Symptom burden in cancer patients: Evaluation of medication risks and development of disease-specific PRO instruments

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Abbreviations

ABDA	*Federal Association of German Pharmacists*
ADR	*Adverse drug reaction*
AE	*Adverse event*
AJCC	*American Joint Committee on Cancer*
ALT	*Alanin amino transferase*
AMTS	*German: Arzneimitteltherapiesicherheit*
ANOVA	*Analysis of Variance*, *Analysis of Variance*
AST	*Aspartate amino transferase*
ATC code	*Anatomical Therapeutical Chemical Classification*
BC	*Breast cancer*
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMI	*Body mass index*
CCI	*Charlson comorbidity index*
CDK4/6	*Cyclin-dependent kinases 4 and 6*
CI	*Confidence interval*
CIM	*Clinical impact method*
CIO	*Center for integrated Oncology*
CKD	*Chronic kidney disease*
CONSORT PRO	*Consolidated Standards of Reporting Trials - PRO extension*
CRP	*C-reactive protein*
CTCAE	*Common Terminology Criteria for Adverse Events*
DDIs	*Drug-drug interactions*
DRPs	*Drug-related problems*
ECOG	*Eastern Cooperative Oncology Group*
eCRF	*Electronic case report form*
EMA	European Medicines Agency
EORTC	*European Organisation for Research and Treatment of Cancer*
ePRO	*Electronic patient-reported Outcome*
EQUATOR	*Enhancing the Quality and Transparency of Helth Research*
ER	*Estrogen receptor*
FACT	*Functional Assessment of Cancer Therapy*
FDA	*Food and Drug Administration*
FEV_1	*Forced expiratory volume during the first second*
fT3	*Triiodothyronine*
fT4	*Thyroxine*
GBA	*Gemeinsamer Bundesausschuss*
GFR	*Glomerular filtration rate*
GGT	*Gamma glutamyl transferase*

HbA1c	*Hemoglobin A1c*
HDL	*High density lipoprotein*
HER2	*Human epidermal receptor 2*
HRQOL	*Health-related quality of life*
IIC	*Inter-item correlation*
INR	*International Normalized Ratio*
IQR	*Interquartile range*
ISPOR	The Professional Society for Health Economics and Outcomes Research
ISS	*International staging system*
KDIGO	*Kidney Disease: Improving Global Outcomes*
LDL	*Low density lipoprotein*
MDBS	*MedicalDataBaseSystems*
MID	*Minimal important difference*
MM	*Multiple myeloma*
PC	*Prostate cancer*
PEF	*Peak expiratory flow*
PIM	*Potential inadequate medication*
PPI	*Proton pump inhibitors*
PR	*Progesterone receptor*
PRO-CTCAE	*Patient-reported outcomes version of the Common Terminoligy Criteria of Adverse Events*
PROs	*Patient-reported outcomes*
PSA	*Prostate-specific antigene*
QLQ-C30	*Quality-of-Life Questionnaire-Core 30*
SCT	*Stem cell transplantation*
SD	*Standard deviation*
SMPC	*Summaries of product characteristics*
SPIRIT-PRO	*Defining standard protocol items for clinical trials - PRO extension*
TNMG	*Tumor, Node, Metastases, Grading*
TSH	*Thyroid-stimulating hormone*
WHO	*World Health Organisation*

Preliminary note

For the sake of clarity and to improve the readability the respective wording “he” is meant to include the female gender.

Furthermore, the author of this work was anxious to consider the copyright of all used texts, figures and data.

1 Introduction

1.1 Patient-reported outcomes in oncology

1.1.1 Patient-reported outcomes in drug development

During the 10 years from 2011 to 2020, every 17 days, a new oncologic drug entered the German market [1]. The added benefit of new active pharmaceutical ingredients in Germany is evaluated by the Federal Joint Committee (*German: Gemeinsamer Bundesausschuss, GBA*) in an early benefit assessment. The patient-relevant outcomes considered are mortality, morbidity, safety, and health-related quality of life (HRQOL) [2]. Whereas hard endpoints for mortality and morbidity like response rate, progression-free survival, and overall survival can be measured objectively, the concept of HRQOL is broad and complex. Core concepts contributing to the HRQOL are disease symptoms, physical function, and symptomatic adverse events [3]. HRQOL and its components are patient-reported outcomes (PROs), which are defined by the US Food and Drug Administration (FDA) as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." [4].

The patient's experience should be a key element in evaluating the benefit of new drugs in oncology. Regulatory agencies as the FDA and the European Medicines Agency (EMA) demand the use of PROs in their guidelines for the development of medicinal products [4-6]. Nevertheless, between 2007 and 2013 only 29% of oncology trials registered at ClinicalTrials.gov included PROs [7], and the level of reporting of PROs in 557 randomized controlled cancer trials between 2004 and 2013 was poor [8].

This displays the gap between desire and reality towards a patient-centered drug development in oncology [9]. To improve the use of PROs in clinical trials, international, consensus-based guidelines were developed based on the methodological framework for guideline development of the EQUATOR network as the SPIRIT-PRO extension (2018) for the inclusion of PROs in clinical trial protocols and the CONSORT PRO extension (2013) for the reporting of PROs in randomized trials [10, 11].

Until now, the challenges in PRO assessment remain, which are the outcomes to be measured, the instruments to be selected, how they are captured electronically and how they have to be analyzed, reported, interpreted and disseminated [12].

1.1.2 Patient-reported outcomes in clinical practice

By measuring PROs clinicians can gain important additional information about their patients. Montazari et al. conducted a review of the literature on HRQOL data as prognostic indicators of survival in cancer patients from 1982 to 2008. They found a positive relation between HRQOL data and the survival duration of cancer patients. As a conclusion they state that baseline data refer to disease-specific characteristics as the general health status and mental setting of the patients. Follow-up data refer to treatment-specific characteristics like the effect of treatment on patient's well-being [13]. This association can be summarized with four possible explanations: 1. HRQOL measures include different items and provide more sensitive information than traditional performance status and toxicity measures, 2. HRQOL data collected at baseline could pick up relevant information earlier than established clinical prognostic factors, 3. HRQOL data are markers of patients' behavior because they relate to diagnosis, treatment and subsequent outcomes of the disease and 4. HRQOL data are markers of individual characteristics such as personality style and adapting coping strategies, which affect the disease process and outcomes in cancer patients [13, 14].

Multiple studies show that systematic monitoring of PROs is associated with improving patient-clinician communication, clinician awareness of symptoms, symptom management and patient satisfaction [15-18]. The core aspect of implementing PROs in clinical practice is the assessment of patients' symptoms and adverse events during treatment.

1.1.3 Assessment of adverse events and symptom monitoring

An adverse event (AE) is defined by the WHO as any untoward medical occurrence with a temporal correlation to the use of a drug. An AE is not necessarily drug-related [19]. If the correlation is not only temporarily but also causally related to the administration of a drug, it is defined as an adverse drug reaction (ADR) [19].

In oncology, AEs are assessed by physicians using the Common Terminology Criteria for Adverse Events (CTCAE) [20]. This physician-reported assessment often differs from the patients' experience. A study by Efficace et al. compared the reporting of symptom severity and health status between 422 patients with chronic myeloid leukemia and their treating physicians. The severity of symptoms was underestimated by physicians most frequently for fatigue (51%), muscle cramps (49%) and musculoskeletal pain (42%), whereas the physicians overestimated the health status in 67% of patient cases [21, 22]. Di Maio et al. analyzed the agreement of the reporting of frequently occurring symptomatic adverse events (anorexia, nausea, vomiting, constipation, diarrhea and hair loss) between physicians and patients in three randomized trials. For patients with toxicity of any severity underreporting of physicians was 41% to 74% and for severe symptoms 13% to 50% [23]. These findings are confirmed by a systematic review in which 28 studies with mixed cancer types including anal, breast, cervical, endometrial, hematological, lung, ovarian, pelvic, pharyngeal, prostate and rectal cancer, were analyzed regarding their association between clinician-based CTCAE and PRO AEs. The association between CTCAE and PROs was poor to moderate and had a large variation across the studies [22].

To address this gap in clinician- versus patient-reporting of symptoms Basch et al. conducted a randomized controlled trial on 766 patients with advanced cancer. Patients in the intervention group underwent a weekly electronic monitoring of PRO symptoms with automated alerts to clinicians. Patients in the control group received standard oncology care. After six months HRQOL improved among 34% of patients in the intervention group and 18% in the control group and worsened among fewer patients in the intervention group (38% vs. 53%; $p < 0.001$). Patients who underwent the electronic PRO symptom monitoring were less frequently admitted to the emergency department (34% vs. 41%; $p = 0.02$) or hospital (45% vs. 49%; $p = 0.08$) and remained longer under therapy (8.2 vs. 6.3 months; $p = 0.002$) [24]. After a median follow-up of seven years the median overall survival was prolonged for five months in the intervention group (31.2 months [95%-Confidence interval (CI) 24.5 – 39.6] vs. 26 months [95%-CI 22.1 – 30.9]; $p = 0.03$) [25]. These findings are affirmed by a further trial by Denis et al. which showed a seven-month benefit for patients with advanced lung cancer, who got an electronic PRO monitoring at home [26].

1.1.4 Development of PRO-CTCAE

To complement the physician-based assessment of AEs the United States National Cancer Institute has developed a PRO version of the CTCAE [27]. Out of the 790 adverse events listed in the CTCAE, 78 were considered to be appropriate to be asked directly from the patients. Plain language terms and up to three items characterizing severity, frequency and interference with daily activities were designed for every symptomatic adverse event and refined in a cognitive interviewing study creating a library consisting of 124 items. The items were evaluated regarding their construct validity, reliability, responsiveness, and between-mode equivalence [28, 29]. Following the Principles of Good Translation and Cultural Adaptation Practice as articulated by ISPOR in 2005 the PRO-CTCAE item library was translated into more than 30 languages [27]. The German translation was conducted by Kirsch et al. at the Institute of Nursing Science of the University of Basel [30, 31]. A PRO-CTCAE core item set containing 31 items for patients with chemotherapy has been validated in German by Hagelstein et al. at the Department of Clinical Pharmacy at the University of Bonn [31]. The complementary nature of PRO-CTCAE to CTCAE was illustrated by the fact that patients' and physicians' answers to PRO-CTCAE questions differ a lot. The agreement was poor and patients tended to grade symptoms severer than physicians [32].

1.2 Medication safety in cancer patients

1.2.1 Medication risks

Drug therapy for cancer patients represents a major challenge. This raises the above-discussed need for enhancing safety in the process of drug development. In clinical trials, ADRs that occur with the intended use of a drug are extensively characterized. However, oncological treatment has become increasingly complex in recent years due to the rapid development of new drugs and more diverse routes of administration, so that a safety culture for the high-risk process of drug therapy is necessary as well. In Germany this has been addressed in the course of five action plans for medication safety since 2008 (*German: Aktionsplan AMTS*) [33].

Since the incidence of most cancer entities rises with age, most cancer patients are older what comes along with comorbidity [34]. Compared to the general population the comorbidity burden of cancer patients is higher [35]. With an increasing comorbidity burden also the

prevalence of polymedication rises [36]. The common definition of polymedication is five or more medicines taken [37]. Hyperpolymedication is defined as the intake of 10 or more medicines [38]. A study by Turner et al. found that polymedication was present in 57% of older cancer patients presented at a medical oncology outpatient clinic in Australia [36]. Nightingale et al. found a prevalence of 84% for polymedication, including 43% of patients with hyperpolymedication in their prospective pilot study [39]. Prithviraj et al. found a prevalence for polymedication of 80% in their study cohort [40]. Although the number of patients with polymedication differs from study to study, polymedication is a highly prevalent problem in older cancer patients [41]. Besides being necessary to control the multiple health conditions of older cancer patients, relations between polymedication and a range of health outcomes including adverse drug events, falls, frailty, hospitalization, postoperative complications, and mortality have been described [42-44].

Polymedication leads to drug-related problems (DRPs) that can harm patients and are very common especially in older cancer patients [45]. A DRP is defined as an event during pharmacotherapy which interferes with a desired health outcome [46]. In a study by Nightingale et al. 41 oncology outpatients $\geq$ 65 years were analyzed and 123 DRPs were detected, amounting to three DRPs per patient. The results of Edwards et al. confirm this number with 3.7 DRPs per patient [47]. DRPs can lead to increased morbidity, unnecessary hospital admissions and mortality [45]. Chan et al. evaluated the characteristics of unplanned hospital admissions due to DRPs and found that 12.4% of unplanned hospital admissions of patients with cancer were associated with a DRP [48]. Common DRPs detected in a retrospective study by Yeoh et al. were potential drug-drug interactions (DDIs) (36.4%), adverse drug events (31.7%) and non-adherence (8.9 %) [45]. A study conducted by Nazer et al. on patients with cancer found that 22.9% of the admissions to the intensive care unit were associated with an adverse drug event and the mortality rate of the admitted patients was 28.1% [49]. Alkan et al. found that severe DDIs are present in 35.1% of cancer patients in general and significantly more inpatients were affected be severe DDIs than outpatients (47.2% vs. 28.3%, $p < 0.001$) [50]. Severe DDIs may occur between anticancer drugs, supportive care medications and comedication for the treatment of comorbidity. Especially older adults with cancer are affected due to polymedication, multimorbidity and organ dysfunctions like an impaired renal function [51]. In a study by Nightingale et al. on an older

cancer outpatient population, 61 to 69% of patients, depending on the used database, showed severe DDIs with an average of 2.2 severe DDIs per patient [51]. Van Leeuwen et al. found 120 potentially clinically relevant DDIs present in 81 patients, amounting to 1.5 DDIs per patient [52].

1.2.2 Pharmaceutical care of oncology patients

In order to minimize the risks described for cancer patients, medication management concepts were developed, a multi-professional cooperation of all disciplines involved in the medication process.

Medication management is a continuously process. The patient's overall medication is analyzed for DRPs (medication review), followed by multiprofessional care of the patient that focuses on reaching predefined treatment goals. According to the available information three types of medication reviews can be defined: simple medication review (type 1), advanced medication review (type 2a or 2b), complete medication review (type 3). The simple medication review (type 1) is based on medication data and basic patient data. The advanced medication review is additionally supported by a patient interview (type 2a) or clinical data (type 2b). Clinical data include diagnoses and laboratory parameters. The complete medication review (type 3) is based on all above-mentioned sources of information [53].

Depending on the type of medication review, classes of DRPs that can be detected within the analysis differ [53]. The classes of DRPs are shown in *Table 1-1*.

Table 1-1 Classes of drug-related problems depending on type of medication review [53]

Drug-related problem	**Type of medication review**			
	1	**2a**	**2b**	**3**
Drug-drug interaction	x	x	x	x
(Pseudo-) double medication	x	x	x	x
Unsuitable or inappropriate dosing interval	x	x	x	x
Unsuitable or inappropriate time of administration	x	x	x	x
Contraindication due to age and gender	x	x	x	x
Administration problem		x		x
Non-adherence		x		x
Unsuitable or inappropriate dosage form		x		x
Drug-food interaction		x		x
Adverse drug reaction		x		x
Unsuitable or inappropriate drug selection according to evidence			x	x
Unsuitable dosage			x	x
Drug without indication			x	x
Indication without drug			x	x
Contraindication due to diseases and allergies			x	x
Unsuitable or inappropriate duration of therapy			x	x

The effect of pharmacist interventions on adult patients with cancer was summarized in a systematic review with 11 included studies by Colombo et al. with the result that the interventions could improve outcome measures like rates of nausea and vomiting control, medication adherence and patient satisfaction but the collective quality of the studies was poor [54]. A positive effect of the interventions could also be shown in the study by Nightingale et al., in which a pharmacist-led, individualized medication review could reduce the number of DPRs per patient by 45.5% (from three at baseline to 1.6 at 60-day follow-up) [55]. The pharmacist-directed seamless care services in the ambulatory oncology clinic of the study by Edwards et al. also had a significant impact on clinical outcomes and processes of patient care [47].

Most research in the field of medication safety in oncology was conducted in an outpatient setting and focuses on long-term effects of pharmaceutical care interventions, for which a positive effect could already be shown as described above. For inpatient oncologic care the information about DRPs and the effect of medication reviews and management is low. It is conceivable that inpatient oncology patients are exposed to distinct medication risks and different challenges are associated with pharmaceutical interventions.

2 Aims and Objectives

This work consists of two projects focusing on the patient-reported symptom burden of cancer patients measured with PRO-CTCAE.

The aim of the first project was to determine sociodemographic, disease-related, and drug therapy-related factors influencing HRQOL in oncology inpatients. The focus was on detecting medication risks with the help of a standardized medication review, including PRO-CTCAE data. The study was conducted retrospectively in a population of oncology inpatients consisting of patients with different tumor entities. The results can help to implement the use of PRO-CTCAE in pharmacist-led medication reviews and multiprofessional care approaches for cancer patients.

The aim of the second project was to develop PRO-CTCAE item sets with high content validity for patients with breast cancer, prostate cancer and multiple myeloma. Therefore, the prevalence and importance of therapy-associated symptoms, as well as their underlying tumor medication and disease-specific data, were recorded within a patient survey. The newly developed PRO-CTCAE item sets are intended to help with the early detection of ADRs. Furthermore, the new PRO-CTCAE item sets should be applicable for use in clinical studies as an instrument for safety measurement.

3 Project I: Factors influencing quality of life in oncology inpatients (ImSEL-PRO)

3.1 Material and methods

3.1.1 Study design

This project was a post-hoc conducted, retrospective study including patients of the database, that was created during the ImSEL-PRO trial (*German: Implementierung eines mobilen Systems zur Erfassung von Lebensqualität, Therapieeffekten und Erkrankungslast durch selbst-berichtete Patientenangaben (PRO) in der stationären onkologischen Routineversorgung*). This trial was conducted at four oncology wards of Helios hospitals in Berlin.

The primary goal of the ImSEL-PRO trial was to implement a multidimensional electronic PRO (ePRO) system in an inpatient setting and evaluate its feasibility. The study was designed as an interventional, multicentric, three-armed trial. Patients were randomly assigned in a 1:1:1 ratio to the three groups A, B, and C. They completed a self-administered questionnaire based on validated PRO measures at hospital admission, one week after, and at hospital discharge. For patients of groups A and B, an optional electronic follow-up four weeks after hospital discharge was possible. Patients in the intervention group A received the PRO questionnaires, including EORTC QLQ-C30 for HRQOL, EORTC IN-PATSAT32 for patient satisfaction, NCCN Distress Thermometer for psychological distress, SCNS-SF34 for supportive care needs, SDM-Q-9 for shared decision making and PRO-CTCAE for symptom burden via tablet computers. The treating physicians could react to graphical processing of the patients' answers to adapt the therapy. No prespecified supportive care concept was designed. Group B received the PRO questionnaires via tablet computers without feedback from the physicians. The control group C received the PRO questionnaires in a paper-based version without feedback. The effect of the ePRO tool on HRQOL, symptom burden, and patients' satisfaction with care was evaluated [56]. The study design is shown in *Figure 3-1.*

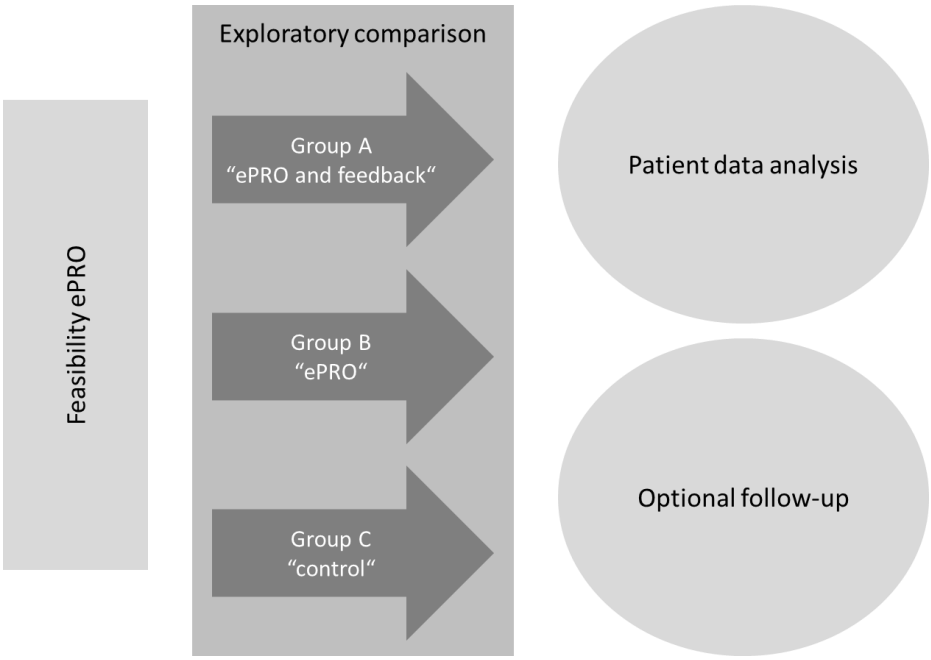

Figure 3-1 Study design of the ImSEL-PRO trial [56]

To determine sociodemographic, disease-related, and drug therapy-related factors influencing changes in the different dimensions of HRQOL from hospital admission to discharge in this population of oncology inpatients multiple linear regression models were built as a result of the retrospective patient data analysis.

The focus was on detecting medication risks with the help of a standardized medication review, including PRO-CTCAE data, and examining their impact on the changes in different dimensions of HRQOL.

3.1.2 Inclusion criteria and patient recruitment

Patients with hematological or oncological cancer entities with an age of 18 years or older were included in the study. They had to be capable of understanding and comprehension. The planned inpatient stay had to be at least three days. Patients were recruited by investigators at a total of four participating centers on the day of inpatient admission.

Patients with no or insufficient documentation of their medication within the database were excluded from the medication reviews and statistical analysis for the retrospective analysis.

For recruitment, patients matching the inclusion criteria were identified by the treating physicians at their inpatient admission to the study centers and were invited to participate. Patients were informed orally and in writing about the nature, significance, and scope of the clinical trial and signed a written informed consent.

3.1.3 Data handling and protection

By law the study is classified as a non-interventional trial according to §4 of the German drug law (*German: Arzneimittelgesetz*) [57], because no prespecified supportive care concept was designed. The trial was approved by the Ethics Committee of Helios Hospital Emil von Behring in Berlin on December 5th 2016 (Eth-48/16) and by the relevant institutions of each participating center.

The collection, transfer, storage, and analysis of personal data within this trial were carried out in accordance with the applicable German and European legal provisions (*German: Datenschutz-Grundverordnung, DSGVO*) [58].

In this project data collection was web-based, using the MedicalDataBaseSystems (MDBS) study database. The patient data documented with the MDBS electronic case report form (eCRF) system, were collected in pseudonymized form. A non-addressable code was used to encrypt patient data. Only physicians and persons authorized by the project management, who were involved in implementing the project, had access to this code. After the end of the trial the data were stored for up to 10 years.

For further data processing within the retrospective study, data were extracted anonymously from the MDBS database in Microsoft® Excel® 2019 (Microsoft Corporation, Redmond, USA) sheets, stored and further processed in a Microsoft® Access® 2019 (Microsoft Corporation, Redmond, USA) database.

3.1.4 Documentation

The time-points of documentation are shown in *Figure 3-2*.

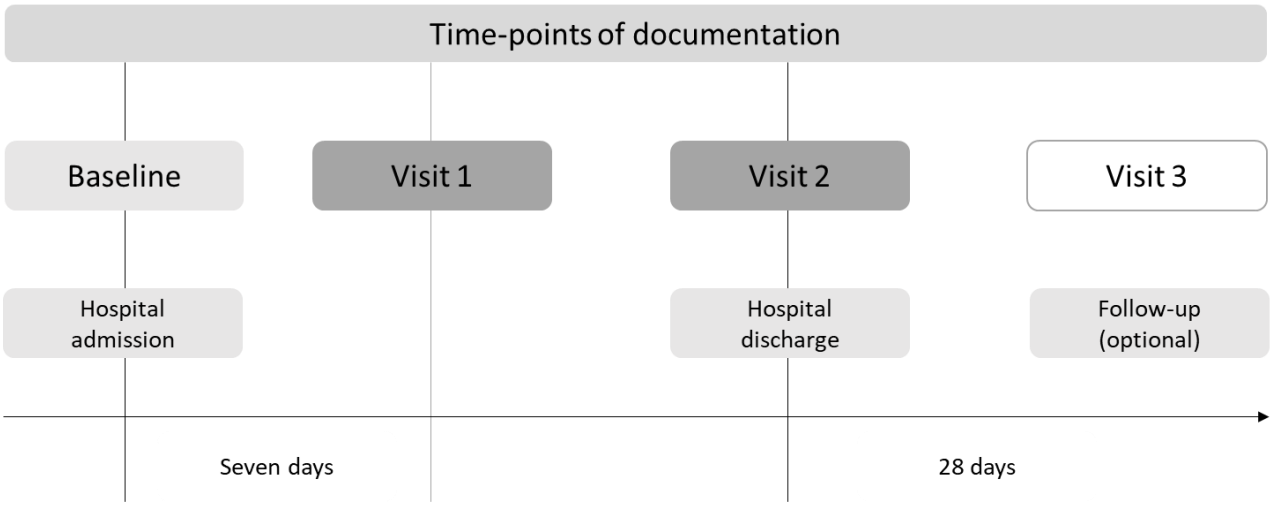

Figure 3-2 Time-points of documentation of the ImSEL-PRO trial

The following data were documented independent of time:

- Pseudonym and study center
- Current therapeutic regimen and tumor therapy: cycle, active ingredients, dosage form, dose, dates of administration, dose reduction, reason for dose reduction
- Concomitant medication and supportive therapy: name of drug/active ingredient, dose, dosage form, type of administration, time of administration, dosage interval, administration instructions, onset, and offset
- Laboratory data and vital parameters (with date of determination)
    - Mandatory: blood pressure, pulse, serum creatinine/cystatin C, glomerular filtration rate (GFR), sodium, potassium, calcium, leukocytes, thrombocytes, neutrophile granulocytes, erythrocytes, hemoglobin, hematocrit
    - Disease-related: INR, FEV_1, PEF, blood glucoses, HbA1c, HDL, LDL, cholesterol, triglycerides, uric acid, CRP, body temperature, AST, ALT, albumin, bilirubin, GGT, TSH, fT3, fT4

Baseline documentation was undertaken at hospital admission and the following data were extracted from the database:

- Recruitment and eligibility criteria
- Sociodemographic parameters: year of birth, age, gender, weight, height, level of education, employment prior to diagnosis, relationship, alcohol use, smoking status
- Disease-characteristics: cancer diagnosis, date of the first diagnosis, histological subtype, ECOG stadium, TNMG classification, therapy intention, therapy of relapses, surgery, radiation, chemotherapy, concomitant diseases, allergies, tube feeding
- Questionnaires: EORTC QLQ-C30, PRO-CTCAE core item set

At visit 1 (seven days after admission), visit 2 (hospital discharge), and visit 3 (28 days after discharge per mail, optional), the following information was documented:

- Questionnaires: EORTC QLQ-C30, PRO-CTCAE core item set

All drugs of the tumor therapy, supportive therapy, and concomitant medication were documented with their Anatomical Therapeutical Chemical Classification (ATC code). The ATC index 2018 of the German Institute for Medical Documentation and Information (*German: Deutsches Institut für Medizinische Dokumentation und Information*) and BfArM was used for classification [59]. All drugs, including electrolyte solutions, over-the-counter drugs, minerals, vitamins, and topical substances, to which an ATC code could be assigned, were included in the analysis of medication risks. Their use in an inpatient setting defines them as relevant for consideration in a medication review.

As a parameter for the kidney function, the creatinine clearance (CL_{KR}) by using the 24-hour urine collection was documented, if available. If only the value for serum creatinine was available, the glomerular filtration rate (GFR) was estimated using the CKD-EPI equation (*Equation 3-1*). Which is the recommended method of the KDIGO guideline on the evaluation of the chronic kidney disease (CKD) and management [60]. It uses the same parameters as the MDRD equation; however, it estimates the eGFR better in higher GFR areas. For the CKD stadiums 3 to 5, there is no essential difference between the equations [60].

$$\mathrm{GFR} = 141 \cdot \min\left(\frac{\mathrm{SCr}}{\kappa}, 1\right)^{\alpha} \cdot \max\left(\frac{\mathrm{SCr}}{\kappa}, 1\right)^{-1{,}209} \cdot 0.993^{\mathrm{age}} \qquad \textit{Equation 3-1}$$

$$\cdot 1.018 \text{ if female}, \qquad \cdot 1.159 \text{ if black}$$

SCr = serum creatinine in mg/dl

κ = 0.7 for females and 0.9 for males

α = -0.329 for females and -0.411 for males

3.1.5 Analysis of medication risks

Based on the documented medication, disease-related, laboratory, and sociodemographic data, retrospective advanced medication reviews type 2b were conducted to identify drug-related problems (DRPs) [53]. To conduct a complete medication review type 3, patient interviews would be mandatory which were not conducted in the study setting. However, patients had the opportunity to report their symptoms under therapy using the PRO-CTCAE questionnaires. This source of information was used to complete the medication reviews. The DRPs were categorized according to the guidance paper on medication analysis and management of the Federal Association of German Pharmacists (ABDA): durg-drug interaction (DDI), (pseudo-) double medication, unsuitable or inappropriate dosing interval, unsuitable or inappropriate time of administration, contraindication due to age and gender, adverse drug reaction (ADR), unsuitable or inappropriate drug selection according to evidence, unsuitable dosage, drug without indication, indication without drugs, contraindication due to diseases and allergies, unsuitable or inappropriate duration of therapy [53].

Administration problems, non-adherence, and drug-food interactions could not be detected during the medication reviews type 2b, because these problems can only be identified based on a patient interview. Unsuitable or inappropriate dosage forms could only be checked in some cases, for example, tube feeding.

The documentation form used for the medication reviews is shown in *Appendix I-A*.

By definition, DRPs include all events or circumstances in drug therapy that actually or only potentially hinder aspired goals in therapy [53, 61]. Because of the retrospective character of this analysis and the lack of further clinical information all DRPs were assumed to be potential. For the scientific evaluation, the complete range of potential DRPs is of interest. For the daily clinical routine, only the DRPs with a need for intervention by health care providers are relevant [62].

DRPs were recorded per medicinal product (= drug) and not per active ingredient. The DRPs DDI and (pseudo-) double medication were recorded per triggering drug pair. For the DRP indication without drugs, no drug could be recorded. In some cases, for the DRP unsuitable or inappropriate drug selection according to evidence, more than one drug was recorded. That for example was the case if the antiemetic supportive therapy was inappropriate because one out of three indicated drugs was missing.

The relevance and need for possible interventions of the DRPs were evaluated during the medication reviews and sorted into the following categories:

- pDRP: potential drug-related problem without need for intervention
- iDRP: potential drug-related problem with need for intervention

The classification of the DRPs was implemented by Vucur et al. in a study on a multi-professional medication management for outpatients with intravenously administered tumor therapy [63, 64]. Additionally, the category PRO-i/pDRP: potential drug-related problem with or without need for intervention in relation to PRO-CTCAE data was built. Because of the retrospective character of the study no interventions for the iDRPs could be carried out.

The medication reviews were conducted by the investigator as a trained clinical pharmacist. They were partially validated by three independent reviewers, who were pharmacists with experience in clinical pharmacy, in order to assure a high interrater reliability [65]. The main focus of the validation was the completeness of the detected DRPs and the categorization according to their needs for intervention (pDRP, iDRP).

3.1.6 Measurement tools and outcome parameters

3.1.6.1 Drug-related problems

To detect the DRPs, relevant guidelines, specialist information, primary and secondary literature, academic books, and databases were used.

DRPs concerning the unsuitable or inappropriate dosing interval, time of administration, dosage, and duration of therapy, as well as contraindications due to age, gender, diseases, and allergies, were mainly identified by the summaries of product characteristics (SMPC) of the EMA and the specialist information of the pharmaceutical companies [66, 67].

If the patients had an impaired GFR of less than 60 ml/min according to the creatinine clearance measured with the 24-hour urine collection method or the estimation of the GFR with the CKD-EPI equation (*Equation 3-1*), the need for dosage adjustment was evaluated using the database "dosing.de" providing assistance in the search for drug-related information on the individual dosing of drugs in adult patients with impaired renal function. In this database, information and recommendations on active ingredients from various literature sources are compiled, processed, and supplemented with information on clinical management [68].

Unsuitable or inappropriate drug selection according to evidence, (pseudo-) double medication, drugs without indication, and indications without drugs were mainly identified by national and international supply guidelines [69].

Of special interest for all DRPs concerning the tumor and supportive therapy were the S3 guideline for supportive therapy in oncology patients (*German: S3-Leitlinie Supportive Therapie bei onkologischen Patienten*), a German chemotherapy manual named "*Das Blaue Buch – Chemotherapie-Manual Hämatologie und Onkologie"* and the guidelines of onkopedia.de by the German Society for Hematology and medical Oncology (*German: Deutsche Gesellschaft für Hämatologie und medizinische Onkologie*) [70-72].

DDIs were identified using the ABDA interaction database and Lexi-Interact. The ABDA interaction database is hosted by the ABDATA Pharma-Daten-Service (Eschborn, Germany). It is a commonly used interaction database in German community and hospital pharmacies [73]. Lexi-Interact is part of the Lexicomp® database providing evidence-based referential drug

information hosted by Wolters Kluwer (Alphen aan den Rijn, Netherlands) and mainly used in hospitals. The underlying monographies are based on international specialist information from the Anglo-American area (mostly USA and Canada) [74]. Both databases were considered for the medication reviews to cover a wider spectrum of possible DDIs in the study population of oncology inpatients. The ABDA database sorts DDIs into eight categories. Lexi-Interact uses five categories. The categories are shown in *Table 3-1.*

Table 3-1 Categories of drug-drug interactions according to the ABDA database and Lexi-Interact [73, 74]

Category	**ABDA database**	**Lexi-Interact**
Contraindication	Serious consequences likely - contraindicated	X – Avoid combination
	Serious consequences likely - contraindicated in certain cases	
	Serious consequences possible - contraindicated as a precautionary measure	
Therapy modification	Concurrent use not recommended	D – Consider therapy modification
Therapy monitoring	Monitoring or adjustment necessary	C – Monitor therapy
	Monitoring or adjustment necessary in certain cases	
	Monitor precautionarily	
No actions needed	Usually, no measures required	B – No action needed
No known interaction		A – No known interaction

For scientific evaluation, all potential DDIs were documented (pDRPs). DDIs of the categories contraindication and therapy modification of both databases were considered as iDRPs with needs for interventions during the medication review.

Potential inadequate medication (PIM) for older patients from 65 years on was identified using the EU(7)-PIM list. The EU(7)-PIM list is an explicit list and includes 282 drugs or drug classes from 34 therapeutic groups. It comprises rationales for selecting the drugs as PIM,

recommended dose adjustments, and therapeutic alternatives. Some drugs are only stated as PIM if they exceed a certain dose (e.g., zopiclone > 3.75 mg) or duration of treatment (e.g., proton pump inhibitors (PPI) > eight weeks) [75]. The EU(7)-PIM list is the most recently developed explicit PIM tool in Europe. It is widely usable across Europe and based on the German PRISCUS list [76], making it the most applicable tool for this study's German cancer inpatient setting. Other explicit tools such as the STOPP/START criteria [77] and the FORTA list [78] containing positive lists or the implicit Medication Appropriateness Index [79] not applicable for the retrospective setting, and the explicit Beers list [80] is aligned to the US. In the documentation for this study the duration of therapy and the dates of onset and offset of a drug were documented. If nothing was documented in this regard, the drug was defined as permanent medication. For example, this was relevant in the evaluation of PPI as PIM. They were considered as PIM if there was no explicit documentation for a duration of therapy under eight weeks.

If patients were supplied with a feeding tube and the perorally administered drugs had to be given via this feeding tube, the tube pass ability of the drugs was checked. For this purpose, the specialist information and the information available at pharmatrix.de were consulted. Pharmatrix.de is hosted by the University Hospital of Tübingen and contains information about the pulverizabilty and suspendability of drugs for their administration via a feeding tube [81].

ADRs were assessed based on laboratory and vital parameters as well as PRO-CTCAE data. The ADR assessment by PRO-CTCAE is explained in section 3.1.6.2. As ADRs are an inherent part of the tumor therapy, not every deviating laboratory value requires action. Therefore, only abnormal laboratory values corresponding to CTCAE grade of 3 or higher were considered. *Table 3-2* shows the CTCAE grade 3 or higher for common adverse events (AEs) [20].

Table 3-2 CTCAE grade 3 or higher for common adverse events [20]

Adverse event	**Laboratory value**	**CTCAE grade ≥ 3**
Anemia	Hemoglobin	< 8.0 g/dL
Neutropenia	Neutrophile granulocytes	< 1.0 G/L
Thrombopenia	Thrombocytes	< 50.0 G/L
Leukopenia	Leukocytes	< 2.0 x 1000/µL
Hypocalcemia	Calcium	< 1.75 mmol/L
Hypokalemia	Potassium	< 3.0 mmol/L
Hyponatremia	Sodium	< 130 mmol/L

Due to the retrospective character of this study, no assessment of the causality of AEs and used drugs could be undertaken because important information for the assessment using the Naranjo Scale or other similar instruments was missing [82]. The recorded ADRs are only reasonable suspicions. Therefore, ADRs were only documented if they were listed in the specialist information of a drug as "frequent" (≥ 1/100 to < 1/10) or "very frequent" (≥ 1/10).

Contraindications to drugs because of abnormal laboratory and vital parameters like an impaired kidney function were assessed using the specialist information. If concomitant diseases like arterial hypertension or diabetes are linked to laboratory and vital parameters, agreement with target values based on national guidelines was checked. Deviations were indications for DRPs.

3.1.6.2 Patient-reported symptom burden

The patient-reported symptom burden was evaluated using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). The PRO-CTCAE item library was developed as a complementary tool to the CTCAE criteria by the US National Cancer Institute. It consists of 124 Items representing 78 symptoms that can be reported best by the patients themselves. The items characterize up to three properties regarding severity, frequency, and interference with daily activities of the symptoms [27]. The items are answered with a verbal five-point Likert scale. The scale for frequency ranges from (0) "never" to (4) "almost constantly". The scale for severity ranges from (0) "none" to (4) "very severe" and the scale for interference with daily activity ranges from (0) "not at all" to (4) "very much". Answers cover the worst expression of the item during the last seven days. The items were evaluated regarding their construct validity, reliability, responsiveness, and between-mode equivalence [28]. The German translation was conducted at the Institute of Nursing Science of the University of Basel, Switzerland. The items were translated by dual forward translation with reconciliation, dual back translation, back translation review, and harmonization. Cognitive testing was done with a sample of cancer patients after allogeneic stem cell transplantation [30]. A PRO-CTCAE core item set containing 31 items representing 12 symptom constructs with 16 symptoms in total for patients with chemotherapy was validated in German by our working group at the University of Bonn [31]. The PRO-CTCAE core item set is based on the recommended symptom set for adult cancer in clinical trials [83]. It was tested for its item quality, reliability, and validity [31]. The PRO-CTCAE core item set with its symptoms and items is shown in *Table 3-3*.

Table 3-3 Symptoms and items of the PRO-CTCAE core item set [31]

Symptom	Number of Items	Items
Difficulty swallowing	1	Severity
Dry mouth	1	Severity
Mouth/throat sores	2	Severity, Interference
General pain	3	Frequency, Severity, Interference
Decreased appetite	2	Severity, Interference
Constipation	1	Severity
Diarrhea	1	Frequency
Nausea	2	Frequency, Severity
Vomiting	2	Frequency, Severity
Insomnia	2	Severity, Interference
Fatigue	2	Severity, Interference
Numbness and tingling	2	Severity, Interference
Shortness of breath	2	Severity, Interference
Concentration	2	Severity, Interference
Anxious	3	Frequency, Severity, Interference
Sad	3	Frequency, Severity, Interference

Since there is no official scoring manual for PRO-CTCAE, scoring was undertaken according to the calculation of the symptom scales of the EORTC QLQ-C30 questionnaire. The same scoring procedure was used in the validation study of the PRO-CTCAE core item set and was established in several other studies [64, 84, 85]. In the first step, the raw score (RS) was calculated with *Equation 3-2*. The RS indicates the mean value of the individual attributes of the symptom scales. In case of missing values, the raw score was only calculated if at least 50% of the attributes were answered [86].

$$RS = \frac{I_1 + I_2 + \ldots + I_n}{n}$$ *Equation 3-2*

I_1 = Value of item 1

I_2 = Value of item 2

I_n = Value of item n

n = Number of items per scale

In the second step, the raw score was linearly transformed to numerical score values ranging from 0 to 100 using *Equation 3-3* [86]. Higher values indicate a higher severity of the symptom. A score of ≥ 75 is defined as a severe symptom burden.

$$Score = \left\{\frac{RS}{Range}\right\} \cdot 100$$ *Equation 3-3*

Range = Difference between maximum and minimum values of the response scale (0 to 4)

As ADRs are an inherent part of the tumor therapy, not every symptomatic toxicity requires action. Therefore, only severe PRO-CTCAE symptoms with a score of ≥ 75 were considered. If the symptom was present at the baseline survey and during the hospital stay at visit 1 and/or visit 2, it could be considered as an indication without drugs, if no drug for the therapy of the symptom was documented although it was recommended by guidelines. The classification as pDRP or iDRP was not always possible because the setting of an indication and the initiation of a therapy is the task of a physician. Did the symptom appear during the hospital stay at visit 1 and/or visit 2, it could be considered as an ADR. If other factors additionally played a role in the assessment, the symptoms could also be assigned to other DRP categories. Symptoms appearing at the online visit 3, 28 days after discharge, were not considered as DRPs, because of the questionable timely relation to the therapy.

The patients included in the study answered the PRO-CTCAE questionnaire in different modes. Patients in study groups A and B answered the electronic tablet computer version, whereas patients in group C answered the paper-based version. Since both administration modes are equal [87], the patients' answers of all three groups were treated equally for the medication

reviews and retrospective analysis. The scoring and graphical presentation for the medication reviews was done post-hoc and in a different way than for the feasibility study of the ePRO tool [56]. A direct comparison of the evaluation methods is therefore not given.

3.1.6.3 Health-related quality of life

Health-related quality of life was assessed using the Quality-of-Life Questionnaire-Core 30 (QLQ-C30) Version 3.0 of the European Organization for Research and Treatment of Cancer (EORTC) [88]. The EORTC QLQ-C30 questionnaire is designed for use in cancer patients in clinical trials. The questionnaire is validated, and a certified German translation is available [88, 89]. It covers the global health status, the global HRQOL, five functional subscales, and nine symptom scales. Every scale consists of one or more items, making the questionnaire composed of 30 items. The questionnaire with its scales and items is shown in *Table 3-4*.

Table 3-4 Scales and items of the EORTC QLQ-C30 questionnaire [88]

Scale	Number of Items	Figure of Items
Global health status	1	29
Global health-related quality of life	1	30
Functional scales		
Physical function	5	1, 2, 3, 4, 5
Role function	2	6, 7
Emotional function	4	21, 22, 23, 24
Cognitive function	2	20, 25
Social function	2	26, 27
Symptom scales		
Fatigue	3	10, 12, 18
Nausea and vomiting	2	14, 15
Pain	2	9, 19
Dyspnea	1	8
Insomnia	1	11
Decreased appetite	1	13
Constipation	1	16
Diarrhea	1	17
Financial difficulties	1	28

The function and symptom scales are answered with verbal 4-point Likert scales ranging from (1) "not at all" to (4) "very much". The scales for the global health status and the global health-related quality of life are answered with verbal-numerical seven-point scales ranging from (1) "very poor" to (7) "excellent".

Scoring the answers to the questionnaire was done using the EORTC QLQ-C30 scoring manual of the EORTC. In the first step, the raw score (RS) was calculated using *Equation 3-2,* analogous to the PRO-CTCAE scoring. The raw score indicates the mean value of the item values of the scales. In case of missing values, the raw score was only calculated if at least 50% of the items were answered [86].

In the second step, the raw score was linearly transformed to numerical score values ranging from 0 to 100 using *Equation 3-4* and *3-5* [86]. High numerical values correspond to a high global HRQOL, to a high level of function for the functional scales, and a high symptom severity for the symptom scales.

Global HRQOL and symptom scales

$$\text{Score} = \left\{\frac{(\text{RS}-1)}{\text{Range}}\right\} \cdot 100 \qquad \textit{Equation 3-4}$$

Functional scales

$$\text{Score} = \left\{1 - \frac{(\text{RS}-1)}{\text{Range}}\right\} \cdot 100 \qquad \textit{Equation 3-5}$$

Range = Difference between maximum and minimum values of the response scale (1 to 4 or 1 to 7)

For this analysis, the differences in the scores from baseline to discharge (visit 2) for global HRQOL and the functional scales physical function, cognitive function and emotional function were calculated and considered as patient-relevant outcomes.

3.1.6.4 Comorbidity

Comorbidity was documented using the Charlson Comorbidity Index (CCI) in its original form. The CCI is a scoring system to assess the one-year mortality risk of patients with 19 underlying conditions deemed relevant concomitant diseases. The conditions are weighted from 1 to 6 points. Since the focus was on describing relevant diseases of the cancer patients, the cancer diagnosis was neglected for calculation of the score [51].

3.1.7 Statistical analysis

Statistical analysis was conducted using Microsoft® Excel® 2019 (Microsoft Corporation, Redmond, USA), IBM® SPSS® Statistics Version 27.0 for Windows (IBM Corporation, Armonk, USA), and R Version 4.0.5 (The R Foundation for Statistical Computing, Vienna, Austria). The analyses with R Version 4.0.5 were conducted by the Institut für Medizinische Biometrie, Informatik und Epidemiologie of the University Hospital Bonn.

3.1.7.1 Descriptive statistics

Descriptive statistics were performed for patient characteristics, medication data, DRPs, and PROs. Mean values with standard deviations (SD) or the median with interquartile range (IQR) were calculated, as applicable. Frequencies were described as absolute numbers and percentages [90, 91].

If the data distribution was presented, the Shapiro-Wilk test for normal distribution was performed, and skewness and kurtosis were calculated to describe the distribution shape [92, 93].

3.1.7.2 Multiple linear regression analysis

For inductive statistics in the multiple linear regression analysis, a p-value of < 0.05 was considered as statistically significant. Confidence intervals (CI) of 95% were calculated.

To explore the influence of sociodemographic, disease-related and drug therapy-related factors on the change of the global HRQOL and functionalities from baseline to hospital discharge (visit 2), multivariate linear regression models were computed using SPSS.

As described in section *3.1.6.3*, the Likert scales of the EORTC QLQ-C30 questionnaire were numerically transformed to values ranging from 0 to 100 so that the values could be used as metric dependent variables for the linear regression analysis. All prespecified independent variables were included in the exploratory multivariate linear regression analysis without applying a selection procedure. *Table 3-5* shows the independent variables and their scale levels.

The statistical significance of the multiple linear regression models was determined using ANOVA. The goodness-of-fit of the multiple linear regression model was evaluated by using R^2 and adjusted R^2. The explanation of variance can be interpreted according to Cohen as follows: 0.02 weak, 0.13 moderate, and 0.26 strong [94].

Table 3-5 *Independent variables of the exploratory multivariate linear regression models and their scale levels.*

Independent variable	**Scale level**
Study group (A, B, C)	Nominal
Age (years)	Metric
Gender (male, female)	Nominal
Educational level (high, low)	Nominal (binary)
Duration of hospital stay (days)	Metric
Type of cancer (solid, hematological)	Nominal (binary)
Time since the first diagnosis of cancer (months)	Metric
Relapse status (yes, no)	Nominal (binary)
ECOG status (0, 1, 2, 3)	Nominal
Concomitant diseases (number)	Metric
Drugs (number)	Metric
DRP total (number)	Metric
iDRP (number)	Metric
PRO-DRP (number)	Metric

The educational level with the expressions “8th class“, “10th class”, “A-levels“, “job training”, and “University” was transformed into a dichotomous variable. “8th class”, “10th class”, and “Job training” were converted to “lower education”. “A-levels” and “University” were converted to “higher education”. The transformation was undertaken to avoid the potential overfitting of the models due to too many nominal dummy variables.

The study center was considered a potential confounder due to general differences in the treated patient cohorts. Therefore, its influence was calculated as a random effect in mixed model analysis.

3.2 Results

3.2.1 Patient recruitment

Patient recruitment at the four participating centers in Berlin took place between July 2017 and February 2019. A total of 185 patients, who matched the inclusion criteria, were included in the study. In the course of the study, 18 patients dropped out of the study. Three patients withdrew their informed consent. In addition, three patients were transferred to other hospitals. Two patients were deceased, and 11 patients dropped out for other reasons. Five patients had to be excluded from the medication review and the secondary analysis because of missing or insufficient documentation in the database. The target sample for the secondary analysis resulted in 162 patients. An overview of the recruitment process is presented in *Figure 3-3*.

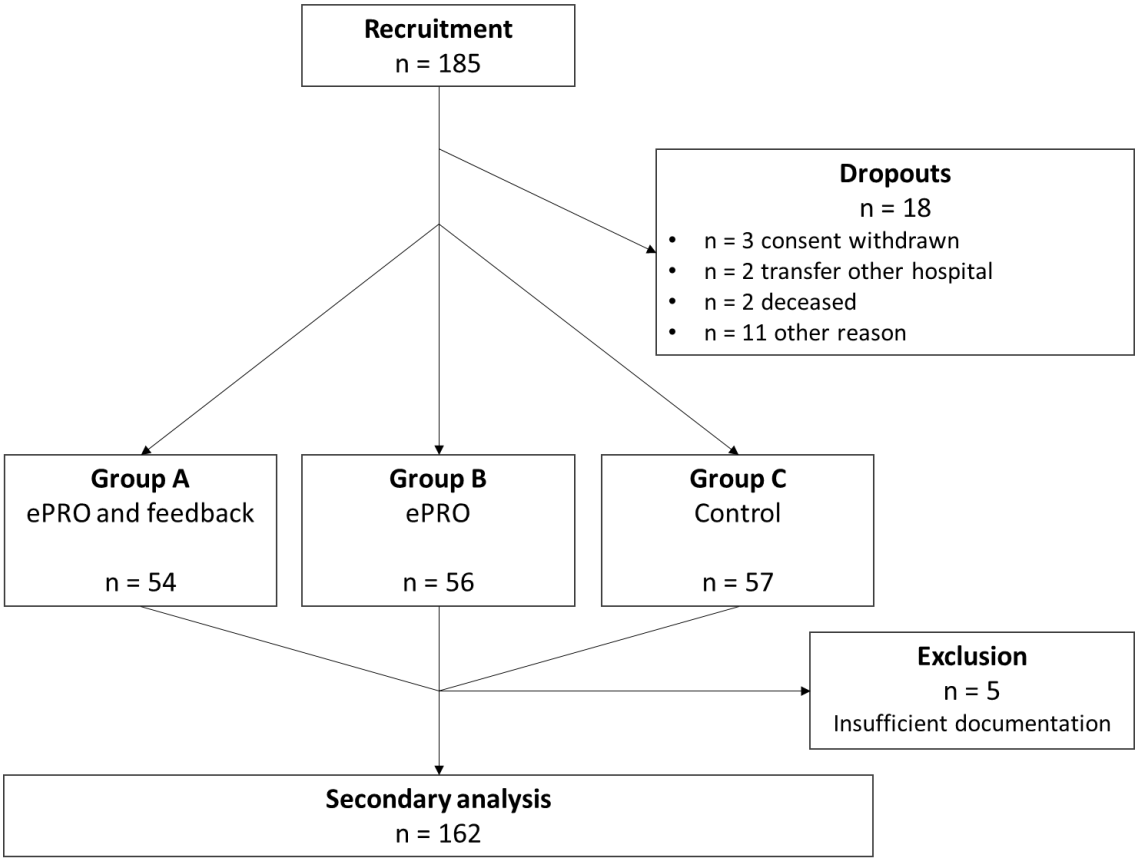

Figure 3-3 Flow chart of patient recruitment for the ImSEL-PRO trial

3.2.2 Patient characteristics

3.2.2.1 Sociodemographic characteristics

The sociodemographic patient characteristics of the population for the secondary analysis are shown in *Table 3-6*.

Table 3-6 Sociodemographic characteristics of the patient population for the secondary analysis of the ImSEL-PRO trial (n = 162)

	Number	Percentage
Center		
Berlin-Buch, station 02	28	17.3
Berlin-Buch, station 03	9	5.6
Bad Saarow	25	15.4
Emil von Behring	100	61.7
Group		
A – ePRO with feedback	50	30.9
B – ePRO	53	32.7
C – Paper-PRO	59	36.4
Hospital stay		
Median [days]	4 (IQR: 7, range: 1 – 73)	
< 7 days	108	66.7
≥ 7 days	54	33.3
Follow-up after 28 days (group B, C)	69	42.6
Gender		
Male	71	43.8
Female	91	56.2
Age		
Median [years]	65.5 (IQR: 18, range: 19 – 88)	
≥ 65 Jahre	86	53.1

Table 3-6 continued

	Number	Percentage
BMI class		
Underweight (<18.5 kg/m^2)	13	8.0
Normalweight (18.5 – 24.9 kg/m^2)	70	43.2
Overweight (25.0 – 29.9 kg/m^2)	50	30.9
Obese (>30.0 kg/m^2)	29	17.9
Educational level		
8th class	9	5.6
10th class	21	13.0
A-levels	8	4.9
Job training	62	38.3
University	60	37.0
Not applicable/missing	2	1.2
Employment prior to diagnosis		
Job seeking	6	3.7
Housewife/ houseman	3	1.9
Retired	77	47.5
Part-time employed	14	8.6
Full-time employed	59	36.4
Not applicable/missing	3	1.9
Relationship status		
Single	26	16.0
Widowed	18	11.1
In steady relationship	17	10.5
Married/registered life partnership	100	61.7
Not applicable/missing	1	0.6

Table 3-6 continued

	Number	Percentage
Alcohol abuse		
Yes, currently	3	1.9
No, not more	15	9.3
No, never	127	78.4
Not known	14	8.6
Not applicable/missing	3	1.9
Smoking status		
Yes, currently	21	13.0
No, not more	63	38.9
No, never	65	40.1
Not known	9	5.6
Not applicable/ missing	4	2.5

IQR = interquartile range, ePRO = electronic patient-reported outcome, BMI = body mass index

3.2.2.2 Oncological and concomitant diseases

Patient characteristics of oncological and concomitant diseases are shown in *Table 3-7*. Most patients (n = 103, 63.6%) had a solid tumor disease. The three most frequently represented tumor entities were lymphoma (n = 31, 19.1%), sarcoma (n = 20, 12.3%) and rectal cancer (n = 16, 9.9%). The biggest part of the tumors were digestive and gastrointestinal entities (n = 49, 30.2%). 123 patients (75.9%) had no relapse of their tumor disease. The median time since the first diagnosis of cancer was four months (IQR: 13.5, range: 0 – 208 months). According to their ECOG status, most patients had a rather good physical condition. The mean number of concomitant diseases was 0.97 (SD: 1.25, range 0 – 6). The three most frequent concomitant diseases were “mild/severe kidney disease” (n = 30), “chronic pulmonary disease” (n = 22) and “secondary tumor disease” (n = 18).

Table 3-7 *Characteristics of oncological and concomitant diseases (n = 162)*

	Number	Percentage
Tumor type		
Hematological	58	35.8
Solid	103	63.6
Not applicable/ missing	1	0.6
Tumor entity*		
Hematological		
Leukemia	15	9.3
Lymphoma	31	19.1
Multiple myeloma	12	7.4
Digestive/gastrointestinal		
Anal	2	1.2
Appendix	1	0.6
Colon	9	5.6
Gallbladder	3	1.9
Gastric	5	3.1
Liver	1	0.6
Pancreatic	10	6.2
Rectal	16	9.9
Small intestine	2	1.2
Gynecological		
Cervical	1	0.6
Gestational trophoblastic tumor	1	0.6
Ovarian	2	1.2
Head and neck		
Esophageal	11	6.8
Oropharyngeal	2	1.2

**Categorized by body location according to the National Cancer Institute*

Table 3-7 *continued (oncological diseases)*

	Number	Percentage
Germ cell		
Extragonadal germ cell	1	0.6
Germ cell	1	0.6
Testicular	1	0.6
Genitourinary		
Prostate	2	1.2
Renal	1	0.6
Musculoskeletal		
Sarcoma	20	12.3
Neuroendocrine		
Neuroendocrine	5	3.1
Unknown primary		
CUP	3	1.9
Not applicable/ missing	3	1.9
Relapse status		
Yes	30	18.5
No	123	75.9
Not applicable/ missing	9	5.6
Time since the first diagnosis of cancer		
Median [months]	4 (IQR: 13.5, range: 0 – 208)	
ECOG		
0	87	53.8
1	53	32.7
2	14	8.6
3	0	0
Not applicable/ missing	8	4.9

Table 3-7 *continued (concomitant diseases)*

	Number	Percentage
Charlson Comorbidity Index (CCI)		
Mean	1.93 (SD: 3.13, range: 0 – 15)	
Score 0	82	50.1
Score 1 – 2	42	25.9
Score 3 – 4	15	9.3
Score ≥ 5	23	14.2
Number of comorbidities		
Mean	0.97 (SD: 1.25, range: 0 – 6)	
Concomitant diseases (from CCI) [number of patients]		
Myocardial infarction	6	3.7
Heart failure	13	8.0
Peripheral arterial disease	4	2.5
Cerebrovascular disease	6	3.7
Dementia	0	0
Chronic pulmonary disease	22	13.6
Collagenosis	4	2.5
Ulcer disease	3	1.9
Mild liver disease	2	1.2
Diabetes mellitus (without organ damage)	13	8.0
Hemiplegia	0	0
Mild/severe kidney disease	30	18.5
Diabetes mellitus (with organ damage)	17	10.5
Secondary tumor disease	18	11.1
Leukemia	1	0.6
Lymphomas	0	0
Mild/severe liver disease	0	0
Secondary metastatic solid tumor disease	17	10.5
AIDS	1	0.6

IQR = interquartile range, SD = standard deviation, CUP = cancer of unknown primary

3.2.2.3 Drug therapy

In total, 1884 drugs, including cancer treatment, supportive and concomitant medication, were used in the population for the secondary analysis during the inpatient stays, amounting to a mean of 11.6 drugs per patient (SD: 5.15, range: 2 – 26, median: 11, IQR: 7). The used drug classes according to their ATC code level 1 and 2 are shown in *Table 3-8*. On ATC code level 1 the most used drug classes were “Alimentary system and metabolism” (A) with 29.2% (n = 551) of used drugs, followed by “Antineoplastic and immunomodulatory agents” (L) with 21.7% (n = 409) of used drugs and “Cardiovascular system” (C) with 9.8% (n = 185) of used drugs. The most used drug classes according to ATC code level 2 were “Antineoplastic agents” (L01) with 19.7% (n = 372), followed by “Antiemetics and anti-nausea agents” (A04) with 8.9% (n = 168) and “Corticosteroids for systematic use” (H02) with 7.2% (n = 136).

Table 3-8 Drug classes according to their Anatomical Therapeutical Chemical (ATC) code level 1 and 2 (n = 1884)

ATC-Class	Number	Percentage
Alimentary system and metabolism (A)	**551**	**29.2**
Stomatologics (A01)	75	4.0
Remedies for acid-related diseases (A02)	113	6.0
Remedies for functional gastrointestinal disorders (A03)	34	1.8
Antiemetics and anti-nausea agents (A04)	168	8.9
Remedies against obstipation (A06)	49	2.6
Antidiarrheal and intestinal antiphlogistics (A07)	25	1.3
Antidiabetics (A10)	24	1.3
Vitamines (A11)	16	0.8
Minerals (A12)	37	2.0
Others	10	0.5

Table 3-8 continued

ATC-Class	Number	Percentage
Blood and hematopoietic organs (B)	**168**	**8.9**
Antithrombotic agents (B01)	100	5.3
Antianemics (B03)	24	1.3
Blood substitutes and perfusion solutions (B05)	44	2.3
Cardiovascular system (C)	**185**	**9.8**
Diuretics (C03)	49	2.6
Beta-adrenoceptor antagonists (C07)	42	2.2
Calcium channel blockers (C08)	19	1.0
Agents acting on the renin-angiotensin system (C09)	48	2.5
Agents affecting lipid metabolism (C10)	20	1.1
Others	7	0.4
Dramatics (D)	**5**	**0.3**
Others	5	0.3
Urogenital system and sex hormones (G)	**11**	**0.6**
Urologics (G04)	10	0.5
Others	1	0.0
Systemic hormone preparations excluding sexual hormones and insulin (H)	**139**	**7.4**
Corticosteroids for systematic use (H02)	136	7.2
Others	3	0.2
Anti-infectives for systemic use (J)	**112**	**5.9**
Antibiotics for systemic use (J01)	66	3.5
Antiviral agents for systemic use (J05)	44	2.3
Others	2	0.1
Antineoplastic and immunomodulatory agents (L)	**409**	**21.7**
Antineoplastic agents (L01)	372	19.7
Immunostimulants (L03)	24	1.3
Immunosuppressants (L04)	12	0.6
Others	1	0.0

Table 3-8 continued

ATC-Class	Number	Percentage
Musculoskeletal system (M)	**40**	**2.1**
Gift medications (M04)	25	1.3
Others	15	0.8
Nervous system (N)	**158**	**8.4**
Analgetics (N02)	111	5.9
Antiepileptic drugs (N03)	15	0.8
Psycholeptics (N05)	14	0.7
Psychoanaleptics (N06)	17	0.9
Others	1	0.0
Antiparasitic agents, insecticides and repellents (P)	**2**	**0.1**
Others	2	0.1
Respiratory tract (R)	**36**	**1.9**
Antihistamincis for systemic use (R06)	28	1.5
Others	8	0.4
Sensory organs (S)	**3**	**0.2**
Others	3	0.2
Varia (V)	**65**	**3.5**
All other therapeutic agents (V03)	52	2.8
Diagnostics (V04)	13	0.7

150 patients (92.6%) exhibited polymedication with five or more drugs during their hospital stay, and 98 patients (60.5%) experienced hyperpolymedication with ten or more drugs.

3.2.3 Drug-related problems

In the course of the medication reviews by the investigator and the validation by the reviewers, a total of 2414 DRPs were detected. This corresponds to 14.9 DRPs per patient (SD: 10.65, range: 1 – 57, median: 12.5, IQR: 13) during the hospital stay. The validation of the DRPs by the three reviewers accounted for 82 proposed changes, of which 35 changes were adopted. The decision to adapt a DRP change was made in focus talks between the investigator and each reviewer. Consensus had to be reached on the following points: Presence of an DRP, category of the DRP, primary source of the DRP including PRO-CTCAE data, need for intervention of the DRP. The largest three categories of DPRs, regardless their need for interventions, were DDI (n = 1489, 61.7%), indication without drugs (n = 384, 15.9%) and unsuitable or inappropriate drug selection according to evidence (n = 202, 8.4%). All categories of DRPs, regardless of their need for interventions, are shown in *Table 3-9*.

Table 3-9 Drug-related problem (DRP) categories regardless their need for interventions (n = 2414)

DRP category	Number	Percentage
Drug-drug interaction	1489	61.7
(Pseudo-) double medication	32	1.3
Unsuitable or inappropriate dosing interval	53	2.2
Unsuitable or inappropriate time of administration	21	0.9
Contraindication due to age and gender	0	0
Adverse drug reaction	71	2.9
Unsuitable or inappropriate drug selection according to evidence	202	8.4
Unsuitable dosage	76	3.1
Drug without indication	59	2.4
Indication without drugs	384	15.9
Contraindication due to diseases and allergies	3	0.1
Unsuitable or inappropriate duration of therapy	15	0.6
Unsuitable or inappropriate dosage form	9	0.4

Of 2414 detected DRPs in total, 1395 (57.8%) were pDRPs without need for intervention, 641 (26.6%) DRPs were iDRPs with the need for intervention, and for 378 (15.7%) DRPs, no exact classification was possible. The iDRPs amounted to 4.0 iDRPs per patient (SD: 2.97, range: 0 – 13, median: 3.0, IQR: 4) during hospital stay. *Figure 3-4* shows the amount of DRPs by the need for intervention.

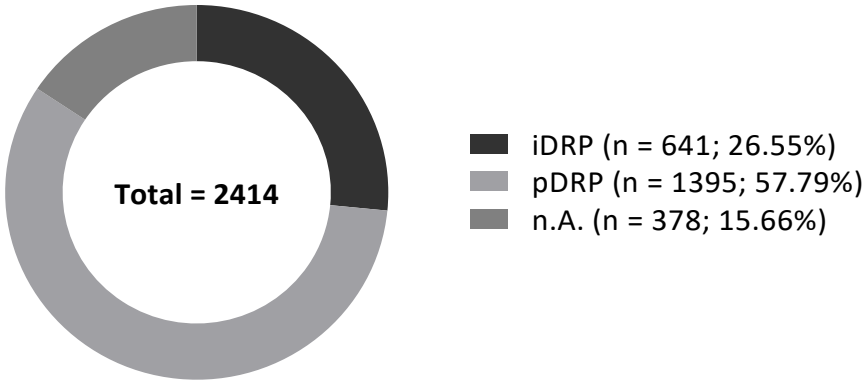

Figure 3-4 Drug-related problems (DRPs) by the need for intervention (n = 2414)

Table 3-10 shows the DRP classes by their need for intervention. “Indication without drugs” was the category with the largest share of iDRPs with 49.0%, followed by a large gap by “Unsuitable or inappropriate drug selection according to evidence” with 12.9%. The most considerable proportion of pDRPs was “Drug-drug interactions”, with 90.9%. “Drug-drug interactions” also exhibited the highest percentage of DRPs (49.5 %) that could not be classified according to their need for intervention. “Indications without drugs” and “Unsuitable dosage” could not be classified in 17.7% and 10.8% of the cases respectively. The following categories were most often categorized as iDRPs: “Contraindication due to diseases and allergies” (100%), “Unsuitable or inappropriate duration of *therapy*” (93.3%), “Unsuitable or inappropriate time of application” (90.5%), “Unsuitable or inappropriate dosing interval” (83.0%), “Indication without drugs” (81.8%), “Adverse drug reaction” (70.4%) and “Drug without indication” (69.5%).

Table 3-10 Drug-related problem (DRP) categories by their need for intervention [n = 2414; n (%)]

DRP category	iDRP	pDRP	n.A.
Drug-drug interaction (n = 1489)	34 (5.3)	1268 (90.9)	187 (49.5)
(Pseudo-) double medication (n = 32)	6 (0.9)	23 (1.6)	3 (0.8)
Unsuitable or inappropriate dosing interval (n = 53)	44 (6.7)	2 (0.1)	7 (1.9)
Unsuitable or inappropriate time of administration (n = 21)	19 (3.0)	0 (0)	2 (0.5)
Contraindication due to age and gender (n = 0)	0 (0)	0 (0)	0 (0)
Adverse drug reaction (n = 71)	50 (7.8)	0 (0)	21 (5.6)
Unsuitable or inappropriate drug selection according to evidence (n = 202)	83 (12.9)	83 (5.9)	36 (9.5)
Unsuitable dosage (n = 76)	32 (5.0)	3 (0.2)	41 (10.8)
Drug without indication (n = 59)	41 (6.4)	5 (0.4)	13 (3.4)
Indication without drugs (n = 384)	314 (49.0)	3 (0.2)	67 (17.7)
Contraindication due to diseases and allergies (n = 3)	3 (0.5)	0 (0)	0 (0)
Unsuitable or inappropriate duration of therapy (n = 15)	14 (2.1)	0 (0)	1 (0.3)
Unsuitable or inappropriate dosage form (n = 9)	1 (0.2)	8 (0.6)	0 (0)
Total	**641 (100)**	**1395 (100)**	**378 (100)**

The main sources for detecting DRPs were the interaction software packages (ADBA database and Lexi-Interact, n = 1489, 61.7%), guidelines (n = 426, 17.7%) and patient-reported symptoms by the PRO-CTCAE core questionnaire (n = 182, 7.5%). All main sources used for detecting the DRPs are shown in *Figure 3-5*.

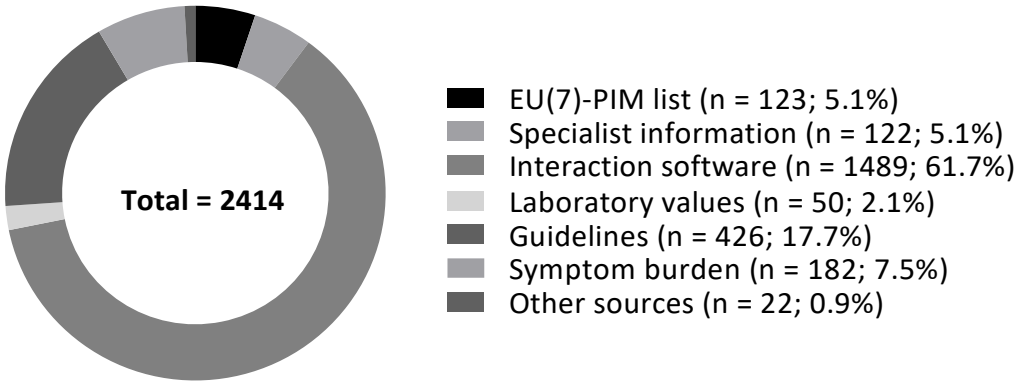

Figure 3-5 Drug-related problems (DRPs) by the main source used for detection (n = 2414)

To detect the 1489 DDIs, the ADBA database and Lexi-Interact were used. Only 25.7% (n = 383) of the DDIs were included in both databases. 62.8% (n = 935) of DDIs were only detected by Lexi-Interact, and the ABDA database only detected 11.5% (n = 171) of the DDIs. Of the 554 DDIs included in the ABDA database, only 1.4% (n = 8) were classified as “contraindicated” (category “contraindication”). For 13.5% (n = 75) of the DDIs, the concurrent use was “not recommended” (category “therapy modification”). The remaining 85.0% (n = 471) of the DDIs were assigned to the lower categories “therapy monitoring” and “no actions needed”, which were not considered as iDRPs in general. Of the 1318 DDIs included in the Lexi-Interact database, 10.2% (n = 135) were classified as “contraindicated” (category “contraindication”). For 18.5% (n = 244) a therapy modification should be considered (category “therapy modification”). The remaining 71.2% (n = 939) of the DDIs were assigned to the lower categories “therapy monitoring”, “no actions needed”, and “no known interaction”, which are not considered as iDRPs in general. The categories of DDIs according to the ABDA database and Lexi-Interact are shown in *Table 3-1*. A comparison of the DDIs of the ABDA database and Lexi-Interact is shown in *Figure 3-6*.

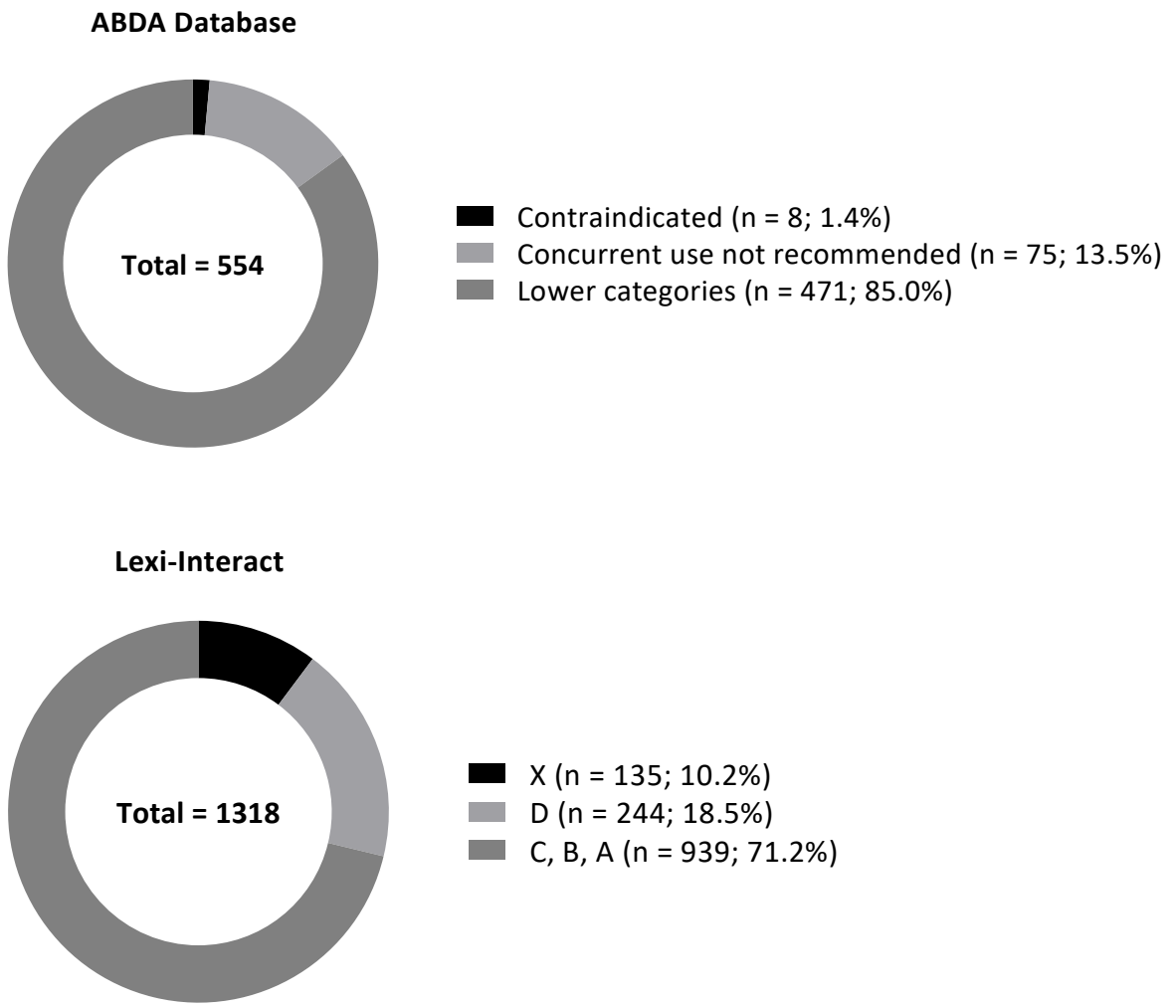

Figure 3-6 Comparison of the Drug-drug interactions (DDIs) of the ABDA database and Lexi-Interact (n = 1489)

182 DRPs were recorded by patient-reported symptoms that were captured with the PRO-CTCAE core questionnaire, amounting to 1.1 PRO-DRPs per patient (SD: 1.33, range: 0 – 6, median: 1.0, IQR: 2). The three main categories of these so-called PRO-DRPs were “indications without drugs” (n = 81, 44.5%), “adverse drug reaction” (n = 55, 30.2%) and “unsuitable or inappropriate drug selection according to evidence” (n = 38, 20.9%). *Figure 3-7* gives an overview of the categories of the PRO-DRPs.

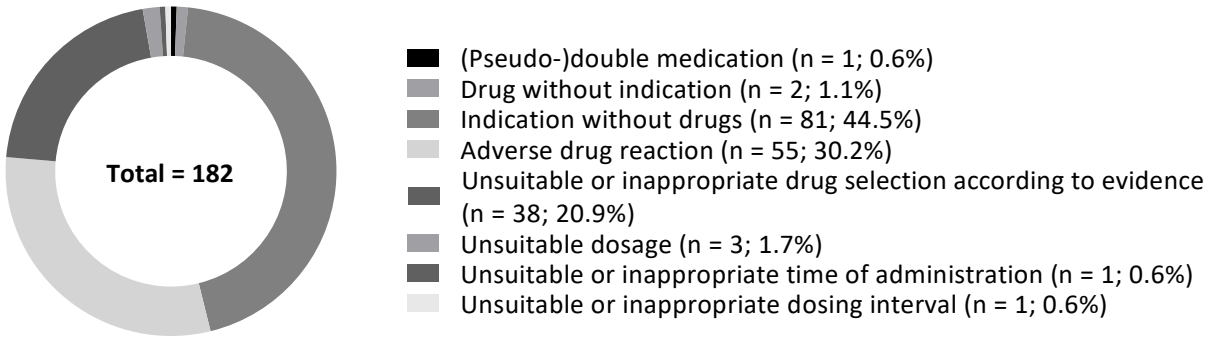

Figure 3-7 Categories of PRO-drug-related problems (PRO-DRPs) (n = 182)

The need for intervention of the PRO-DRPs can be quantified as follows: 75.8% (n = 138) of PRO-DRPs were classified as PRO-iDRPs with the need for intervention, and only 2.2% (n = 4) were classified as PRO-pDRPs without the need for intervention. In 22.0% (n = 40) of cases, the need for intervention of the PRO-DRPs could not be classified. Of the 641 iDRP in total, 21.5% were iPRO-DRP.

3.2.4 Patient-reported outcomes

The patient-reported outcome measures that were taken into account for the secondary analysis of the ImSEL-PRO study were the patient-reported symptom burden collected with the PRO-CTCAE core questionnaire and the health-related quality of life raised with the EORTC QLQ-C30 questionnaire.

3.2.4.1 Patient-reported symptom burden (PRO-CTCAE)

The patient-reported symptom burden raised with the PRO-CTCAE core item set was used for the medication reviews. The PRO-CTCAE core questionnaire contains 31 items for 16 different symptoms.

439 PRO-CTCAE core questionnaires were administered to the 162 patients during the study. One patient did not receive questionnaires at baseline, visit 2 and visit 3. 89.5% (n = 393) of questionnaires were answered completely, 5.2% (n = 23) of questionnaires were only

answered partially, and 5.2% (n = 23) of questionnaires were not answered at all. The answers to the questionnaires were scored on a symptom basis according to the *Equations 3-2* and *3-3.* Therefore, a maximum of 7024 symptom scores should have been calculated for the 439 used PRO-CTCAE questionnaires, each containing 16 symptoms. Due to missing values, 5.5% (n = 387) of the symptom scores could not be calculated.

Of the 439 questionnaires 36.7% (n = 161) were administered at baseline, 12.3% (n = 54) at visit 1 during the hospital stay, 36.0% (n = 158) at visit 2 at discharge and 15.0% (n = 66) at visit 3, 28 days after discharge.

PRO-CTCAE symptoms with a high score of $\geq$ 75 at baseline, visit 1, and/or visit 2 were considered during the medication reviews. 373 questionnaires were administered on these time-points, resulting in 5968 symptoms for which scores were calculated. Of the scores 10.4% (n = 618) were high $\geq$ 75 and 87.2% (n = 5303) were low < 75. 2.5% (n = 147) of scores could not be calculated due to missing values and could not be used for the detection of DRPs in the course of the medication reviews. At baseline, the rate of high scores $\geq$ 75 was 9.2% (n = 236 of 2576), at visit 1 15.3% (n = 132 of 864) and at visit 2 9.9% (n = 250 of 2528). Related to the patient population of 162, the number of severe symptoms per patient could be calculated for the time-points baseline and visit 2. At these time-points, the questionnaires were administered to every patient in the study. At baseline, 1.47 (SD: 2.03, range: 0 – 12, median: 1, IQR: 2) severe symptoms with a score $\geq$ 75 occurred per patient in the patient population. At visit 2, the number was 1.58 (SD: 2.32, range: 0 – 10, median: 1, IQR: 2) severe symptoms $\geq$ 75 per patient.

The distribution of the scores for all 16 symptoms of the PRO-CTCAE core questionnaire is shown in *Figure 3-8* to *Figure 3-11*.

Across all visits “Fatigue” (n = 99, 26.5%) was the most often occurring severe patient-reported symptom, followed by “Decreased appetite” (n = 65, 17.4%) and “Insomnia” (n = 57, 15.3%). At baseline, prior treatment in the hospital, “Fatigue” (n = 39, 24.2%) was the most prevalent severe symptom too, occurring in a similar proportion of patients as across all visits. “General pain” (n = 24, 14.9%) and “Insomnia” (n = 23, 14.3%) were the second and third most frequent appearing symptoms at baseline. At visit 1, only patients who stayed for at least seven days (n = 54) completed the questionnaires. The severe symptoms that were exhibited most

frequently were “Fatigue” (n = 20, 37.0%), “Decreased appetite” (n = 19, 35.2%) and “Nausea” (n = 16, 29.6%). “Fatigue” and “Decreased appetite” occurred with a higher percentage in the patient subpopulation with longer hospital stays, who received the questionnaires at visit 1. The three most prevalent severe symptoms didn’t change much at visit 2 with “Fatigue” (n = 40, 25.3%) followed by “Decreased appetite” (n = 28, 17.7%) and “Insomnia” (n = 25, 15.8%).

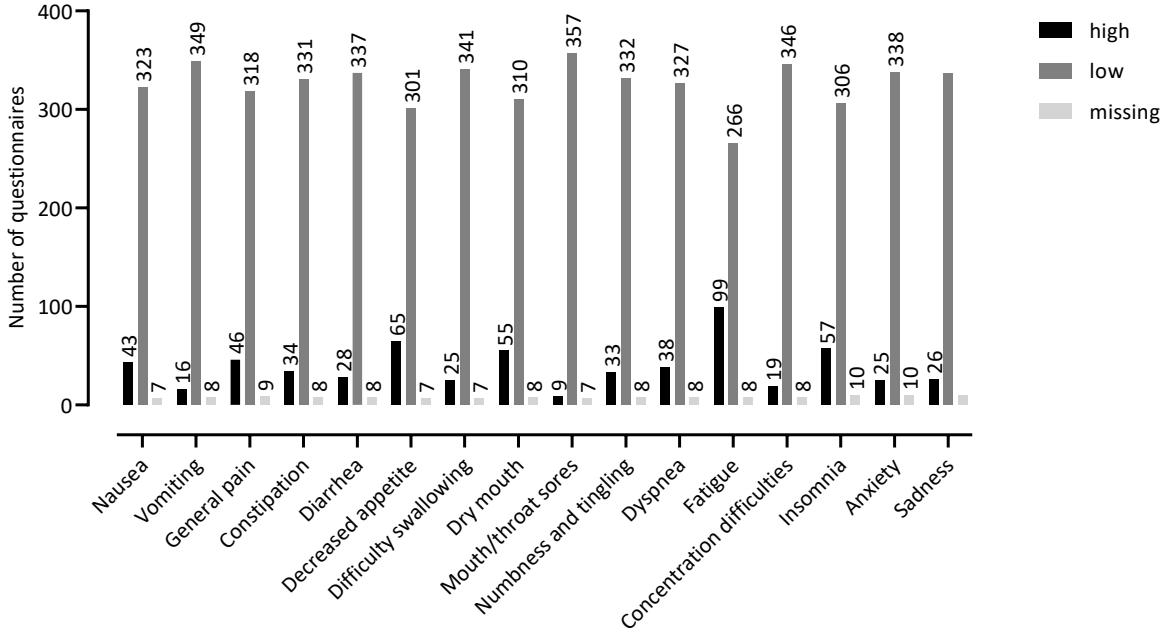

Figure 3-8 *Distribution of the scores of the 16 symptoms of the PRO-CTCAE core questionnaire at baseline, visit 1, and visit 2 counted individually for every time-point (categories high ≥ 75, low < 75, missing; n = 373)*

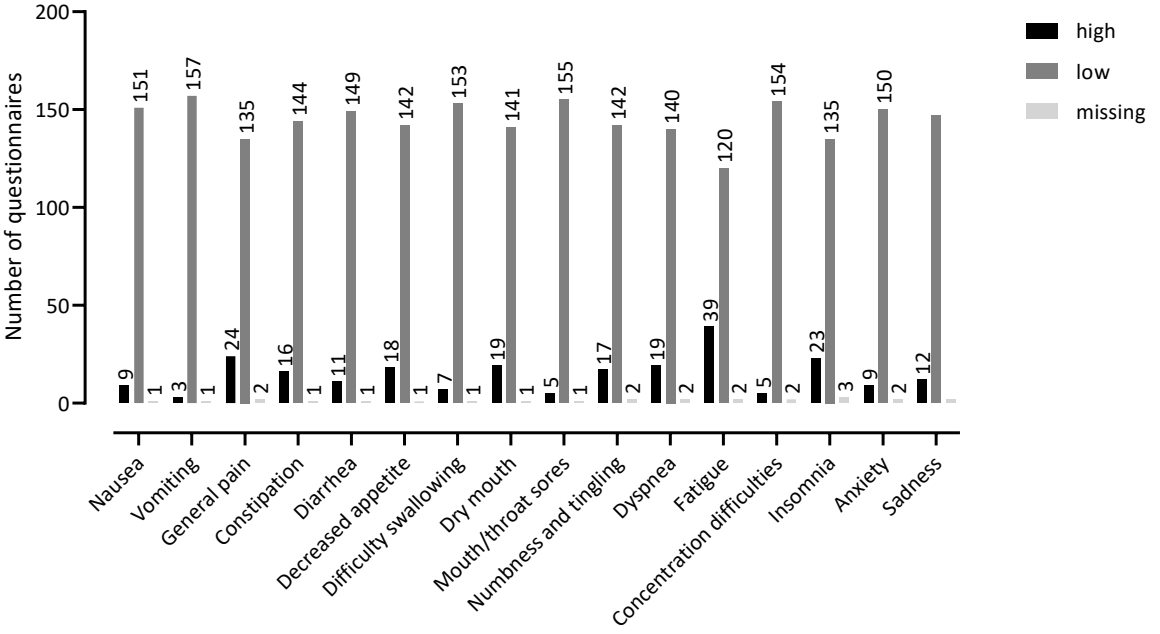

Figure 3-9 *Distribution of the scores of the 16 symptoms of the PRO-CTCAE core questionnaire at baseline (categories high ≥ 75, low < 75, missing; n = 161)*

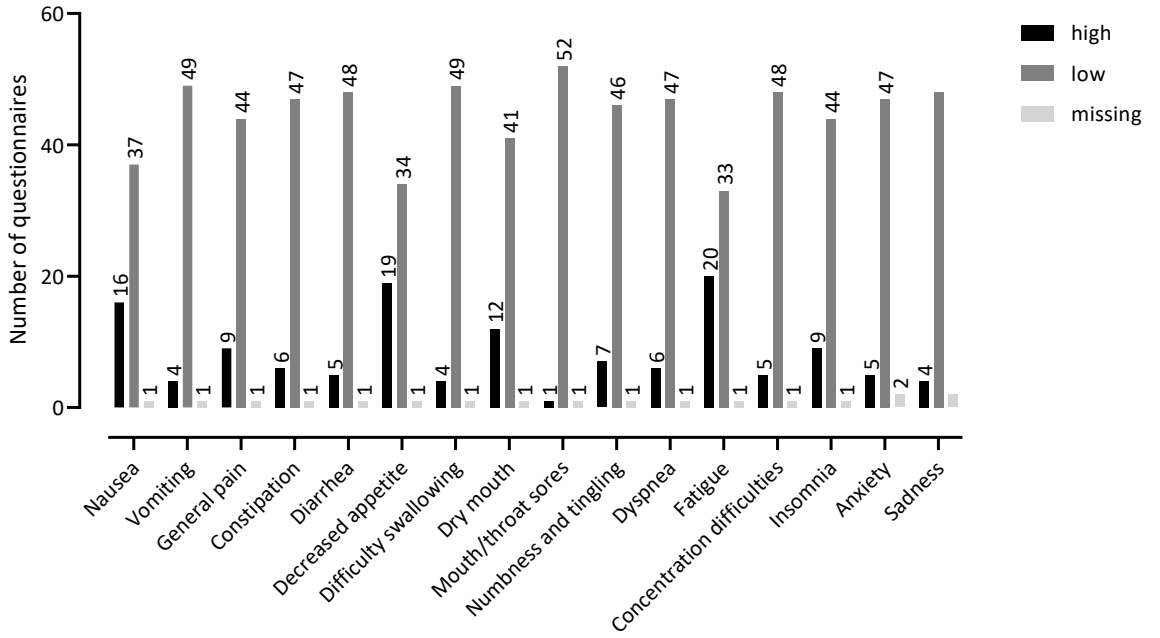

Figure 3-10 Distribution of the scores of the 16 symptoms of the PRO-CTCAE core questionnaire at visit 1 (categories high ≥ 75, low < 75, missing; n = 54)

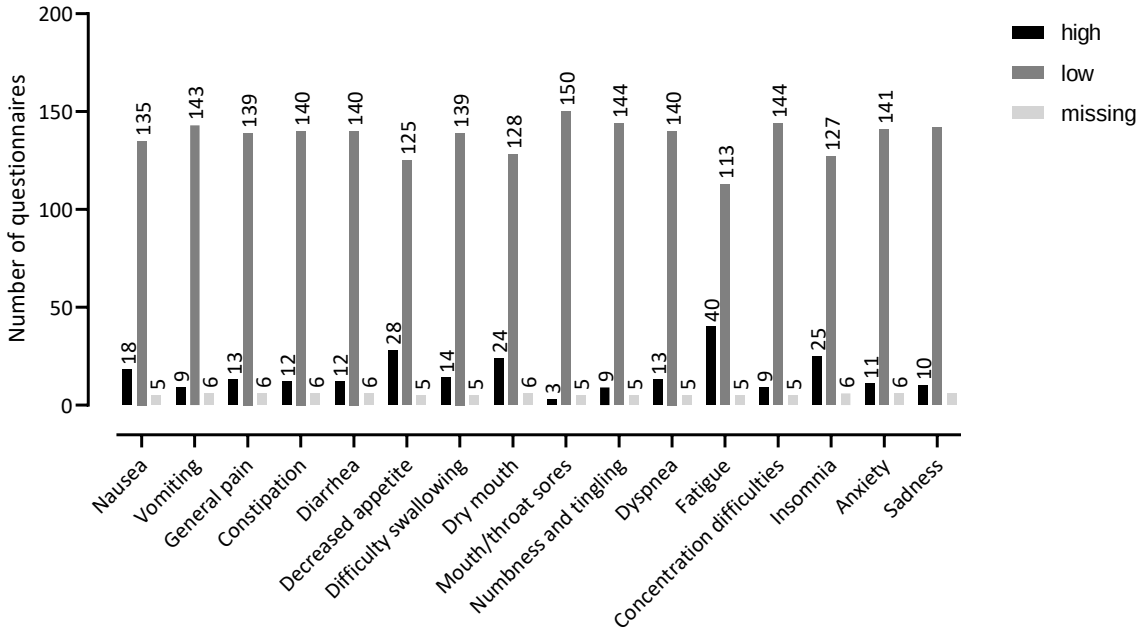

Figure 3-11 Distribution of the scores of the 16 symptoms of the PRO-CTCAE core questionnaire at visit 2 (categories high ≥ 75, low < 75, missing; n = 158)

3.2.4.2 Health-related quality of life (EORTC QLQ-C30)

Health-related quality of life was assessed using the EORTC QLQ-C30 questionnaire. A total of 439 EORTC QLQ-C30 questionnaires were administered to the 162 patients during the study. One patient did not receive questionnaires at baseline, visit 2 and visit 3. 82.9% (n = 364) of questionnaires were answered completely, 12.3% (n = 54) of questionnaires were only answered partially, and 4.8% (n = 21) of questionnaires were not answered at all.

Of the 439 questionnaires, 26.7% (n = 161) were administered at baseline, 12.3% (n = 54) at visit 1 during the hospital stay, 36.0% (n = 158) at visit 2 at discharge and 15.0% (n = 66) at visit 3, 28 days after discharge.

Changes in the scales global HRQOL, physical function, cognitive function, and emotional function from baseline to hospital discharge (visit 2) were used as dependent variables in the multivariate regression analysis. The changes in the scales of the 162 patients couldn´t be calculated in 5.6% (n = 9) of cases for the global health-related quality of life, cognitive and emotional function, and in 6.2% (n = 10) of cases for the physical function due to missing values.

The mean changes of the scales from baseline to visit 2 are shown in *Table 3-11*. The mean values of the global HRQOL, physical function, and cognitive function indicate a negative trend for the differences between baseline and visit 2. In contrast, the mean for the emotional function shows a positive trend. The standard deviations and ranges of the values are high and show a large scatter.

Table 3-11 Mean changes of the EORTC QLQ-C30 scales from baseline (BL) to visit 2 (V2)

Change in scale from BL to V2	Median	IQR	Mean	SD	Minimum	Maximum
Global health-related quality of life	0	25.0	-3.5	18.1	-58.0	50.0
Physical function	0	20.0	-3.7	17.0	-73.0	67.0
Cognitive function	0	16.7	-1.2	18.8	-67.0	67.0
Emotional function	0	25.0	4.5	17.6	-50.0	67.0

IQR = interquartile range, SD = standard deviation

The distribution of the changes in the scales from baseline to visit 2 is shown in the histograms of *Figure 3-12* to *Figure 3-15*.

The biggest proportion of values for the difference of global HRQOL from baseline to visit 2 (n = 45, 29.4%) shows bin centers of 0 in the histogram with a bin width of 10 ranging from -5 to +5. With bin centers of -10 (n = 30, 19.6%) and -20 (n = 24, 15.7%) about one third of the patients shows a reasonable decrease in their global HRQOL and 12 patients (7.8%) showed an even greater decrease with bin centers of -30, -40, -50 and -60. In contrast, the numbers of patients with an increasing global HRQOL were as follows: 17 patients (11.1%) had an increase with a bin center of +10 and 18 patients (11.8%) with +20. A greater increase with bin centers of +30, +40, and +50 had seven patients (4.6%). The significant Shapiro-Wilk test showed that the values are not distributed normally. Data are left-skewed (skewness -0.18), and the peak is sharper compared to normal distribution (kurtosis 1.62).

Regarding the physical function subscale, 34 patients (22.4%) were in the group with a bin center of 0. 43 patients (28.3%) had a bin center of -10 and nine patients (5.6%) of -20. 12

patients (7.9%) had a lager decrease in their physical function of -30 and -40. 42 patients (27.6%) had a moderate increase with a bin center of 10 and seven patients (4.6%) with a bin center of +20. Only one patient (0.7%) had a significant increase with a bin center of 30. The significant Shapiro-Wilk test shows that the values are not distributed normally. Data are left-skewed (skewness -0.81), and the peak is sharper compared to normal distribution (kurtosis 4.61).

Looking at the cognitive function subscale, about half of the patients had no major change from baseline to visit 2 (n = 76, 49.7%). The other half splits to decreases (n = 38, 24.8%) and increases (n = 35, 22.9%) of mostly +/-20 and +/-30. The significant Shapiro-Wilk test shows that the values are not distributed normally. Data are left-skewed (skewness -0.41), and the peak is sharper compared to normal distribution (kurtosis 2.92).

In terms of the emotional function, besides 36 patients (23.5%) with a bin center of 0, 38 patients (24.8%) were grouped to the bin centers of -10 and -20, whereas 52 patients (34.0%) were grouped to +10 and +20. The number of patients with a greater increase of +30, +40 and +50 was higher with a number of 21 (13.7%) than the number of patients with a greater decrease of -30, -40 and -50 (n = 5, 3.3%). The significant Shapiro-Wilk test shows that the values are not distributed normally. Data are right-skewed (skewness 0.24), and the peak is sharper compared to normal distribution (kurtosis 1.58).

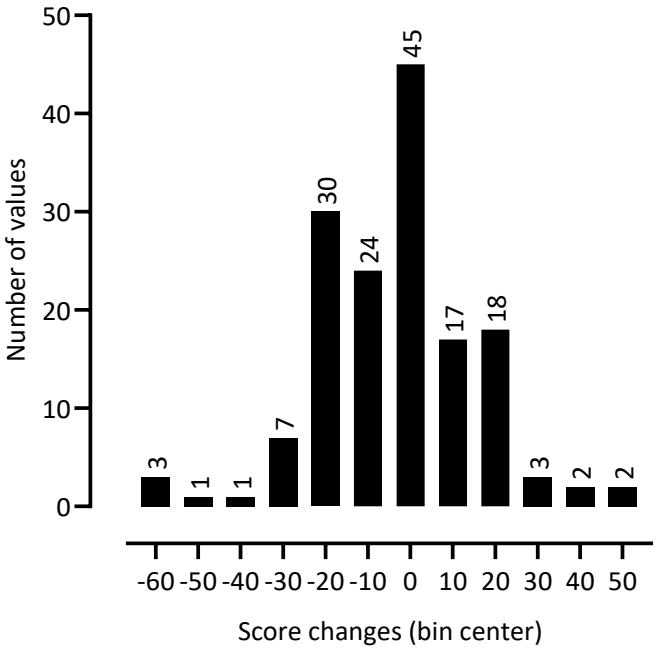

Figure 3-12 Histogram of the distribution of the score changes in global HRQOL from baseline to visit 2 (n = 153)

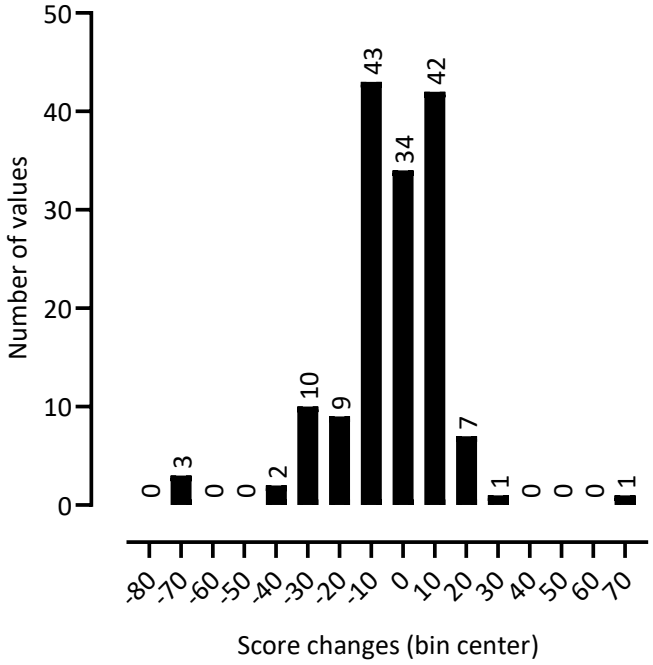

Figure 3-13 Histogram of the distribution of the score changes in physical function from baseline to visit 2 (n = 152)

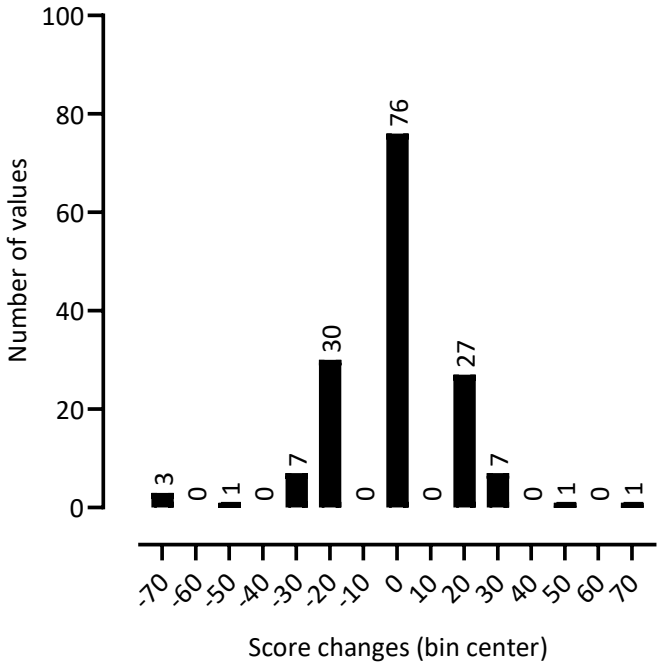

Figure 3-14 Histogram of the distribution of the score changes in cognitive function from baseline to visit 2 (n = 153)

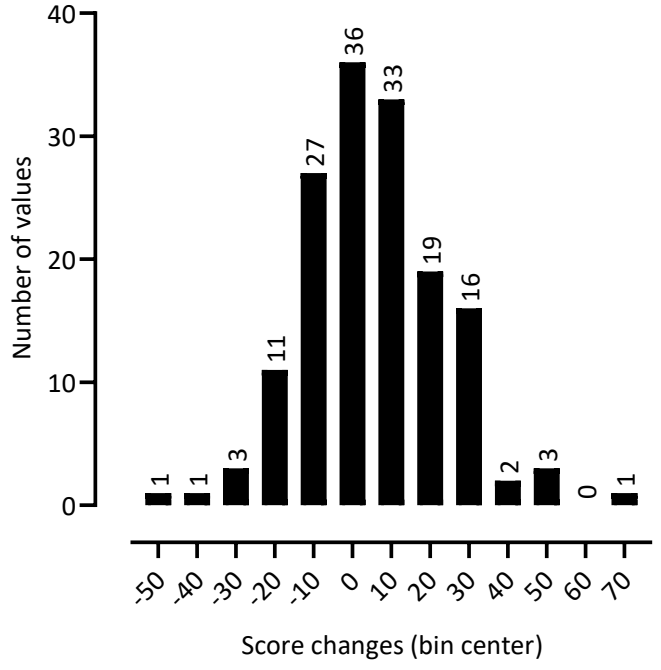

Figure 3-15 Histogram of the distribution of the score changes in emotional function from baseline to visit 2 (n = 153)

3.2.5 Multiple linear regression models

To explore the influence of sociodemographic, disease-related, and drug therapy-related factors on the change of the global health-related quality of life and the subscales, physical function, cognitive function, and emotional function of the EORTC QLQ-C30 questionnaire from baseline to hospital discharge (visit 2), multivariate linear regression models were computed. The independent variables with their scale levels are shown in *Table 3-5*.

In the run-up to the analysis, the variable “study center” was considered as a potential confounder due to general differences in the characteristics of the treated patients. Its influence was considered as a random effect in a mixed model analysis. The center level variation in the analysis for the global HRQOL was very low, with a SD of 0.00293. Therefore, the calculation of multiple linear regression models was deemed sufficient. Since the functional scales are subscales of the global HRQOL, the mixed model analysis was performed only for the global HRQOL.

A strong linear correlation was found between the variables “drugs (number)” and “DRP total (number)” with a high Pearson correlation coefficient of 0.818 [94]. Therefore, the variable “DRP total (number)” was excluded from the analysis to avoid multicollinearity.

The results of the multiple linear regression models describing the change of global HRQOL and the physical function subscale of the EORTC QLQ-C30 questionnaire are shown in *Table 3-12* and *Table 3-13*.

Table 3-12 Multiple linear regression model describing the effect of covariates on the change of the global HRQOL scale of the EORTC QLQ-C30 questionnaire from baseline to visit 2

Covariate	Effect	SE	p	95% CI	
(Constant)	-24.54	11.08	0.029	-46.47	-2.61
Study group B	-4.85	3.77	0.202	-12.31	2.62
Study group C	-6.20	3.54	0.083	-13.22	0.81
Age (years)	0.23	0.13	0.088	-0.04	0.49
Gender (female)	0.76	3.21	0.814	-5.59	7.11
Educational level (low)	1.44	3.02	0.635	-4.54	7.41
Duration of hospital stay (days)	-0.34	0.19	0.082	-0.71	0.04
Type of cancer (solid)	-0.29	3.87	0.940	-7.94	7.36
Time since first diagnosis of cancer (months)	0.04	0.05	0.415	-0.06	0.15
Relapse status (no)	11.06	4.38	0.013*	2.38	19.73
ECOG status 1	2.83	3.55	0.426	-4.19	9.85
ECOG status 2	10.85	5.91	0.069	-0.85	22.54
Concomitant diseases (number)	-1.32	1.41	0.350	-4.12	1.47
Drugs (number)	0.18	0.36	0.613	-0.53	0.89
iDRP (number)	-0.10	0.72	0.896	-1.53	1.34
PRO-DRP (number)	-0.30	1.43	0.833	-3.13	2.53

SE = standard error

The ANOVA revealed that the model contains significant covariates (p = 0.031). The included independent variables describe 8.6% of the variance of the dependent variable (R^2 = 0.184, adjusted R^2 = 0.086). The model for global HRQOL shows a weak to moderate variance explanation. The variable “relapse status” significantly influenced the change in global HRQOL (p = 0.013). Patients without a current relapse of their tumor disease show an increase of 11.06 points on the global HRQOL scale of the EORTC QLQ-C30 questionnaire from baseline to hospital discharge (visit 2). The changes in the metric variables (age, time since the first diagnosis of cancer, drugs, duration of hospital stay, concomitant diseases, iDRP, and PRO-DRP) count per unit, whereas changes in the nominal variables (gender, educational level,

ECOG status 1 and 2, study group B and C and type of cancer) are compared to their other expressions as reference.

Table 3-13 Multiple linear regression model describing the effect of covariates on the change of the physical function scale of the EORTC QLQ-C30 questionnaire from baseline to visit 2

Covariate	**Effect**	**SE**	**p**	**95% CI**	
(Constant)	-12.06	10.47	0.252	-32.78	8.67
Study group B	-6.08	3.59	0.093	-13.19	1.03
Study group C	-4.44	3.37	0.190	-11.12	2.23
Age (years)	0.15	0.13	0.245	-0.10	0.40
Gender (female)	-0.17	3.04	0.957	-6.17	5.84
Educational level (low)	-3.11	2.86	0.279	-8.77	2.55
Duration of hospital stay (days)	-0.48	0.18	0.009*	-0.84	-0.12
Type of cancer (solid)	1.79	3.71	0.630	-5.55	9.14
Time since first diagnosis of cancer (months)	0.05	0.05	0.299	-0.05	0.15
Relapse status (no)	1.49	4.14	0.720	-6.71	9.68
ECOG status 1	1.17	3.36	0.728	-5.47	7.81
ECOG status 2	4.33	5.61	0.441	-6.76	15.42
Concomitant diseases (number)	-0.83	1.34	0.540	-3.48	1.83
Drugs (number)	0.52	0.34	0.135	-0.16	1.20
iDRP (number)	-0.05	0.69	0.942	-1.41	1.31
PRO-DRP (number)	-0.88	1.35	0.516	-3.55	1.79

SE = standard error

The ANOVA revealed that the model contains significant covariates (p = 0.009). The included independent variables describe 11.6% of the variance of the dependent variable (R^2 = 0.211, adjusted R^2 = 0.116). It shows a weak to moderate variance explanation. The variable “Duration of hospital stay (days)” was shown to have a significant influence on the change in

physical function ($p = 0.009$). With every day the patients stay in the hospital, the physical function scale of the EORTS QLQ-C30 questionnaire decreases by 0.48 points.

For the models describing the changes of the cognitive and emotional function scales, the ANOVA did not show a significant result ($p = 0.122$ and $p = 0.210$ respectively). The results are shown in *Appendix I-B*.

3.3 Discussion

3.3.1 Study design

The ImSEL-PRO trial was conducted to evaluate the feasibility of a multidimensional ePRO system and to implement it in an inpatient oncology setting. The primary analysis results indicate that the ePRO tool is feasible, but some results were not as predicted. The satisfaction with care received by the physicians was significantly lower in the intervention group A than in the control group C. Group B showed the highest satisfaction with care. The symptom burden and global HRQOL did not change significantly between the groups A, B, and C during hospital stay. These findings indicate shortcomings in the feedback on the ePRO measures by the treating physicians since there was no predefined supportive care concept designed for the study [56].

This secondary analysis was conducted to identify possible explanations for the counterintuitive findings of the primary analysis. Therefore, retrospective medication reviews were undertaken to determine the underlying DRPs of the patient population and provide possible solutions. Medication reviews were performed by a pharmacist, including PROs derived from the ePRO tool. Furthermore, sociodemographic, disease-related, and drug therapy-related factors influencing the HRQOL of the patients, regardless of their study group affiliation, were determined in a multivariate regression analysis. The results can serve as a basis for designing interdisciplinary and risk-adapted supportive care concepts for cancer inpatients as feedback to ePRO measures.

A strength of this study is that it is the first study in a German oncology inpatient setting evaluation DRPs using PROs. It can contribute to implementing PRO instruments such as PRO-CTCAE with its focus on therapy-related symptomatic toxicity in the routine of pharmacist-led medication reviews in German hospitals. Due to the lack of pharmacists in German hospitals, personal patient interviews are not always possible. Data on the number of pharmacists per patient bed are limited. In 2010 0.31 pharmacists per 100 patient beds worked in German hospitals, whereas in the UK there were 4.35 pharmacists per 100 patient beds [95]. In Germany only about one-third of the pharmacists worked directly at the wards and, in most cases, at surgical wards [96]. PRO data can contribute to closing this gap and making first-hand patient information available for German hospital pharmacists.

A limitation of this study is that medication reviews could only be conducted retrospectively, and interventions could not be undertaken. Although trained study nurses collected the underlying patient data in a standardized eCRF, missing information could not be obtained retrospectively. The feasibility and efficacy of PRO-based medication reviews should be evaluated in further prospective studies with parallel-group design.

3.3.2 Patient characteristics

Patients with broadly defined inclusion criteria were included in the study. However, for the secondary analysis, five additional patients had to be excluded from the study population due to no or insufficient documentation in the eCRF, which was the basis for the secondary analysis. Therefore, the patient population of the secondary analysis is not exactly comparable to the one of the feasibility study.

By far, most patients were recruited at Helios Hospital Emil von Behring (n = 100, 61.7%), which is also the study center of the study's initiator. The reasons for the differences in patient recruitment and their consequences on the conduction of the study and the physicians' compliance are not known. Nevertheless, the variable “Study center” was considered to be a confounder for the multivariate regression analysis. With a median hospital stay of only four days (IQR: 7, range: 1 – 73) and 66.7% (n = 108) of patients staying less than seven days, the hospital stays were short. Considering that EORTC QLQ-C30 and PRO-CTCAE are meant to be answered every seven days, the short hospital stays have probably affected the differences in the scores from baseline to hospital discharge. The median age of 65.5 years (IQR: 18, range: 19 – 88) corresponds to the fact that the incidence of developing cancer rises rapidly once the age of about 60 years is reached, and the mean age of disease onset is about 70 years. More patients were female (n = 91, 56.2%), which is notable because usually more men than women suffer from cancer. Regarding the risk factors for cancer like obesity, smoking, and alcohol abuse, the patient population did not show significant anomalies [97].

Most patients (n = 103, 63.6%) had a solid tumor disease and most tumors were located in the digestive and gastrointestinal tract (n = 49, 30.2%). The most frequent hematological diseases in the patient population were lymphoma (n = 31, 19.1%). This reflects the finding that colorectal cancer is the solid tumor disease and lymphoma is the hematological tumor disease

that occur gender-independent most frequently. Breast cancer, as the most prevalent female cancer entity, was not represented in the patient population, and prostate cancer, as the most prevalent male cancer entity, was only present in two cases [97]. In general, the patients were rather on the beginning of their disease, as the median time since the first diagnosis of cancer was four months. Still, a broad range from newly diagnosed up to over 17 years since diagnosis was covered (IQR: 13.5, range: 0 – 208 months). Most patients had no relapse of their tumor disease (n = 123, 75.9%). Their physical condition was rather good with a majority of patients with a ECOG status of 0 (n = 87, 53.8%) and 1 (n = 53, 32.7%). It is also remarkable that the patients only showed about one concomitant disease per patient. In contrast, the number of concomitant diseases in a study by Yeoh et al. amounted to three concomitant diseases per patient [45].

The patients received a mean of 11.6 drugs per patient (SD: 5.15, range: 2 – 26, median: 11, IQR: 7), including cancer treatment, supportive and concomitant medication. This number includes all drugs that were administered during the hospital stay, even if they were only used for a short duration, such as antiemetic prophylaxis or antibiotic therapy. The drugs were documented time-independent at the point of discharge. That's why not all drugs were necessarily administered together and during the whole time period. No differentiation in drugs before and after hospital admission was possible. This approach may have led to an overestimation of the number of drugs. Nevertheless, every administered drug can cause a DRP. In a previous study from our working group in patients with head and neck cancer in an ambulatory setting, the patients received an average of 3.2 (SD 2.6, median 2.5, IQR 4.0, range 0 – 9) drugs before starting tumor therapy. Patients were treated for six therapy cycles, and the average number of drugs rose to 10.2 (SD 2.7, median 9.5, IQR 3.5, range 6 – 16) in the first cycle and 13.7 (SD 3.9, median 14.0, IQR 6.0, range 5 – 20) in the sixth cycle [63, 64]. In another study from our working group medication risks were evaluated in older cancer inpatients [84]. The patients received a median of five drugs (SD 3.5) as long-term medication before the start of the cancer treatment. After the start of cancer treatment, patients received an additional of median six drugs (IQR 2.3, range 1 – 12), including cancer and supportive treatment [84]. Two studies by Nightingale et al. detected a mean of 9.8 respectively, 10.4 medications per patient including prescription drugs, non-prescription drugs, and herbal drugs [51, 55]. Prithwiraj et al. detected 7.3 drugs including prescribed and non-prescribed drugs per patient in their studies with older cancer patients [40]. Although the number of drugs prior to

cancer treatment could not be raised in the present study, the number of drugs during the cancer treatment corresponds to that of other studies. Almost every patient (n = 150, 92.6%) exhibited polymedication with five or more drugs during hospital stay, and more than half of the patients (n = 98, 60.5%) experienced hyperpolymedication with ten or more drugs. The general high proportion of patients with polymedication is congruent with the findings of other studies [36, 39, 40]. In contrast, the number of patients with hyperpolymedication is slightly higher (60.5% vs. 43%) in this study [39].

3.3.3 Drug-related problems

Because the medication reviews and relevance assessments of the DRPs were conducted by the research associate, who also performed the analysis of the results, the potential for bias arises. Intrarater reliability and interrater reliability represent suitable quality criteria for the precision of a method. This refers to the agreement of the results if a method is repeatedly applied by the same person (intrarater reliability) or by two independent persons (interrater reliability) [65, 98]. To ensure high precision of the medication reviews and the relevance assessments of the DRPs, they were partially validated by three independent reviewers. The reviewers proposed 82 changes, of which 35 changes were adopted after the focus talks. Regarding the 2414 in total detected DRPs, the change rate only amounts to 1.4%, and the interrater reliability can be assumed to be very good. The second quality criterion, intrarater reliability, could not be evaluated.

The detected DRPs amount to 14.9 DRPs per patient (SD: 10.65, range: 1 – 57, median: 12.5, IQR: 13) during hospital stay, regardless of the need for intervention. Only about one-quarter of the DRPs (n = 641, 26.6%) was considered iDRPs, which corresponds to 4.0 iDRPs per patient (SD: 2.97, range: 0 – 13, median: 3.0, IQR: 4). Due to missing information or the lack of opportunity to talk to patients and physicians, a reasonable number of DRPs could not be classified as iDRP or pDRP (n = 378, 15.7%). The DRP categorization in pDRP and iDRP was implemented and used in the study by Vucur et al [64]. The proportion of iDRPs in this sample of head and neck cancer patients was higher than in the present study and ranged between 45.1% and 49.0%, dependent on the cycle of therapy, and the number of iDRPs per patient ranged from 4.8 in the first therapy cycle to 6.9 in the fifth therapy cycle [64]. The difference between the proportion of iDRPs can be explained by methodological differences in DDI

detection. The number of 4.0 iDRPs per patient found in the present study was lower than the number of Vucur et al., but it corresponds to the study of Nightingale et al. with three DRPs per patient and Edwards et al. showing 3.7 DRPs per patient [47, 55]. Since these two studies were conducted prospectively, it can be assumed that only relevant DRPs were documented, and the number can be referred to the iDRPs of the present study.

In the present study, a huge number of DRPs were DDIs (n = 1489, 61.7%). Only 5.3% were classified as iDRPs, whereas Vucur et al. reported between 11.9% in therapy cycle 1 and 25.5% in therapy cycle 6 [64]. The DDIs were assessed with different tools. Vucur et al. used the ABDA database to identify DDIs, and the present study used the ABDA database and Lexi-Interact. Remarkably is that only a small amount of DDIs was detected with both databases simultaneously (n = 383, 25.7%). Most DDIs were detected by Lexi-Interact (n = 935, 62.8%). Only a very small proportion was detected with the ABDA database (n = 171, 11.5%), and only 14.9% of these were assigned to the relevant categories “contraindication” and “therapy modification”. Compared to that, 28.7% of the DDIs of Lexi-Interact were classified as “contraindication” or “therapy modification”. DDIs of the categories “contraindication” and “therapy modification” were not necessarily iDRPs. Severe DDIs may occur, but the drug combination might be necessary to achieve therapeutic goals, as it is often the case if myelosuppressing chemotherapeutic agents of a therapy regimen are applied simultaneously. The discrepancies between the DDIs detected by the ABDA database and Lexi-Interact also indicate that the ABDA database is underreporting DDIs related to cancer therapy. In contrast, Lexi-Interact overreports DDIs, especially those between anticancer drugs and DDIs involving metamizole. The drug is commonly used in Germany as an analgesic. In the US, it is not licensed because of the very rare ADR called agranulocytosis [99]. This circumstance illustrates that, on the one hand, Lexi-Interact is one of the best performing DDI programs, as shown by Khesthi et al. [100]. On the other hand, local conditions play an essential role in evaluating DDIs.

An innovative approach to the medication reviews conducted for the present study was the inclusion of patient-reported symptoms. To conduct a complete medication review type 3, talking to the patients would be mandatory. The advanced medication reviews type 2b were complemented by the PRO-CTCAE data, which are recorded directly from the patients. As ADRs are an inherent part of tumor therapy, not every symptomatic toxicity requires action.

For this purpose, only severe PRO-CTCAE symptoms with a score of ≥ 75 were considered. Due to the retrospective character of the medication reviews, the high threshold value should have also ensured that only most reasonable symptoms are considered. Due to the short duration of hospital stays during the present study, it is possible that symptoms that occur over a longer time period in less pronounced expression, but that are bothersome were not taken into account [101]. In total, the amount of detected PRO-DRPs was relatively small (n = 182, 7.5%), but with 75.8% (n = 138) iDRPs, the proportion of iDRPs was three times higher in comparison to the regular DRPs. Taking into account that 641 DRPs were iDRPs, 21.5% of iDRPs were detected on basis of the PRO-CTCAE data. This emphasizes the importance of PRO data as additional information for advanced medication reviews type 2b.

3.3.4 Patient-reported outcomes

The two PRO instruments that were considered for the secondary analysis of the ImSEL-PRO trial were the PRO-CTCAE core questionnaire and the EORTC QLQ-C30 questionnaire. As described in section *3.3.3*, the PRO-CTCAE core questionnaire was implemented in the medication reviews. The EORTC QLQ-C30 questionnaire was used as HRQOL outcome for the multivariate regression analysis, which will be discussed in section *3.3.5*.

Both questionnaires were answered with a reasonably high rate. The PRO-CTCAE core questionnaires were entirely answered with a higher rate of 89.5% than the EORTC QLQ-C30 questionnaire with 82.9%. To detect DRPs, only the symptom scores from the questionnaires administered at baseline, visit 1, and visit 2 were considered. Only 2.5% of the relevant PRO-CTCAE symptom scores could not be calculated due to missing values. The difference from baseline to visit 2 of the global HRQOL scale and its subscales from the EORTC QLQ-C30 questionnaire was used for the multivariate regression models. The differences could not be calculated in 5.6% (global HRQOL, cognitive and emotional function) and 6.2% (physical function) of cases, respectively due to missing values. The low numbers of missing values indicate that the results are not biased since a missing rate of about 5 to 10% is accepted in statistical analyses [102].

About one-tenth of the PRO-CTCAE scores (n = 618, 10.4%) were high with a value ≥ 75, amounting to about 1.5 severe PRO-CTCAE symptoms per patient at the time-points baseline

(mean: 1.47, SD: 2.03, range: 0 – 12, median: 1, IQR: 2) and visit 2 (mean: 1.58, SD: 2.32, range: 0 – 10, median: 1, IQR: 2). For visit 1, the calculation of PRO-CTCAE symptoms per patient was not useful because only patients with a hospital stay of at least seven days received the questionnaires at this time-point. Comparing these numbers to the number of 1.1 PRO-DRPs per patient (SD: 1.33, range: 0 – 6, median: 1.0, IQR: 2) shows that about three-fourths of the severe PRO-CTCAE symptoms resulted in a PRO-DRP. Cross-visits "Fatigue" (n = 99, 26.5%) was the most often occurring severe patient-reported symptom, followed by "Decreased appetite" (n = 65, 17.4%) and "Insomnia" (n = 57, 15.3%). The overall view does not differ greatly throughout the different time-points. At baseline "General pain" (n = 24, 14.9%) and at visit 1 "Nausea" (n = 16, 29.6 %) completed the most frequently occurring symptoms. "Fatigue" and "Decreased appetite" occurred in the patient subpopulation with longer hospital stays, who received the questionnaires at visit 1 with a higher percentage. In general, the rate of high PRO-CTCAE scores $\geq$ 75 was at 15.3% highest at visit 1 (n = 132 of 864), indicating that patients with a longer hospital stay developed more symptoms after seven days at the hospital than patients with a shorter hospital stay. The results of Pearce et al. affirm the finding that fatigue is the most common symptom in cancer patients. They conducted a cohort study on self-reported chemotherapy side effects [103]. A literature synthesis by Reilly et al. on the prevalence and severity of symptoms in patients receiving anticancer treatment identified fatigue, insomnia, pain, dry mouth, and anorexia as the top five prevalent symptoms and fatigue, insomnia, anorexia, dry mouth and pain as the top five symptoms for severity [104]. Except for nausea, these were also the most severe occurring symptoms in the population of the current study. Nausea present, especially at visit 1, was ranked place 10 in the analysis of Reilly et al. [104].

The mean differences in the scales of the EORTC QLQ-C30 questionnaire from baseline to hospital discharge (visit 2) were relatively low, with values under ±5 (*Table 3-11*). A negative trend can be observed for global HRQOL, physical function, and cognitive function. Emotional function shows a positive trend and seems to improve during the treatment at the hospital. This reflects the picture shown by the primary analysis, in which no difference in the changes in HRQOL between the three study groups could be shown [56]. All distributions are significantly different from a normal distribution, and with the exception of emotional function, rather left-skewed and much sharper distributed than the normal distribution. This

means that the values of the differences in the HRQOL scales are grouped around zero and show a tendency to improving values.

The most minor changes in the scores, that can be considered clinically meaningful for patients, are called minimal important difference (MID). For the EORTC QLQ-C30 questionnaire, the MID for the global HRQOL and its subscales were evaluated in a study in patients with non-small-cell lung cancer. Two methods were used to determine the MID: An anchor-based approach using the WHO performance status and the weight change of the patients as clinical anchors and a distribution-based approach. The results differed according to the used method and for improvement and deterioration of the scores [105]. A further study in patients with advanced cancer used the global health status scale and the global HRQOL scale of the EORTC QLQ-C30 questionnaire as clinical anchors to determine the MIDs for its subscales [106]. The calculated MIDs for the different scales of the EORTC QLQ-C30 questionnaire according to the anchor-based methods are shown in *Table 3-14*. The German IQWIG used a different approach to evaluate relevant changes in PRO scales. To detect relevant changes that can be felt with sufficient certainty, a response threshold of 15% of the scale range was defined [2].

Table 3-14 Comparison of the minimal important differences (MIDs) for the scales of the EORTC QLQ-C30 questionnaire [105, 106]

Study	Method	MID improvement				MID deterioration			
		QOL	**PF**	**CF**	**EF**	**QOL**	**PF**	**CF**	**EF**
Maringwa et al.	**Clinical anchor-based**								
	WHO performance status	9	9	-	-	4	4	-	-
	5% to <20% weight change	4	5	-	-	4	6	-	-
Bedard et al.	**PRO anchor-based**								
	Overall health status	-	10.1	9.1	14.7	-	7.2	0.3	12.2
	Global HRQOL	-	2.1	9.5	13.2	-	6.1	-1.8	13.2

QOL = global HRQOL, PF = Physical function, CF = Cognitive function, EF = Emotional function; MID = Minimal important difference; 5% to <20% weight change: weight gain for MID improvement, weight loss for MID deterioration; Values referring to the EORTC QLQ-C30 scales from 0 – 100

Taking into account the differences in the methods and the different MID values for improvement and deterioration, a general evaluation of changes in the EORTC QLQ-C30 scales is not possible. However, as an approximation, values between five and 10 can be assumed to be small patient-relevant changes. Values between 10 and 20 indicate a moderate difference, and values above 20 indicate a significant difference [107, 108]. Therefore, it is possible to assume that all patients distributed to bin centers ±10 or higher (*Figure 3-12* to *Figure 3-15)* experienced patient-relevant changes in their HRQOL. In terms of global HRQOL, this could have affected 70.6% of patients, 77.6% of patients for physical function, 50.3% of patients for cognitive function, and 76.5% of patients for emotional function in our study.

3.3.5 Multiple linear regression models

In order to explore how sociodemographic, disease-related and drug therapy-related factors influence the change of the global HRQOL and the subscales, physical function, cognitive

function and emotional function of the EORTC QLQ-C30 questionnaire from baseline to hospital discharge (visit 2), multivariate linear regression analyses were performed

The above-mentioned scales of the EORTC QLQ-C30 questionnaire were chosen because they reflect parts of the construct of HRQOL and are most likely to be affected by the oncological inpatient treatment as part of the study. The scales role function and social function were not used because they can only be evaluated in the everyday home environment. The symptom scales were not considered because the PRO-CTCAE symptom burden was already used as part of the medication reviews and the symptom scales of EORTC QLQ-C30 and PRO-CTCAE show a high grade of consistency [109].

For the global HRQOL and physical function, multiple linear regression models describing the variance of the changes from baseline to hospital discharge (visit 2) were found to contain significant covariates (*Table 3-12* and *Table 3-13*). In contrast, the models for cognitive function and emotional function were not significant predictors (*Appendix I-B*). This could be because cognitive function and emotional function are more complex constructs of HRQOL requiring a longer time period to change than for example, physical function. Therefore, it can be assumed that the sample size of the study population was too small and the duration between the time points of the surveys was too short to show a significant change in these subscales of HRQOL. It is possible that the model for global HRQOL and physical function are affected by these circumstances as well, but the included independent variables explain the variance of the dependent variables global HRQOL (8.6%) and physical function (11.6%) in a weak to moderate extent [94].

Within the model for global HRQOL, only the variable “Relapse status (no)” had a significant influence on the change of global HRQOL. This finding aligns with the expectation that patients with no relapse of their oncological disease benefit most from the treatment during their hospital stay. For most cancer types, the treatment possibilities are best in the early stages of the disease and decrease with relapses. The increase of 11.06 points on the global HRQOL scale in patients with no relapse is above the MID value and indicates a moderate patient-relevant difference (*Table 3-14* and section *3.3.4*).

Regarding the model for physical function, the variable “Duration of hospital stay (days)” has a negative influence on physical function. The deterioration of physical function by 0.48 points per day spent in the hospital is not unexpected. The inpatient setting itself and therapy-related

adverse events like nausea and myelosuppression, triggered by various anticancer drugs, affect the patients´ physical function during the hospital stay, especially if they appear closely after the treatment.

The study group could not be identified as a significant covariate on any of the endpoints examined. The variables “Study group B” and “Study group C” only show a negative trend. This could indicate that global HRQOL and physical function in the intervention group A of our study increased.

Compared to the current study, Zimmermann et al. detected age, performance status (ECOG), survival time, and treatment status as disease-related determinants of HRQOL in patients with cancer [110]. The variables “Relapse status” and “Duration of hospital stay”, related to the treatment status, were determinants of general HRQOL and/or physical function as well. Whether socio-demographic factors influence HRQOL in cancer patients is not clearly established, and no socio-demographic factor was detected within the analysis of this study [111-113].

3.4 Conclusions

This secondary analysis of the ImSEL-PRO trial describes underlying DRPs in a German cancer inpatient population. Data on DRPs in cancer inpatients are limited since most studies on pharmaceutical care are conducted on cancer outpatients. The patient population of the current trial showed a high proportion of patients with polymedication or even hyperpolymedication, indicating that these patients benefit from medication reviews. In general, the number of detected DRPs was large, but the number of iDRPs was comparable to the findings of other studies. In performing the medication reviews, PRO symptoms provided important additional information, and PRO-DRPs were classified in most cases as iPRO-DRPs. The use of different DDI databases with underlying specialist information from the US and Germany, showed the regional differences in detecting and evaluating DDIs. The description of the underlying problems can serve as basis for designing interdisciplinary and risk-adapted supportive care concepts for German cancer inpatients.

In the primary analysis of the HRQOL of the ImSEL-PRO trial patients, no significant difference between the three study groups could be found. The evaluation of the HRQOL without grouping of the patients indicates that a high proportion of patients could still have experienced patient-relevant changes in their HRQOL. The multiple linear regression models for the global HRQOL and the physical function of the EORTC QLQ-C30 questionnaire provide significant explanations for the changes in HRQOL of the study population. The study group was not identified as significant covariate.

The study population in the ImSEL-PRO trial consisted of cancer patients with many different types of cancer. What the patients had in common was that they were treated with cytotoxic chemotherapeutics for their oncological disease. Therefore, the PRO-CTCAE core item set for patients under chemotherapy, was suitable for detecting symptomatic toxicity. For different cancer types, treatment options differ significantly, leading to distinct toxicity patterns. To detect entity-specific symptoms more effectively, PRO-CTCAE item sets tailored to individual cancer types are needed.

4 Project II: Development of tumor disease-specific PRO-CTCAE item sets

4.1 Material and methods

4.1.1 Study design

This project was a multicentric patient survey with breast cancer, prostate cancer, and multiple myeloma patients. The aim was to develop tumor entity-specific PRO-CTCAE item sets based on the prevalence and importance of therapy-associated symptoms and their underlying tumor medication and disease-specific data. The survey was conducted at the Center for Integrated Oncology (CIO) of the University Hospital in Bonn, the Johanniter Hospital in Bonn, and the University Cancer Center of the University Hospital in Dresden.

Although a validated PRO-CTCAE core item set for patients under chemotherapy already exists [31], the treatment options differ a lot among tumor types. Therapies are not only based on chemotherapeutic agents anymore since new drugs with unique mechanisms of action entered the marked in the recent years.

Breast cancer is the most frequently diagnosed malign tumor entity in women. The five-year relative survival rate for all patients is very good with the available treatment options, with 88% [97]. For treatment, a broad spectrum of drugs is used for different stages of the disease, including chemotherapeutics (anthracyclines, bendamustine, capecitabine, cyclophosphamide, eribulin, everolimus, 5-fluorouracil, gemcitabine, platinum derivates, taxanes, vinorelbine), endocrine therapeutics (anastrozole, exemestane, fulvestrant, GnRH analogs, letrozole, tamoxifen), targeted therapeutics against HER2 (lapatinib, pertuzumab, trastuzumab, trastuzumab emtansine), antiangiogenetic therapy (bevacizumab) and the newly developed inhibitors of the cyclin-dependent kinases 4 and 6 (palbociclib and ribociclib) [114].

Prostate cancer is the most often occurring cancer type in men. With the available treatment options the five-year relative survival rate for all patients is very good at 89 % [97]. Drug therapy consists mainly of endocrine therapeutics for androgen deprivation (GnRH agonists and antagonists, flutamide, nilutamide, bicalutamide, and the newly developed antiandrogens

enzalutamide and abiraterone acetate) and chemotherapeutics (docetaxel and the newly developed cabazitaxel) depending on the stadium of the disease [115].

Multiple myeloma is one of the most frequently occurring hematological neoplasms. The prognosis is compared to breast and prostate cancer worse. The five-year relative survival rate for all patients is about 55% [97]. Curative treatment only succeeds in rare cases with autologous stem cell transplantation. But newly approved pharmaceuticals have improved the prognosis of patients throughout the last years [97]. The drug therapy consists of chemotherapeutics (bendamustine, cyclophosphamide, doxorubicin, and melphalan) and drug classes that are only used in multiple myeloma patients: proteasome inhibitors (bortezomib, carfilzomib, and ixazomib), immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide). The two monoclonal antibodies, elotuzumab and daratumumab, and the histone deacetylase inhibitor panobinostat complete the drug portfolio used for the different stages of the disease with or without autologous stem cell transplantation [116].

Due to the different drug classes used for treatment, patients of the above-mentioned three tumor entities should receive tailored PRO-CTCAE questionnaires to cover the relevant spectrum of symptomatic adverse events. Additionally, PRO-CTCAE item sets for patients under treatment with immune checkpoint inhibitors and patients with colorectal cancer were developed within two master theses accompanying this work [117, 118]. Immune checkpoint inhibitors are a new pillar of cancer therapy and are used in many tumor diseases. Therefore, the PRO-CTCAE item set was not developed entity but therapy specific. Colorectal cancer is a tumor entity of interest, because it is the second-frequent tumor disease in women and the third-frequent in men and associated with a high mortality [97].

4.1.2 Inclusion criteria and patient recruitment

Cancer patients with breast cancer, prostate cancer, and multiple myeloma of at least 18 years with active treatment of their disease were included in the study. They had to be linguistically, physically, and mentally capable of completing the patient questionnaire independently. Patients with insufficient knowledge of the German language were excluded from the study

because all relevant documents and information were in German. A prespecified sample of 100 patients for every tumor entity should be included consecutively in the study.

For recruitment, patients matching the inclusion criteria were identified by the treating physicians and the investigator or research associates at their regular appointments at the study centers and were invited to participate. Patients were informed orally and in writing about the nature, significance, and scope of the patient survey and signed a written informed consent. The patient information and formular for informed consent are shown in *Appendix II-A1 and II-A2*.

4.1.3 Data handling and protection

By law the study is classified as a non-interventional trial according to §4 of the German drug law (*German: Arzneimittelgesetz*) [57] because participating in the patient survey did not influence the medical treatment. The study was approved by the Ethics Committee of the Medical Faculty of the University of Bonn on January 10th 2018 (Lfd. Nr. 405/17) and by the relevant institutions of each participating center.

The collection, transfer, storage, and analysis of personal data within this trial were carried out in accordance with the applicable German and European legal provisions (*German: Datenschutz-Grundverordnung, DSGVO*) [58].

Data collection in this project was paper-based, using the patient questionnaires and documentation forms for treatment and medical information. The patient data were documented in pseudonymized form and were assigned a non-addressable code. The pseudonymized documents were separated from the informed consent forms and were transferred to the Department of Clinical Pharmacy of the University of Bonn for further storage and analysis. The key document linking the patients´ names and the pseudonyms remained in the study centers. It was destroyed after the end of the study for anonymization of the patient data. Only the investigator and the research associates, who were involved in the study centers of the project, had access to this document. The data analysis and further storage were conducted with the anonymized data. After the end of the trial, the anonymized data are stored for up to 10 years.

For further data processing, the anonymized data were transferred in a Microsoft® Access® 2019 (Microsoft Corporation, Redmond, USA) database and Microsoft® Excel® 2019 (Microsoft Corporation, Redmond, USA) sheets.

4.1.4 Data collection

Data assessed within this project were collected with the self-administered patient questionnaires and the documentation forms.

4.1.4.1 Patient questionnaire

The complete PRO-CTCAE question pool with 124 items for 78 symptoms is too extensive to be used in complete form for prevalence recording and relevance assessment of the individual symptoms in a patient survey. Therefore, the questionnaire described below was used in this project to minimize the time burden for patients.

The used patient questionnaire consisted of two parts. In the first part, patients were asked to answer whether the 78 symptoms had ever occurred during their tumor therapy and whether they thought that the symptoms should be asked in a questionnaire for patients suffering from their tumor disease. In this study, the symptoms “Nail ridging” and “Nail discoloration” were condensed to one item, resulting in 77 questions in the patient questionnaire. Two symptoms were only relevant for male patients, and five symptoms are only relevant for female patients. The questions about the occurrence of the symptoms could be answered with “Yes” or “No”. The questions about the importance of the symptoms could be answered with “Yes”, “No”, or “I don’t know”. This procedure was adapted from the Guidelines for Developing Questionnaire Modules of the EORTC Quality of Life Group [119]. The terms of the symptoms corresponded to those of the validated German PRO-CTCAE translation and were grouped according to indications that were understandable for the patient. An example of how the administered questionnaire looked like is given in *Figure 4-1*.

Symptome des Magen-Darm-Traktes	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Appetitmangel	Ja	Nein	Ja	Nein	Weiß nicht
2. Übelkeit	Ja	Nein	Ja	Nein	Weiß nicht
3. Erbrechen	Ja	Nein	Ja	Nein	Weiß nicht
4. Verstopfung (Obstipation)	Ja	Nein	Ja	Nein	Weiß nicht

Figure 4-1 Example questions from the patient questionnaire

The second part of the questionnaire contained 13 questions on sociodemographic data (age, gender, height, weight, relationship status, educational level, employment status), the characteristics of tumor disease (diagnosis, date of the first diagnosis), and tumor therapy (occurrence of severe AE, type of current treatment, current therapy situation), which were essential for the characterization of the study populations underlying the newly developed PRO-CTCAE item sets.

The investigator or research associates handed out the patient questionnaires at the study centers. To ensure a proper filling process, patients were taught orally and by a written introduction on the first side of the questionnaire how to answer the questionnaire correctly. The research associates could be contacted at any time if problems or questions occurred. To minimize the burden on the patients, the questionnaire was completed during the waiting time before the treatment or during the treatment, if the nature of the treatment permitted this.

The patient questionnaire is shown in *Appendix II-A3*.

4.1.4.2 Documentation form

The patient populations forming the basis for the newly developed entity-specific PRO-CTCAE item sets needed to be characterized in detail to describe for which disease stages and therapy regimens the PRO-CTCAE item sets are valid in content.

Therefore, additional information to the patient questionnaires was collected using documentation forms that health care professionals filled in at the study centers.

The following disease-specific characteristics were documented in general: diagnosis, the first date of diagnosis, and relapse status. For breast cancer and prostate cancer, the number and type of metastases, as well as the TNM classification, were noted [114-116]. Cancer-specific characteristics were documented as follows:

- breast cancer: staging (according to AJCC), hormone receptor status for estrogen receptor (ER) and progesterone receptor (PR), HER2 receptor status [114]
- prostate cancer: last PSA value (ng/ml), Gleason scores and Gleason grade group, prognostic group (according to AJCC) [115]
- Multiple myeloma: staging (according to ISS) [116]

The current and previous tumor therapy was documented with the following specifications: therapy intention (curative or palliative; adjuvant or neoadjuvant), simultaneous radiation, simultaneous surgery, or other kinds of treatment such as stem cell transplantation. The administered anticancer drugs were documented by active ingredient or trade name, strength, route of administration, and dosage. The same drug was documented multiple times if it was administered during several past and present therapy lines. The current administration of supportive drugs for the following indications was reported: anemia, neutropenia, nausea and emesis, constipation, diarrhea, mucositis, skin toxicity, peripheral neuropathy, bone complications, pain, gastric ulcer prophylaxis, psychological problems, anticoagulation and other indications by a free text field.

The documentation forms were completed by health care professionals in the study centers. At the Center for Integrated Oncology (CIO) of the University Hospital in Bonn and the Johanniter Hospital in Bonn, the documentation was done by the investigator as a trained clinical pharmacist. The documentation at the University Cancer Center of the University Hospital in Dresden was performed by an oncologist. In the run-up to data collection, the procedure for filling in the documentation forms was discussed to ensure a consistent practice.

The documentation forms are shown in *Appendix II-A4*.

4.1.5 Item selection

To build the entity-specific PRO-CTCAE item sets, the most prevalent and most relevant symptoms of the patient questionnaire needed to be identified. An approach based on the clinical impact method (CIM) was used for the item selection. The CIM focuses on the severity and relevance of items rated by the patients and is applicable for small sample sizes, as a prespecified number of 100 patients per tumor entity should be included in the study [120]. Annette Rudolph implemented the used method in her master thesis [117]. The approach is described in the following sections.

4.1.5.1 Scoring and symptom ranking

To create the clinical impact in the CIM, patients rate the severity and the importance of the questionnaire items. The ratings are combined by adding the mean importance rating per item and the mean severity rating per item using *Equation 4-1* [120].

$$CI = I + S \qquad \textit{Equation 4-1}$$

I: Symptom importance
S: Symptom severity

In this study, the CIM was modified. Instead of the symptom severity, the symptom prevalence was used. The scales were scored with “Yes” = 1 and “No” = 0 for the symptom prevalence and with “Yes” = 1, “No” = 0, and “I don’t know” = 0.5 for the symptom importance. In the first step, two separate scores for the symptom prevalence and the symptom importance were calculated. The values for every symptom were added and divided by the number of completed questionnaires to avoid distortions due to missing values. By doing so, the values of the scores displayed values between 0 and 1. The values were ranked from 1 (highest score) to 77 (lowest score). In the second step, the rankings for the symptom prevalence (1 to 77) and the symptom importance (1 to 77) were summed to the combined prevalence-importance score. According to their combined score, the symptoms were then ranked from lowest to

highest. Symptoms with a lower combined score exhibited a higher prevalence and importance.

For the item selection, the symptoms with the lowest combined scores were translated into PRO-CTCAE items until a maximum of 40 PRO-CTCAE items was reached. For every PRO-CTCAE symptom, up to three items are available. The items of one symptom were not split in the selection process. The cut-off value of 40 items for the PRO-CTCAE item sets was chosen because it is considered as a not too burdensome number of questions for patients that can be asked every seven days [28].

4.1.5.2 Item redundancy analysis

The symptoms for the maximum of 40 PRO-CTCAE items were investigated for inter-item correlations to investigate redundancies among the selected symptoms and further shorten the questionnaires.

To investigate the association between the symptom items, the φ coefficient by Karl Pearson was used. It measures the correlation between two binary variables. Based on a 2x2 contingency table, it compares equal answers of two variables with all possible solutions (*Equation 4-2*).

$$\varphi = \frac{\mathbf{n}_{\mathbf{yes-yes}} \cdot \mathbf{n}_{\mathbf{no-no}} - \mathbf{n}_{\mathbf{yes-no}} \cdot \mathbf{n}_{\mathbf{no-yes}}}{\sqrt{\mathbf{n}_{\mathbf{yes-any\ answer}} \cdot \mathbf{n}_{\mathbf{no-any\ answer}} \cdot \mathbf{n}_{\mathbf{any\ answer-no}} \cdot \mathbf{n}_{\mathbf{any\ answer-yes}}}} \qquad \textit{Equation 4-2}$$

The φ coefficient can take values between -1 and +1. Values around 0 indicate a weak correlation. Values of ±1 indicate a perfect positive or negative correlation. Values of ±0.8 or higher indicate a strong correlation between the two variables [121].

The response options for the questions on symptom prevalence (“Yes” and “No”) are dichotomous. The response scale for the questions on symptom importance (“Yes”, “No”, and “I don’t know”) was translated to the dichotomous answers “Yes” and “not Yes” (including “No” and “I don’t know”) in the course of the item-redundancy analysis.

Pairs of symptom items with a φ value of ≥ ±0.8 indicated possible redundancies. To analyze the significance of these correlations and to uncover random correlations, Fisher´s exact test was conducted. Fisher´s exact test is a non-parametric test of independence based on a 2xn contingency table. Fisher´s exact test is more robust in small sample sizes than the χ^2 test and can be used if the conditions for the χ^2 test are not fulfilled [122, 123]. Symptom pairs with statistically significant high φ values were discussed in a focus group for exclusion from the new PRO-CTCAE item sets.

4.1.6 Statistical analysis

Descriptive statistics were performed for patient characteristics and medication data. As applicable, mean values with standard deviations (SD) or the median with interquartile range (IQR) were calculated. Frequencies were described as absolute numbers and percentages.

For inductive statistics in the item-redundancy analysis, a p-value of < 0.05 was considered statistically significant. Confidence intervals (CI) of 95% were calculated.

Statistical analysis was conducted using Microsoft® Excel® 2019 (Microsoft Corporation, Redmond, USA) and IBM® SPSS® Statistics Version 27.0 for Windows (IBM Corporation, Armonk, USA).

4.2 Results

4.2.1 Patient recruitment

Patients were recruited between February and December 2018 at the Center for Integrated Oncology (CIO) of the University Hospital in Bonn and the Johanniter Hospital Bonn. Patient recruitment at the University Cancer Center of the University Hospital in Dresden took place between January and April 2019. In total, 274 patients were recruited, of these 101 patients with breast cancer, 107 with multiple myeloma, and 66 with prostate cancer.

4.2.2 Patient characteristics

4.2.2.1 Sociodemographic characteristics

The sociodemographic patient characteristics of the populations for the three tumor entities breast cancer (BC), multiple myeloma (MM), and prostate cancer (PC) that were asked within the patient questionnaire are shown in *Table 4-1*. In general, most patients were recruited at the CIO Bonn (n = 121, 44.2%) and the University Hospital Dresden (n = 120, 43.8%), whereas only a small number of patients was recruited at the Johanniter Hospital Bonn (n = 33, 12.0%). Breast cancer patients were mostly recruited at the CIO Bonn (n = 80, 79.2%). Multiple myeloma and prostate cancer patients were mostly recruited at the University Hospital Dresden (MM: n = 60, 56.1%; PC: n = 60, 90.9%).

Table 4-1 Sociodemographic characteristics of the study populations [n (%)]

	BC	MM	PC
Number of patients	**101**	**107**	**66**
Study center			
CIO Bonn	80 (79.2)	35 (32.7)	6 (9.1)
Johanniter Hospital Bonn	21 (20.8)	12 (11.2)	0 (0)
University Hospital Dresden	0 (0)	60 (56.1)	60 (90.9)
Gender			
Male	0 (0)	67 (62.6)	66 (100)
Female	101 (100)	40 (37.4)	0 (0)
Age			
Median [years]	58 (IQR: 16, range: 28 – 84, mean 58.0, SD 11.4)	62 (IQR: 13, range: 33 – 83, mean: 62.0, SD: 9.1)	76 (IQR: 8, range: 59 – 94, mean: 74.5, SD: 6.9)
Educational level			
Elementary school certificate	4 (4.0)	4 (3.7)	0 (0)
Secondary school certificate	4 (4.0)	7 (6.5)	0 (0)
Middle school certificate	31 (30.7)	11 (10.3)	0 (0)
Journeyman exam	9 (8.9)	28 (26.2)	17 (25.8)
High school diploma	11 (10.9)	7 (6.5)	1 (1.5)
Master craftsman exam	1 (1.0)	11 (10.3)	15 (22.7)
University of applied sciences degree	12 (11.9)	13 (12.1)	11 (16.7)
University degree	20 (19.8)	23 (21.5)	17 (25.8)
Higher university degree (e.g., Ph.D.)	4 (4.0)	3 (2.8)	5 (7.6)
Missing/not applicable	5 (5.0)	0 (0)	0 (0)

Table 4-1 continued

	BC	MM	PC
Employment status			
Housewife/ houseman	19 (18.8)	4 (3.7)	0 (0)
Student	1 (1.0)	0 (0)	0 (0)
Civil servant	4 (4.0)	4 (3.7)	2 (3.0)
Retired	39 (38.6)	68 (63.6)	58 (87.9)
Employee	33 (32.7)	19 (17.8)	3 (4.5)
Self-employed	2 (2.0)	8 (7.5)	2 (3.0)
Laborer	0 (0)	4 (3.7)	0 (0)
Craftsman	0 (0)	0 (0)	1 (1.5)
Missing/not applicable	3 (3.0)	0 (0)	0 (0)
Relationship status			
single	9 (8.9)	12 (11.2)	0 (0)
Married/registered life partnership	68 (67.3)	84 (78.5)	57 (86.4)
Divorced	12 (11.9)	6 (5.6)	2 (3.0)
Widowed	11 (10.9)	5 (4.7)	7 (10.6)
Missing/not applicable	1 (1.0)	0 (0)	0 (0)

BC = breast cancer, MM = multiple Myeloma, PC = prostate cancer, IQR = interquartile range, SD = standard deviation

4.2.2.2 Oncological diseases

General patient characteristics about the oncological diseases asked within the patient questionnaire are shown in *Table 4-2*.

Table 4-2 General characteristics of oncological diseases of the study populations [n (%)]

	BC	**MM**	**PC**
Number of patients	**101**	**107**	**66**
Time since the first diagnosis of cancer			
Median [months]	14 (IQR: 67, range: 1 – 506, mean: 59, SD: 86.9)	59 (IQR: 69, range: 2 – 255, mean: 63.7, SD: 52.8)	27 (IQR: 60, range: 1 – 190, mean: 41.7, SD: 43.3)
Current therapy situation			
Outpatient therapy	101 (100)	87 (81.3)	56 (84.9)
Inpatient therapy	0 (0)	20 (18.7)	10 (15.1)
Discontinuation of therapy due to ADR			
Yes	14 (13.9)	17 (15.9)	8 (12.1)
No	87 (86.1)	90 (84.1)	58 (87.9)
Type of current tumor therapy [number of patients]			
Oral medication	34 (33.7)	73 (68.2)	35 (53.0)
Intravenous medication	93 (92.1)	71 (66.4)	44 (66.7)
Radiation	18 (17.8)	7 (6.5)	32 (48.5)
Surgery	23 (22.8)	4 (3.7)	5 (7.6)
Active surveillance	1 (1.0)	16 (15.0)	4 (6.1)

BC = breast cancer, MM = multiple Myeloma, PC = prostate cancer, IQR = interquartile range, SD = standard deviation, ADR = Adverse drug reaction

Tumor disease-specific characteristics for breast cancer, multiple myeloma, and prostate cancer documented in the documentation forms are shown in *Table 4-3* to *Table 4-5.*

Table 4-3 Tumor disease-specific characteristics for breast cancer (n = 101)

Breast Cancer	**Number**	**Percentage**
Metastases		
Patients with metastases	54	53.5
Type of metastases [number of patients]		
Liver		
Bone	20	19.8
Lung	34	33.7
Ovary	15	14.9
Peritoneum	4	4.0
Brain	3	3.0
Pleura	3	3.0
Other	7	6.9
	6	5.9
Metastases per patient		
Mean	0.9 (SD: 0.9, median: 1, IQR: 1, range: 0 – 4)	
Relapse		
Patients with relapse	22	21.8
Number of relapses		
1 Relapse	15	14.9
2 Relapses	4	4.0
3 Relapses	1	1.0
Missing/not applicable	2	2.0

Table 4-3 continued

Breast Cancer	**Number**	**Percentage**
Tumor characteristics		
Estrogen receptor positive	65	64.4
Progesterone receptor-positive	46	45.6
HER2 positive	44	43.6
Therapy situation	**Current, [n (%)]**	**Former, [n (%)]**
Curative	32 (31.7)	14 (13.7)
Palliative	53 (52.5)	20 (19.8)
Missing/ not applicable	16 (15.8)	67 (66.3)
Adjuvant	52 (51.5)	28 (27.7)
Neoadjuvant	23 (22.8)	18 (17.8)
Missing/ not applicable	25 (24.8)	55 (54.5)
Radiation additional	21 (20.8)	43 (42.6)
Surgery additional	20 (19.8)	51 (50.5)
Other therapies additional	0 (0)	0 (0)

IQR = interquartile range, SD = standard deviation, HER2 = human epidermal receptor 2

Table 4-4 Tumor disease-specific characteristics for multiple myeloma (n = 107)

Multiple myeloma	**Number**	**Percentage**
Relapse		
Patients with relapse	27	25.2
Number of relapses		
1 Relapse	22	20.6
2 Relapses	1	0.9
3 Relapses	2	1.9
Missing/not applicable	2	1.9
Therapy situation	**Current, [n (%)]**	**Former, [n (%)]**
Curative	35 (32.7)	48 (44.9)
Palliative	68 (63.6)	51 (47.7)
Missing/not applicable	4 (3.7)	8 (7.5)
Radiation	3 (2.8)	39 (36.4)
Surgery	0 (0)	14 (13.1)
Autologous SCT	14 (13.1)	≥ 1x 77 (72.0)
		2x 12 (11.2)
		3x 3 (2.8)
Allogenic SCT	0 (0)	4 (3.7)

SCT = stem cell transplantation

Table 4-5 Tumor disease-specific characteristics for prostate cancer (n = 66)

Prostate cancer	**Number**	**Percentage**
Metastases		
Patients with metastases	20	30.3
Type of metastases [number of patients]		
Bone	20	30.3
Peritoneum	1	1.5
Metastases per patient Mean	0.3 (SD: 0.5, median: 0, IQR: 1, range: 0 – 2)	
Relapse		
Patients with relapse	18	27.3
Number of relapses		
1 Relapse	6	9.1
2 Relapses	8	12.1
3 Relapses	1	1.5
Missing/not applicable	3	4.5
Tumor characteristics		
Gleason grade group		
Group 1 (lowest risk)	2	3.0
Group 2	7	10.6
Group 3	13	19.7
Group 4	10	15.2
Group 5 (highest risk)	26	39.4
Missing/not applicable	8	12.1

Table 4-5 continued

Prostate cancer	**Number**	**Percentage**
Therapy situation	Current, [n (%)]	Former, [n (%)]
Curative	24 (36.4)	31 (47.0)
Palliative	30 (45.5)	10 (15.2)
Missing/ not applicable	12 (18.2)	25 (37.9)
Adjuvant	3 (4.5)	1 (1.5)
Neoadjuvant	0 (0)	2 (3.0)
Missing/not applicable	63 (95.5)	63 (95.5)
Radiation	29 (43.9)	28 (42.4)
Surgery	1 (1.5)	28 (42.4)
Other therapies	9 (13.6)	2 (3.0)

IQR = interquartile range, SD = standard deviation

4.2.2.3 Drug therapy

Tumor therapy-specific characteristics for breast cancer, multiple myeloma, and prostate cancer patients, as documented in the documentation forms, are described in the following.

Overall, the highest number of active ingredients used per patient was a mean of 7.7 (SD: 4.1, median: 7, IQR: 5, range 0 – 24) in the multiple myeloma patients, followed by the breast cancer patients with a mean of 5.8 (SD: 3.4, median: 5, IQR: 4, range: 0 – 17). The prostate cancer patients received only a mean of 1.9 (SD: 1.6, median: 2, IQR: 1, range 0 – 7) active ingredients per patient. Medication data was missing for four multiple myeloma patients, one breast cancer patient, and 11 prostate cancer patients. The used drug classes for the three tumor entities are shown in *Figure 4-2*.

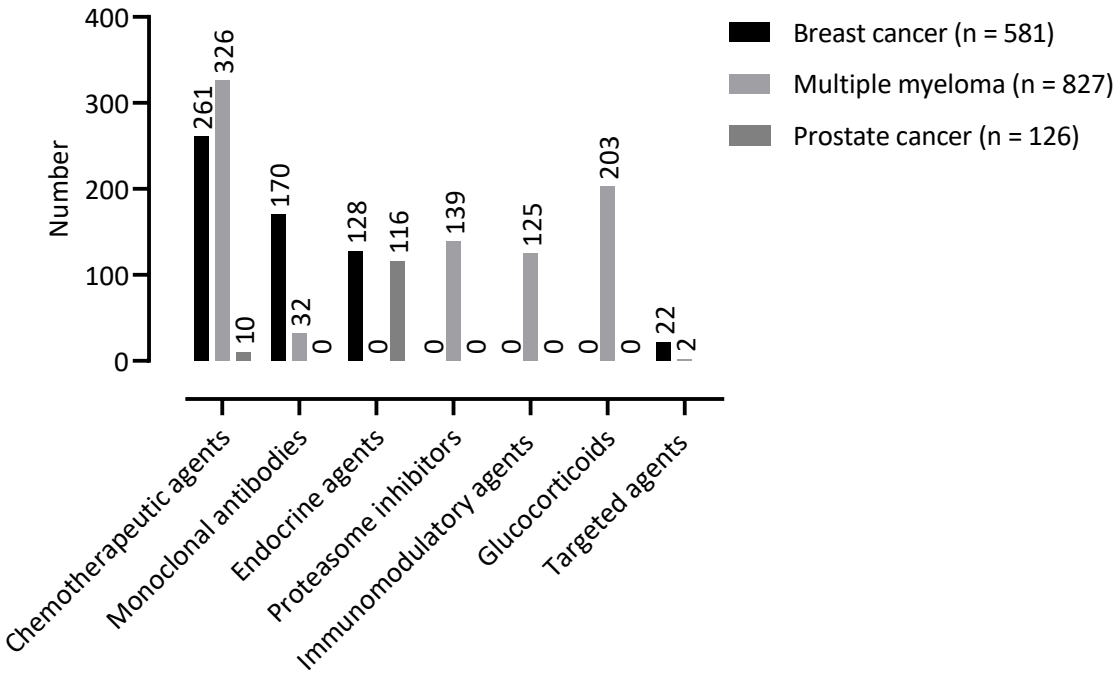

Figure 4-2 Drug classes used in the therapy of the participating breast cancer (n = 101), multiple myeloma (n = 107) and prostate cancer (n = 66) patients

The used active ingredients for the different drug classes in the three tumor entities are shown in *Table 4-6* to *Table 4-8*.

Of the 581 administered drugs of the breast cancer patients, 41.5% (n = 241) were administered during the current therapy. The most used active ingredients in total were trastuzumab (n = 91, 15.7%), cyclophosphamide (n = 69, 11.9%), epirubicin (n = 68, 11.7%), pertuzumab (n = 55, 9.5%), and docetaxel (n = 44, 7.6%). The distribution of the active ingredients to the current and former therapy of the patients is displayed in *Table 4-6*.

Table 4-6 Active ingredients used in the 101 breast cancer patients in the current and former drug therapy [n (%)]

Active ingredients	Total	Current therapy	Former Therapy
Targeted agents			
Everolimus	4 (0.7)	1 (0.4)	3 (0.9)
Lapatinib	4 (0.7)	1 (0.4)	3 (0.9)
Palbociclib	14 (2.4)	10 (4.1)	4 (1.2)
Total	*22 (3.8)*	*12 (5.0)*	*10 (2.9)*
Endocrine agents			
Anastrozole	5 (0.9)	1 (0.4)	4 (1.2)
Choriogonadotropin alfa	1 (0.2)	0 (0)	1 (0.3)
Exemestane	12 (2.1)	1 (0.4)	11 (3.2)
Follitropin alfa	1 (0.2)	1 (0.4)	0 (0)
Fulvestrant	24 (4.1)	15 (6.2)	9 (2.7)
Ganirelix	1 (0.2)	1 (0.4)	0 (0)
Goserelin	1 (0.2)	1 (0.4)	0 (0)
Letrozole	38 (6.5)	15 (6.2)	23 (6.8)
Leuprorelin	1 (0.2)	1 (0.4)	0 (0)
Menotropin	1 (0.2)	1 (0.4)	0 (0)
Tamoxifen	43 (7.4)	17 (7.1)	26 (7.7)
Total	*128 (22.0)*	*54 (22.4)*	*74 (21.8)*
Monoclonal antibodies			
Bevacizumab	18 (3.1)	9 (3.7)	9 (2.7)
Pertuzumab	55 (9.5)	26 (10.8)	29 (8.5)
Trastuzumab	91 (15.7)	44 (18.3)	47 (13.8)
Trastuzumab emtansine	6 (1.0)	2 (0.8)	4 (1.2)
Total	*170 (29.3)*	*81 (33.6)*	*89 (26.2)*

Table 4-6 continued

Active ingredients	Total	Current therapy	Former Therapy
Chemotherapeutics			
Capecitabine	12 (2.1)	1 (0.4)	11 (3.2)
Carboplatin	3 (0.5)	2 (0.8)	1 (0.3)
Cyclophosphamide	69 (11.9)	29 (12.0)	40 (11.8)
Docetaxel	44 (7.6)	9 (3.7)	35 (10.3)
Doxorubicin	2 (0.3)	0 (0)	2 (0.6)
Epirubicin	68 (11.7)	29 (12.0)	39 (11.5)
Eribulin	2 (0.3)	2 (0.8)	0 (0)
Fluorouracil	13 (2.2)	0 (0)	13 (3.8)
Methotrexate	4 (0.7)	0 (0)	4 (1.2)
Paclitaxel	41 (7.1)	21 (8.7)	20 (5.9)
TACE	1 (0.2)	0 (0)	1 (0.3)
Vinorelbine	2 (0.3)	1 (0.4)	1 (0.3)
Total	*261 (44.9)*	*94 (39.0)*	*167 (49.1)*
Overall total	**581 (100)**	**241 (100)**	**340 (58.5)**

Of the 827 administered drugs of the multiple myeloma patients, only 15.6% (n = 129) were adminisered during the current therapy. The most used active ingredients in total were dexamethasone (n = 199, 24.1%), bortezomib (n = 124, 15.0%), cyclophosphamide (n = 113, 13.7%), melphalan (n = 111, 13.4%), and lenalidomide (n = 110, 13.3%). The distribution of the active ingredients to the current and former therapy of the patients is displayed in *Table 4-7*.

Table 4-7 Active ingredients used in the 107 multiple myeloma patients in the current and former drug therapy [n (%)]

Active ingredients	Total	Current therapy	Former therapy
Targeted agents			
Panobinostat	1 (0.1)	0 (0)	1 (0.1)
Venetocalx	1 (0.1)	0 (0)	1 (0.1)
Total	*2 (0.2)*	*0 (0)*	*2 (0.3)*
Monoclonal antibodies			
Daratumumab	21 (2.5)	9 (7.0)	12 (1.7)
Elotuzumab	7 (0.8)	4 (3.1)	3 (0.4)
Rituximab	1 (0.1)	0 (0)	1 (0.1)
Study Anti CD38 AB	3 (0.4)	1 (0.8)	2 (0.3)
Total	*32 (3.9)*	*14 (10.9)*	*18 (2.6)*
Chemotherapeutics			
Bendamustine	5 (0.6)	1 (0.8)	4 (0.6)
Cyclophosphamide	113 (13.7)	6 (4.7)	107 (15.3)
Cytarabine	1 (0.1)	0 (0)	1 (0.1)
Doxorubicin	78 (9.4)	0 (0)	78 (11.2)
Etoposide	8 (1.0)	0 (0)	8 (1.2)
Fludarabine	3 (0.4)	1 (0.8)	2 (0.3)
Idarubicin	2 (0.2)	0 (0)	2 (0.3)
Melphalan	111 (13.4)	14 (10.9)	97 (13.9)
Treosulfan	3 (0.4)	1 (0.8)	2 (0.3)
Vincristine	2 (0.2)	0 (0)	2 (0.3)
Total	*326 (39.4)*	*23 (17.8)*	*303 (43.4)*
Proteasome inhibitors			
Bortezomib	124 (15.0)	16 (12.4)	108 (15.5)
Carfilzomib	14 (1.7)	7 (5.4)	7 (1.0)
Ixazomib	1 (0.1)	1 (0.8)	0 (0)
Total	*139 (16.8)*	*24 (18.6)*	*115 (16.5)*

Table 4-7 continued

Active ingredients	Total	Current therapy	Former therapy
Immunomodulatory agents			
Lenalidomide	110 (13.3)	32 (24.8)	78 (11.2)
Pomalidomide	7 (0.8)	3 (2.3)	4 (0.6)
Thalidomide	8 (1.0)	0 (0)	8 (1.2)
Total	*125 (15.1)*	*35 (27.1)*	*90 (12.9)*
Glucocorticoids			
Dexamethasone	199 (24.1)	32 (24.8)	167 (23.9)
Prednisolone	2 (0.2)	0 (0)	2 (0.3)
Prednisone	2 (0.2)	1 (0.8)	1 (0.1)
Total	*203 (24.6)*	*33 (25.6)*	*170 (24.4)*
Overall total	**827 (100)**	**129 (100)**	**698 (100)**

Of the 126 administered drugs of the prostate cancer patients, 42.9% (n = 54) were administered during the current therapy. The most used active ingredients in total were not further specified LH-RH analogs (n = 32, 25.4%), bicalutamide (n = 24, 19.1%), leuprorelin (n = 23, 18.3%), degarelix (n = 12, 9.5%) and abiraterone acetate (n = 10, 7.9%). The distribution of the active ingredients to the current and former therapy of the patients is displayed in *Table 4-8*.

Table 4-8 Active ingredients used in the 66 prostate cancer patients in the current and former drug therapy [n (%)]

Active ingredients	Total	Current therapy	Former therapy
Chemotherapeutics			
Cabazitaxel	4 (3.2)	2 (3.7)	2 (2.8)
Docetaxel	6 (4.8)	1 (1.9)	5 (6.9)
Total	*10 (7.9)*	*3 (5.6)*	*7 (9.7)*
Endocrine agents			
Abiraterone acetate	10 (7.9)	6 (11.1)	4 (5.6)
Bicalutamide	24 (19.1)	7 (13.0)	17 (23.6)
Buserelin	2 (1.6)	1 (1.9)	1 (1.4)
Degarelix	12 (9.5)	5 (9.3)	7 (9.7)
Enzalutamide	6 (4.8)	3 (5.6)	3 (4.2)
Finasteride	2 (1.6)	1 (1.9)	1 (1.4)
Flutamide	1 (0.8)	0 (0)	1 (1.4)
GnRH antagonist	2 (1.6)	1 (1.9)	1 (1.4)
Goserelin	1 (0.8)	0 (0)	1 (1.4)
Leuprorelin	23 (18.3)	11 (20.4)	12 (16.7)
LH-RH analog	32 (25.4)	15 (27.8)	17 (23.6)
Triptorelin	1 (0.8)	1 (1.9)	0 (0)
Total	*116 (92.1)*	*51 (94.4)*	*65 (90.3)*
Overall total	**126 (100)**	**54 (100)**	**72 (57.1)**

The indications for which the patients received supportive drug therapy during their current therapy cycle are displayed in *Table 4-9*.

Breast cancer patients were treated for a mean of 1.7 indications for supportive care (SD: 1.7, median: 1, IQR: 1, range: 0 – 6). They received most frequently care for nausea and emesis (n = 41, 24.3%), bone complications (n = 40, 23.7%), and gastric ulcer prophylaxis (n = 18, 10.7%). Multiple myeloma patients were treated also for a mean of 1.7 supportive care indications (SD: 1.5, median: 1, IQR: 2, range: 0 – 6), most frequently for bone complications (n = 48, 26.5%), gastric ulcer prophylaxis (n = 43, 23.8%) and pain (n = 34, 18.8%). Prostate cancer

patients were only treated for a mean of 0.4 supportive care indications (SD: 0.9, median: 0, IQR: 0, range: 0 – 4), the most frequently for bone complications (n = 7, 25.9%), gastric ulcer prophylaxis (n = 6, 22.2%) and pain (n = 5, 18.5%).

Table 4-9 Current supportive care by indication for breast cancer (n = 101), multiple myeloma (n = 107) and prostate cancer patients (n = 66) [n (%)]

Indication	BC	MM	PC
Anemia	0 (0)	1 (0.6)	0 (0)
Neutropenia	12 (7.1)	11 (6.1)	0 (0)
Nausea und emesis	41 (24.3)	10 (5.5)	1 (3.7)
Diarrhea	4 (2.4)	2 (1.1)	0 (0)
Constipation	7 (4.1)	13 (7.2)	4 (14.8)
Mucositis	11 (6.5)	0 (0)	0 (0)
Skin toxicity	5 (3.0)	0 (0)	0 (0)
Peripheral neuropathy	0 (0)	3 (1.7)	0 (0)
Bone complications	40 (23.7)	48 (26.5)	7 (25.9)
Pain	17 (10.1)	34 (18.8)	5 (18.5)
Gastric ulcer prophylaxis	18 (10.7)	43 (23.8)	6 (22.2)
Psychological problems	2 (1.2)	8 (4.4)	1 (3.7)
Anticoagulation	12 (7.1)	7 (3.9)	3 (11.1)
Total	**169 (100)**	**181 (100)**	**27 (100)**

BC = breast cancer, MM = multiple Myeloma, PC = prostate cancer

4.2.3 Completion of questionnaires

In total, 101 patient questionnaires were completed by patients with breast cancer, 107 by patients with multiple myeloma and 66 by patients with prostate cancer at the three different study centers.

Missing values occurred if patients did not answer a question at all or not clear enough by marking an answer on the paper-based questionnaires.

Within the 101 questionnaires filled in by the breast cancer patients, the questions regarding the prevalence of the symptoms were not answered in 2.2% of cases (mean number of cases 2.2, SD 3.17, range 0 – 16). The questions about the importance of the symptoms were not answered in 4.2% of cases (mean number of cases 4.2, SD 1.52, range 1 – 10).

For the 107 questionnaires of the multiple myeloma patients, the missing values amount to 0.8% of cases (mean number of cases 0.9, SD 1.38, range 0 – 6) for the prevalence questions and 1.6% of cases (mean number of cases 1.7, SD 1.29, range 0 – 6) for the importance questions.

For the 66 questionnaires of the prostate cancer patients, the missing values amount to 0.2% of cases (mean number of cases 0.1, SD 0.31, range 0 – 1) for the prevalence questions and 5.6% of cases (mean number of cases 3.7, SD 1.77, range 1 – 7) for the importance questions.

4.2.4 Scoring and symptom ranking

For data analysis, the PRO-CTCAE symptoms of the patient questionnaire were numbered from 1 to 77, as listed in the patient questionnaire. The PRO-CTCAE library and symptom numbers can be found in *Appendix II-B1 and II-B2*.

4.2.4.1 Breast cancer

Prevalence of symptoms

A median of 27 symptoms per patient (IRQ 31, range 4 – 53) occurred in the sample of 101 breast cancer patients. The symptom that appeared most often was “Hair loss” (Number 24) in 86 patients.

Figure 4-3 gives an overview of the prevalence scores displaying the relative frequency of the symptom prevalence. Higher scores indicate higher frequency. All prevalence score values are shown in *Appendix II-B3*.

The female breast cancer patients did not answer the symptoms number 64 and 65 concerning only male patients.

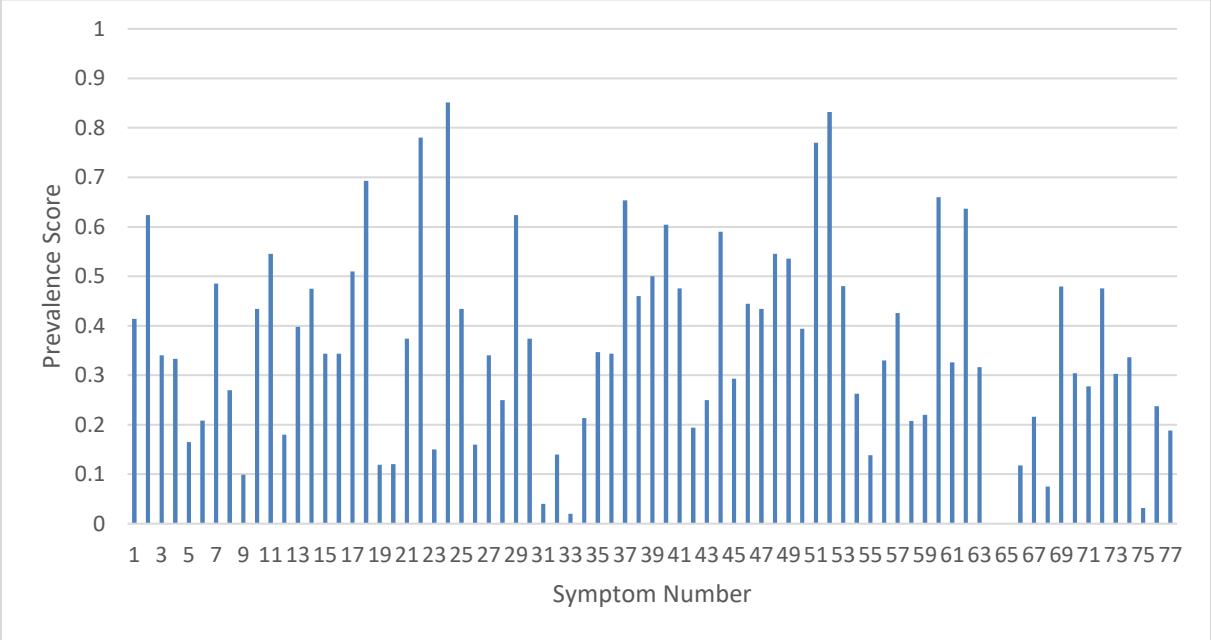

Figure 4-3 Symptom prevalence scores of the breast cancer patients (n = 101)

Importance of symptoms

A median of 46 symptoms per patient (IQR 36, range 0 – 75) was considered important in the sample of 101 breast cancer patients.

Figure 4-4 gives an overview of the importance scores displaying the relative importance of the symptoms. Higher scores indicate higher importance. All importance score values are shown in *Appendix II-B4*.

The female breast cancer patients did not answer the symptoms number 64 and 65 concerning only male patients.

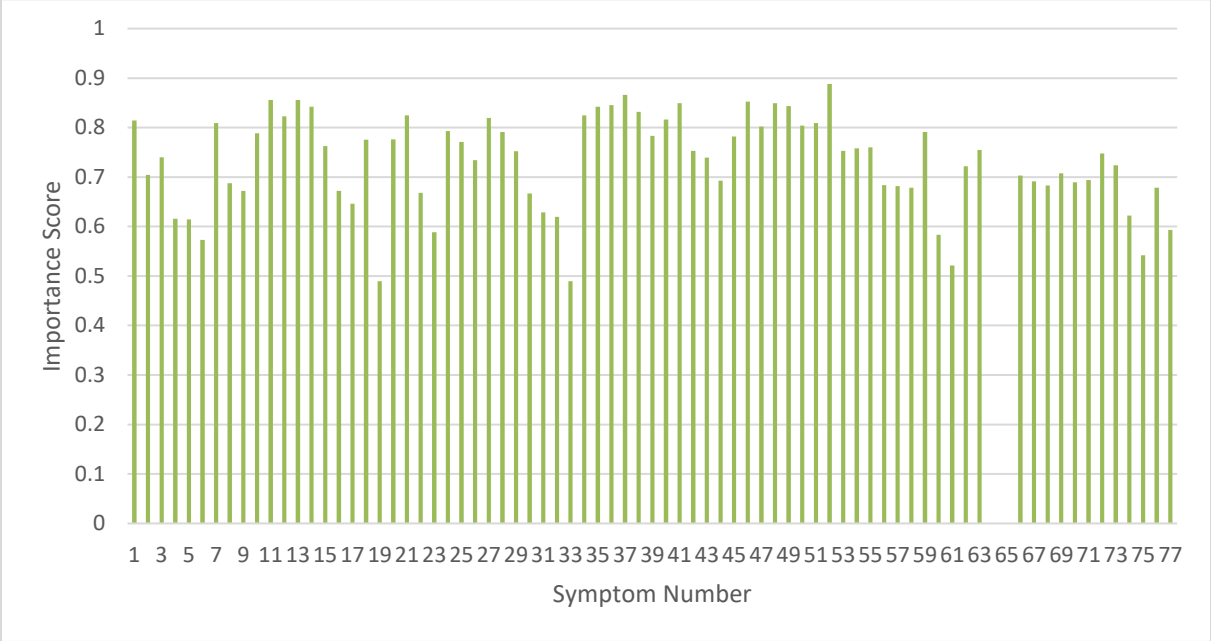

Figure 4-4 Symptom importance scores of the breast cancer patients (n = 101)

Combined prevalence-importance scores

Figure 4-5 gives an overview of the combined prevalence-importance scores displaying the relative clinical impact of the symptoms. Lower scores indicate higher clinical impact. All combined prevalence-importance score values are shown in *Appendix II-B5*.

The female breast cancer patients did not answer the symptoms number 64 and 65 concerning only male patients.

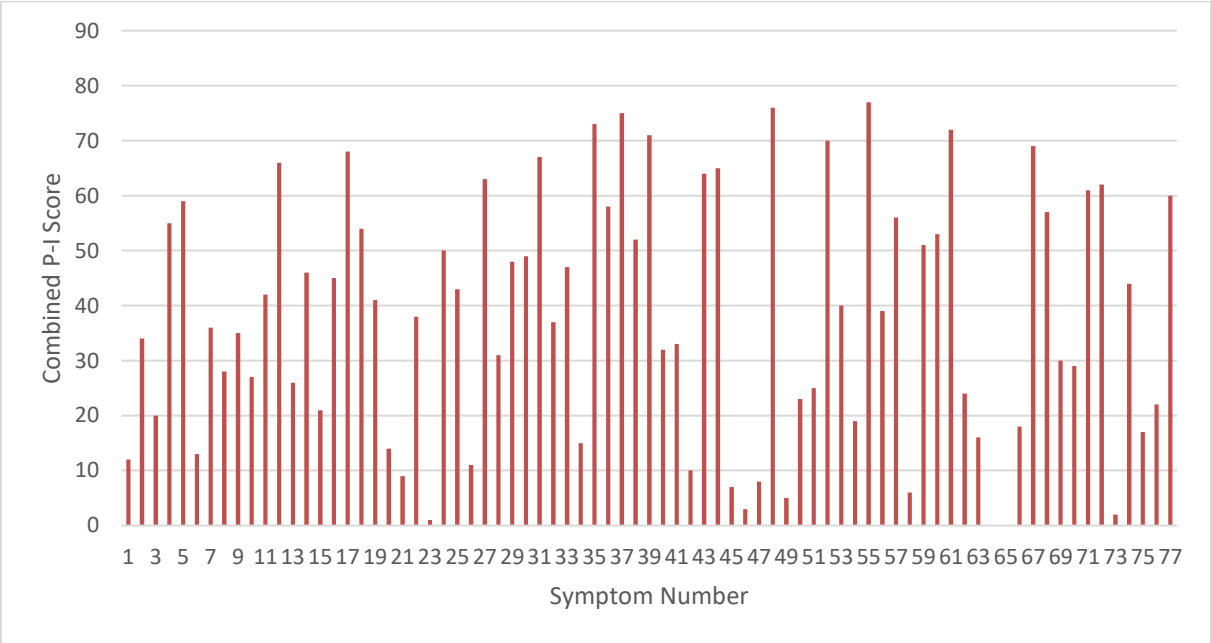

Figure 4-5 Combined prevalence-importance scores of the breast cancer patients (n = 101)

Based on the combined prevalence-importance scores, 21 symptoms were translated into 39 PRO-CTCAE items to build the PRO-CTCAE breast cancer item set. *Table 4-10* shows the selected items for the PRO-CTCAE breast cancer item set ranked by their combined score.

Table 4-10 PRO-CTCAE breast cancer item set including 39 items for 21 symptoms

PRO-CTCAE term	Symptom Number	Combined score	Attributes
Fatigue	52	3	S, I
Numbness and tingling	37	9	S, I
Nausea	11	16	F, S
Muscle pain	48	19	F, S, I
Insomnia	51	23	S, I
Hair loss	24	24	P
Joint pain	49	24	F, S, I
Blurred vision	41	27	S, I
Concentration	40	28	S, I
General pain	46	30	F, S, I
Diarrhea	14	33	F
Constipation	13	34	S
Taste changes	18	35	S
Dizziness	38	36	S, I
Shortness of breath	7	37	S, I
Heart palpitations	36	44	F, S
Memory	39	44	S, I
Swelling	35	45	F, S, I
Rash	21	46	P
Nail ridging*	29	47	P
Nail discoloration*	29	47	P

** Symptoms were combined in the patient questionnaire*

F: frequency; S: severity; I: interference; P: presence/absence/amount

4.2.4.2 Multiple myeloma

Prevalence of symptoms

A median of 28 symptoms per patient (IRQ 14, range 7 – 61) occurred in the sample of 107 multiple myeloma patients. The symptom that appeared most often was “Fatigue” (Number 52) in 92 patients.

Figure 4-6 gives an overview of the prevalence scores displaying the relative frequency of the symptom prevalence. Higher scores indicate higher frequency. All prevalence score values are shown in *Appendix II-B6*.

Male patients only answered the symptoms number 64 and 65. The symptoms 66 to 70 were only answered by female patients.

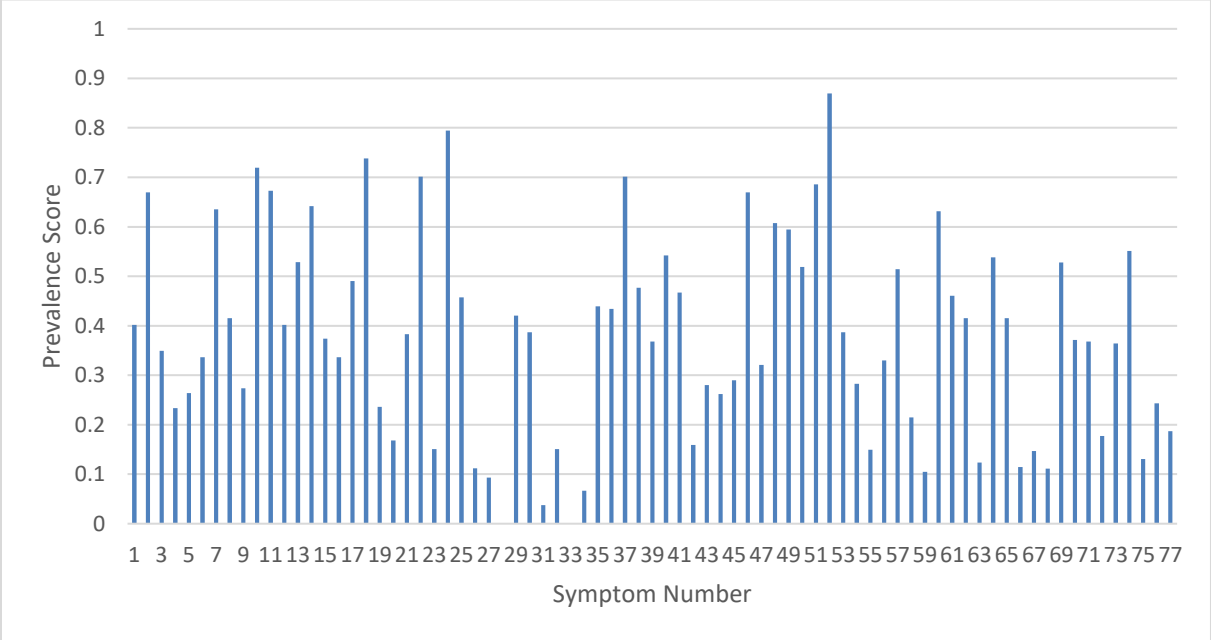

Figure 4-6 Symptom prevalence scores of the multiple myeloma patients (n = 107)

Importance of symptoms

A median of 48 symptoms per patient (IQR 32, range 0 – 75) was considered as important in the sample of 107 multiple myeloma patients.

Figure 4-7 gives an overview of the importance scores displaying the relative importance of the symptoms. Higher scores indicate higher importance. All importance score values are shown in *Appendix II-B7*.

The symptoms numbers 64 and 65 were only answered by male patients. The symptoms 66 to 70 were only answered by female patients.

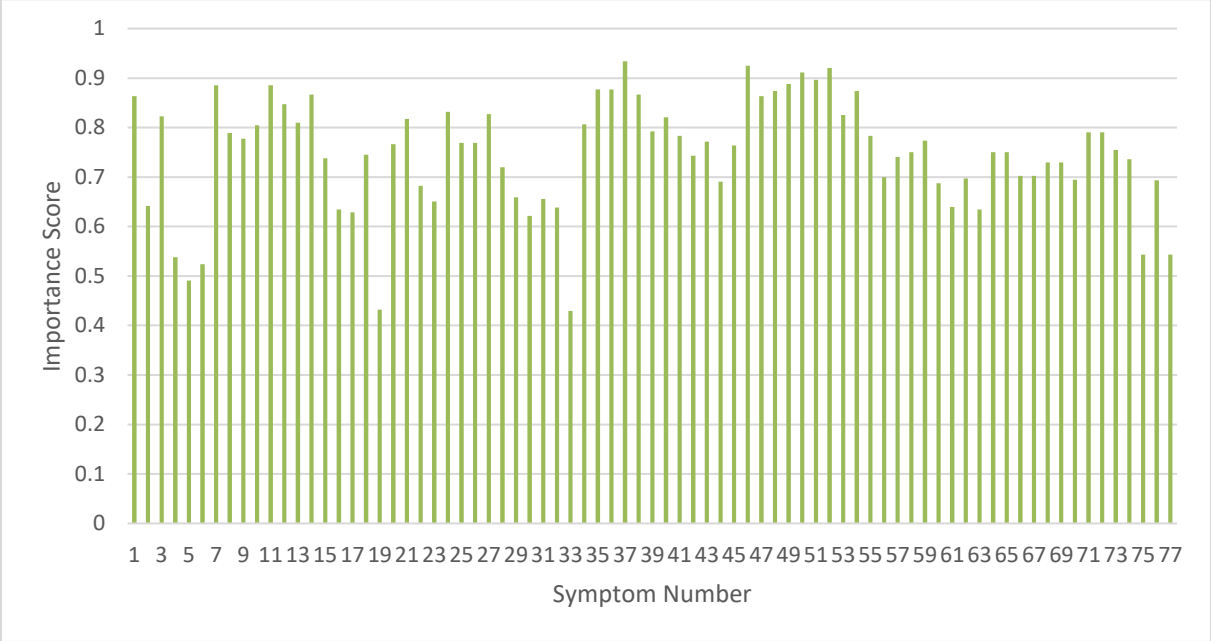

Figure 4-7 Symptom importance scores of the multiple myeloma patients (n = 107)

Combined prevalence-importance scores

Figure 4-8 gives an overview of the combined prevalence-importance scores displaying the relative clinical impact of the symptoms. Lower scores indicate higher clinical impact. All combined prevalence-importance score values are shown in *Appendix II-B8*.

The symptoms numbers 64 and 65 were only answered by male patients. The symptoms 66 to 70 were only answered by female patients.

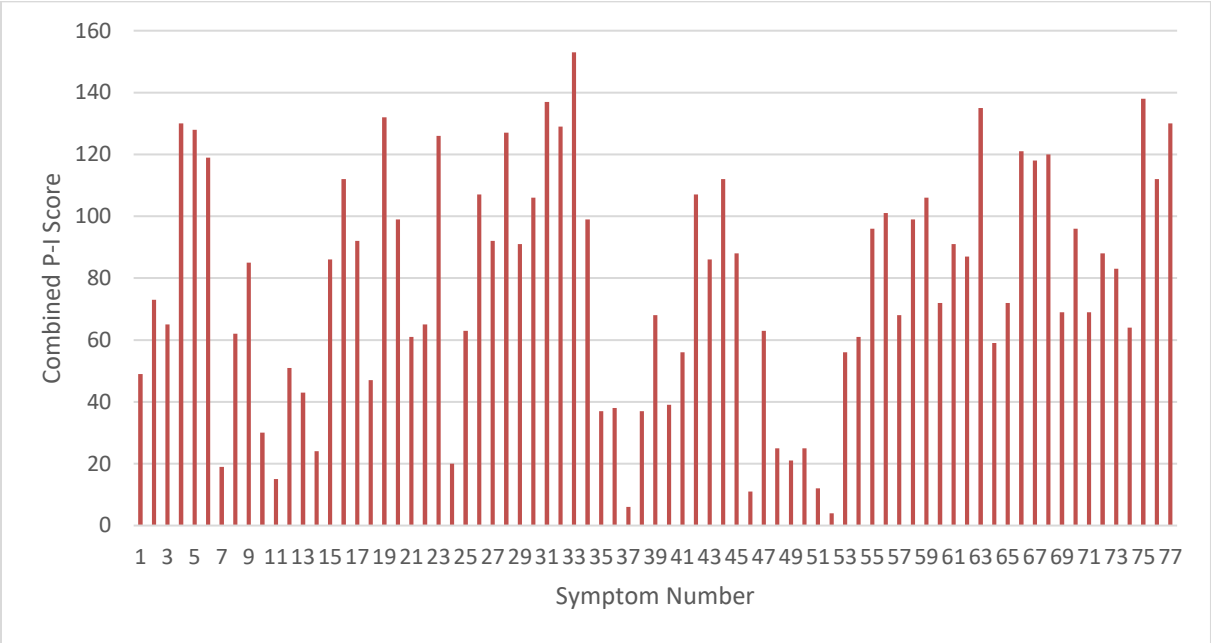

Figure 4-8 *Combined prevalence-importance scores of the multiple myeloma patients (n = 107)*

Based on the combined prevalence-importance scores, 19 symptoms were translated into 39 PRO-CTCAE items to build the PRO-CTCAE multiple myeloma item set. *Table 4-11* shows the selected items for the PRO-CTCAE multiple myeloma item set ranked by their combined score.

Table 4-11 PRO-CTCAE multiple myeloma item set including 39 items for 19 symptoms

PRO-CTCAE term	Symptom Number	Combined score	Attributes
Fatigue	52	4	S, I
Numbness and tingling	37	6	S, I
General pain	46	11	F, S, I
Insomnia	51	12	S, I
Nausea	11	15	F, S
Shortness of breath	7	19	S, I
Hair loss	24	20	P
Joint pain	49	21	F, S, I
Diarrhea	14	24	F
Muscle pain	48	25	F, S, I
Anxious	50	25	F, S, I
Decreased appetite	10	30	S, I
Swelling	35	37	F, S, I
Dizziness	38	37	S, I
Heart palpitations	36	38	F, S
Concentration	40	39	S, I
Constipation	13	43	S
Taste changes	18	47	S
Mouth/throat sores	1	49	S, I

F: frequency; S: severity; I: interference; P: presence/absence/amount

4.2.4.3 Prostate cancer

Prevalence of symptoms

A median of 20 symptoms per patient (IRQ 13, range 4 – 51) occurred in the sample of 66 prostate cancer patients. The symptom that appeared most often was “Achieve and maintain erection” (Number 64) in 59 patients.

Figure 4-9 gives an overview of the prevalence scores displaying the relative frequency of the symptom prevalence. Higher scores indicate higher frequency. All prevalence score values are shown in *Appendix II-B9*.

The symptoms 66 to 70 concerning only female patients were not answered by the male prostate cancer patients.

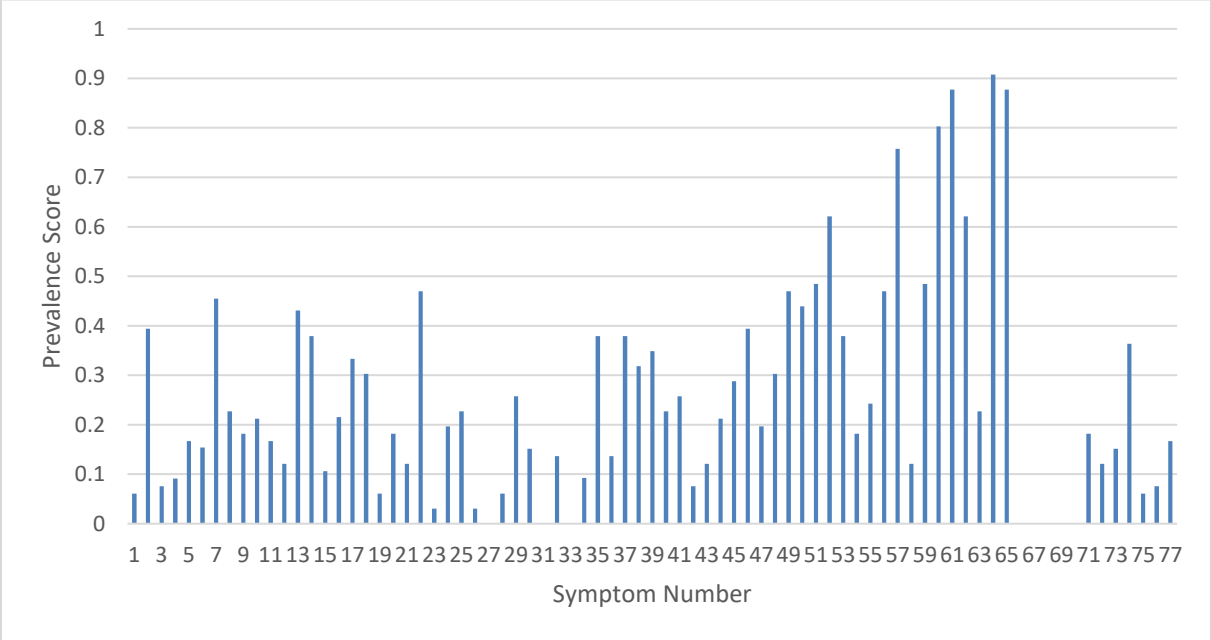

Figure 4-9 Symptom prevalence scores of the prostate cancer patients (n = 66)

Importance of symptoms

A median of 46 symptoms per patient (IQR 26, range 0 – 72) was considered as important in the sample of 66 prostate cancer patients.

Figure 4-10 gives an overview of the importance scores displaying the relative importance of the symptoms. Higher scores indicate higher importance. All importance score values are shown in *Appendix II-B10*.

The symptoms 66 to 70 concerning only female patients were not answered by the male PC patients.

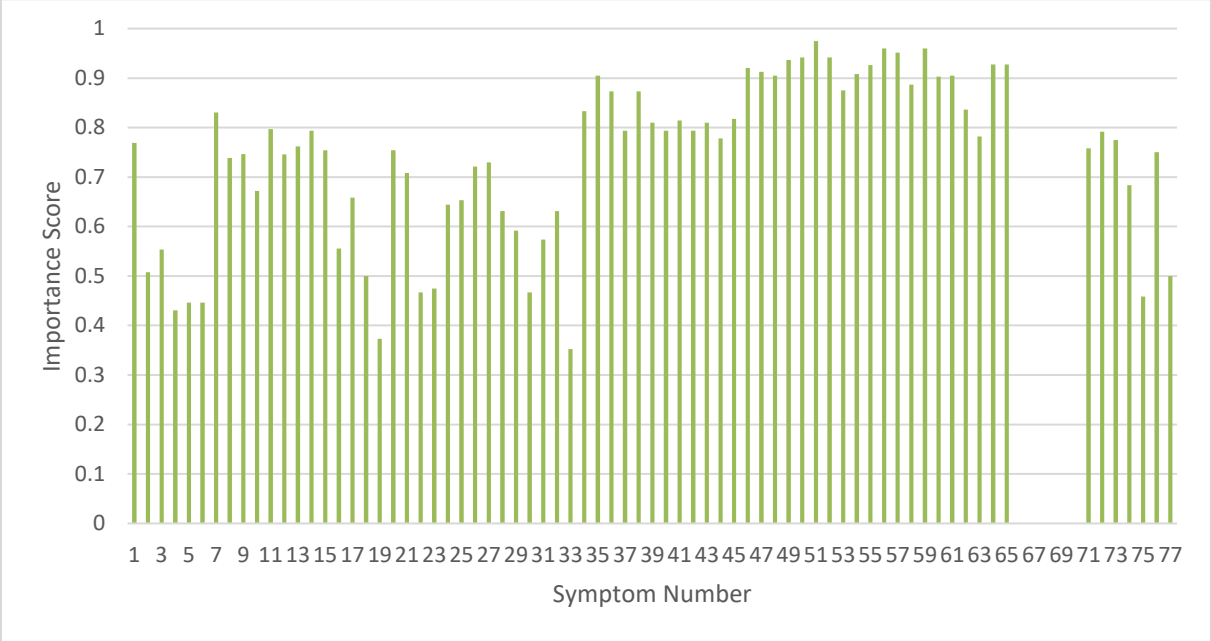

Figure 4-10 Symptom importance scores of the prostate cancer patients (n = 66)

Combined prevalence-importance scores

Figure 4-11 gives an overview of the combined prevalence-importance scores displaying the relative clinical impact of the symptoms. Lower scores indicate higher clinical impact. All combined prevalence-importance score values are shown in *Appendix II-B11*.

The symptoms 66 to 70 concerning only female patients were not answered by the male prostate cancer patients.

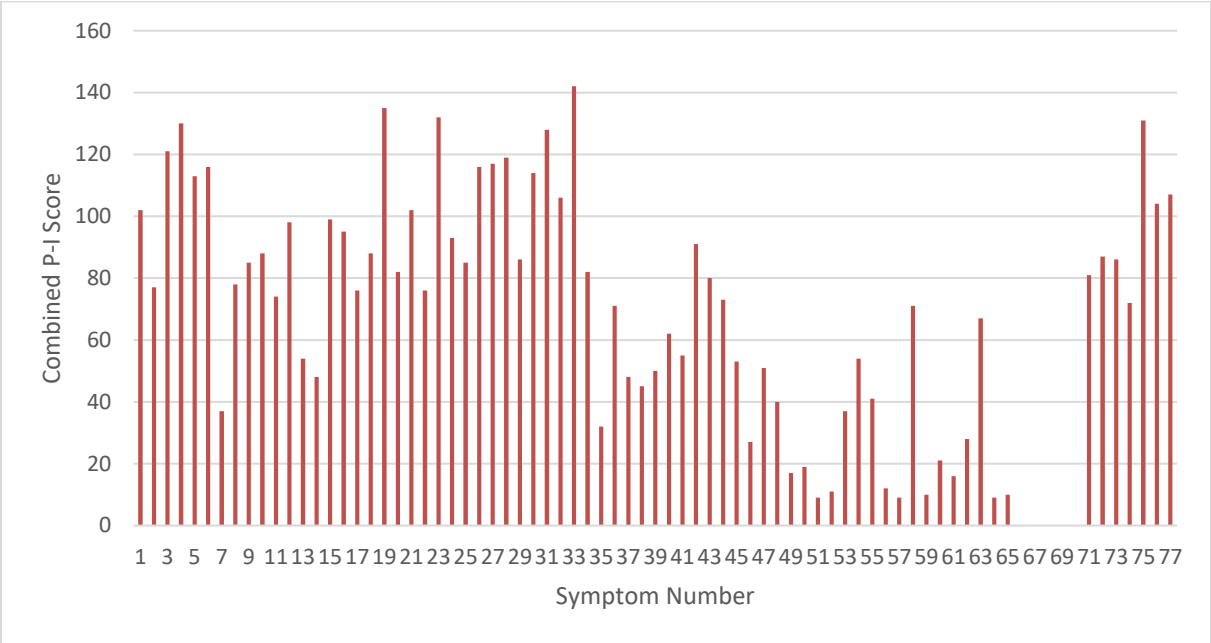

Figure 4-11 Combined prevalence-importance scores of the prostate cancer patients (n = 66)

Based on the combined prevalence-importance scores, 19 symptoms were translated into 40 PRO-CTCAE items to build the PRO-CTCAE prostate cancer item set. *Table 4-12* shows the selected items for the PRO-CTCAE prostate cancer item set ranked by their combined score.

Table 4-12 PRO-CTCAE prostate cancer item set including 40 items for 19 symptoms

PRO-CTCAE term	Symptom Number	Combined score	Attributes
Insomnia	51	9	S, I
Urinary frequency	57	9	F, I
Achieve and maintain erection	64	9	S
Urinary incontinence	59	10	F, I
Ejaculation	65	10	F
Fatigue	52	11	S, I
Urinary urgency	56	12	F, I
Unable to have orgasm	61	16	P, P
Joint pain	49	21	F, S, I
Anxious	50	19	F, S, I
Decreased libido	60	21	S
General pain	46	27	F, S, I
Hot flashes	62	28	F, S
Swelling	35	32	F, S, I
Shortness of breath	7	37	S, I
Sad	53	37	F, S, I
Muscle pain	48	40	F, S, I
Painful urination	55	41	S
Dizziness	38	45	S, I

F: frequency; S: severity; I: interference; P: presence/absence/amount

4.2.5 Item redundancy analysis

The patient questionnaires' items, which were translated into the tumor entity-specific PRO-CTCAE item sets, were analyzed for possible redundancies. For the item redundancy analysis, inter-item correlation (IIC) matrices based on the φ coefficient were formed for the symptom prevalence and symptom importance questions of the three tumor entities.

4.2.5.1 Breast cancer

Prevalence of symptoms

Figure 4-12 shows the φ coefficient matrix for the symptom prevalence. The observed φ correlations are relatively low, with values of < 0.5. Only the symptom pairs “General pain (46) and Joint pain (49)”, “Muscle pain (48) and Joint pain (49)” and “General pain (46) and Muscle pain (48)” showed moderate correlations with a φ value ≥ 0.5. Nevertheless, the Fisher´s exact test for independence provided significant results for both symptom pairs, supporting the hypothesis that the correlations are not random. The results of the χ2-test are shown in *Table 4-13*. The correlations between the symptoms were deemed pathophysiologically plausible during the discussion in the expert board because they all affect the symptom cluster pain.

Symptom	7	11	13	14	18	21	24	29	35	36	37	38	39	40	41	46	48	49	51	52
7	x	0.30	0.16	0.05	0.22	0.02	0.13	-0.02	0.17	0.34	0.12	0.24	0.40	0.26	0.15	0.17	0.17	0.11	0.16	0.12
11		x	0.23	0.33	0.15	0.07	0.18	0.05	0.15	0.26	0.05	0.32	0.27	0.20	0.02	0.24	0.02	-0.03	0.36	0.23
13			x	0.03	0.12	0.24	0.15	-0.08	0.17	0.13	0.11	0.17	0.16	0.09	0.05	0.19	0.08	0.10	0.13	0.13
14				x	0.23	0.14	0.27	0.34	0.19	0.05	0.09	0.17	0.29	0.29	0.17	0.09	0.04	0.12	0.28	0.17
18					x	0.19	0.39	0.37	0.12	0.03	0.24	0.01	0.31	0.25	0.12	0.17	0.13	0.14	0.15	0.27
21						x	0.33	0.14	-0.08	0.03	0.14	0.03	0.19	0.28	0.25	0.07	0.22	0.12	0.08	0.24
24							x	0.25	0.13	-0.07	0.16	-0.09	0.12	0.35	0.06	0.07	0.10	-0.11	0.10	0.26
29								x	0.18	-0.15	0.34	0.00	0.23	0.17	0.17	0.20	0.32	0.24	0.16	0.03
35									x	0.22	0.22	0.04	0.13	0.21	-0.03	0.17	0.23	0.19	0.09	-0.01
36										x	0.21	0.32	0.17	0.02	0.18	0.19	0.28	0.25	0.20	0.16
37											x	0.28	0.21	0.18	0.15	0.24	0.37	0.20	0.15	0.17
38												x	0.40	0.16	0.26	0.40	0.32	0.32	0.26	0.20
39													x	0.49	0.28	0.27	0.18	0.18	0.25	0.06
40														x	0.12	0.10	0.09	0.12	0.20	0.29
41															x	0.19	0.28	0.32	0.19	0.32
46																x	0.50	0.50	0.16	0.19
48																	x	0.52	0.17	0.15
49																		x	0.16	0.17
51																			x	0.39
52																				x

± 0.0 – 0.49

± 0.5 – 0.69

± 0.7 – 1.0

Figure 4-12 φ coefficient matrix for symptom prevalence of the breast cancer patients (n = 101)

Table 4-13 χ2-test for symptom prevalence of the breast cancer patients (n = 101) with a φ coefficient ≥ 0.5

Symptoms	**φ coefficient**	**Fisher´s exact test**
46 and 49	0.50	0.000*
48 and 49	0.52	0.000*
46 and 48	0.50	0.000*

* $p < 0.05$: statistically significant

Importance of symptoms

Figure 4-13 shows the φ coefficient matrix for the symptom importance. The observed φ values are, in general, on a higher level than for the symptom prevalence. A high correlation with a value of ≥ 0.8 was found for the symptom pairs “Memory (39) and Concentration (40)” and “Muscle pain (48) and Joint pain (49)”. Fisher´s exact test for independence provided significant results for both symptom pairs, supporting the hypothesis that the correlations are not random. The results of the χ2-test are shown in *Table 4-14*. The correlations between the symptoms were deemed pathophysiologically plausible because they affect symptoms of the same symptom clusters.

Symptom	7	11	13	14	18	21	24	29	35	36	37	38	39	40	41	46	48	49	51	52
7	x	0.41	0.42	0.46	0.47	0.52	0.43	0.41	0.47	0.51	0.46	0.49	0.30	0.39	0.42	0.56	0.56	0.48	0.37	0.40
11		x	0.67	0.65	0.52	0.64	0.39	0.34	0.44	0.68	0.57	0.69	0.36	0.40	0.54	0.52	0.36	0.34	0.45	0.65
13			x	0.72	0.41	0.70	0.46	0.46	0.51	0.66	0.69	0.60	0.43	0.42	0.43	0.70	0.52	0.49	0.57	0.60
14				x	0.50	0.71	0.44	0.43	0.59	0.76	0.64	0.61	0.40	0.45	0.60	0.52	0.49	0.53	0.61	0.58
18					x	0.41	0.51	0.52	0.34	0.38	0.51	0.47	0.52	0.43	0.48	0.34	0.32	0.30	0.42	0.47
21						x	0.45	0.38	0.54	0.77	0.60	0.66	0.38	0.43	0.58	0.58	0.45	0.43	0.50	0.54
24							x	0.64	0.45	0.38	0.50	0.36	0.48	0.37	0.42	0.52	0.45	0.49	0.48	0.46
29								x	0.44	0.32	0.42	0.41	0.44	0.41	0.48	0.47	0.45	0.48	0.66	0.47
35									x	0.71	0.62	0.49	0.36	0.41	0.49	0.54	0.66	0.70	0.45	0.41
36										x	0.60	0.66	0.35	0.40	0.53	0.56	0.56	0.60	0.49	0.58
37											x	0.75	0.61	0.65	0.66	0.69	0.63	0.69	0.56	0.48
38												x	0.60	0.66	0.76	0.60	0.53	0.54	0.52	0.49
39													x	0.82	0.50	0.41	0.34	0.33	0.53	0.29
40														x	0.67	0.38	0.37	0.42	0.54	0.33
41															x	0.45	0.52	0.56	0.59	0.60
46																x	0.67	0.65	0.50	0.58
48																	x	0.84	0.47	0.49
49																		x	0.46	0.39
51																			x	0.63
52																				x

± 0.0 – 0.49

± 0.5 – 0.69

± 0.7 – 1.0

Figure 4-13 φ coefficient matrix for symptom importance of the breast cancer patients (n = 101)

Table 4-14 χ2-test for symptom importance of the breast cancer patients (n = 101) with a φ coefficient ≥ 0.8

Symptoms	φ coefficient	Fisher´s exact test
39 and 40	0.82	0.000*
48 and 49	0.84	0.000*

* p < 0.05: statistically significant

4.2.5.2 Multiple myeloma

Prevalence of symptoms

Figure 4-14 shows the φ coefficient matrix for the symptom prevalence. The observed φ correlations are relatively low, with values of < 0.5. Only the symptom pair "Muscle pain (48) and Joint pain (49)" showed a moderate correlation with a φ value ≥ 0.5. Nevertheless, the Fisher´s exact test for independence provided a significant result, supporting the hypothesis that the correlation is not random. The result of the χ2-test is shown in *Table 4-15*. The correlation between the symptoms was deemed pathophysiologically plausible because they both affect the symptom cluster pain.

Symptom	1	7	10	11	13	14	18	24	35	36	37	38	40	46	48	49	50	51	52
1	x	-0.01	0.09	0.08	0.13	0.18	0.10	0.23	0.08	0.15	0.24	0.21	0.07	0.20	0.11	0.12	-0.05	0.06	0.04
7		x	0.26	0.26	0.06	0.12	0.21	-0.05	0.28	0.14	0.14	0.06	0.08	0.17	0.19	0.09	0.09	0.09	0.11
10			x	0.41	0.04	0.23	0.39	0.30	0.26	-0.02	0.14	0.05	0.14	0.18	0.14	0.08	0.23	0.09	0.25
11				x	0.26	0.23	0.27	0.29	0.26	-0.01	0.28	0.27	0.00	0.32	0.38	0.28	0.29	0.26	0.26
13					x	0.00	0.08	-0.02	0.10	0.02	0.04	0.17	0.11	0.31	0.20	0.08	0.05	0.18	0.13
14						x	0.27	0.30	0.14	0.15	0.32	0.00	0.14	0.22	0.16	0.14	0.00	0.23	0.06
18							x	0.07	0.23	0.14	0.26	0.14	0.35	0.22	0.18	0.07	0.15	0.17	0.40
24								x	0.03	0.12	0.12	0.21	0.14	0.38	0.30	0.29	0.16	0.16	0.21
35									x	0.18	0.29	0.17	0.17	0.26	0.02	0.20	-0.02	0.03	0.01
36										x	0.08	0.13	-0.03	0.16	0.07	0.08	-0.10	0.07	-0.05
37											x	0.22	0.10	0.11	0.19	0.21	-0.10	0.12	0.11
38												x	0.05	0.19	0.19	0.30	0.23	0.21	0.32
40													x	0.21	0.22	0.10	0.09	0.22	0.20
46														x	0.42	0.24	0.14	0.19	0.14
48															x	0.51	0.19	0.17	0.31
49																x	0.00	0.13	0.19
50																	x	0.08	0.24
51																		x	0.22
52																			x

± 0.0 – 0.49

± 0.5 – 0.69

± 0.7 – 1.0

Figure 4-14 *φ coefficient matrix for symptom prevalence of the multiple myeloma patients (n = 107)*

Table 4-15 *χ2-test for symptom prevalence of the multiple myeloma patients (n = 107) with a φ coefficient ≥ 0.5*

Symptoms	**φ coefficient**	**Fisher´s exact test**
48 and 49	0.51	0.000*

* $p < 0.05$: statistically significant

Importance of symptoms

Figure 4-15 shows the φ coefficient matrix for the symptom importance. The observed φ values are, in general, on a higher level than for the symptom prevalence. A high correlation with a value of ≥ 0.8 was found for the symptom pair "Swelling (35) and Heart palpitations (36)". Fisher´s exact test for independence provided a significant result, supporting the hypothesis that the correlation is not random. The result of the χ2-test is shown in *Table 4-16*. The correlation between the symptoms was deemed pathophysiologically possible, but the plausibility is questionable. Edema and heart palpitations can appear both because of cardiovascular issues, but edema can have other origins as well.

Symptom	1	7	10	11	13	14	18	24	35	36	37	38	40	46	48	49	50	51	52
1	1	7	10	11	13	14	18	24	35	36	37	38	40	46	48	49	50	51	52
7	x	0.29	0.46	0.45	0.34	0.41	0.36	0.48	0.37	0.31	0.45	0.46	0.44	0.45	0.37	0.30	0.53	0.39	0.35
10		x	0.29	0.28	0.33	0.32	0.39	0.23	0.40	0.40	0.49	0.51	0.33	0.38	0.21	0.31	0.21	0.23	0.30
11			x	0.55	0.40	0.43	0.58	0.46	0.40	0.29	0.53	0.43	0.32	0.36	0.20	0.33	0.34	0.39	0.36
13				x	0.48	0.66	0.50	0.39	0.43	0.43	0.49	0.47	0.38	0.46	0.38	0.47	0.32	0.58	0.46
14					x	0.57	0.38	0.34	0.49	0.60	0.45	0.36	0.35	0.48	0.35	0.26	0.27	0.20	0.22
18						x	0.37	0.41	0.39	0.39	0.40	0.54	0.43	0.30	0.23	0.31	0.30	0.34	0.23
24							x	0.46	0.28	0.24	0.34	0.41	0.41	0.37	0.33	0.38	0.32	0.38	0.25
35								x	0.35	0.30	0.31	0.44	0.38	0.42	0.30	0.34	0.44	0.39	0.35
36									x	0.82	0.64	0.56	0.54	0.68	0.53	0.57	0.49	0.45	0.46
37										x	0.57	0.56	0.54	0.68	0.61	0.60	0.45	0.40	0.39
38											x	0.48	0.45	0.59	0.42	0.45	0.49	0.53	0.59
40												x	0.52	0.38	0.27	0.43	0.47	0.49	0.45
46													x	0.42	0.44	0.49	0.42	0.38	0.35
48														x	0.75	0.65	0.54	0.33	0.39
49															x	0.76	0.49	0.32	0.32
50																x	0.53	0.49	0.43
51																	x	0.53	0.46
52																		x	0.74

± 0.0 – 0.49

± 0.5 – 0.69

± 0.7 – 1.0

Figure 4-15 φ coefficient matrix for symptom importance of the multiple myeloma patients (n = 107)

Table 4-16 χ2-test for symptom importance of the multiple myeloma patients (n = 107) with a φ coefficient ≥ 0.8

Symptoms	φ coefficient	Fisher´s exact test
35 and 36	0.82	0.000*

* p < 0.05: statistically significant

4.2.5.3 Prostate cancer

Prevalence of symptoms

Figure 4-16 shows the φ coefficient matrix for the symptom prevalence. The observed φ correlations are relatively low, with values of < 0.5. The symptom pairs "Decreased libido (60) and delayed orgasm (61)", "Decreased libido (60) and "Achieve and maintain erection (64)" and "Achieve and maintain erection (64) and Ejaculation (65)" showed a moderate correlation with φ values ≥ 0.5. Nevertheless, the Fisher´s exact test for independence provided significant results, supporting the hypothesis that the correlations are not random. The results of the χ2-tests are shown in *Table 4-17*. The correlations between the symptoms were deemed pathophysiologically possible because they all affect the symptom cluster of sexual function.

Symptom	7	35	38	46	48	49	50	51	52	53	55	56	57	59	60	61	62	64	65
7	x	0.35	0.10	0.14	0.26	0.12	0.11	0.09	0.27	-0.02	0.05	0.18	0.09	-0.03	0.22	0.16	0.02	0.30	0.25
35		x	0.14	0.14	0.30	0.20	0.32	-0.01	0.22	0.16	-0.15	-0.17	-0.14	0.12	0.07	0.10	0.03	0.03	0.01
38			x	0.05	0.12	0.27	0.18	-0.08	0.27	0.00	-0.01	0.01	0.01	-0.01	0.01	0.05	0.00	-0.02	0.05
46				x	0.41	0.17	0.29	0.09	0.31	0.27	0.05	-0.01	0.02	0.09	0.09	0.21	0.44	0.04	0.02
48					x	0.37	0.28	0.09	0.31	0.03	0.09	0.11	-0.01	-0.05	-0.01	0.05	0.18	0.10	-0.06
49						x	0.08	0.00	0.05	-0.17	0.03	-0.16	0.04	0.00	0.08	0.07	0.17	0.08	-0.03
50							x	0.06	0.31	0.44	-0.07	-0.04	0.00	0.00	0.06	0.15	0.06	0.07	-0.04
51								x	0.13	0.18	0.09	0.12	0.20	-0.03	0.02	-0.01	0.20	-0.01	0.09
52									x	0.03	0.00	0.11	0.07	0.13	0.08	0.10	0.16	-0.02	0.00
53										x	0.07	0.08	0.00	-0.20	-0.01	0.01	0.03	-0.08	0.10
55											x	0.32	0.24	-0.20	0.10	0.11	0.08	-0.07	0.00
56												x	0.39	-0.12	0.08	0.16	0.05	-0.03	0.16
57													x	-0.09	0.08	0.00	0.07	-0.06	-0.11
59														x	0.25	0.26	0.13	0.20	0.26
60															x	0.52	0.08	0.51	0.40
61																x	0.20	0.37	0.43
62																	x	0.09	-0.09
64																		x	0.69
65																			x

± 0.0 – 0.49

± 0.5 – 0.69

± 0.7 – 1.0

Figure 4-16 φ coefficient matrix for symptom prevalence of the prostate cancer patients (n = 66)

Table 4-17 χ2-test for symptom prevalence of the prostate cancer patients (n = 66) with a φ coefficient ≥ 0.5

Symptoms	φ coefficient	Fisher´s exact test
60 and 61	0.52	0.000*
60 and 64	0.51	0.001*
64 and 65	0.69	0.000*

* p < 0.05: statistically significant

Importance of symptoms

Figure 4-17 shows the φ coefficient matrix for the symptom importance. The observed φ values are, in general, on a higher level, than for the symptom prevalence. Compared to the other tumor entities, the prostate cancer symptom importance matrix shows the greatest number of high φ values. Some correlations amount to a φ coefficient of 1.000. A high correlation with a value of ≥ 0.8 was found for the symptom pairs “General pain (46) and Joint pain (49)”, “Muscle pain (48) and Joint pain (49), “Anxious (50) and Fatigue (52)”, “Painful urination (55) and Urinary urgency (56)”, “Painful urination (55) and Urinary frequency (57)”, “Painful urination (55) and Urinary incontinence (59)”, “Urinary urgency (56) and Urinary incontinence (59)”, “Decreased libido (60) and delayed orgasm (61)”, “Decreased libido (60) and Achieve and maintain erection (64)”, “Decreased libido (60) and Ejaculation (65)”, “Delayed orgasm (61) and Achieve and maintain erection (64)”, “Delayed orgasm (61) and Ejaculation (65)” and “Achieve and maintain erection (64) and Ejaculation (65)”. Fisher´s exact test for independence provided significant results, supporting the hypothesis that the correlations are not random. The results of the χ2-test are shown in *Table 4-18*. The correlations between the symptoms were deemed to be pathophysiologically plausible. The symptom pairs affect the different symptom clusters of pain, urinary tract, and sexual function. For the symptom pair “Anxious (50) and Fatigue (52)”, an overlapping is plausible. However, fatigue is a multifactorial construct including not only psychological components.

Symptom	7	35	38	46	48	49	50	51	52	53	55	56	57	59	60	61	62	64	65
7	x	0.39	0.46	0.26	0.11	0.18	0.21	0.24	0.21	0.18	0.14	0.10	0.23	0.10	0.14	0.15	0.20	0.10	0.10
35		x	0.73	0.43	0.53	0.49	0.17	0.33	0.17	0.31	0.29	0.21	0.21	0.21	0.07	0.07	0.34	-0.02	-0.02
38			x	0.34	0.30	0.39	0.39	0.46	0.39	0.34	0.47	0.31	0.46	0.31	0.45	0.45	0.33	0.42	0.42
46				x	0.78	0.92	0.26	0.43	0.26	0.30	0.19	0.27	0.27	0.27	-0.02	-0.02	0.27	0.02	0.02
48					x	0.85	0.23	0.39	0.23	0.40	0.17	0.24	0.24	0.24	-0.04	-0.04	0.34	-0.01	-0.01
49						x	0.30	0.48	0.30	0.35	0.23	0.30	0.30	0.30	0.01	0.01	0.32	0.04	0.04
50							x	0.69	0.82	0.75	0.64	0.56	0.78	0.56	0.35	0.30	0.42	0.36	0.36
51								x	0.69	0.51	0.63	0.76	0.76	0.76	0.31	0.31	0.44	0.36	0.36
52									x	0.60	0.64	0.56	0.78	0.56	0.35	0.30	0.28	0.36	0.36
53										x	0.43	0.38	0.55	0.38	0.19	0.16	0.46	0.22	0.22
55											x	0.83	0.83	0.83	0.67	0.67	0.29	0.62	0.62
56												x	0.78	1.00	0.51	0.51	0.38	0.59	0.59
57													x	0.78	0.51	0.51	0.38	0.59	0.59
59														x	0.51	0.51	0.38	0.59	0.59
60															x	1.00	0.26	0.88	0.88
61																x	0.26	0.88	0.88
62																	x	0.34	0.34
64																		x	1.00
65																			x

± 0.0 – 0.49

± 0.5 – 0.69

± 0.7 – 1.0

Figure 4-17 φ coefficient matrix for symptom importance of the prostate cancer patients (n = 66)

Table 4-18 χ2-test for symptom importance of the prostate cancer patients (n = 66) with a φ coefficient ≥ 0.8

Symptoms	φ coefficient	Fisher´s exact test
46 and 49	0.92	0.000*
48 and 49	0.85	0.000*
50 and 52	0.82	0.000*
55 and 56	0.83	0.000*
55 and 57	0.83	0.000*
55 and 59	0.83	0.000*
56 and 59	1.00	0.000*
60 and 61	1.00	0.000*
60 and 64	0.88	0.000*
60 and 65	0.88	0.000*
61 and 64	0.88	0.000*
61 and 65	0.88	0.000*
64 and 65	1.00	0.000*

* $p < 0.05$: statistically significant

4.3 Discussion

4.3.1 Study design

The aim of this project was to develop PRO-CTCAE item sets with high content validity for patients with breast cancer, prostate cancer, and multiple myeloma. As the largest European organization for developing HRQOL questionnaires for cancer patients, the EORTC guidelines for developing questionnaire modules are a broadly accepted standard. The procedure for developing the tumor entity specific PRO-CTCAE item sets was derived from these guidelines. The guidelines include four phases of the development process: 1. Generation of relevant HRQOL issues, 2. Converting the HRQOL issues into an item set, 3. Pre-testing of the item set, and 4. Large-scale international field testing [119].

While developing the PRO-CTCAE item library by the US National Cancer Institute, the above-mentioned steps have already been taken for the item library in general. From the CTCAE catalog containing 790 adverse events, 78 symptomatic adverse events (AEs) relevant to cancer patients, in general, were derived (Phase 1). Plain language terms and up to three items characterizing severity, frequency, and interference with daily activities were designed for every symptomatic AE and refined in a cognitive interviewing study creating a library consisting of 124 items (Phase 2). The items were evaluated for construct validity, reliability, responsiveness, and between-mode equivalence (Phase 3 and 4) [28, 29, 87]. The PRO-CTCAE item library was translated into more than 30 languages, including a German translation. [20, 23].

Despite being a valid PRO instrument in general, PRO-CTCAE has one weakness. The complete PRO-CTCAE question pool with 124 items is too extensive to be administered in complete form. This circumstance raises the question which symptoms are relevant to patients with different cancer entities. The question refers to phase 1 of the development process in which the foundation for high content validity of the PRO tool is laid. For compiling the relevant HRQOL issues, three sources should be used: literature, patients, and healthcare professionals. Based on the preexisting PRO-CTCAE symptom pool derived from literature, the tool of choice was a patient survey. PRO-CTCAE is a tool for detecting symptomatic AEs, and it is known that the physician-reported assessment often differs from the patients' experience and perception [21, 22]. Therefore, the patient perspective was chosen over the perspective

of healthcare professionals, which is also encouraged by the EORTC guidelines [119]. As the PRO-CTCAE symptom terms are prespecified and well understandable for patients, no semi-structured interviews but a questionnaire-based patient survey on the prevalence and importance of the symptoms was conducted.

4.3.2 Patient characteristics

Patients with broadly defined inclusion criteria were recruited in three study centers. The sample size for psychometric validation studies is only rarely justified a priori, but 100 patients are considered as a minimum. Since only content validity was part of this study, the number was considered sufficient [124]. The prespecified number of 100 was not reached for the patients with prostate cancer (n = 66) within the recruitment period. This limitation of the study arises from the fact that fewer patients than expected could be recruited at the CIO Bonn (n = 6, 9.1%), and no patients could be recruited at the Johanniter Hospital Bonn. An explanation is that prostate cancer patients are mostly treated in oncology practice and not as out- or inpatients at hospitals. The prostate cancer patients (n = 60, 90.9%) and the multiple myeloma patients (n = 60, 56.1%) were mostly recruited at the University Hospital Dresden. The hospital offers a special consultation for multiple myeloma patients, which explains the large number recruited in this center. In the day clinic of the CIO Bonn, patients with different cancer types are treated, but a great proportion of them are breast cancer patients. Therefore, most breast cancer patients were recruited at the CIO Bonn (n = 80, 79.2%). Since the prespecified number was reached after recruitment at the CIO Bonn and the Johanniter Hospital Bonn, no breast cancer patients were recruited at the University Hospital in Dresden. In general, most patients were recruited at CIO Bonn (n = 121, 44.2%) and University Hospital Dresden (n = 120, 44.2%) as these are big national cancer centers.

More multiple myeloma patients were male (n = 67, 62.6%) than female. This refers to the fact that, in general, 55% of multiple myeloma patients in Germany are male. The breast cancer patients and multiple myeloma patients were younger than the mean age of disease onset in Germany (BC: 58 vs. 64 years, MM: 62 vs. 74 years). The prostate cancer patients were older than the mean age of disease onset in Germany (76 vs. 71 years) [97].

Thus, according to their age, the study populations don't represent the typical German patient populations.

Oncological disease-specific characteristics

Almost all recruited patients were treated in an outpatient setting (BC: n = 101, 100%; MM: n = 87, 81.3%; PC: n = 56, 84.9%) and had a long experience with their disease. Time from the first diagnosis ranged from 14 months of the breast cancer patients and 27 months of the multiple myeloma patients to 59 months of the prostate cancer patients.

Looking at the disease-specific characteristics of the breast cancer patients, it is noteworthy that with 53.5% more patients than usual had already developed distant metastases. Usually, 20% of patients develop distant metastases. The metastases were most often located in bones (n = 34), liver (n = 20), and lung (n = 15), which are also the most frequently occurring metastases. The incidence of locoregional relapses is 5 to 10% within 10 years [114]. In the present sample, 21.8% had a relapse of their disease. Regarding molecular subtypes the subtypes ER (64.4%), PR (45.6%) and HER2 (43.6%) were present in the patient population. The current therapy intention was palliative and adjuvant in most cases.

The multiple myeloma patients show the following disease-specific characteristics: 25.2% had a disease relapse, most of them one. In addition, 13.1% were undergoing autologous SCT during the survey, 72.0% received at least one autologous SCT during former therapy lines. In comparison, 22.2% of multiple myeloma patients in Europe received an autologous SCT [125].

Regarding the disease-specific characteristics, of the prostate cancer patients, about one-third had metastases. Almost all metastases were located in bones since bone metastases are frequently caused by prostate cancer [126]. 27.3% of the patients had a relapse of their disease. Most patients belonged to the high-risk Gleason grade group 5. In most cases, the current therapy situation was palliative. The disease-specific characteristics of prostate cancer patients show a population with progressed diseases. This is also reflected by the old age of the patients and the long durations since the first diagnosis of the disease.

Drug therapy-specific characteristics

Although only patients with active treatment of their disease were included in the study, data on drug therapy are missing for some patients. For the breast cancer and multiple myeloma patients the numbers are small (1.0% and 3.7% respectively). For prostate cancer patients, the number is rather high (16.7%). The missing values do not seem to be randomly distributed as prostate cancer is far more affected than breast cancer or multiple myeloma. The missing data ratio is above 5 to 10%, the acceptable threshold for missing values [102]. A possible explanation for this is varying quality of documentation in the study centers. Most prostate cancer patients were recruited mostly at only one study center (90.9%) with different structural conditions.

In the comparison between the three tumor entities, it is noteworthy that multiple myeloma patients and breast cancer patients received a lot more active ingredients per patient for their tumor therapy than the prostate cancer patients in general. The numbers relate to the entire time period from diagnosis of the disease to the time-point of the patient survey. Taking the duration since the first diagnosis of the disease into account, which is far longer for the prostate cancer patients than for the other tumor entities, indicates that the prostate cancer patients received a far smaller variety of drugs, and therapy changes occurred less frequently. Nevertheless, the number should be treated with caution as it could be biased by the high rate of missing data for prostate cancer patients.

Of 1534 administered drugs in total for the three tumor entities, 38.9% were classical chemotherapeutic agents, and chemotherapeutics were less than half of the used drugs in breast cancer and multiple myeloma patients. For the prostate cancer patients, chemotherapeutics were only used in rare cases. This shows that chemotherapy is still important, but modern anticancer therapies include many more options. Therefore, entity-specific PRO-CTCAE item sets for individual cancer types are needed.

Drug therapy-specific characteristics were collected to describe the patient population for which the PRO-CTCAE item sets are valid. Taking a closer look at the active ingredients used for the breast cancer patients, it is notable that besides the classical chemotherapeutic agents cyclophosphamide, epirubicin, and docetaxel that are used in a lot of chemotherapeutic regimens the monoclonal antibodies against HER2 trastuzumab and pertuzumab that are used

in the adjuvant treatment of HER2-positive diseases are under the most frequently administered active ingredients. The list also includes the endocrine agents tamoxifen and letrozole, the antiangiogenetic monoclonal antibody bevacizumab and the CDK4/6 inhibitor palbociclib. The CDK4/6 inhibitors are the newest developed drug class for breast cancer treatment. Still, ribociclib approved in August 2017 and abemaciclib authorized in September 2018 were not used within the patient sample as ribociclib had not reached the standard of care in the recruiting centers and abemaciclib was just authorized at the end of the recruitment period [127-129]. The adverse event profiles of palbociclib and ribociclib differ in some cases, e.g., ribociclib causes severe hepatobiliary toxicity that could result in a different pattern of symptomatic adverse events [127, 128, 130]. This fact illustrates that the representation of the underlying drugs of the patient population surveyed for the PRO-CTCAE item sets is crucial in terms of validity since changes in therapy could introduce new symptomatic adverse events that are not covered by the PRO-CTCAE item set.

The dominating active ingredients used within the multiple myeloma patients were entity-specific drug classes like dexamethasone, bortezomib, and lenalidomide that are used in combination therapy regimes for induction, consolidation and maintenance therapy and the chemotherapeutics cyclophosphamide and melphalan that are used in combination therapy regimes and for high-dose therapy in the course of autologous stem cell transplantation [116]. Of interest is that bortezomib is the only proteasome inhibitor used frequently within the study population. The newly developed carfilzomib, which has been introduced to the market in 2015, was only used rarely. Ixazomib, the newest authorized proteasome inhibitor in 2016, was only used in one case [131, 132]. The same applies to the immunomodulatory drugs, as thalidomide and pomalidomide were seldom used. This can be explained by the fact that except for the obsolete thalidomide, the drugs are used for the second- and third-line treatment [116]. This also refers to the monoclonal antibodies daratumumab (authorization 2016) and elotuzumab (authorization 2016), as well as the targeted drug panobinostat (authorization 2015) that are underrepresented in the study sample. Thus, symptomatic adverse events caused by these drugs are not adequately represented in the PRO-CTCAE item set for multiple myeloma.

Over 90% of active ingredients of the prostate cancer patients were endocrine agents. Not further specified LH-RH analogs and the LH-RH analog leuprorelin as well as the androgen

receptor antagonist bicalutamide were most frequently used for androgen deprivation therapy as established drugs. The antiandrogens abiraterone acetate that was authorized by the EMA in 2011 and Enzalutamide that entered the market in 2013 were represented in the study population in a reasonably high proportion [133, 134].

After the recruitment period ending in April 2019, newly authorized drugs like the selective tyrosine kinase inhibitor of HER2 tucatinib for the treatment of breast cancer (February 2021) or the antibody-active ingredient-conjugate belantamab-mafodotin against the B-cell maturation antigen (BCAM) for the treatment of multiple myeloma (August 2020) entered the market [135]. The constant introduction of new drugs and evidence-based treatment changes may change the profile of symptomatic adverse events. Thus, the content validity of the PRO-CTCAE item sets should be constantly reviewed.

Another therapy-related factor influencing the experienced symptomatic adverse events is that patients are treated with supportive medication to prevent or mitigate adverse drug reactions. Within this project, only the supportive medication of the current cancer therapy could be taken into account, as the documentation of supportive medication from former therapy lines was not feasible. The number and kind of indications for which the patients received supportive medication differs. In accordance with the findings for cancer treatment, prostate cancer patients received supportive care for fewer indications than breast cancer and multiple myeloma patients. Breast cancer patients most frequently received supportive medication for nausea and emesis. Which are frequent adverse events under cancer therapy. Despite guideline-compliant therapy, vomiting still occurs in 20 to 30% of patients during chemotherapy and nausea in 40 to 50% of patients even more frequently [70, 136]. As emetogenic chemotherapeutics mainly cause nausea and emesis, this finding could be linked to the fact that breast cancer patients received more chemotherapeutics in their current cancer therapy than multiple myeloma and prostate cancer patients [70]. The high number of breast cancer patients treated for bone complications is consistent with the considerable proportion of patients with bone metastases within the study population. As bone complications are common in multiple myeloma and bone metastases are the most frequently developed metastases in prostate cancer, it was also the indication for which most patients across the tumor entities were treated [70].

4.3.3 Item selection

The rate of missing values for the questions regarding the prevalence and importance of the symptoms ranged from 0.2% (prevalence question, prostate cancer patients) to 5.6% (importance question, prostate cancer patients). With the exception of the importance question of the prostate cancer patients, all missing value rates were less than 5%, indicating an acceptable number of missing values within this patient survey. A possible reason for this is that the patients were looked after during the survey by a research associate because the surveys were conducted at the study centers and not at home.

The goal of item selection was to reduce the number of items for the entity-specific PRO-CTCAE item sets to a maximum of 40. The EORTC QLQ-C30 (30 items) plus entity-specific modules like QLQ-MY20 (multiple myeloma, 20 items), QLQ-BR23 (breast cancer, 23 items), or QLQ-PR25 (prostate cancer, 25 items) contain about 50 items [88]. But they cover a broad range of aspects of HRQOL, whereas PRO-CTCAE focuses on symptomatic adverse events. The questionnaires Functional Assessment of Cancer Therapy (FACT) questionnaires of the FACIT group consist of 27 items for the FACT-G (general) questionnaire, 37 items for the FACT-B (breast cancer), 41 items for the FACT-MM (multiple myeloma), and 39 items for FACT-P (prostate cancer) [137]. In general, it is recommended that the answering of a PRO questionnaire should be limited to 10 to 15 minutes or less if the questionnaire is administered repeatedly to minimize the response burden for patients [138]. Answering a 28-item PRO-CTCAE questionnaire takes four to six minutes [28]. Therefore, a number of 40 items was chosen as a cut-off because it is considered a not too burdensome number of questions.

A striking observation during the data analysis was the discrepancy in the prevalence and importance scores, as importance scores were much higher in general throughout all cancer entities. The question about prevalence refers to symptoms that actually occurred throughout cancer therapy. The question on the importance of the symptoms also applies to symptoms that are in the perception of patients important but did not necessarily occur during therapy. *Table 4-19* shows the top 10 symptoms of the three tumor entities significantly affected by this discrepancy. Thus, bothersome symptoms that did not actually occur during therapy could be part of the PRO-CTCAE item sets. Out of the PRO-CTCAE item set for breast cancer, the symptoms “Constipation”, “Heart palpitations” and “Swelling” are examples, and the symptom “Painful urination” of the PRO-CTCAE prostate cancer item set. No symptom of the

PRO-CTCAE multiple myeloma item set is affected. Nevertheless, the mentioned symptoms are plausible parts of the item sets. “Constipation” is a widely occurring symptom in cancer patients, and cardiotoxic effects coming along with “Heart palpitations” and “Swelling” are part of breast cancer treatment with taxane derivates, anthracyclines, and trastuzumab [103, 139]. “Painful urination” is a well-known symptom in prostate cancer patients [140, 141].

Table 4-19 Top 10 symptoms with the most significant differences in prevalence and importance scores

Breast cancer	**Diff.**	**Multiple myeloma**	**Diff.**	**Prostate cancer**	**Diff.**
Vomiting	-47	Hand-foot-syndrome#	-54	Radiation skin reaction#	-36
Radiation skin reaction#	-44	Radiation skin reaction#	-49	Change in usual urine color	-35
Fecal incontinence	-39	Discouraged	-39	Heart palpitations	-31
Painful urination#	-34	Urinary incontinency	-38	Flashing lights	-31
Urinary incontinency	-31	Painful urination#	-34	Discouraged	-28
Constipation	-28	Hives	-33	Headache	-27
Heart palpitations	-28	Headache	-33	Mouth/throat sores	-26
Nail loss	-28	Nosebleed	-32	Visual floaters	-26
Swelling	-25	Nail loss	-25	Hand-foot-syndrome#	-23
Hand-foot-syndrome#	-24	Difficulty swallowing	-23	**Painful urination#**	-21
Flashing lights	-24	Fecal incontinence	-23	-	

Diff.: difference of importance and prevalence scores; #: top 10 in all three tumor entities; ***BOLD****: selected for the entity specific PRO-CTCAE item set*

Comparing the three tumor entity-specific PRO-CTCAE item sets, some symptoms appear in all three item sets, which is the case for “Fatigue”, “Muscle pain”, “Insomnia”, “Joint pain”, “General pain”, “Dizziness”, “Shortness of breath,” and “Swelling”. This is not surprising since fatigue as a multifactorial syndrome is the most frequently observed symptom across most tumor entities, which is also the case for mood-related symptoms like insomnia and pain-

related symptoms [104]. In particular, the breast cancer and multiple myeloma PRO-CTCAE item set have symptoms in common. This is the case for 16 symptoms, including the above-mentioned symptoms and further frequently occurring symptoms like “Numbness and tingling”, “Nausea”, and “Hair loss”. The PRO-CTCAE breast cancer item set includes five of 21 (23.8%) symptoms that are not included in the other item sets. The PRO-CTCAE multiple myeloma item set contains only two of 19 (10.5%) and the prostate cancer item set 10 of 19 (52.6%) exclusive symptoms. The unique symptoms of the PRO-CTCAE prostate cancer item set belong to the urogenital and hormonally-related symptoms group. *Table 4-20* shows the comparison of the entity specific PRO-CTCAE item sets.

Although the breast cancer and multiple myeloma PRO-CTCAE item set have a lot of symptoms in common, they differ from the PRO-CTCAE core item set that was designed and validated. for patients under chemotherapy [31]. Of the 16 symptoms included in the PRO-CTCAE core item set, nine are included in the breast cancer item set, and 12 are included in the multiple myeloma item set. The PRO-CTCAE prostate cancer set shares six symptoms with the core item set. Symptoms of the core item set that are included in neither entity-specific item set are “Difficulty swallowing”, “Dry mouth”, and “Vomiting”. The only oral symptom included in an entity-specific item set was “Mouth/throat sores” in the multiple myeloma item set, indicating that the participating patients did not rate oral symptoms as that important. This is noteworthy since “Dry mouth” was ranked a top five symptom for prevalence and severity in the study of Reilly et al. [104]. Instead of “Vomiting”, “Nausea” was included in the breast cancer and multiple myeloma item set. Nausea usually appears before or together with vomiting. Nausea can occur over a long period with differing strengths and affects the quality of life of persons without being accompanied by vomiting [101]. Moreover, vomiting can be effectively prevented by antiemetic prophylaxis, which the patients receive as supportive care. Therefore, it is plausible that “Nausea” had a higher prevalence than “Vomiting” within the patient survey across the tumor entities.

Table 4-20 Comparison of the entity specific PRO-CTCAE item sets according to the rank of the symptoms

Breast cancer	**Rank**	**Multiple myeloma**	**Rank**	**Prostate cancer**	**Rank**
Fatigue#§	1	Fatigue#§	1	Insomnia#§	1
Numbness and tingling*§	2	Numbness and tingling*§	2	**Urinary frequency**	1
Nausea*§	3	General pain#§	3	**Achieve and maintain erection**	1
Muscle pain#	4	Insomnia#§	4	**Urinary incontinence**	4
Insomnia#§	5	Nausea*§	5	**Ejaculation**	4
Hair loss*	6	Shortness of breath#§	6	Fatigue#§	6
Joint pain#	6	Hair loss*	7	**Urinary urgency**	7
Blurred vision	8	Joint pain#	8	**Unable to have orgasm**	8
Concentration*§	9	Diarrhea*§	9	Joint pain#	9
General pain#§	10	Muscle pain#	10	Anxious*§	10
Diarrhea*§	11	Anxious*§	10	**Decreased libido**	11
Constipation*§	12	**Decreased appetite**§	12	General pain#§	12
Taste changes*	13	Swelling	13	**Hot flashes**	13
Dizziness#	14	Dizziness#	13	Swelling#	14
Shortness of breath#§	15	Heart palpitations*	15	Shortness of breath#§	15
Heart palpitations*	16	Concentration*§	16	**Sad**§	15
Memory	16	Constipation*§	17	Muscle pain#	17
Swelling#	18	Taste changes*	18	**Painful urination**	18
Rash	19	**Mouth/throat sores**§	19	Dizziness#	19
Nail ridging+	20				
Nail discoloration+	20				

*#: Part of all three PRO-CTCAE item sets; *: Part of two of three PRO-CTCAE item sets; **BOLD**: Part of only one PRO-CTCAE item set; §: Part of the PRO-CTCAE core item set; +: Symptoms were combined in the patient questionnaire*

The item redundancy analysis with the φ coefficient and Fisher´s exact test for the prevalence and importance of the symptoms revealed some possible redundancies. High inter-item correlations indicating a redundancy of symptoms appear more often in relation to the importance of the symptoms. This effect can be explained as analogs to the discrepancies in the scores. The question about prevalence refers to symptoms that actually occurred, whereas the question on importance also applies to symptoms that are in the perception of patients important but had not necessarily actually occurred during their therapy.

High correlations with a φ coefficient of 0.8 or higher did not appear regarding the prevalence of symptoms throughout the three tumor entities. Nevertheless, the few correlations with a moderate φ coefficient of 0.5 or higher still led to significant correlations and revealed possible plausible redundancies. In terms of breast cancer and multiple myeloma, pain-related symptoms were involved. Regarding prostate cancer, symptom pairs of the group of sexual and hormonally related symptoms that are pathophysiologically linked closely together showed plausible redundancies in their prevalence.

For the importance of symptoms, high correlations with a φ coefficient of 0.8 or higher were observed. For breast cancer, also pain-related symptoms showed a high and plausible correlation for importance, matching the high correlation for prevalence. Also, the symptom pair memory and concentration showed a plausible correlation, but it is not reflected by redundancy in the prevalence of the symptoms. The same applies to swelling and heart palpitations for multiple myeloma. Compared to the other tumor entities, prostate cancer symptom importance showed the greatest number of high φ values. Three symptom clusters with possibly redundant symptom pairs were found for which redundancy is pathophysiologically highly plausible. Symptom pairs of the cluster of sexual and hormonally-related symptoms were detected matching the possible redundancies found for the symptom prevalence. Urogenital symptoms are another cluster that showed highly correlating pairs for symptom importance, but the redundancies were not reflected by symptom prevalence. The same is true for the cluster of pain symptoms as these symptoms showed correlations for prevalence in breast cancer and multiple myeloma but not prostate cancer.

In particular, pathophysiologically plausible symptom pairs showing possible redundancies for prevalence and importance, like the pain-related symptoms of the breast cancer patients and the cluster of sexual and hormonally-related symptoms of the prostate cancer patients, were

discussed for exclusion of the PRO-CTCAE item sets. Which symptoms of the redundant pairs should be removed and which effect the exclusion would show is unclear. To make this final decision, further evaluation of the PRO-CTCAE item sets is necessary as the development of the content-valid PRO-CTCAE item sets must be followed by a validation study to determine their psychometric quality criteria reliability and construct validity, as it was conducted for the PRO-CTCAE core item set [31]. In terms of measuring the reliability of a questionnaire, internal consistency can be determined for each scale of the PRO-CTCAE item sets using Cronbach´s alpha [142]. Values range from 0 to 1, with 1 representing perfect reliability. To evaluate which items negatively influence the reliability of a scale, Alpha-if-item-deleted values can be calculated. By doing so, items of a questionnaire are excluded step-by-step, and Cronbach´s alpha is calculated again. If Cronbach´s alpha increases, the removal of the item indicates higher reliability of the scale [143].

Despite taking only the content validity into account and further validation of the PRO-CTCAE item sets is necessary to meet the requirements of regulatory authorities for the use of the PRO-CTCAE item sets in clinical studies, this study has another limitation. The entity-specific PRO-CTCAE item sets for breast cancer, multiple myeloma, and prostate cancer are designed to be valid for all patients of an entity. Patients are treated differently, according to their stages of disease and clinical situation. For example, the treatment of breast cancer patients differs a lot over time. After diagnosis, adjuvant or neoadjuvant chemotherapy is combined with surgery and radiation. After this initial phase, adjuvant treatment with endocrine therapeutics and anti-HER2 antibodies is carried out over years. Over time, the AE profile and the HRQOL of patients change, leading to the importance of developing PRO-CTCAE item sets for different therapy situations within one tumor entity. For multiple myeloma, this could also be the case for patients being eligible and ineligible for an autologous stem cell transplantation and for patients needing a second- or third-line therapy because of a relapse of the disease.

4.4 Conclusions

This patient survey resulted in differences in patterns of symptomatic adverse events of patients with breast cancer, multiple myeloma, and prostate cancer. Based on the patients´ answers to the questions about prevalence and importance of the symptoms of the PRO-CTCAE item library, tumor entity-specific PRO-CTCAE item sets with high content validity were developed.

The PRO-CTCAE item sets have some symptoms in common, which is especially the case for symptoms occurring frequently across the different cancer types. The PRO-CTCAE prostate cancer item set includes the most unique symptoms not included in the other PRO-CTCAE item sets. The breast cancer and multiple myeloma PRO-CTCAE item sets have more symptoms in common, but they both differ significantly from the PRO-CTCAE core item set for patients under chemotherapy. The size of the PRO-CTCAE item sets was limited to 40 PRO-CTCAE items because this was considered a not too burdensome number of questions.

The item redundancy analysis identified symptoms of the PRO-CTCAE item sets that may be redundant. The PRO-CTCAE prostate cancer item set was shown to exhibit the most possible redundancies, whereas this was the case for only few symptoms of the breast cancer and multiple myeloma PRO-CTCAE item sets.

In the course of the study, patients' cancer disease data and cancer medications were documented to know for which disease stages and therapies the PRO-CTCAE item sets are valid. The information is important because not all relevant disease characteristics and therapy options were equally represented by the patient populations. Furthermore, over time, new drug approvals and evidence-based therapy changes will lead to changes in the symptomatic adverse event pattern experienced by the patients.

5 Outlook

To improve medication safety in cancer patients, they should be treated within a best practice model. In healthcare, best practice is defined as the optimization of a care process using evidence-based decision making for patients to ensure ongoing quality assurance [144]. The results of the secondary analysis of the ImSEL-PRO trial can serve as basis for designing interdisciplinary and risk-adapted supportive care concepts as best practice models for German cancer inpatients. The electronic assessment of PRO measures, pharmacist-led medication reviews and other components like psychooncological care and therapeutic drug monitoring, can be combined in complex interventions to improve health outcomes of the patients. Complex interventions should be developed and evaluated in a phased approach including qualitative and quantitative methods. In the first phase, components of the intervention and their underlying mechanism by which they influence outcomes must be identified [145]. After identifying individual components, the following questions need to be answered in the further development process: What is the trigger for an intervention? (e.g. PRO-CTCAE symptom over defined cut-off value as trigger for symptom management, polymedication as trigger for medication review); how is the intervention conducted? (e.g. performing a symptom management, type of medication review performed and implementation of solutions); and which patient-relevant outcomes should be measured? (e.g., HRQOL, therapy discontinuation, adherence to treatment). Subsequently, exploratory and randomized controlled trials should be conducted to evaluate the effectiveness of the complex intervention.

PRO-CTCAE questionnaires can be used for the assessment of symptomatic adverse events in clinical practice and drug development. Regulatory authorities like the FDA and EMA require validated PRO questionnaires for the use in clinical trials. In order to validate the quality and psychometric criteria of the new PRO-CTCAE item sets for breast cancer, multiple myeloma, and prostate cancer, further studies are required. The validation of the PRO-CTCAE item set for multiple myeloma is currently ongoing in a multicentre, one-time survey using a browser-based application. Within the survey, patients complete the PRO-CTCAE item set for multiple myeloma and the corresponding EORTC questionnaires. A further challenge will be the development of subgroup PRO-CTCAE item sets for the different therapy situations within one

tumor entity. Besides the PRO-CTCAE item sets for breast cancer, multiple myeloma and prostate cancer, PRO-CTCAE item sets for colorectal cancer and patients under therapy with immune checkpoint inhibitors have already been developed and the development of a PRO-CTCAE item set for patients with sarcoma is currently ongoing.

6 Summary

In oncology, adverse events are usually documented using the Common Terminology Criteria for Adverse Events (CTCAE). This physician-reported assessment can be supported by patient-reported outcomes (PRO) that play an increasing role in clinical drug development and practice. The National Cancer Institute (NCI) has developed a PRO version of the CTCAE criteria (PRO-CTCAE) for the detection of symptomatic adverse events in cancer patients. To minimize medication risks like adverse events for cancer patients, pharmacist-led medication reviews and medication management can be provided. This work consists of two projects focusing on the patient-reported symptom burden of cancer patients measured with PRO-CTCAE.

The aim of the first project was to determine sociodemographic, disease-related, and drug therapy-related factors influencing health-related quality of life (HRQOL) in oncology inpatients. The focus was on detecting medication risks with the help of a standardized medication review, including PRO-CTCAE data. The study was conducted retrospectively in a population of oncology inpatients at four study centers. The median age of the 162 patients was 65.5 years. They had various hematological and solid cancer diseases and received a mean of 11.6 drugs per patient. 92.6% of patients exhibited polymedication with five or more drugs. In the course of medication reviews a mean of 4.0 drug-related problems (DRPs) with need for intervention was detected per patient. 21.5% of those DRPs were identified based on PRO-CTCAE data. Multiple linear regression models describing changes of HRQOL from baseline to hospital discharge were found for the global HRQOL and the physical function of the patients including the relapse status (global HRQOL) and the duration of hospital stay (physical function) as covariates. The results may support the implementation of PRO-CTCAE in pharmacist-led medication reviews and multiprofessional care approaches for cancer patients.

The aim of the second project was to develop PRO-CTCAE item sets with high content validity for patients with breast cancer, prostate cancer and multiple myeloma. Therefore, the prevalence and importance of therapy-associated symptoms, as well as their underlying tumor medication and disease-specific data, were assessed within a patient survey. In order to select PRO-CTCAE items for each tumor entity, individual symptoms were ranked on the

basis of prevalence and importance. 101 patients with breast cancer, 107 with multiple myeloma, and 66 with prostate cancer were recruited at three study centers. The final breast cancer item set contains 21 symptoms, the multiple myeloma and prostate cancer item set 19 symptoms each. The symptoms with the highest rankings across the item sets were fatigue and sleep disorders. An item redundancy analysis identified symptoms of the PRO-CTCAE item sets that may be redundant. The PRO-CTCAE prostate cancer item set exhibited the most possible redundancies. After further validation studies, the new PRO-CTCAE item sets will be applicable for use in clinical studies as instruments for safety assessment.

Based on the results of the two projects, complex interventions to improve health outcomes of cancer patients can be developed, combining electronic recording of PROs and medication reviews with other safety-increasing measures.

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8 Appendix

Appendix Project I

Appendix Project II

Appendix I-A: Documentation form for medication reviews

Leitfaden zur Medikationsanalyse

ImSEL-PRO-ID	Datum

Erfassen relevanter Medikationsdaten und klinischer Daten

1.	**Erfassen der Gesamtmedikation** Aktuelle Gesamtmedikation für den ersten Applikationstag der Tumortherapie auf Station zusammenstellen (inklusive Tumortherapie, Supportivtherapie, Dauermedikation sowie Bedarfsmedikation)	☐
2.	**Aufbereiten der Symptomlast** Symptome mit einem Symptomscore ≥ 75 für die Studienzeitpunkte Baseline, Visite 1 bzw. Visite 2 zusammenstellen (Baseline → Aktuelle Grundbeschwerden; Visite 1 bzw. Visite 2 → Potentielle Nebenwirkungen)	☐
3.	**Auswahl der Labordaten und Vitalparameter** Auffällige Vitalparameter und Labordaten außerhalb des Referenzbereiches zusammenstellen	☐

Analyse der Gesamtmedikation

4.	**Interaktionen** Interaktionscheck mittels ABDA-Datenbank und Lexicomp® Drug Interactions durchführen; Ergebnisübersicht ausdrucken; Interaktionen mit entsprechenden Maßnahmen dokumentieren	☐
5.	**Indikation** Arzneistoffe zu Indikationsgebieten zuordnen; auf Vollständigkeit (Arzneimittel ohne Indikation, Indikation ohne Arzneimittel) prüfen; therapeutischen Zweck für Off-Label-Einsatz ausschließen	☐
6.	**(Pseudo-)Doppelmedikation** Auf Doppelverordnungen (Arzneistoffe, Arzneistoffklassen) prüfen; therapeutischen Zweck möglicher Doppelverordnungen ausschließen	☐
7.	**Kontraindikationen** Auf Kontraindikationen hinsichtlich Alter, Geschlecht, Begleiterkrankungen und Allergien prüfen	☐
8.	**Dosierung** Kreatinin-Clearance ≤ 60 ml/min → Dosisanpassung bei Niereninsuffizienz (DANI) Child Pugh Score A, B, C → Dosisanpassung bei Leberinsuffizienz (DALI) Auf inadäquate Dosierung (Unterdosierung, Überdosierung) prüfen	☐
9.	**Dosierungsintervall** Auf ungeeignete oder unzweckmäßige Dosierungsintervalle prüfen	☐
10.	**Einnahmezeitpunkt** Auf sinnhafte Einnahmezeitpunkte (Zeitabstand zum Essen, Zeitabstand zu anderen Arzneimitteln) prüfen	☐
11.	**Therapiedauer** Auf Einhaltung der empfohlenen Therapiedauer prüfen	☐
12.	**Darreichungsform** Ernährungssonde → Sondenfähige Darreichungsform Auf ungeeignete oder unzweckmäßige Darreichungsformen prüfen	☐
13.	**Arzneimittelauswahl** Alter ≥ 65 Jahre → EU(7)-PIM-Liste Arzneimittelauswahl mit Hilfe vorhandener Evidenz (Leitlinien, Originalliteratur) prüfen	☐
14.	**Nebenwirkungen** Auf plausible Nebenwirkungen auch mittels Symptomlast sowie Vitalparameter und Labordaten prüfen; dabei nur plausible sehr häufige bzw. häufige Nebenwirkungen berücksichtigen	☐

Dokumentation aller potentiellen arzneimittelbezogenen Probleme in der Datenbank

Appendix I-B: Multiple linear regression analysis

Table I-B.1 Multiple linear regression model describing the effect of covariates on the change of the cognitive function scale of the EORTC QLQ-C30 questionnaire from baseline to visit 2 (ANOVA p = 0.122; R^2 = 0.151, adjusted R^2 = 0.049)

Covariate	Effect	SE	p	95% CI	
(Constant)	-15.30	12.01	0.205	-39.06	8.47
Study group B	-1.82	4.09	0.657	-9.91	6.27
Study group C	3.67	3.84	0.342	-3.94	11.27
Age (years)	0.02	0.14	0.892	-0.27	0.31
Gender (female)	-3.44	3.48	0.325	-10.32	3.45
Educational level (low)	-0.59	3.27	0.858	-7.06	5.89
Duration of hospital stay (days)	0.22	0.21	0.301	-0.20	0.62
Type of cancer (solid)	-0.29	4.19	0.944	-8.58	7.99
Time since first diagnosis of cancer (months)	0.11	0.06	0.053	0.00	0.23
Relapse status (no)	9.17	4.75	0.056	-0.23	18.57
ECOG status 1	0.06	3.84	0.988	-7.55	7.67
ECOG status 2	6.42	6.40	0.318	-6.25	19.10
Concomitant diseases (number)	-0.46	1.53	0.766	-3.49	2.57
Drugs (number)	0.74	0.39	0.059	-0.03	1.51
iDRP (number)	-1.70	0.78	0.032	-3.25	-0.15
PRO-DRP (number)	0.90	1.55	0.562	-2.16	3.97

SE = standard error

Table I-B.2 Multiple linear regression model describing the effect of covariates on the change of the emotional function scale of the EORTC QLQ-C30 questionnaire from baseline to visit 2 (ANOVA p = 0.210; R^2 = 0.135, adjusted R^2 = 0.031)

Covariate	**Effect**	**SE**	**p**	**95% CI**	
(Constant)	19.75	11.24	0.081	-2.49	41.99
Study group B	-1.12	3.83	0.771	-8.69	6.46
Study group C	5.81	3.59	0.109	-1.31	12.92
Age (years)	-0.15	0.14	0.280	-0.41	0.12
Gender (female)	-3.94	3.25	0.228	-10.38	2.50
Educational level (low)	3.41	3.06	0.267	-2.65	9.47
Duration of hospital stay (days)	-0.13	0.19	0.505	-0.51	0.25
Type of cancer (solid)	1.04	3.92	0.791	-6.72	8.80
Time since first diagnosis of cancer (months)	-0.08	0.05	0.150	-0.18	0.03
Relapse status (no)	-4.42	4.44	0.322	-13.21	4.38
ECOG status 1	-4.61	3.60	0.203	-11.76	2.51
ECOG status 2	11.04	5.99	0.068	-0.82	22.90
Concomitant diseases (number)	0.05	1.43	0.973	-2.79	2.88
Drugs (number)	-0.04	0.37	0.907	-0.77	0.68
iDRP (number)	-0.23	0.73	0.753	-1.68	1.22
PRO-DRP (number)	-0.08	1.45	0.957	-2.95	2.79

SE = standard error

Appendix II-A1: Patient information

RHEINISCHE FRIEDRICH-WILHELMS-UNIVERSITÄT BONN
Pharmazeutisches Institut
Klinische Pharmazie
Leitung: Prof. Dr. Ulrich Jaehde

Patienteninformation zur wissenschaftlichen Untersuchung

„Auswahl patientenrelevanter Symptome zur Entwicklung entitätsspezifischer PRO-CTCAE-Fragebögen für Patienten mit Multiplem Myelom oder Prostatakarzinom“

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Sehr geehrte Patientin, sehr geehrter Patient,

Zurzeit werden Sie im Universitätsklinikum Dresden wegen Ihrer Krebserkrankung behandelt. In einem Forschungsprojekt entwickeln wir Fragebögen, mit dem wir herausfinden möchten, wie sehr Krebspatientinnen und –Patienten **von Nebenwirkungen ihrer Therapie** betroffen sind. Die Fragebögen sollen zukünftig dazu beitragen, Maßnahmen zur möglichst frühzeitigen Erkennung und Behandlung von Nebenwirkungen weiter zu entwickeln.

Um die Fragebögen bestmöglich anpassen zu können, wollen wir zunächst erfassen, unter welchen Symptomen Patientinnen und Patienten dieser Krebsarten leiden und welche Symptome als so wichtig empfunden werden, dass sie bei Patienten mit der jeweiligen Krebserkrankung in einem Fragebogen regelmäßig abgefragt werden sollten.

Wenn Sie sich für die Teilnahme an diesem Projekt entscheiden, bitten wir Sie, den **beiliegenden Fragebogen** auszufüllen. Am Anfang des Fragebogens ist genau erklärt, wie die verschiedenen Teile des Fragebogens ausgefüllt werden sollen. Die Bearbeitung des Fragebogens wird etwa **15 Minuten** in Anspruch nehmen.

Neben Ihren Symptomen ist es notwendig, zu erfassen, welche Form der Krebserkrankung Sie haben, welche Therapie Sie bisher erhalten haben und in welchem Stadium sie sich befindet. Diese Daten werden, im Falle Ihrer Zustimmung, aus Ihrer Patientenakte entnommen und durch einen wissenschaftlichen Mitarbeiter der Universität Bonn verarbeitet und ausgewertet.

Die von Ihnen gemachten Angaben und die Daten Ihrer Krankenakte werden streng vertraulich behandelt. Ihre persönlichen Daten werden **pseudonymisiert**, d.h. Ihrem Namen und Geburtsdatum wird eine Patientennummer zugeordnet. Ihre persönlichen Daten und das Pseudonym werden in einem Dokument hinterlegt. Ohne Einsicht in dieses Dokument ist kein Rückschluss auf Ihre Identität möglich. Es wird nach dem Ende der Studie vernichtet, sodass ab diesem Zeitpunkt die Auswertung der Daten anonym erfolgt. Dazu benötigen wir aus datenschutzrechtlichen Gründen Ihre **Unterschrift** auf der beiliegenden Einwilligungserklärung. Selbstverständlich können Sie Ihre Einwilligung zu einem späteren Zeitpunkt ohne Angabe von Gründen widerrufen. **Dabei können Sie auch eine Einsicht, sowie die Berichtigung oder eine Löschung Ihrer personenbezogenen Daten verlangen**. Nach Abschluss der Datenerhebung, etwa zwei Monate nach Studienbeginn, werden die Daten anonymisiert. Damit wird verhindert, dass Ihre Daten mit Ihrer Person in Verbindung gebracht werden können. **Ab diesem Zeitpunkt ist jedoch auch eine Einsicht, eine Berichtigung oder eine Löschung Ihrer Daten nicht mehr möglich.**

Im Falle von Verstößen gegen das Datenschutzrecht haben Sie das Recht sich bei einer zuständigen Datenschutzaufsichtsbehörde zu beschweren. Die Kontaktdaten der zuständigen Behörden und Personen finden Sie auf der Rückseite dieser Patienteninformation.

Ob Sie an der Studie teilnehmen oder nicht, hat keinerlei Auswirkungen auf Ihre derzeitige und zukünftige ärztliche Behandlung. Für Sie selbst entstehen durch diese Erhebung keine direkten Vorteile. Durch Ihre Mitarbeit an unserem Projekt können Sie jedoch wesentlich dazu beitragen, dass in Zukunft Strategien zur Vermeidung von Nebenwirkungen und zu einem besseren Umgang mit Nebenwirkungen entwickelt werden können.

Vielen Dank für Ihre Unterstützung!

Dr. Katharina Schütte
(Studienärztin Dresden)

Dipl.-Psych. Leopold Hentschel
(Studienkoordination)

Apotheker Maximilian Günther
(Wissenschaftlicher Mitarbeiter)

Prof. Dr. Ulrich Jaehde
(Projektleiter)

Kontaktdaten der zuständigen Datenschutzaufsichtsbehörden und –verantwortlichen:

Für die Datenverarbeitung in diesem Projekt verantwortliche Person
Prof. Dr. Ulrich Jaehde
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Datenschutzbeauftragter der Rheinischen Friedrich-Wilhelms-Universität Bonn
Dr. Jörg Hartmann
Genscherallee 3
53113 Bonn
Tel.: 0228/736758
E-Mail: joerg.hartmann@uni-bonn.de

Datenschutzbeauftragte des Universitätsklinikum Carl Gustav Carus an der TU Dresden
Katrin Piehler
01304 Dresden
Tel.: 0351/4583245

Appendic II-A2: Informed consent

UNIVERSITÄT BONN
RHEINISCHE FRIEDRICH-WILHELMS-UNIVERSITÄT BONN
Pharmazeutisches Institut
Klinische Pharmazie
Leitung: Prof. Dr. Ulrich Jaehde

Einwilligungserklärung

Vorname, Name: _____

Geburtsdatum: _____

Das Original dieser Einwilligungserklärung verbleibt bei den Unterlagen. Eine Kopie der Einwilligungserklärung wird dem Patienten ausgehändigt.

Hiermit erkläre ich, dass ich die Patienteninformation zur wissenschaftlichen Untersuchung

„Auswahl patientenrelevanter Symptome zur Entwicklung entitätsspezifischer PRO-CTCAE-Fragebögen für Patienten mit Multiplem Myelom oder Prostatakarzinom“

und diese Einwilligungserklärung in Kopie erhalten habe.

○ Ich wurde ausreichend mündlich und schriftlich über die wissenschaftliche Untersuchung informiert.

○ Ich weiß, dass ich jederzeit meine Einwilligung, ohne Angaben von Gründen, widerrufen kann, ohne dass dies für mich nachteilige Folgen hat. Beim Widerruf meiner Einwilligung, an der Studie teilzunehmen, habe ich das Recht, die Löschung aller meiner bis dahin gespeicherten personenbezogenen Daten zu verlangen.

○ Ich weiß, dass ich das Recht habe, Auskunft über meine persönlichen Daten zu erhalten, sowie gegebenenfalls deren Berichtigung zu verlangen. Auf Wunsch kann ich eine unentgeltliche Kopie meiner Daten erhalten.

○ Mir ist bewusst, dass meine Daten am Ende der Erhebung, in etwa drei Monaten, anonymisiert werden und dass danach die Zuordnung zu meiner Person und damit eine Auskunft über die Daten, deren Berichtigung oder Löschung nicht mehr möglich ist.

◯ **Mir ist bekannt, dass ich bei Verstößen gegen das Datenschutzrecht ein Beschwerderecht beim Sächsischen Datenschutzbeauftragten habe.**

◯ **Ich bin damit einverstanden, dass meine Angaben, Krankheitsdaten und personenbezogenen Daten, einschließlich Daten zu Symptomen, die das Sexualleben betreffen, im Rahmen der wissenschaftlichen Untersuchung in pseudonymer Form erhoben werden und durch einen wissenschaftlichen Mitarbeiter der Universität Bonn ausgewertet werden. Es wird gewährleistet, dass meine persönlichen Daten nicht an Dritte weitergegeben werden. Bei der Veröffentlichung in einer wissenschaftlichen Zeitschrift wird aus den Daten nicht hervorgehen, wer an dieser Untersuchung teilgenommen hat. Meine persönlichen Daten unterliegen dem Datenschutzgesetz.**

◯ Mit der vorstehend geschilderten Vorgehensweise bin ich einverstanden und bestätige dies mit meiner Unterschrift.

_____ , den _____ _____

(Ort) (Datum) (Unterschrift Patientin/Patient)

_____

(Name aufklärende Person)

_____ , den _____ _____

(Ort) (Datum) (Unterschrift aufklärende Person)

Appendix II-A3: Patient questionnaire

UNIVERSITÄT BONN
RHEINISCHE FRIEDRICH-WILHELMS-UNIVERSITÄT BONN
Pharmazeutisches Institut
Klinische Pharmazie
Leitung: Prof. Dr. Ulrich Jaehde

Patientennummer: _____

Fragebogen zur Auswahl patientenrelevanter Symptome zur Entwicklung entitätsspezifischer PRO-CTCAE-Fragebögen für Patienten mit Multiplem Myelom oder Prostatakarzinom

Sehr geehrte Patientin, sehr geehrter Patient,

mit dem vorliegenden Fragebogen möchten wir Sie bitten, uns bei der Entwicklung eines **Fragebogens zum Erkennen** von subjektiv empfundenen **Symptomen und Nebenwirkungen** der Krebstherapie bei Patienten mit Ihrer Krebserkrankung zu unterstützen.

Der Fragebogen kann innerhalb **von 15 Minuten** ausgefüllt werden.

- Im ersten Teil des Fragebogens bitten wir Sie, für alle Symptome anzukreuzen, ob diese in der Zeit Ihrer Krebstherapie jemals aufgetreten sind. Ist ein Symptom aufgetreten, kreuzen Sie bitte das Feld „**Ja**“ an. Ist das Symptom während der Therapie bisher nicht aufgetreten, bitte das Feld „**Nein**“ ankreuzen.
  Außerdem bitten wir Sie, einzuschätzen, ob das jeweilige Symptom bei Krebspatienten mit Ihrer Tumordiagnose in einem Fragebogen abgefragt werden sollte. Kreuzen Sie dazu bitte eine der Antworten „**Ja**“, „**Nein**“, oder „**Weiß nicht**“ an.
- Im zweiten Teil des Fragebogens werden **allgemeine Angaben** zu Ihrer Person abgefragt, die für die Einordnung Ihrer Antworten bei der wissenschaftlichen Auswertung von Bedeutung sind.

Bitte füllen Sie den Fragebogen **vollständig** aus, da dies für die Auswertung sehr wichtig ist.

Mit Ihrer ausdrücklichen Zustimmung wird zusätzlich zu diesem Fragebogen aus Ihrer Patientenakte erfasst, welche **Medikamente** Sie für die Therapie Ihrer Krebserkrankung erhalten und in welchem **Stadium** sich Ihre Erkrankung befindet. Die Daten aus dem Fragebogen werden dann zusammen mit dieser Information wissenschaftlich ausgewertet.

Die Auswertung Ihrer Angaben erfolgt **pseudonymisiert**, d.h. Ihrem Namen und Geburtsdatum wird eine Patientennummer zugeordnet. Die von Ihnen gemachten Angaben werden streng vertraulich behandelt und können Ihrer Person ohne Kenntnis des Schlüssels nicht zugeordnet werden. Notieren Sie deshalb bitte weder Name noch Anschrift auf dem Bogen.

Vielen Dank für Ihre Unterstützung!

Dr. Katharina Schütte
(Ärztlicher Leiter Dresden)

Dipl.-Psych. Leopold Hentschel
(Studienkoordination Dresden)

Apotheker Maximilian Günther
(Wissenschaftlicher Mitarbeiter)

Prof. Dr. Ulrich Jaehde
(Projektleiter)

Version: 30.11.2018

Patientennummer: _____

Teil 1: Fragebogen zu Symptomen

Bitte **kreuzen** Sie für jedes Symptom an, ob es während Ihrer Krebstherapie aufgetreten ist und ob es in einem Fragebogen abgefragt werden sollte.

Symptome in Mund und Rachen	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Wunde oder offene Stellen in Mund oder Hals (Mucositis)	Ja	Nein	Ja	Nein	Weiß nicht
2. Mundtrockenheit	Ja	Nein	Ja	Nein	Weiß nicht
3. Schwierigkeiten beim Schlucken	Ja	Nein	Ja	Nein	Weiß nicht
4. Rissige Mundwinkel	Ja	Nein	Ja	Nein	Weiß nicht
5. Veränderungen der Stimme	Ja	Nein	Ja	Nein	Weiß nicht
6. Heiserkeit	Ja	Nein	Ja	Nein	Weiß nicht

Symptome der Atemwege	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Kurzatmigkeit (Dyspnoe)	Ja	Nein	Ja	Nein	Weiß nicht
2. Husten	Ja	Nein	Ja	Nein	Weiß nicht
3. Pfeifendes Atemgeräusch der Lunge (Giemen)	Ja	Nein	Ja	Nein	Weiß nicht

Symptome des Magen-Darm-Traktes	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Appetitmangel	Ja	Nein	Ja	Nein	Weiß nicht
2. Übelkeit	Ja	Nein	Ja	Nein	Weiß nicht
3. Erbrechen	Ja	Nein	Ja	Nein	Weiß nicht
4. Verstopfung (Obstipation)	Ja	Nein	Ja	Nein	Weiß nicht
5. Durchfall (Diarrhöe)	Ja	Nein	Ja	Nein	Weiß nicht
6. Bauchschmerzen	Ja	Nein	Ja	Nein	Weiß nicht
7. Sodbrennen	Ja	Nein	Ja	Nein	Weiß nicht
8. Blähungen (Flatulenz)	Ja	Nein	Ja	Nein	Weiß nicht
9. Geschmacksveränderungen beim Essen oder Trinken	Ja	Nein	Ja	Nein	Weiß nicht
10. Schluckauf	Ja	Nein	Ja	Nein	Weiß nicht
11. Stuhlgang nicht kontrollieren oder halten können (Stuhlinkontinenz)	Ja	Nein	Ja	Nein	Weiß nicht

Patientennummer: _____

Symptome der Haut	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Hautausschlag	Ja	Nein	Ja	Nein	Weiß nicht
2. Trockene Haut	Ja	Nein	Ja	Nein	Weiß nicht
3. Akne oder Pickel im Gesicht oder auf dem Brustkorb	Ja	Nein	Ja	Nein	Weiß nicht
4. Haarausfall	Ja	Nein	Ja	Nein	Weiß nicht
5. Juckreiz	Ja	Nein	Ja	Nein	Weiß nicht
6. Juckende, rote Hautschwellung (Nesselfieber)	Ja	Nein	Ja	Nein	Weiß nicht
7. Hautausschlag an Händen oder Füßen, der Brennen, Abschälen der Haut, Rötung oder Schmerzen verursachen kann (Hand-Fuß-Syndrom)	Ja	Nein	Ja	Nein	Weiß nicht
8. Verlust von Finger- oder Fußnägeln	Ja	Nein	Ja	Nein	Weiß nicht
9. Veränderungen der Finger- oder Fußnägel (Furchen, Unebenheiten oder Farbveränderungen der Nägel)	Ja	Nein	Ja	Nein	Weiß nicht
10. Erhöhte Sonnenempfindlichkeit der Haut	Ja	Nein	Ja	Nein	Weiß nicht
11. Druckstellen (Dekubitus)	Ja	Nein	Ja	Nein	Weiß nicht
12. Dunkle Veränderungen der Haut	Ja	Nein	Ja	Nein	Weiß nicht
13. Dehnungsstreifen	Ja	Nein	Ja	Nein	Weiß nicht
14. Hautverbrennungen nach Bestrahlung	Ja	Nein	Ja	Nein	Weiß nicht

Symptome des Herz-Kreislauf-Systems	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Geschwollene Arme oder Beine	Ja	Nein	Ja	Nein	Weiß nicht
2. Herzklopfen, -Rasen oder unregelmäßiger Puls (Palpitation)	Ja	Nein	Ja	Nein	Weiß nicht

Symptome des Nervensystems und des Gedächtnisses	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Taubheit oder Kribbeln in Händen oder Füßen	Ja	Nein	Ja	Nein	Weiß nicht
2. Schwindel	Ja	Nein	Ja	Nein	Weiß nicht
3. Vergesslichkeit	Ja	Nein	Ja	Nein	Weiß nicht
4. Konzentrationsprobleme	Ja	Nein	Ja	Nein	Weiß nicht

Patientennummer: _____

Symptome der Augen und Ohren	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Verschwommenes Sehen	Ja	Nein	Ja	Nein	Weiß nicht
2. Blitze vor den Augen	Ja	Nein	Ja	Nein	Weiß nicht
3. Schwimmende Punkte, Linien oder Flecken vor den Augen (Mouches volantes)	Ja	Nein	Ja	Nein	Weiß nicht
4. Tränende Augen	Ja	Nein	Ja	Nein	Weiß nicht
5. Ohrengeräusche (z.B. Pfeifen)	Ja	Nein	Ja	Nein	Weiß nicht

Schmerzsymptome	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Schmerzen, generell	Ja	Nein	Ja	Nein	Weiß nicht
2. Kopfschmerzen	Ja	Nein	Ja	Nein	Weiß nicht
3. Muskelschmerzen	Ja	Nein	Ja	Nein	Weiß nicht
4. Gelenkschmerzen (z.B. Ellenbogen, Knie, Schultern)	Ja	Nein	Ja	Nein	Weiß nicht

Psychische Symptome	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Angst	Ja	Nein	Ja	Nein	Weiß nicht
2. Schlafstörungen (Probleme beim Ein- oder Durchschlafen oder zu frühes Aufwachen)	Ja	Nein	Ja	Nein	Weiß nicht
3. Müdigkeit, Erschöpfung oder fehlende Energie (Fatigue)	Ja	Nein	Ja	Nein	Weiß nicht
4. Traurigkeit	Ja	Nein	Ja	Nein	Weiß nicht
5. Mutlosigkeit (Gefühl, dass einen nichts aufmuntern kann)	Ja	Nein	Ja	Nein	Weiß nicht

Patientennummer: _____

Symptome der Harnwege und Sexualorgane	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Schmerzen beim Wasserlassen	Ja	Nein	Ja	Nein	Weiß nicht
2. Plötzlicher starker Drang zum Wasserlassen	Ja	Nein	Ja	Nein	Weiß nicht
3. Häufiges Wasserlassen	Ja	Nein	Ja	Nein	Weiß nicht
4. Ungewöhnliche Veränderung der Urinfarbe	Ja	Nein	Ja	Nein	Weiß nicht
5. Urin nicht halten können (Urininkontinenz)	Ja	Nein	Ja	Nein	Weiß nicht
6. Weniger Interesse an Sexualität	Ja	Nein	Ja	Nein	Weiß nicht
7. Es dauert zu lange oder ist nicht möglich, einen Orgasmus zu bekommen	Ja	Nein	Ja	Nein	Weiß nicht
8. Hitzewallungen	Ja	Nein	Ja	Nein	Weiß nicht
9. Schwellung oder Druckempfindlichkeit der Brust	Ja	Nein	Ja	Nein	Weiß nicht
Symptome, die nur Männer betreffen					
1. Probleme, eine Erektion zu bekommen oder zu halten	Ja	Nein	Ja	Nein	Weiß nicht
2. Probleme, einen Samenerguss zu bekommen	Ja	Nein	Ja	Nein	Weiß nicht
Symptome, die nur Frauen betreffen					
1. Unregelmäßige Regelblutung	Ja	Nein	Ja	Nein	Weiß nicht
2. Ausbleiben einer erwarteten Regelblutung	Ja	Nein	Ja	Nein	Weiß nicht
3. Ungewöhnlicher Ausfluss aus der Scheide	Ja	Nein	Ja	Nein	Weiß nicht
4. Scheidentrockenheit	Ja	Nein	Ja	Nein	Weiß nicht
5. Schmerzen der Scheide beim Geschlechtsverkehr	Ja	Nein	Ja	Nein	Weiß nicht

Verschiedene Symptome	*Ist das Symptom bei Ihnen aufgetreten?*		*Soll das Symptom in einem Fragebogen abgefragt werden?*		
1. Mehr blaue Flecken	Ja	Nein	Ja	Nein	Weiß nicht
2. Nasenbluten	Ja	Nein	Ja	Nein	Weiß nicht
3. Schüttelfrost	Ja	Nein	Ja	Nein	Weiß nicht
4. Verstärktes Schwitzen nicht in Verbindung mit Hitzewallungen	Ja	Nein	Ja	Nein	Weiß nicht
5. Vermindertes Schwitzen	Ja	Nein	Ja	Nein	Weiß nicht
6. Schmerzen, Schwellung oder Rötung an der Einstichstelle einer Infusion/Injektion	Ja	Nein	Ja	Nein	Weiß nicht
7. Stärkerer Körpergeruch	Ja	Nein	Ja	Nein	Weiß nicht

Teil 2: Allgemeine Angaben

Patientennummer: _____

Bitte machen Sie folgende Angaben zu Ihrer Person. Falls nötig, bitte **ankreuzen**.

1.	**Lebensalter in Jahren**	_____	
2.	**Geschlecht**	◯ Männlich	◯ Weiblich
3.	**Größe in Metern (ca.)**	_____	
4.	**Gewicht in Kilogramm (ca.)**	_____	
5.	**Familienstand**	◯ Ledig	◯ Verheiratet/ Lebensgemeinschaft
		◯ Geschieden	◯ Verwitwet
6.	**Höchster Ausbildungsabschluss**	◯ Volksschulabschluss	◯ Hauptschulabschluss
		◯ Mittlere Reife/ Fachhochschulreife	◯ Gesellenprüfung
		◯ Abitur (Hochschulreife)	◯ Meistertitel
		◯ Fachhochschulabschluss	◯ Hochschulabschluss
		◯ Höherer universitärer Abschluss (Dr., Priv. Doz., Prof., etc.)	
7.	**Aktueller Beruf**	◯ Hausfrau/-Mann	◯ Schüler/-in / Student/-in
		◯ Beamter/-r	◯ Rentner/-in
		◯ Angestellte/-r	◯ Selbstständige/-r
		◯ Arbeiter/-in	◯ Handwerker/-in
8.	**Diagnose**	◯ Prostatakrebs	◯ Multiples Myelom
9.	**Zeitpunkt der Diagnose (Monat/Jahr)**	_____/_____	
10.	**Wurden Sie vor dieser Therapie schon mit anderen Krebsmedikamenten behandelt?**	◯ Ja	◯ Nein
11.	**Mussten Sie eine oder mehrere Krebstherapien aufgrund von Nebenwirkungen abbrechen?**	◯ Ja	◯ Nein
		Wenn ja, wegen welcher Nebenwirkung(en)?	_____

1.	**Art der aktuellen Krebstherapie (Mehrfachnennungen sind möglich)**	◯	Orale Medikamente (z.B. Tabletten, Kapseln)	◯ Intravenöse Medikamente (z.B. Infusion, Spritze)
		◯	Bestrahlung	◯ Operation
		◯	Aktive Überwachung ohne Therapie	
2.	**Aktuelle Therapiesituation**	◯	Stationäre Behandlung	◯ Ambulante Behandlung

Vielen Dank für Ihre Unterstützung!

Appendix II-A4: Documentation form

UNIVERSITÄT BONN
RHEINISCHE FRIEDRICH-WILHELMS-UNIVERSITÄT BONN
Pharmazeutisches Institut
Klinische Pharmazie
Leitung: Prof. Dr. Ulrich Jaehde

Patientennummer: _____

Dokumentationsformular zur Auswahl patientenrelevanter Symptome zur Entwicklung entitätsspezifischer PRO-CTCAE-Fragebögen für Patienten mit Multiplem Myelom oder Prostatakarzinom

Tumorerkrankung

Diagnose: _____ **Erstdiagnose (Datum)**: _____

Metastasierung: ◯ Ja ◯ Nein

Wenn Ja, Art der Metastasen: _____

Rezidiv: ◯ Ja ◯ Nein

Wenn Ja, um das wievielte Rezidiv handelt es sich? _____

Tumorklassifizierung: *nur für zutreffende Tumorentität ausfüllen!*

Multiples Myelom

1) Stadium (ISS):_____
2) Stadium (Salmon & Durie): _____

Prostatakarzinom

1) TNM: T: _____ N: _____ M: _____
2) Letzter PSA-Wert (ng/ml):_____
3) Gleason-Score:_____+_____ Gleason-Grade-Gruppe:_____
4) Prognostische Gruppierung (AJCC): _____

Tumortherapie

Aktuelle Tumortherapie

Therapieintention	◯ Kurativ	◯ Palliativ
	◯ Adjuvant	◯ Neoadjuvant
Simultane Strahlentherapie	◯ Ja	◯ Nein
Operation	◯ Ja	◯ Nein

Andere Therapieform: _____

Tumortherapeutika (Wirkstoff und Handelsname)	**Stärke**	**Applikation**	**Zyklus**
1.			
2.			
3.			
4.			
5.			

Aktuelle Supportivtherapie für folgende Indikationen (zutreffendes bitte ankreuzen)

Anämie	◯	**Neutropenie**	◯
Nausea und Emesis	◯	**Diarrhoe**	◯
Obstipation	◯	**Obstipation**	◯
Mucositis	◯	**Hauttoxizität**	◯
Periphere Neuropathie (CIPN)	◯	**Ossäre Komplikationen**	◯
Schmerzen	◯	**Magenprotektion**	◯
Psychische Probleme/ Schlafstörungen	◯	**Antikoagulation**	◯

Weitere Indikationen:

Patientennummer: _____

Frühere Tumortherapie

Therapieintention	◯ Kurativ	◯ Palliativ
	◯ Adjuvant	◯ Neoadjuvant
Simultane Strahlentherapie	◯ Ja	◯ Nein
Operation	◯ Ja	◯ Nein

Andere Therapieform: _____

Tumortherapeutika (Wirkstoff und Handelsname)	**Stärke**	**Applikation**	**Zyklus**
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			

Appendix II-B1: PRO-CTCAE item library

Patient-Reported Outcomes version Of The Common Terminology Criteria For Adverse Events (PRO-CTCAE™)

QUICK GUIDE TO THE ITEM LIBRARY*

Oral	
Dry mouth	S
Difficulty swallowing	S
Mouth/throat sores	SI
Cracking at the corners of the mouth (cheilosis/cheilitis)	S
Voice quality changes	P
Hoarseness	S

Gastrointestinal	
Taste changes	S
Decreased appetite	SI
Nausea	FS
Vomiting	FS
Heartburn	FS
Gas	P
Bloating	FS
Hiccups	FS
Constipation	S
Diarrhea	F
Abdominal pain	FSI
Fecal incontinence	FI

Respiratory	
Shortness of breath	SI
Cough	SI
Wheezing	S

Cardio/Circulatory	
Swelling	FSI
Heart palpitations	FS

Cutaneous	
Rash	P
Skin dryness	S
Acne	S
Hair loss	A
Itching	S
Hives	P
Hand-foot syndrome	S
Nail loss	P
Nail ridging	P
Nail discoloration	P
Sensitivity to sunlight	P
Bed/pressure sores	P
Radiation skin reaction	S
Skin darkening	P
Stretch marks	P

Neurological	
Numbness & tingling	SI
Dizziness	SI

Visual/Perceptual	
Blurred vision	SI
Flashing lights	P
Visual floaters	P
Watery eyes	SI
Ringing in ears	S

Attention/Memory	
Concentration	SI
Memory	SI

Pain	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

Sleep/Wake	
Insomnia	SI
Fatigue	SI

Mood	
Anxious	FSI
Discouraged	FSI
Sad	FSI

Genitourinary	
Irregular periods/vaginal bleeding	P
Missed expected menstrual period	P
Vaginal discharge	A
Vaginal dryness	S
Painful urination	S
Urinary urgency	FI
Urinary frequency	FI
Change in usual urine color	P
Urinary incontinence	FI

Sexual	
Achieve and maintain erection	S
Ejaculation	F
Decreased libido	S
Delayed orgasm	P
Unable to have orgasm	P
Pain w/sexual intercourse	S

Miscellaneous	
Breast swelling and tenderness	S
Bruising	P
Chills	FS
Increased sweating	FS
Decreased sweating	P
Hot flashes	FS
Nosebleed	FS
Pain and swelling at injection site	P
Body odor	S

Attributes	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence
A: Amount	

NIH National Cancer Institute

*Complete library of items available at: https://healthcaredelivery.cancer.gov/pro-ctcae

Version date: 3/11/2020

Appendix II-B2: PRO-CTCAE symptom numbering

Symptom in the questionnaire	PRO-CTCAE term
Oral symptoms	
1. Mucositis	Mouth/throat sores
2. Mundtrockenheit	Dry mouth
3. Schwierigkeiten beim Schlucken	Difficulty swallowing
4. Rissige Mundwinkel	Cracking at the corners of the mouth
5. Stimmveränderungen	Voice quality changes
6. Heiserkeit	Hoarsness
Respiratory symptoms	
7. Kurzatmigkeit	Shortness of breath
8. Husten	Cough
9. Giemen	Weezing
Gastrointestinal symptoms	
10. Appetitmangel	Decreased appetite
11. Übelkeit	Nausea
12. Erbrechen	Vomiting
13. Verstopfung	Constipation
14. Durchfall	Diarrhea
15. Bauchschmerzen	Abdominal pain
16. Sodbrennen	Heartburn
17. Blähungen	Bloating
18. Geschmacksveränderungen	Taste changes
19. Schluckauf	Hiccups
20. Stuhlinkontinenz	Fecal incontinence
Cutaneous symptoms	
21. Hautausschlag	Rash
22. Trockene Haut	Dry skin
23. Akne	Acne
24. Haarausfall	Hair loss
25. Juckreiz	Itching
26. Nesselfieber	Hives
27. Hand-Fuß-Syndrom	Hand-foot-syndrome
28. Verlust von Finger-/Fußnägeln	Nail loss
29. Veränderungen von Finger-/Fußnägeln	Nail ridging/dicoloration
30. Sonnenempfindlichkeit	Sensitivity to sunlight
31. Druckstellen	Bed/pressure sores
32. Dunkle Hautveränderungen	Skin darkening

33. Dehnungsstreifen	Stretch marks
34. Hautverbrennungen nach Bestrahlung	Radiation skin reaction

Cardio/circulatory symptoms

35. Geschwollene Gliedmaßen	Swelling
36. Palpitationen	Heart palpitations

Symptoms of the nervous system

37. Taubheit/Kribbeln in Händen/Füßen	Numbness & tingling
38. Schwindel	Dizziness
39. Vergesslichkeit	Memory
40. Konzentrationsprobleme	Concentration

Perceptual symptoms

41. Verschwommenes Sehen	Blurred vision
42. Blitze vor den Augen	Flashing lights
43. Mouches volantes	Visual floaters
44. Tränende Augen	Watery eyes
45. Ohrengeräusche	Ringing in ears

Pain-related symptoms

46. Schmerzen, generell	General pain
47. Kopfschmerzen	Headache
48. Muskelschmerzen	Muscle pain
49. Gelenkschmerzen	Joint pain

Mood-related symptoms

50. Angst	Anxious
51. Schlafstörungen	Insomnia
52. Fatigue	Fatigue
53. Traurigkeit	Sad
54. Mutlosigkeit	Discouraged

Urogenital symptoms

55. Schmerzen beim Wasserlassen	Painful urination
56. Plötzlicher starker Drang zum Wasserlassen	Urinary urgency
57. Häufiges Wasserlassen	Urinary frequency
58. Ungewöhnliche Veränderung der Urinfarbe	Change in usual urine colour
59. Urininkontinenz	Urinary incontinence
60. Weniger Interesse an Sexualität	Decreased libido
61. Ausbleibender Orgasmus	Unable to have orgasm

62. Hitzewallungen	Hot flashes
63. Schwellung/Druckempfindlichkeit der Brust	Breast swelling and tenderness

Symptoms regarding only male patients

64. Erektionsprobleme	Achieve and maintain erection
65. Ejakulationsprobleme	Ejaculation

Symptoms regarding only female patients

66. Unregelmäßige Regelblutungen	Irregular periods/vaginal bleeding
67. Ausbleibende Regelblutung	Missed expected menstrual period
68. Ungewöhnlicher Ausfluss	Vaginal discharge
69. Scheidentrockenheit	Vaginal dryness
70. Schmerzen beim Geschlechtsverkehr	Pain w/sexual intercourse

Miscellaneous symptoms

71. Vermehrt blaue Flecken	Bruising
72. Nasenbluten	Nosebleed
73. Schüttelfrost	Chills
74. Verstärktes Schwitzen	Increased sweating
75. Vermindertes Schwitzen	Decreased sweating
76. Schmerzen/Schwellung/Rötung an der Injektionsstelle	Pain and swelling at injection site
77. Verstärkter Körpergeruch	Body odor

Appendix II-B3: Breast cancer – symptom prevalence

Symptom Number	PRO-CTCAE term	Prevalence Score
1	Mouth/throat sores	0.414
2	Dry mouth	0.624
3	Difficulty swallowing	0.340
4	Cracking at the corners of the mouth	0.333
5	Voice quality changes	0.165
6	Hoarsness	0.208
7	Shortness of breath	0.485
8	Cough	0.270
9	Weezing	0.099
10	Decreased appetite	0.434
11	Nausea	0.545
12	Vomiting	0.180
13	Constipation	0.398
14	Diarrhea	0.475
15	Abdominal pain	0.343
16	Heartburn	0.343
17	Bloating	0.510
18	Taste changes	0.693
19	Hiccups	0.119
20	Fecal incontinence	0.120
21	Rash	0.374
22	Dry skin	0.780
23	Acne	0.150
24	Hair loss	0.851
25	Itching	0.434
26	Hives	0.160
27	Hand-foot-syndrome	0.340
28	Nail loss	0.250
29	Nail ridging/dicoloration	0.624
30	Sensitivity to sunlight	0.374
31	Bed/pressure sores	0.040
32	Skin darkening	0.140
33	Stretch marks	0.020

Symptom Number	PRO-CTCAE term	Prevalence Score
34	Radiation skin reaction	0.213
35	Swelling	0.347
36	Heart palpitations	0.343
37	Numbness & tingling	0.653
38	Dizziness	0.460
39	Memory	0.500
40	Concentration	0.604
41	Blurred vision	0.475
42	Flashing lights	0.194
43	Visual floaters	0.250
44	Watery eyes	0.590
45	Ringing in ears	0.293
46	General pain	0.444
47	Headache	0.434
48	Muscle pain	0.545
49	Joint pain	0.535
50	Anxious	0.394
51	Insomnia	0.770
52	Fatigue	0.832
53	Sad	0.480
54	Discouraged	0.263
55	Painful urination	0.139
56	Urinary urgency	0.330
57	Urinary frequency	0.426
58	Change in usual urine colour	0.208
59	Urinary incontinence	0.220
60	Decreased libido	0.660
61	Unable to have orgasm	0.326
62	Hot flashes	0.636
63	Breast swelling and tenderness	0.316
64	Achieve and maintain erection	0.000
65	Ejaculation	0.000
66	Irregular periods/vaginal bleeding	0.118
67	Missed expected menstrual period	0.216
68	Vaginal discharge	0.075

Symptom Number	PRO-CTCAE term	Prevalence Score
69	Vaginal dryness	0.479
70	Pain w/sexual intercourse	0.304
71	Bruising	0.277
72	Nosebleed	0.475
73	Chills	0.303
74	Increased sweating	0.337
75	Decreased sweating	0.032
76	Pain and swelling at injection site	0.238
77	Body odor	0.188

Appendix II-B4: Breast cancer – symptom importance

Symptom Number	PRO-CTCAE term	Importance Score
1	Mouth/throat sores	0.814
2	Dry mouth	0.704
3	Difficulty swallowing	0.740
4	Cracking at the corners of the mouth	0.616
5	Voice quality changes	0.615
6	Hoarsness	0.573
7	Shortness of breath	0.809
8	Cough	0.688
9	Weezing	0.672
10	Decreased appetite	0.789
11	Nausea	0.856
12	Vomiting	0.823
13	Constipation	0.856
14	Diarrhea	0.842
15	Abdominal pain	0.763
16	Heartburn	0.672
17	Bloating	0.646
18	Taste changes	0.776
19	Hiccups	0.490
20	Fecal incontinence	0.776
21	Rash	0.825
22	Dry skin	0.668
23	Acne	0.589
24	Hair loss	0.793
25	Itching	0.771
26	Hives	0.734
27	Hand-foot-syndrome	0.820
28	Nail loss	0.791
29	Nail ridging/dicoloration	0.753
30	Sensitivity to sunlight	0.667
31	Bed/pressure sores	0.629
32	Skin darkening	0.620
33	Stretch marks	0.490

Symptom Number	PRO-CTCAE term	Importance Score
34	Radiation skin reaction	0.825
35	Swelling	0.842
36	Heart palpitations	0.845
37	Numbness & tingling	0.866
38	Dizziness	0.832
39	Memory	0.784
40	Concentration	0.816
41	Blurred vision	0.849
42	Flashing lights	0.753
43	Visual floaters	0.740
44	Watery eyes	0.693
45	Ringing in ears	0.782
46	General pain	0.853
47	Headache	0.802
48	Muscle pain	0.849
49	Joint pain	0.844
50	Anxious	0.804
51	Insomnia	0.809
52	Fatigue	0.888
53	Sad	0.753
54	Discouraged	0.758
55	Painful urination	0.760
56	Urinary urgency	0.684
57	Urinary frequency	0.682
58	Change in usual urine colour	0.679
59	Urinary incontinence	0.791
60	Decreased libido	0.583
61	Unable to have orgasm	0.521
62	Hot flashes	0.722
63	Breast swelling and tenderness	0.755
64	Achieve and maintain erection	0.000
65	Ejaculation	0.000
66	Irregular periods/vaginal bleeding	0.703
67	Missed expected menstrual period	0.691
68	Vaginal discharge	0.683

Symptom Number	PRO-CTCAE term	Importance Score
69	Vaginal dryness	0.707
70	Pain w/sexual intercourse	0.689
71	Bruising	0.694
72	Nosebleed	0.747
73	Chills	0.724
74	Increased sweating	0.622
75	Decreased sweating	0.542
76	Pain and swelling at injection site	0.679
77	Body odor	0.593

Appendix II-B5: Breast cancer – combined prevalence-importance scores

Symptom Number	PRO-CTCAE term	Combined P-I Score
1	Mouth/throat sores	48
2	Dry mouth	55
3	Difficulty swallowing	79
4	Cracking at the corners of the mouth	108
5	Voice quality changes	130
6	Hoarsness	129
7	Shortness of breath	37
8	Cough	102
9	Weezing	129
10	Decreased appetite	52
11	Nausea	16
12	Vomiting	77
13	Constipation	34
14	Diarrhea	33
15	Abdominal pain	68
16	Heartburn	94
17	Bloating	78
18	Taste changes	35
19	Hiccups	144
20	Fecal incontinence	97
21	Rash	46
22	Dry skin	63
23	Acne	134
24	Hair loss	24
25	Itching	57
26	Hives	106
27	Hand-foot-syndrome	56
28	Nail loss	76
29	Nail ridging/dicoloration	47
30	Sensitivity to sunlight	94
31	Bed/pressure sores	136
32	Skin darkening	131
33	Stretch marks	149

Symptom Number	PRO-CTCAE term	Combined P-I Score
34	Radiation skin reaction	70
35	Swelling	45
36	Heart palpitations	44
37	Numbness & tingling	9
38	Dizziness	36
39	Memory	44
40	Concentration	28
41	Blurred vision	27
42	Flashing lights	96
43	Visual floaters	93
44	Watery eyes	61
45	Ringing in ears	76
46	General pain	30
47	Headache	48
48	Muscle pain	19
49	Joint pain	24
50	Anxious	53
51	Insomnia	23
52	Fatigue	3
53	Sad	56
54	Discouraged	85
55	Painful urination	100
56	Urinary urgency	96
57	Urinary frequency	84
58	Change in usual urine colour	115
59	Urinary incontinence	79
60	Decreased libido	76
61	Unable to have orgasm	117
62	Hot flashes	52
63	Breast swelling and tenderness	80
64	Achieve and maintain erection	152
65	Ejaculation	152
66	Irregular periods/vaginal bleeding	117
67	Missed expected menstrual period	106
68	Vaginal discharge	126

Symptom Number	PRO-CTCAE term	Combined P-I Score
69	Vaginal dryness	65
70	Pain w/sexual intercourse	97
71	Bruising	97
72	Nosebleed	60
73	Chills	90
74	Increased sweating	105
75	Decreased sweating	146
76	Pain and swelling at injection site	110
77	Body odor	129

Appendix II-B6: Multiple myeloma – symptom prevalence

Symptom Number	PRO-CTCAE term	Prevalence Score
1	Mouth/throat sores	0.402
2	Dry mouth	0.670
3	Difficulty swallowing	0.349
4	Cracking at the corners of the mouth	0.234
5	Voice quality changes	0.264
6	Hoarsness	0.336
7	Shortness of breath	0.636
8	Cough	0.415
9	Weezing	0.274
10	Decreased appetite	0.720
11	Nausea	0.673
12	Vomiting	0.402
13	Constipation	0.528
14	Diarrhea	0.642
15	Abdominal pain	0.374
16	Heartburn	0.336
17	Bloating	0.491
18	Taste changes	0.738
19	Hiccups	0.236
20	Fecal incontinence	0.168
21	Rash	0.383
22	Dry skin	0.701
23	Acne	0.151
24	Hair loss	0.794
25	Itching	0.457
26	Hives	0.112
27	Hand-foot-syndrome	0.093
28	Nail loss	0.000
29	Nail ridging/dicoloration	0.421
30	Sensitivity to sunlight	0.387
31	Bed/pressure sores	0.037
32	Skin darkening	0.151
33	Stretch marks	0.000

Symptom Number	PRO-CTCAE term	Prevalence Score
34	Radiation skin reaction	0.067
35	Swelling	0.439
36	Heart palpitations	0.434
37	Numbness & tingling	0.701
38	Dizziness	0.477
39	Memory	0.368
40	Concentration	0.542
41	Blurred vision	0.467
42	Flashing lights	0.159
43	Visual floaters	0.280
44	Watery eyes	0.262
45	Ringing in ears	0.290
46	General pain	0.670
47	Headache	0.321
48	Muscle pain	0.607
49	Joint pain	0.594
50	Anxious	0.519
51	Insomnia	0.686
52	Fatigue	0.869
53	Sad	0.387
54	Discouraged	0.283
55	Painful urination	0.150
56	Urinary urgency	0.330
57	Urinary frequency	0.514
58	Change in usual urine colour	0.215
59	Urinary incontinence	0.105
60	Decreased libido	0.631
61	Unable to have orgasm	0.461
62	Hot flashes	0.415
63	Breast swelling and tenderness	0.124
64	Achieve and maintain erection	0.538
65	Ejaculation	0.415
66	Irregular periods/vaginal bleeding	0.114
67	Missed expected menstrual period	0.147
68	Vaginal discharge	0.111

Symptom Number	PRO-CTCAE term	Prevalence Score
69	Vaginal dryness	0.528
70	Pain w/sexual intercourse	0.371
71	Bruising	0.368
72	Nosebleed	0.178
73	Chills	0.364
74	Increased sweating	0.551
75	Decreased sweating	0.131
76	Pain and swelling at injection site	0.243
77	Body odor	0.187

Appendix II-B7: Multiple myeloma – symptom importance

Symptom Number	PRO-CTCAE term	Importance Score
1	Mouth/throat sores	0.863
2	Dry mouth	0.642
3	Difficulty swallowing	0.822
4	Cracking at the corners of the mouth	0.538
5	Voice quality changes	0.491
6	Hoarsness	0.524
7	Shortness of breath	0.886
8	Cough	0.789
9	Weezing	0.777
10	Decreased appetite	0.805
11	Nausea	0.886
12	Vomiting	0.848
13	Constipation	0.810
14	Diarrhea	0.867
15	Abdominal pain	0.738
16	Heartburn	0.635
17	Bloating	0.629
18	Taste changes	0.745
19	Hiccups	0.432
20	Fecal incontinence	0.767
21	Rash	0.818
22	Dry skin	0.682
23	Acne	0.651
24	Hair loss	0.832
25	Itching	0.769
26	Hives	0.769
27	Hand-foot-syndrome	0.827
28	Nail loss	0.720
29	Nail ridging/dicoloration	0.659
30	Sensitivity to sunlight	0.621
31	Bed/pressure sores	0.656
32	Skin darkening	0.638
33	Stretch marks	0.429

Symptom Number	PRO-CTCAE term	Importance Score
34	Radiation skin reaction	0.807
35	Swelling	0.877
36	Heart palpitations	0.877
37	Numbness & tingling	0.934
38	Dizziness	0.867
39	Memory	0.792
40	Concentration	0.821
41	Blurred vision	0.783
42	Flashing lights	0.743
43	Visual floaters	0.771
44	Watery eyes	0.690
45	Ringing in ears	0.764
46	General pain	0.925
47	Headache	0.863
48	Muscle pain	0.874
49	Joint pain	0.888
50	Anxious	0.911
51	Insomnia	0.896
52	Fatigue	0.921
53	Sad	0.825
54	Discouraged	0.874
55	Painful urination	0.783
56	Urinary urgency	0.700
57	Urinary frequency	0.740
58	Change in usual urine colour	0.750
59	Urinary incontinence	0.774
60	Decreased libido	0.688
61	Unable to have orgasm	0.639
62	Hot flashes	0.697
63	Breast swelling and tenderness	0.635
64	Achieve and maintain erection	0.750
65	Ejaculation	0.750
66	Irregular periods/vaginal bleeding	0.703
67	Missed expected menstrual period	0.703
68	Vaginal discharge	0.730

Symptom Number	PRO-CTCAE term	Importance Score
69	Vaginal dryness	0.730
70	Pain w/sexual intercourse	0.694
71	Bruising	0.790
72	Nosebleed	0.790
73	Chills	0.755
74	Increased sweating	0.736
75	Decreased sweating	0.543
76	Pain and swelling at injection site	0.693
77	Body odor	0.543

Appendix II-B8: Multiple myeloma – combined prevalence-importance score

Symptom Number	PRO-CTCAE term	Combined P-I Score
1	Mouth/throat sores	49
2	Dry mouth	73
3	Difficulty swallowing	65
4	Cracking at the corners of the mouth	130
5	Voice quality changes	128
6	Hoarsness	119
7	Shortness of breath	19
8	Cough	62
9	Weezing	85
10	Decreased appetite	30
11	Nausea	15
12	Vomiting	51
13	Constipation	43
14	Diarrhea	24
15	Abdominal pain	86
16	Heartburn	112
17	Bloating	92
18	Taste changes	47
19	Hiccups	132
20	Fecal incontinence	99
21	Rash	61
22	Dry skin	65
23	Acne	126
24	Hair loss	20
25	Itching	63
26	Hives	107
27	Hand-foot-syndrome	92
28	Nail loss	127
29	Nail ridging/dicoloration	91
30	Sensitivity to sunlight	106
31	Bed/pressure sores	137
32	Skin darkening	129
33	Stretch marks	153

Symptom Number	PRO-CTCAE term	Combined P-I Score
34	Radiation skin reaction	99
35	Swelling	37
36	Heart palpitations	38
37	Numbness & tingling	6
38	Dizziness	37
39	Memory	68
40	Concentration	39
41	Blurred vision	56
42	Flashing lights	107
43	Visual floaters	86
44	Watery eyes	112
45	Ringing in ears	88
46	General pain	11
47	Headache	63
48	Muscle pain	25
49	Joint pain	21
50	Anxious	25
51	Insomnia	12
52	Fatigue	4
53	Sad	56
54	Discouraged	61
55	Painful urination	96
56	Urinary urgency	101
57	Urinary frequency	68
58	Change in usual urine colour	99
59	Urinary incontinence	106
60	Decreased libido	72
61	Unable to have orgasm	91
62	Hot flashes	87
63	Breast swelling and tenderness	135
64	Achieve and maintain erection	59
65	Ejaculation	72
66	Irregular periods/vaginal bleeding	121
67	Missed expected menstrual period	118
68	Vaginal discharge	120

Symptom Number	PRO-CTCAE term	Combined P-I Score
69	Vaginal dryness	69
70	Pain w/sexual intercourse	96
71	Bruising	69
72	Nosebleed	88
73	Chills	83
74	Increased sweating	64
75	Decreased sweating	138
76	Pain and swelling at injection site	112
77	Body odor	130

Appendix II-B9: Prostate cancer – symptom prevalence

Symptom Number	PRO-CTCAE term	Prevalence Score
1	Mouth/throat sores	0.061
2	Dry mouth	0.394
3	Difficulty swallowing	0.076
4	Cracking at the corners of the mouth	0.091
5	Voice quality changes	0.167
6	Hoarsness	0.154
7	Shortness of breath	0.455
8	Cough	0.227
9	Weezing	0.182
10	Decreased appetite	0.212
11	Nausea	0.167
12	Vomiting	0.121
13	Constipation	0.431
14	Diarrhea	0.379
15	Abdominal pain	0.106
16	Heartburn	0.215
17	Bloating	0.333
18	Taste changes	0.303
19	Hiccups	0.061
20	Fecal incontinence	0.182
21	Rash	0.121
22	Dry skin	0.470
23	Acne	0.030
24	Hair loss	0.197
25	Itching	0.227
26	Hives	0.030
27	Hand-foot-syndrome	0.000
28	Nail loss	0.061
29	Nail ridging/dicoloration	0.258
30	Sensitivity to sunlight	0.152
31	Bed/pressure sores	0.000
32	Skin darkening	0.136
33	Stretch marks	0.000

Symptom Number	PRO-CTCAE term	Prevalence Score
34	Radiation skin reaction	0.092
35	Swelling	0.379
36	Heart palpitations	0.136
37	Numbness & tingling	0.379
38	Dizziness	0.318
39	Memory	0.348
40	Concentration	0.227
41	Blurred vision	0.258
42	Flashing lights	0.076
43	Visual floaters	0.121
44	Watery eyes	0.212
45	Ringing in ears	0.288
46	General pain	0.394
47	Headache	0.197
48	Muscle pain	0.303
49	Joint pain	0.470
50	Anxious	0.439
51	Insomnia	0.485
52	Fatigue	0.621
53	Sad	0.379
54	Discouraged	0.182
55	Painful urination	0.242
56	Urinary urgency	0.470
57	Urinary frequency	0.758
58	Change in usual urine colour	0.121
59	Urinary incontinence	0.485
60	Decreased libido	0.803
61	Unable to have orgasm	0.877
62	Hot flashes	0.621
63	Breast swelling and tenderness	0.227
64	Achieve and maintain erection	0.908
65	Ejaculation	0.877
66	Irregular periods/vaginal bleeding	0.000
67	Missed expected menstrual period	0.000
68	Vaginal discharge	0.000

Symptom Number	PRO-CTCAE term	Prevalence Score
69	Vaginal dryness	0.000
70	Pain w/sexual intercourse	0.000
71	Bruising	0.182
72	Nosebleed	0.121
73	Chills	0.152
74	Increased sweating	0.364
75	Decreased sweating	0.061
76	Pain and swelling at injection site	0.076
77	Body odor	0.167

Appendix II-B10: Prostate cancer – symptom importance

Symptom Number	PRO-CTCAE term	Importance Score
1	Mouth/throat sores	0.769
2	Dry mouth	0.508
3	Difficulty swallowing	0.554
4	Cracking at the corners of the mouth	0.431
5	Voice quality changes	0.446
6	Hoarsness	0.446
7	Shortness of breath	0.831
8	Cough	0.738
9	Weezing	0.746
10	Decreased appetite	0.672
11	Nausea	0.797
12	Vomiting	0.746
13	Constipation	0.762
14	Diarrhea	0.794
15	Abdominal pain	0.754
16	Heartburn	0.556
17	Bloating	0.659
18	Taste changes	0.500
19	Hiccups	0.373
20	Fecal incontinence	0.754
21	Rash	0.708
22	Dry skin	0.467
23	Acne	0.475
24	Hair loss	0.644
25	Itching	0.653
26	Hives	0.721
27	Hand-foot-syndrome	0.730
28	Nail loss	0.631
29	Nail ridging/dicoloration	0.592
30	Sensitivity to sunlight	0.467
31	Bed/pressure sores	0.574
32	Skin darkening	0.631
33	Stretch marks	0.352

Symptom Number	PRO-CTCAE term	Importance Score
34	Radiation skin reaction	0.833
35	Swelling	0.905
36	Heart palpitations	0.873
37	Numbness & tingling	0.794
38	Dizziness	0.873
39	Memory	0.810
40	Concentration	0.794
41	Blurred vision	0.815
42	Flashing lights	0.794
43	Visual floaters	0.810
44	Watery eyes	0.778
45	Ringing in ears	0.817
46	General pain	0.921
47	Headache	0.913
48	Muscle pain	0.905
49	Joint pain	0.937
50	Anxious	0.942
51	Insomnia	0.975
52	Fatigue	0.942
53	Sad	0.875
54	Discouraged	0.908
55	Painful urination	0.926
56	Urinary urgency	0.960
57	Urinary frequency	0.952
58	Change in usual urine colour	0.887
59	Urinary incontinence	0.960
60	Decreased libido	0.903
61	Unable to have orgasm	0.905
62	Hot flashes	0.836
63	Breast swelling and tenderness	0.782
64	Achieve and maintain erection	0.927
65	Ejaculation	0.927
66	Irregular periods/vaginal bleeding	0.000
67	Missed expected menstrual period	0.000
68	Vaginal discharge	0.000

Symptom Number	PRO-CTCAE term	Importance Score
69	Vaginal dryness	0.000
70	Pain w/sexual intercourse	0.000
71	Bruising	0.758
72	Nosebleed	0.792
73	Chills	0.775
74	Increased sweating	0.683
75	Decreased sweating	0.458
76	Pain and swelling at injection site	0.750
77	Body odor	0.500

Prostate cancer – combined prevalence-importance scores

Symptom Number	PRO-CTCAE term	Combined P-I Score
1	Mouth/throat sores	102
2	Dry mouth	77
3	Difficulty swallowing	121
4	Cracking at the corners of the mouth	130
5	Voice quality changes	113
6	Hoarsness	116
7	Shortness of breath	37
8	Cough	78
9	Weezing	85
10	Decreased appetite	88
11	Nausea	74
12	Vomiting	98
13	Constipation	54
14	Diarrhea	48
15	Abdominal pain	99
16	Heartburn	95
17	Bloating	76
18	Taste changes	88
19	Hiccups	135
20	Fecal incontinence	82
21	Rash	102
22	Dry skin	76
23	Acne	132
24	Hair loss	93
25	Itching	85
26	Hives	116
27	Hand-foot-syndrome	117
28	Nail loss	119
29	Nail ridging/dicoloration	86
30	Sensitivity to sunlight	114
31	Bed/pressure sores	128
32	Skin darkening	106
33	Stretch marks	142

Symptom Number	PRO-CTCAE term	Combined P-I Score
34	Radiation skin reaction	82
35	Swelling	32
36	Heart palpitations	71
37	Numbness & tingling	48
38	Dizziness	45
39	Memory	50
40	Concentration	62
41	Blurred vision	55
42	Flashing lights	91
43	Visual floaters	80
44	Watery eyes	73
45	Ringing in ears	53
46	General pain	27
47	Headache	51
48	Muscle pain	40
49	Joint pain	17
50	Anxious	19
51	Insomnia	9
52	Fatigue	11
53	Sad	37
54	Discouraged	54
55	Painful urination	41
56	Urinary urgency	12
57	Urinary frequency	9
58	Change in usual urine colour	71
59	Urinary incontinence	10
60	Decreased libido	21
61	Unable to have orgasm	16
62	Hot flashes	28
63	Breast swelling and tenderness	67
64	Achieve and maintain erection	9
65	Ejaculation	10
66	Irregular periods/vaginal bleeding	143
67	Missed expected menstrual period	143
68	Vaginal discharge	143

Symptom Number	PRO-CTCAE term	Combined P-I Score
69	Vaginal dryness	143
70	Pain w/sexual intercourse	143
71	Bruising	81
72	Nosebleed	87
73	Chills	86
74	Increased sweating	72
75	Decreased sweating	131
76	Pain and swelling at injection site	104
77	Body odor	107