the electronic version of the submitted thesis, entitled

Models to optimise medication safety in elderly and oncology inpatients

is congruent with the printed version both in content and format.

Munich, 28.06.2018

Place, date

Ana Šarčević

Signature doctoral candidate

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dean's Office
Medical Faculty

Affidavit

Šarčević, Ana

Surname, first name

Street

Zip code, town

Country

I hereby declare, that the submitted thesis entitled

Models to optimise medication safety in elderly and oncology inpatients

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

Munich, 28.06.2018

Place, date

Ana Šarčević

Signature doctoral candidate