IDENTIFICATION OF RISKS FOR DRUG-RELATED PROBLEMS

Inauguraldissertation

zur Erlangung der Würde eines Doktors der Philosophie

vorgelegt

der Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

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aus Basel (BS), Ballwil (LU)

Basel 2015

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät

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Dekan

To my family

Acknowledgements

The presented work was conducted at the Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, at the University of Basel under the supervision of Prof. Dr. Kurt Hersberger and Dr. Markus Lampert. I am deeply thankful for the support of the following persons. This research project would not have been possible without them.

First, I would like to express my deepest gratitude to Dr. Markus Lampert who supervised this thesis with great commitment and enthusiasm. Thank you Markus, for your valuable scientific and non-scientific support and your trust and for sharing my “unrealistically optimistic” ideas. I own you a huge part of my personal development be that in the area of research, education or clinical pharmacy.

Many important thanks go to Prof. Dr. Kurt Hersberger for his watching over this thesis. Thank you Kurt for your valuable ideas and inputs. I am admiring your talent to create such a pleasant and familiar working atmosphere in our team. I enjoyed being a PhD-student in the PCRG-group, it was great to learn from your pharmaceutical expertise and to take part in all the national and international scientific exchanges and all the great team events.

Further thank goes to Prof. Dr. David Schwappach for accepting the co-reference and his interest in my thesis as well as to Prof. Dr. Matthias Hamburger for acting as chair at the defence.

I would also like to thank the Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA) for their financial support of this thesis.

Many thousand thanks to all my dear colleagues from the Pharmaceutical Care Research Group (PCRG) for the great working atmosphere. Most cordial thanks to Kurt’s Gang: Fabienne Böni, Markus Messerli, Samuel Allemann, Karen Maes, Corinna Metaxas and Dominik Stämpfli for being a second little family to me during the last years. Thank you for all the great working- and non-working hours we spent together, for all your unconditional support and care.

Furthermore, I would like to thank the whole team of the Basel Pharmacoepidemiology Unit for the great collaboration and all the good times at the ESCP conferences, the afterworks and in the Chalet. Thank you Julia and Saskia for the 24/7 availability in our technical and

motivational help chat and for your valuable friendship. Thank you Marlene for your motivation during the last months.

Many thanks to the whole team of the hospital pharmacy of the Kantonsspital Baselland, Bruderholz for the great three years. Special thanks to Maya von Moos, Andrea Studer, Charlotte Rapp and Seraina Mengiardi-Nemec for being such lovely team members.

Thank you to the expert panel for participating in project B and to all the people from the Kantonsspital Baselland, Standort Bruderholz and Liestal, who enabled the conduction of the patient interviews.

A huge thank you to the whole team of the hospital pharmacy at the University Hospital of Basel for the warm welcoming last year. Many cordial thanks go to Prof. Dr. Christoph Meier for being such a motivating and supportive head. I am looking forward to continuing my work in your team. A special thank goes to my colleagues from the division of clinical pharmacy. Thank you Delia, Sibylle, Patrick, Andy, Julian, Balbina, Stephan, Samantha and Daphne for your great support that gave me a lot of relief in the last months.

Many thanks to my master students Regina Tremp, Dominik Stämpfli, Nadine Mory and Timon Stolz for their excellent work.

Many thanks to Ben Basger and April Stockfleet for the English proof reading, Michael Mittag for his support in analysis and statistics, Dr. Katja Suter for her advices on how to conduct systematic literature reviews as well as Balbina Preston and Christina Ernstberger for the participation in the patient interviews.

Finally, my deepest gratitude goes to my amazing family and closest friends. Thank you, to my parents for your unconditional support in every minute of my life. It would have been impossible to finish this thesis without your care during the last weeks. Many thanks to Muriel, my favourite little sister. Thank you to my friends, Alina, Marina, Judith, Stephanie, Simone, Isabella, Mark and Melanie for being always at my side and care for me, even when my life was completely taken up with work.

Table of Contents

Abbreviations

A	Ambulatory patients
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
BMQ	Beliefs about medicines questionnaire
CP	Clinical Pharmacy
CRF	Case Report Form
DART	Drug Associated Risk Tool
Dp	Delphi technique
DRP	Drug-related Problem
eGFR	estimated glomerular filtration rate
El	Elderly
Ex	Expert panel
GSASA	Swiss Association of public health administration and hospital pharmacists
H	Hospitalized patients
IP	Inappropriate prescribing
IQR	Interquartile range
Lit	Literature search
MAI	Medication Appropriateness Index
ME	Medication Error
MESH	Medical Subheading
MMAS	Morisky Medication Adherence Scale
MMSE	Mini Mental State Examination
MMT	Micro Mental Test
MR	Medication Review

MRP	Medication Related Problem
n.a.	Not applicable
NGT	Nominal Group Technique
NRS	Nutritional Risk Screening
n.s.	Not specified
NSAID	Non-steroidal anti-inflammatory drugs
PIM	Potentially inappropriate medication
RD	RAND Appropriateness method
RF	Risk factor
φ	Phi-coefficient
χ2	Chi-square

Summary

Drug-related problems (DRPs) are defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes. The term DRP is an 'umbrella' term that includes medication errors (MEs), adverse drug events (ADEs) and adverse drug reactions (ADRs). A ME is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer. An ADE is an injury - whether or not causally related to the use of a drug - and an ADR is any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological functions. DRPs are common and occur at every stage of care. They are responsible for patient harm and cause substantial additional healthcare cost. A considerable amount of DRPs is judged by the literature as preventable.

Inappropriate prescribing (IP) constitutes a major risk for the occurrence of DRPs and is highly prevalent, especially in the elderly, where polymorbidity and polypharmacy are often part of everyday life. An appropriate prescription of medication should "maximize efficacy and safety, minimise cost, and respect patient's preferences".

Clinical pharmacy (CP) is an area of pharmacy with the aim of developing and promoting the appropriate, safe and cost-effective use of therapeutic products. A clinical pharmacist assumes responsibility for managing medication therapy in direct patient care. CP services for in-patients have a beneficial effect on patient safety by reducing medication errors and ADEs; they are effective in improving the patients knowledge about drug therapy and their adherence. The involvement of a clinical pharmacist who provides clinical pharmacy services such as patient counselling and medication review has proved to be a successful approach to support the physician in reducing IP.

Numerous tools for the assessment of IP have been published and can be a valuable aid during the physicians prescribing process or a medication review of a pharmacist. Until today a comprehensive and structured overview of existing tools has not been available.

In most European countries, staffing restrictions are a major barrier for the development of CP services. At the same time, an impressively growing drug market and an increasing number of elderly patients with complex polypharmacy demand the need for clinical pharmacists. To meet the requirements of optimising patient's drug therapies while at the same time dealing with limited capacity, pharmacists are forced to target their clinical activities to those patients who are most likely to benefit from them – that is, to focus on those who are at the highest risk of experiencing DRPs.

This thesis aimed to create a comprehensive overview on available tools for the assessment of IP. In a second part, a risk assessment tool for the occurrence of DRPs should be developed to enable pharmacists to target their clinical activities on high-risk patients.

In **project A,** a systematic literature search on PUBMED resulted in 46 tools for the assessment of IP, all different in terms of IP content, structure and length, targeted health care settings (hospital care, ambulatory care, long-term care) and patient groups (elderly, all age), development method (literature review, expert panels and/or consensus techniques) and extent of validation. By outlining the characteristics of each tool in a highly structured manner, we created a survey, which did not identify a single ideal tool but who revealed their strengths and weaknesses what may help readers to choose one, either for research purposes or for use in daily practice, according to the situation in which it is intended to be applied.

In **project B** we developed a risk assessment tool, to support pharmacists in focussing their clinical activities. The development of such a risk assessment tool required in a first step an identification of risk factors (RFs). As RFs for the occurrence of DRPs are numerous, they cannot be fully covered by an IP assessment tool.

In **project B1** we therefore intended to get a broader impression on possible RFs for the occurrence of DRPs. We conducted a multidisciplinary expert panel, using the nominal group technique (NGT) and a qualitative analysis to gather risk factors for DRPs. The literature was searched for additional risk factors. Gathered factors from the literature search and the NGT were assembled and validated in a two-round Delphi questionnaire. This approach resulted in a final list of 27 RFs judged by the experts to be "important" or "rather important" for the occurrence of DRPs.

In **project B2** we developed the Drug Associated Risk Tool (DART) out of the RFs that we identified in project B1. We conducted a prospective validation study with 164 patients and validated the DART concerning feasibility, acceptability and reliability of patients answers. Feasibility and acceptability of the DART were satisfactory. Compared to other risk assessment tools, summarized in a separate **overview B3,** the DART reached a high overall specificity of 95% and a slightly low overall sensitivity of 58%.

From the results and experiences of this thesis the following conclusions could be drawn:

- Inappropriate prescribing (IP) is a major risk for the occurrence of DRPs. The avoidance of IP should not only be the task of the physician but shared between different healthcare providers in order to guarantee the most appropriate therapy. Tools for the assessment of IP can provide a useful aid to evaluate the appropriateness of a therapy, during a medication review, or during the process of prescribing itself.
- Inappropriate prescribing assessment tools are numerous. They show a large variety in structure, degree of comprehensiveness and extend of validation. By providing an overview of published assessment tools, this thesis may assist healthcare providers to choose a tool, either for research purposes or for use in daily practice, according to the situation in which it is intended to be applied.
- The Drug Associated Risk Tool (DART) is a promising approach for clinical pharmacists to assess patients at risk for the development of DRPs and thereby target their clinical pharmacy activities to those patients who benefit the most thereof.
- The DART is based on a combination of a systematic literature search, with the professional experience and knowledge of a multidisciplinary expert panel, which enabled the comprehensive finding of risk factors for DRPs representing the real-life situation in the Swiss healthcare setting.
- A first technical validation of the DART was successful and supported the concept of a patient self-assessment. Compared to similar self-assessment tools, the DART has comparable complexity and comprehensiveness, has an appealing design and shows a satisfactory validation concerning feasibility, acceptability and reliability of patients' answers.

We saw a lower sensitivity of the DART compared to similar risk self-assessments. We proposed potential issues that might have affected the sensitivity of our tool: The understandability of the questions, the accuracy of medical histories and medical data and the reliability of patient answers. A rephrasing of the statements with very low sensitivity values with the aim of improving the understanding of the question followed by a second validation with a most accurate medication list is recommended. A validation with clinical outcomes is crucial to prove the concept of our risk assessment.

General Introduction

Drug-related problems

"Medical advance offers the hope of bringing benefits to patients but also has the potential to do harm if not used appropriately. Knowing when and how to treat patients is particularly important in the prescribing of drugs as populations' age and multi-morbidity becomes more prevalent" Duerden, 2013 [1].

In the late 1950s, the German pharmaceutical company Chemie-Gruenenthal launched thalidomide as a new sedative and tranquilizer. The new drug was very effective and discovered to also be effective for the treatment of morning sickness in pregnant women. Thalidomide became one of the world's largest selling drugs, advertised as "completely safe" [2]. Two years after its' release, patients started to develop peripheral neuropathy after taking the drug. Shortly thereafter, thalidomide was connected with an epidemic of severe birth defects in children whose mothers had taken the drug during pregnancy. The prescription of thalidomide was named as the largest man-made medical disaster in history causing damage to over 10000 children [3]. Intensive discussions on the preventability of this tragedy were responsible for an increasing awareness of drug-related harm and led to efforts for the improvement of drug safety.

Researchers began to evaluate the occurrence of drug-related problems (DRPs) in primary and secondary care. DRPs are defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes [4]. The term DRP is an "umbrella" term that includes medication errors (MEs), adverse drug events (ADEs) and adverse drug reactions (ADRs). Table 1 shows current definitions used in this thesis.

Table 1: Definition and terms associated with DRPs

MEDICATION ERROR (ME)	Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer [5]
ADVERSE DRUG EVENT (ADE)	An injury—whether or not causally related to the use of a drug [6]
ADVERSE DRUG REACTION (ADR)	Any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological functions. An ADR is defined as non-preventable [7].

Miller at al. [8] prospectively analysed 7014 hospital admissions between 1969 and 1972. Data were collected in seven hospitals in the USA, Canada and Israel and revealed that ADRs were the main cause of admission or at least strongly influenced the admission of 260 (3.7%) patients. With the similar aim of describing the frequency and pattern of drug-related morbidity resulting in hospital admission ,Nelson and Talbot [9], reviewed 452 newly hospitalized patients charts. They concluded that 16.2% of the patients were hospitalised due to DRPs. The authors judged 50% of drug-related admissions as definitely preventable. A study from the UK of Pirmohamed et al. (2004) screened 18820 hospital admissions, with 1225 (6.5%) of the admissions related to the occurrence of an ADR [10]. However, issues with the definition of medication safety terms cast doubt on a statement that more than 70% of the ADRs could have been potentially or definitely avoided. This was because ADRs, which form a subset of adverse drug events (ADEs), have been defined as non-preventable (cf. table 1). Despite numerous research projects demonstrating the problems of medication-related injury, international interest in patient safety remained limited. A turning point in the subject came in the year 1999, when the US Institute of Medicine issued their report “To err is human”[11]. This report was based upon an analysis of multiple studies by a variety of organizations, and showed that medical errors cause up to 98,000 deaths and more than 1 million injuries each year. This publication had a big impact on the recognition of medication management problems.

Differences between definitions of medication safety terms in the literature has led to frequent confusion between researchers. The following example illustrates the complexity of the classification: A patient receiving oral anticoagulation therapy develops a gastrointestinal bleed. If the use of oral anticoagulation in this patient was appropriate (correct dosage, indication and appropriate monitoring), this may be classified as an ADR, a non-preventable event due to an inherent risk of gastrointestinal bleeding with oral anticoagulation. If the bleeding occurred because of a wrong usage of the drug (e.g. overdosage, no monitoring, contraindication present), classification would consist of an ADE, as it would have been preventable. The often incorrect use of DRP associated terms complicates a proper comparison of the results from research articles. The illustration in figure 1 should facilitate the understanding of the different subterms.

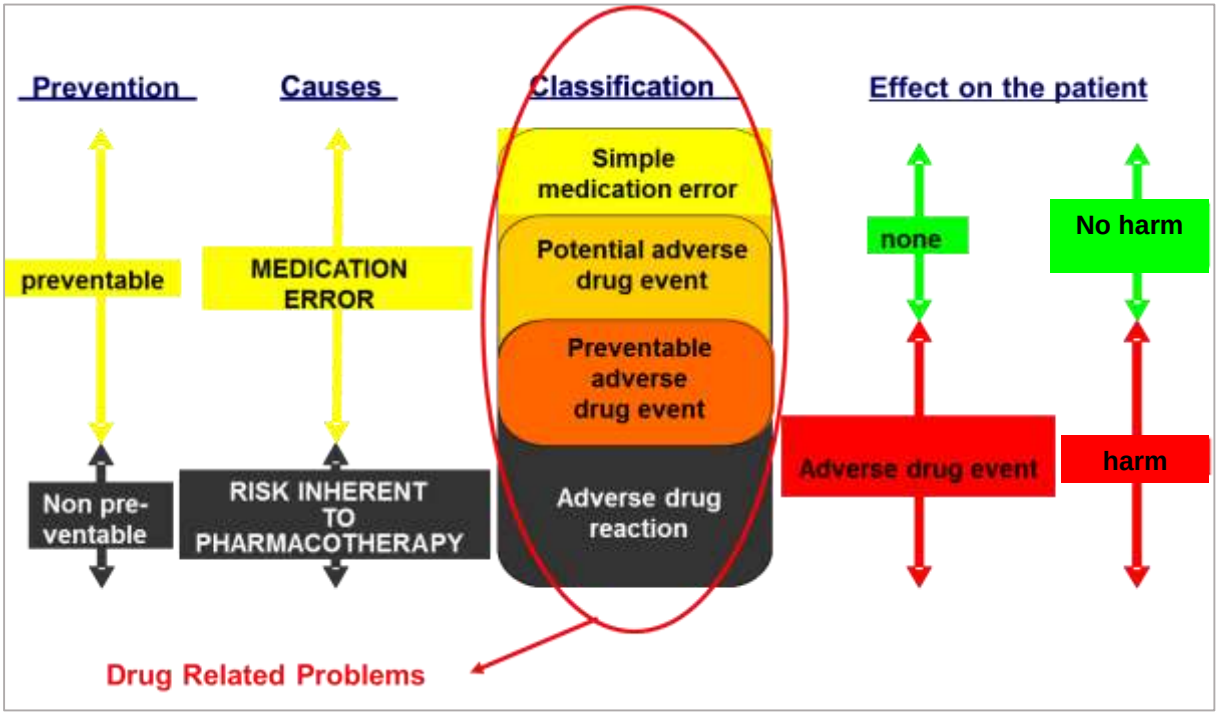

Figure 1: Illustration of DRPs and associated terms (modified from Otero et al. [12])

Today, many studies have shown that DRPs occur at every stage of care. Five to 15% of all hospital admissions are drug-related and largely preventable [13-15]. The occurrence of DRPs continues during hospitalization. In a systematic review covering the decade from 1991 to 2001, Krähenbühl-Melcher et al [16] showed that approximately 6% of all hospitalized patients experienced an ADE and in 3% of the affected patients, the adverse event was fatal. Five to 10% of all drug prescriptions or drug applications were erroneous. Schlienger et al. [17] investigated in a prospective study the incidence of ADEs on the medical ward of a Swiss

university hospital. ADEs occurred in about 15% of all patients. During hospital stay, the medication of a patient undergoes many changes. Almost every patient receives new medicines added to his existing treatment, with others being stopped [18]. Approximately 60% of drugs change at the time of discharge with half of the medications on the discharge prescription being new to the patient [19]. Paulino et al. [18] published a study where 112 community pharmacies from all over Europe took part. The pharmacists interviewed 445 patients with a prescription after hospital discharge and found DRPs in 277 (64%) of these patients. According to a recent Swiss study, 27% of the discharge prescriptions contained at least one DRP and 34% of the prescriptions showed qualitative deficiencies like illegible drug names, missing/unclear drug form or dosage [20]. In a Swiss thesis from 2001, patients during home-interviews, after being discharged, reported handling difficulties (8%), side effects (21,6%), and gaps in drug supply (24%) and the researcher discovered potentially harmful drug-drug interactions in 22.4% of the cases [19]. Williams et al [21] confirmed, that with a better management of seamless care, including medication management, 59% of all unplanned readmissions would be avoidable.

Patients experiencing an ADE showed an almost doubled risk of death [22]. Besides human suffering, DRPs cause substantial additional cost and a prolonged length of hospital stay. Bates et al. [23] stated that an ADE resulted in 2.2 additional days of hospital stay and additional costs of $3244. Many other researchers support Bates findings, clearly indicating the increasing economic burden and the prolonged length of hospital stay, regardless of whether the studies focused on DRPs, ADEs or ADRs [22, 24-28].

Inappropriate prescribing

" The appropriate prescription of medication should maximize efficacy and safety, minimise cost, and respect patient's preferences" Barber 1995 [29].

A major risk for the occurrence of drug-related problems (DRPs) constitutes inappropriate prescribing (IP). DRPs resulting in actual and potential ADEs occur throughout the entire medication process, half of these at the stage of prescription (49%) [30]. Choosing the most appropriate medication for each patient in order to achieve desired therapeutic outcomes is a challenge for healthcare professionals in their daily practice [31]. Trained to prescribe in a

rational way, they consider evidence-based guidelines for the most effective treatments with the best benefit-risk ratios. This of course is an essential part of prescribing. However, when focusing on appropriate prescribing instead of rational prescribing, patient's preferences should be incorporated in every decision[29] even when, from a rational point of view, an appropriate prescription might not always be the most effective one. This also implies the omission of drugs, which may otherwise have been indicated according to current guidelines, with the aim of reducing a patient's drug burden and promote drug adherence.

According to Spinewine [32] inappropriate prescribing (IP) can be grouped in three subcategories [33, 34]:

- Underprescribing – the omission of a medication that is needed (no therapy prescribed for a given indication)
- Overprescribing – the prescription of a medication that is clinically not indicated (resulting in unnecessary therapy).
- Misprescribing – the incorrect prescription of an indicated medication – for example, a wrong dosage or duration of therapy; a drug-drug, drug-food or drug-disease interaction, or the selection of a drug where better alternatives (better benefit-risk ratio / better cost-effectiveness ratio) would be preferable.

Inappropriate prescribing (IP) is highly prevalent, especially in the elderly, where polymorbidity and polypharmacy are part of everyday life. In a retrospective Irish population study in 2010 [35], Cahir et al. screened 338,801 electronic patient charts and found the prevalence of IP in primary care to be 36%. A retrospective cross-sectional study of 2707 elderly receiving home care services across 11 European countries documented the prevalence of potentially inappropriate prescribing [36]. By using validated explicit criteria like the Beers criteria [37] and McLeods criteria [38] they identified 19.8% of patients with at least one inappropriate medication. These European findings are comparable with data from the USA [39, 40], where the prevalence of IP among community-dwelling elderly has been reported to be 21% [39]. A recent Swiss study revealed similar results by screening claims data from the largest health insurance in the country, which revealed that 21% of community dwelling elderly received at least one potentially inappropriate drug [41].

The act of prescribing is mainly the task of the physician. Different approaches have been evaluated in order to support physicians in reducing IP, as summarized by Spinewine et al. [32]:

- Educational approaches including printed information material and interactive courses may improve prescribers' knowledge about appropriate prescribing and improve prescribing behaviour. The more personalised, interactive and multidisciplinary the approaches are the more effective they are. Educational interventions have to be repeated frequently in order to be sustainable. The covering of the broad topic of appropriate prescribing is time consuming. Therefore, educational interventions are often restricted to certain diseases or special groups of drugs.
- Computerized decision support systems (CDSS) and/or computerized physician order entry (CPOE) can serve as an electronic support at the time of prescribing. If the system is linked to clinical data, it is possible to cover all categories of IP. The implementation is time-consuming, as all relevant data and information need to be entered and regularly updated. Generally, the integration of a new system to existing working processes might be challenging. The system needs to be easy to use, with avoidance of high volumes of warnings, because the physician tends to override them.
- A comprehensive assessment of drug therapy by an interdisciplinary team, usually composed of physicians (often geriatricians), nurses, pharmacists and other specialized health-care professionals is an expensive and complex approach. Nevertheless, if successful, patients' therapy benefits from the different competences of each healthcare professional, potentially resulting in a very comprehensive medication review (MR).
- Involvement of a clinical pharmacist who provides clinical pharmacy services such as patient counselling and medication review has been proved to reduce IP. The clinical pharmacist needs training in conducting medication reviews. Some expertise in geriatric pharmacotherapy might be a benefit because the occurrence of IP increases in the elderly. A close collaboration with the prescriber and full access to the clinical record of the patient are necessary for a successful implementation.

A combination of the mentioned interventions has proved to be more effective than one single approach.

A medication review (MR) is “an evaluation of patient‘s medicines with the aim of managing the risk and optimizing the outcome of medicine therapy by detecting, solving and preventing DRPs” [42]. It can be provided by physicians, pharmacists and nurses, in primary and secondary care. A recently published study summarized the evidence of MRs [43]. The author concluded that there is evidence that MR improves outcomes of prescribing such as reduced polypharmacy and an appropriate choice of medicines. However, there is still no evidence for the reduction of “harder outcomes” such as hospitalization and mortality [44].

There are numerous tools for the assessment and evaluation of the appropriateness of prescribing. Usually developed by literature review, expert panels and/or consensus techniques, they can serve as an aid for physicians, pharmacists and other healthcare providers during their medication review. Tools differ in terms of structure, length and content, use in different healthcare settings and in particular patient groups. They can be grouped roughly into implicit (judgement- based) and explicit (criterion-based) tools, and tools showing a combination of both approaches. Chang and Chan [45] compared different criteria for the assessment of IP in the elderly and concluded that not all of the criteria considered the same drugs as inappropriate. This also depended upon the availability of the drugs in different countries.

The consideration of whether to choose explicit or implicit criteria can be important, as they may provide different findings. In a US study, Steinman et al. [46], evaluated the drug prescribing quality by using both - the explicit Beers Criteria and the implicit MAI in the same cohort of patients. The two tools provided substantially different results (cf. figure 2). Based on his observations, Steinman concluded that, because using a single tool may fail to capture the overall quality of a patient’s medication regimen, it would seem prudent to consider employing multiple tools to capture the range of quality problems that may be present in medication prescribing [46]. A tool using both approaches (explicit AND implicit) can serve as an alternative to the use of multiple tools.

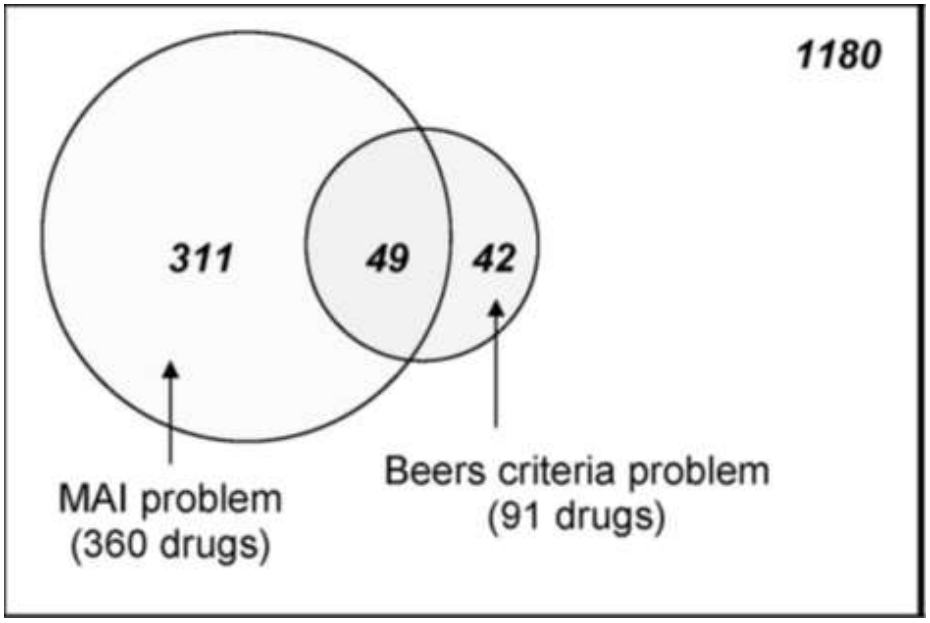

Figure 2: Concordance of drug-level measures of prescribing quality for 1582 drugs. Circles are proportional to the number of drug quality problems identified. Numbers represent the number of drugs within each category. The area of the box outside the circles represents the number of drugs without any prescribing problem [46]. Reprinted by permission from Wolters Kluwer Health, Inc.

Despite a wide selection of different tools, their use in the daily clinical setting is very limited. Most tools are very comprehensive and appear more suitable for research purpose. Numerous pages of guidelines make it impossible to assess a patient's drug therapy in a short amount of time. Further, validation in terms of demonstrating a significant relation between inappropriate drug use and adverse drug outcomes is often missing.

Validation is the confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled [47]. During the development process of a tool some technical aspects of validation should be considered like the appropriateness, acceptability, feasibility, interpretability and reliability of a tool [48]. After a successful technical validation, it is important to validate a tool concerning clinical outcomes. An assessment tool for IP might fulfil all aspects of a technical validation but its application remains questionable if the tool has no proven effect on adverse outcomes (e.g. reduction of rehospitalisation, morbidity, mortality).

A comprehensive and structured overview of existing tools for the assessment of IP has not been available. The aim of project A of this thesis was to conduct a systematic literature review to provide an overview of published assessment tools. This approach may help healthcare professionals to choose the most suitable tool, either for research purposes or for daily practice use, according to its intended application.

Clinical Pharmacy

The profession of pharmacy has experienced significant development over the past 50 years. While the traditional role of the ancient “apothecary” was characterized by the manufacturing and selling of drugs, his importance waned when the development of drugs became more and more the task of the pharmaceutical industry. Downgraded from the important role of the drug manufacturer to the profession of a simple drug dispenser, pharmacists saw themselves needing to redefine their professional activities. Clinical pharmacy (CP) had its beginning in the early 1960s in the USA when pharmacists began to change their focus from the product to the patient [49].

The Swiss Association of public health administration and hospital pharmacists (GSASA) defined clinical pharmacy as an area of pharmacy with the aim of developing and promoting the appropriate, safe and cost-effective use of therapeutic products. In the hospital setting, clinical pharmacy includes direct patient oriented pharmaceutical activities, implemented on patient care wards in collaboration with other healthcare professionals [50]. According to the definition of the American College of Clinical Pharmacy, a clinical pharmacist assumes responsibility for managing medication therapy in direct patient care. He is an expert in the therapeutic use of medication and provides drug therapy evaluations and recommendations to the patient and healthcare providers. Thereby he practices independently and/or as a consultant in collaboration with other healthcare professionals [51]. This definition encompasses appropriate and inappropriate prescribing. CP is not necessarily linked to the hospital environment. It can be provided by community pharmacies to nursing homes, in home-based care services and in other settings where drugs are prescribed and used. It should be emphasized that CP is not synonymous with hospital pharmacy. While the basic work of a hospital pharmacist includes activities such as logistic supply, quality control and

manufacturing of drugs, the focus of attention of the clinical pharmacist moves from a focus on the drug to that of the single patient.

Clinical pharmacy services are multifaceted and occur at every point of care. A selection of core activities of the clinical pharmacists are [50]:

- Provision of counselling activity and drug information for healthcare professionals.
- Participation on ward rounds in an interdisciplinary team of healthcare professionals in order to improve a patients' drug therapy.
- Performing medication reviews, defined as a "structured, critical examinations of patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication related problems and reducing waste" [52].
- Medication reconciliation: The process of identifying the most accurate list of all medications that the patient is taking including name, dosage, frequency, and route, by comparing the medical record to an external list of medications obtained from a patient, hospital, or other provider [53].
- Education of healthcare professionals; enhancing drug therapy knowledge and improving prescribing behaviour.
- Educating patients; improving patients' knowledge and awareness of their drug therapy.
- Monitoring and improving patients' adherence.
- Assurance of seamless care.
- Provision of therapeutic drug monitoring for high-risk drugs.

There are more and more studies available evidencing the positive clinical, humanistic and economic benefit of CP services provided to hospitalized patients. A systematic review covering the time from 1985 to 2005 [54] and a large observational study from 2005 [55] support the use of clinical pharmacists. They both concluded that CP services for in-patients have a beneficial effect on patient safety by reducing medication errors and ADEs; they are effective in improving the patients' knowledge about drug therapy and their adherence, and the use of inappropriate medicines decreases. A comprehensive systematic review by Chisholm et al [56] examined the effect of pharmacist-provided direct patient care. After having screened over 56,000 titles and abstracts, there were 298 full texts included in this review. The results provided clear evidence concerning the favourable effect of pharmacists

on patient care. Patients treated by a care team including a pharmacist showed significantly better therapeutic and safety outcomes compared to those without pharmacists in their care teams. Favourable effects were demonstrated on blood pressure measurements, International Normalized Ratio values, glycated haemoglobin (HbA1c) - and lipid levels. Mortality, readmissions, inpatient length of stay and emergency department visits decreased, as well as MEs and ADEs. Pharmacists' effects on humanistic outcomes such as medication adherence, patient satisfaction and knowledge showed variable results. Their benefit was less obvious, but the evidence remained positive with the most favourable data concerning the enhancement of patient knowledge about medication and disease states. CP also proved to be cost-effective [57]. An economic review [58], calculated a mean cost-benefit ratio of 1:4,68. In a more recent study [59], data assessed over a one-year period in 2012 confirmed former findings; pharmacist interventions in hospitals provided substantial cost-avoidance to the healthcare payer.

While nowadays the clinical pharmacy is well implemented in the USA, this specialized field of pharmacy is only in the beginning stages in most European countries. Only the UK and Ireland have developed CP services to a significant extent. In 71% of all US hospitals, pharmacists are integrated to such an extent, that they review and approve almost all medication prescriptions before the administration of the first dose, except those arising in emergencies. However, the level to which European hospital pharmacists document their clinical activities is low. Because of this, collected data from Europe do not provide detailed information about the involvement of clinical pharmacists. Statistics collected on the number of pharmacists per hospital and their activities on the ward identify notable differences across Europe, such that we appear far from providing CP services as the USA [60].

Staffing restrictions are a major barrier for the development of CP services. In most countries, the economic pressure on healthcare providers is pronounced. A European survey performed by the European Association of Hospital Pharmacists (EAHP) [60] revealed important differences between countries in allocation of human resources to hospital pharmacies. The number of pharmacists (full time equivalents) per 100 bed ranged from 0.24 in Bosnia-Herzegovina to 4.35 in the United Kingdom (cf. figure 3). These data suggest that the greater the number of employed pharmacists, the greater the time spent on clinical services, such as daily patient ward visits.

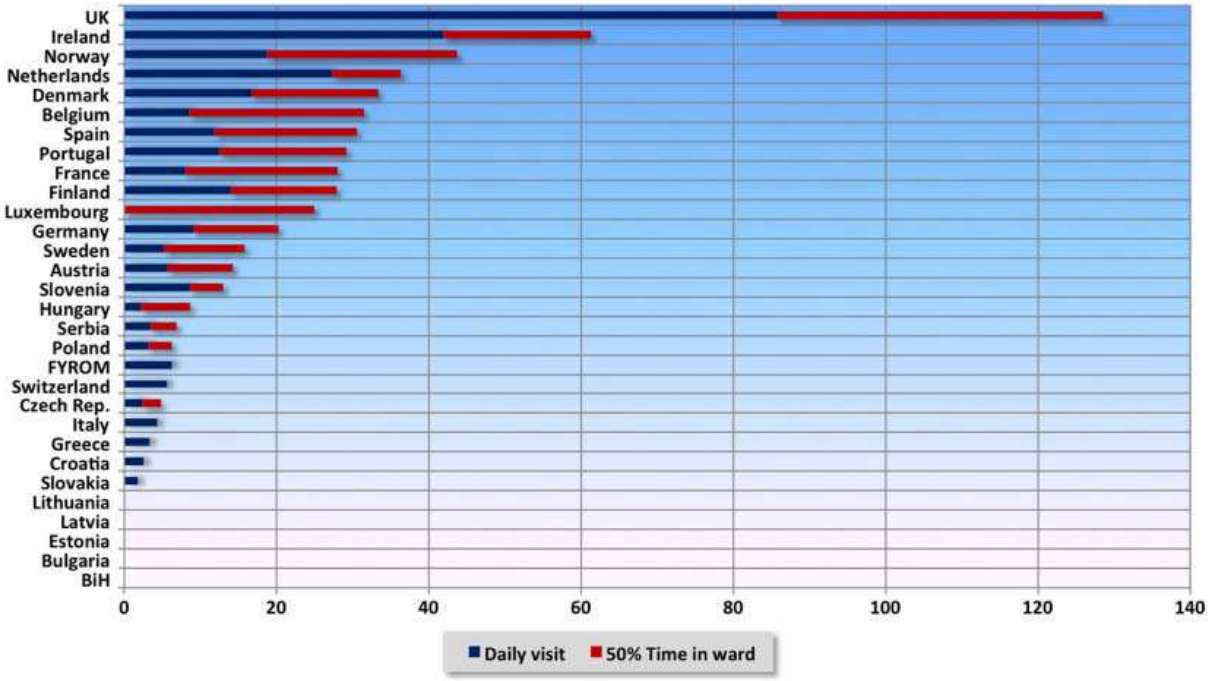

Figure 3: Percentage of pharmacies with either daily visits on the wards by pharmacists or having pharmacists working at least 50% of their time on the ward. Total may be >100% when both services are provided [60]. Reprinted by permission from BMJ Publishing Group Ltd.

To provide CP services effectively and efficiently, pharmacists must have adequate skills and knowledge. Education and training at both pre- and postgraduate levels is essential. The number of specific programs for clinical pharmacists is continuously growing, but in many European countries there is still a lack of well-trained specialists in the field to meet increased needs. In Switzerland, most CP services take place in the hospital setting and the number of activities varies greatly from one hospital to another. Figure 4 shows the regional differences in the provision of CP services. A recent online survey among all hospital pharmacies affiliated with the national professional society revealed that 69 persons (22%) out of 307 employed hospital pharmacists had a formal specialisation in CP. Twenty-eight of these have both a hospital and clinical pharmacy specialisation and 146 had a masters degree in pharmacy [61].

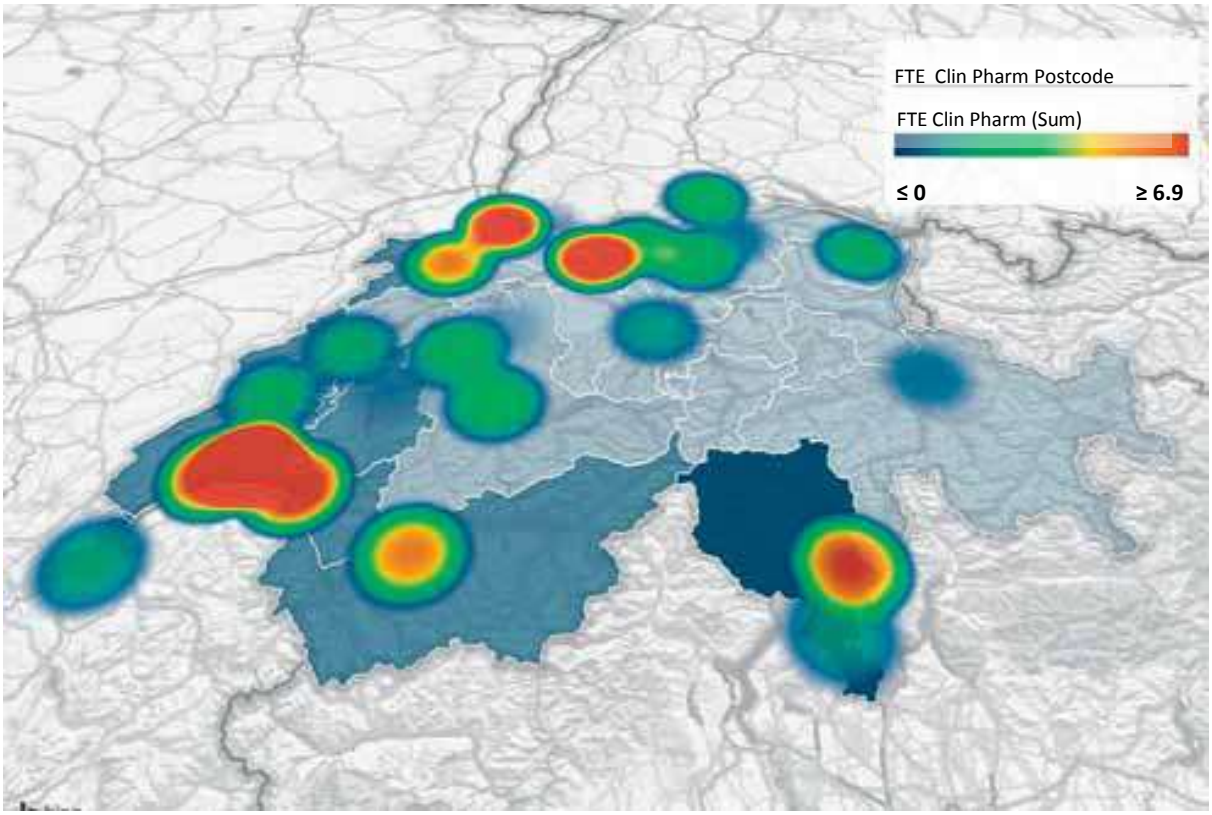

Figure 4: Extend of clinical pharmacy services in the various language areas (French, German, Italian); FTE: Full time equivalent [62]

Risk Assessment

"The goal of risk identification is to ensure that the patients who will most likely benefit from these services are identified, thereby enhancing the cost effectiveness of these interventions" Coleman 2003 [63].

An impressively growing drug market and an increasing number of elderly patients with complex polypharmacy demand the need for clinical pharmacists. The dilemma of increased pharmaceutical needs versus the limited resources available requires good management of CP services. To meet the requirements of optimising patient's drug therapies while at the same time dealing with limited capacity, pharmacists are forced to target their clinical activities to those patients who are most likely to benefit from them – that is, to focus on those who are at the highest risk of experiencing DRPs.

The identification of patients who are mostly at high risk of DRPs would allow clinical pharmacists to be more target-oriented. This does not mean that clinical pharmacy should neglect standard care. It can rather be seen as a reallocation of available resources when additional capacities are not available. Clinical pharmacists could provide individualised care for patients who were at higher risk, and reduce their care in patients who were at lower risk (cf. figure 5).

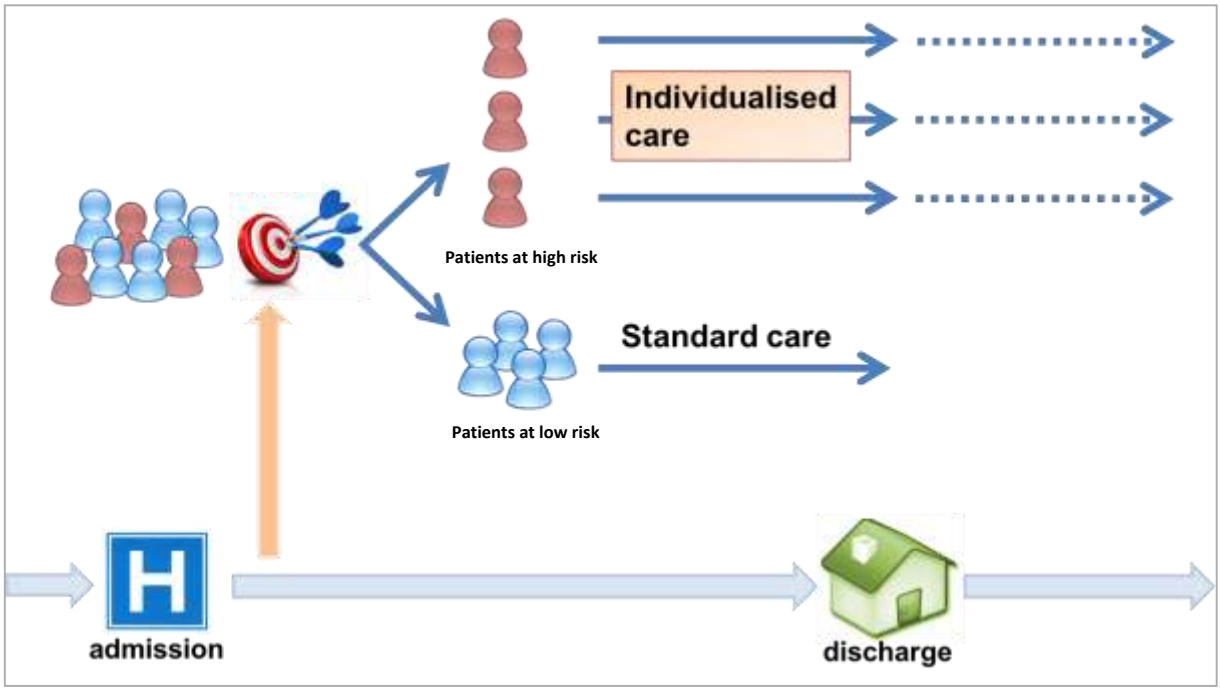

Figure 5: The identification of patients at risk allows clinical pharmacists to target clinical pharmacy activities.

The identification of patients at risk requires the identification of risk factors (RFs) for the development of DRPs. Literature serves as a valuable source for the collection of RFs. However, published studies appear very heterogeneous depending on the study design (e.g. prospective, retrospective), the study setting (e.g. ambulatory care, nursing homes or hospitals), the study population (e.g. all patients, elderly, patients with particular chronic diseases), the outcomes upon which the authors focused (e.g. DRPs, ADEs, ADRs, hospital admission) and the way data were collected (e.g. by pharmacist, physician, nurse). Although a comparison of findings is difficult, a literature search can provide an overview of the current research and of RFs judged as the most important ones. However, data from the literature might not fully reflect the current problems of practicing healthcare providers, especially when the information comes from another country with a completely different healthcare

system. The consultation of an expert panel, consisting of actively practicing healthcare professionals may reveal valuable RFs, seen in daily practice but not mentioned in most research projects.

Once RFs are identified, patient showing these factors then need to be screened in a reliable way by using as little CP resources as possible. The approach of risk assessments has proved successful in other areas of care. One of the best-known risk assessments is the Nutritional Risk Screening (NRS) [64], designed in 1999. This identifies patients who are likely to benefit from nutritional support, which will then provide an improved clinical outcome, i.e., they are at-risk of nutrition-related complications and/or other indices of worsened outcome if untreated. The screening characterizes patients by scoring the components 'undernutrition' and 'severity of disease' in four categories (absent, mild, moderate and severe). The patient can have a score of 0–3 for each component, a total score of 0–6, and any patient with a total score of three or higher is considered at risk for undernutrition and is believed to benefit from nutritional support. The NRS has been well implemented in primary and secondary care. A validation study has proved the association of a high NRS score with negative clinical outcomes like increased mortality, higher rate of complications and longer lengths of hospital stay [65].

A similar approach may also be promising in the area of medication safety. An easy-to-use risk assessment tool appears to be a reliable way to screen patients at risk of DRPs who may benefit from targeted clinical pharmacy services.

Rational and approach

The percentage of old and very old persons in the community increases constantly [66]. Advances in medical science and technology have converted formerly fatal acute diseases into survivable events, often resulting in chronic health conditions [67]. Chronic health conditions often require polypharmacy and the growing pharmaceutical industry supports intensive therapies by continuously developing new innovative drugs. Polypharmacy is a well-known risk factors for the occurrence of DRPs [16]. The adverse outcomes of DRPs have been the subject of many research projects. The different understanding of DRPs, the various and sometimes incorrect use of the term DRP and its associated concepts, and the heterogeneity of study designs and outcome measures has complicated a detailed comparison of existing data. However, evidence clearly indicates that DRPs lead to patient harm and increasing healthcare costs. A large number of DRPs are known to be preventable with targeted interventions [13]. Inappropriate prescribing (IP), as a major contributing risk for DRPs, is a prevalent cause for the occurrence of adverse outcomes. The association of IP with patient harm and an economic burden has been proven by various studies [32].

The employment of clinical pharmacists has shown to be efficient in reducing IP and the occurrence of DRPs and proved to be cost-effective [54, 55]. The clinical pharmacist with his focus on the patient's therapy rather than on the drug itself may be the healthcare professional of choice to improve medication safety in primary and secondary care. Restricted resources and time limits activities of pharmacists. Targeting CP activities is crucial to prevent the development of DRPs in the most effective way.

This thesis aims to identify RFs for the development of DRPs. We approached this aim in two major steps:

In **project A** we conducted a systematic literature review to provide a comprehensive overview of assessment tools for inappropriate prescribing (IP). A structured mapping was intended to facilitate orientation and assist healthcare professionals in comparing existing tools and choosing the most suitable one for their work and research. To our knowledge, no similar overview has been published so far.

Inappropriate prescribing is a major risk for DRPs. However, an IP assessment tool cannot fully cover the broad range of risk factors (RFs). There is a high need for a screening tool that takes the full range of RFs into consideration. In **project B1** we intended to create a basis for such a tool and therefore get a broad impression on possible RFs for the occurrence of DRPs. The strategy of using a combination of current evidence from the literature with the professional experience of healthcare providers should serve as comprehensive approach to identify a list of important RFs for DRPs that accurately reflect the reality of daily practise. Out of this list, a screening tool should be developed for the detection of patients at risk **(project B2).** This risk assessment should allow pharmacists to target their clinical activities where they are needed most. The tool should be validated regarding feasibility, acceptability and the reliability of patients answers by calculating sensitivity and specificity.

Parallel to project B1 and B2, we aimed to search the literature for already existing tools. This approach may provide ideas for the development of our risk assessment tool. Results are shown in the **overview B3**. A synopsis of the rational is listed below and serves as an overview of the thesis.

A condensed overview of the projects and aims of the thesis

A INAPPROPRIATE PRESCRIBING

PROJECT A: INAPPROPRIATE PRESCRIBING: A SYSTEMATIC OVERVIEW OF PUBLISHED ASSESSMENT TOOLS

The aim of this project was to create a comprehensive and structured overview of existing tools for the assessment of inappropriate prescribing.

B ASSESSMENT OF PATIENTS AT RISK FOR THE DEVELOPMENT OF DRUG-RELATED PROBLEMS

PROJECT B1: DETERMINATION OF RISK FACTORS FOR DRUG-RELATED PROBLEMS: A MULTIDISCIPLINARY TRIANGULATION PROCESS

With project B1 we aimed to assess risk factors for the occurrence of DRPs with the intention to use them as a basis for the further development of a screening tool to identify patients at risk for DRPs.

PROJECT B2: THE DRUG ASSOCIATED RISK TOOL – DART: A NEW INSTRUMENT TO SCREEN PATIENTS AT RISK FOR DRUG-RELATED PROBLEMS

The aim of this study was to create a self-assessment questionnaire out of the identified risk factors from project B1 and to validate the questionnaire regarding feasibility, acceptability, and the reliability of the patients' answers.

B3: HOW TO DETECT PATIENTS AT RISK FOR DRUG-RELATED PROBLEMS: AN OVERVIEW ON EXISTING SCREENING TOOLS

In this part we aimed to create a structured overview on existing tools to screen for patients at risk for DRPs.

PROJECT A: Inappropriate prescribing

Introduction

Inappropriate prescribing (IP) is prevalent in primary and secondary care and has a clearly demonstrated association with negative outcomes. The consequences of IP are the occurrence of ADEs and increased morbidity, mortality and healthcare utilization [32, 68-70]. It is not surprising that IP is responsible for an increased economic burden. Cahir et al. [35] estimated the total expenditure due to IP to be 45.6 million euros for one year. Many screening tools have been developed to detect and measure IP and assist prescribers with prescribing guidelines for their daily clinical practice. The first screening tool, developed in 1991 in the USA, was the Beers criteria [71]. These explicit criteria consisted of a list of drugs to avoid in elderly nursing home residents. They have been regularly updated, the most recent in 2014 [37, 72, 73]. In 1992, Hanlon et al. developed the Medication Appropriateness Index (MAI) [74] in the USA. In contrast to the explicit criteria of Beers, the MAI was an implicit tool, which demonstrated a different approach by providing ten questions to the prescriber in order to assess the appropriateness of a patients' therapy. Since then researchers have developed numerous new assessment tools, which have often been derived from existing tools and adapted in structure and content. The growing range of tools complicates the orientation in this field of research.

In project A of this thesis, we aimed to provide a comprehensive and structured overview of all existing IP assessment tools, what – to our knowledge – has not been done so far. By conducting a systematic literature review, we intended to find all published assessment tools. A structured mapping was designed to highlight their characteristics and allow a comparison of the structure and the content of these tools. The compilation might help healthcare professionals choose the appropriate tool or combination of tools for their own purposes and raise awareness of advantages and limitations of IP assessment tools. Thus, this overview might contribute to improving their prescribing behaviour in daily practice.

PROJECT A1;

Inappropriate prescribing: A systematic overview of assessment tools

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European Journal of Clinical Pharmacology (2014) 70:1–11

DOI 10.1007/s00228-013-1575-8

Abstract

Background: Criteria to assess the appropriateness of prescriptions might serve as a helpful guideline during professional training and in daily practice, with the aim to improve a patient's pharmacotherapy.

Objective: To create a comprehensive and structured overview of existing tools to assess inappropriate prescribing.

Method: Systematic literature search in Pubmed (1991–2013). The following properties of the tools were extracted and mapped in a structured way: approach (explicit, implicit), development method (consensus technique, expert panel, literature based), focused patient group, healthcare setting, and covered aspects of inappropriate prescribing.

Results: The literature search resulted in 46 tools to assess inappropriate prescribing. Twenty-eight (61%) of 46 tools were explicit, 8 (17%) were implicit and 10 (22%) used a mixed approach. Thirty-six (78%) tools named older people as target patients and 10 (22%) tools did not specify the target age group. Four (8.5%) tools were designed to detect inappropriate prescribing in hospitalised patients, 9 (19.5%) focused on patients in ambulatory care and 6 (13%) were developed for use in long-term care. Twenty-seven (59%) tools did not specify the healthcare setting. Consensus methods were applied in the development of 19 tools (41%), the others were based on either simple expert panels (13; 28%) or on a literature search (11; 24%). For three tools (7%) the development method was not described.

Conclusion: This overview reveals the characteristics of 46 assessment tools and can serve as a summary to assist readers in choosing a tool, either for research purposes or for daily practice use.

Keywords: Drug-related problems, inappropriate prescribing, assessment tool, drug safety

Introduction

The appropriate prescription of medication should "maximize efficacy and safety, minimize cost, and respect patient's preferences"[29]. Choosing the most appropriate medication for each patient in order to achieve desired therapeutic outcomes is a challenge for healthcare professionals in their daily practice [31]. Criteria to assess the appropriateness of prescriptions and to improve a patient's pharmacotherapy might serve as a helpful guideline during professional training and on the job on a daily basis. In recent years, with inappropriate prescribing becoming an important public health concern, different tools to assess inappropriate prescribing have been developed and published. These tools show major differences in structure and content. They can be grouped roughly into implicit (judgement-based) and explicit (criterion-based) tools, and tools showing a combination of both approaches.

Explicit tools are usually developed from published reviews, expert opinions, and consensus techniques. These criterion-based tools are mostly drug-oriented and/or disease-oriented and can be applied with little or no clinical judgement [32]. Explicit criteria are generally used as rigid standards and neither address individual differences among patients, nor the complexity and appropriateness of entire medication regimens [31]. They need to be updated regularly to ensure their conclusiveness. Furthermore, each country has specific guidelines, standards and approved medications, which makes a country specific adaption of explicit criteria necessary. The advantages are the lower cost of application and a higher degree of fairness in ensuring a more equal care [75]. Implicit tools are judgement-based, patient-specific, and consider the patient's entire medication regimen [31]. Implicit criteria often depend on the user's knowledge, experience and attitude. They can also take into account patients' preferences. However, they may be time-consuming and can have low reliability [32].

The combination of both explicit and implicit criteria enables to link the advantages of each approach. Explicit guidelines serve as background to supply user's clinical judgement of patient's medication and implicit questions provide a patient specific approach with mostly a small number of items.

Creating a valid tool for the assessment of the appropriateness of a medication requires adequate evidence. In areas of healthcare where higher levels of evidence (e.g. controlled

trials) are missing, consensus techniques are useful methods to develop an evidence base. These group facilitation techniques were developed to explore the level of consensus among a group of experts, whereby consensus is reached by summarizing many opinions into a single, agreed-upon, refined opinion [76]. Combining expert opinions with evidence from the literature seems to be a good approach to create a valid, useful tool. Types of consensus techniques are the RAND appropriateness method, the Delphi technique and the nominal group technique (NGT). The RAND combines current scientific evidence with the opinion of elected experts. Panelists rate, meet for discussion and then re-rate issues of interest. The Delphi technique consists of multiple questionnaire rounds with feedback to the panelists between rounds and uses evidence-based literature as a basis but omits expert meetings. The NGT is widely used to generate and prioritize ideas but usually has no initial review of the current scientific literature [76].

Several publications summarize and compare selected existing tools to assess the appropriateness of prescribing [31, 45, 77-81], but a comprehensive overview is still missing. The existing publications either focus on specific patient groups or only show just a small comparison of the most popular tools. Therefore, the objective of this study is to provide a systematic literature search to create a comprehensive and structured overview of all existing tools. A mapping will highlight their characteristics and will allow a comparison of the structure and the content of these tools.

Methods

Pubmed database search included the time period from January 1, 1991, to March 19, 2013. The search strategy contained the following terms and combinations: Inappropriate Prescribing [MESH] OR inappropriate prescribing [All Fields] OR inappropriate prescribing/classification [All Fields] OR inappropriate prescribing/economics [All Fields] OR inappropriate prescribing/ethics [All Fields] OR inappropriate prescribing/ history [All Fields] OR inappropriate prescribing/methods [All Fields] OR inappropriate prescribing/mortality [All Fields] OR inappropriate prescribing/nursing [All Fields] OR inappropriate prescribing/psychology [All Fields] OR inappropriate prescribing/trends [All Fields] OR inappropriate prescribing/utilization [All Fields] OR inappropriate prescribings [All Fields] OR inappropriate prescription [All Fields] OR inappropriate prescriptions [All Fields]. The MESH term “Inappropriate prescribing” was introduced only in 2011. Prior to this, “inappropriate

prescribing" was included in the broadly defined MESH term "Drug therapy". We limited the search to studies in adults. Articles must have been published in English or German. The database search was completed with a manual search from the reference lists of included articles. The reviewer (RT) assessed publications for eligibility by title and abstract screening. Each article showing uncertainty regarding inclusion or exclusion criteria was discussed between three of the authors (RT, CK, ML).

Inclusion and exclusion criteria

We included articles describing tools or computerised decision support systems to assess inappropriate prescribing, updated versions of already published tools and adaptations of an already published tool if its further development was based on new expert consensus. We defined the following exclusion criteria: Tools restricted to specific therapeutic classes (e.g., benzodiazepines, antibiotics, etc.), or specific diseases, tools targeted to children, adaption of already published tools to computerised decision support systems, medication review techniques which did not use a tool, educational interventions to improve prescribing practice, validation studies of previously published tools, and general guidelines or recommendations to assess inappropriate prescribing.

Mapping of the tools

We grouped the tools in three main domains (explicit, implicit and mixed tools). In every domain, tools were ordered according the strength of evidence of their development method (consensus technique, expert panel, literature based). To highlight the characteristics of the tools we listed all properties in a structured way. We categorised inappropriate prescribing according to Spinewine [32] into underprescribing, overprescribing and misprescribing and defined these terms as follows [33, 34]:

Underprescribing: The omission of a medication that is needed (no therapy for a given indication)

Overprescribing: The prescription of a medication that is clinically not indicated (unnecessary therapy)

Misprescribing: The incorrect prescription of an indicated medication.

We further divided misprescribing in:

- Drug choice: Better alternatives are available (better risk-benefit ratio or better cost-effectiveness)
- Dosage: Prescribed dose too low, too high, or not correctly adapted to patient characteristics (e.g. renal function, body weight.)
- Duration of therapy: Duration of therapy too long or too short
- Duplication: Inappropriate prescription of drugs of the same pharmacological class
- Drug-Disease, Drug-Drug, Drug-Food Interactions: Combination of a drug with another drug, with food or with a medical condition with a potential or manifest negative impact on the therapeutic outcome

We listed the focused patient group (elderly, all age), and healthcare setting (hospital care, ambulatory care, long-term care). In addition, we added adherence, cost-effectiveness and whether the tool suggested alternative therapies to the inappropriate ones. The aspect of adherence represents, to a certain extent, the patients' preferences. Intentional non-adherence reflects patients' unwillingness to take their medication, mostly caused by a therapy regimen which does not respect their preferences and, according to Barber's definition [29] is therefore inappropriate.

Results

A total of 716 articles was identified through database search. The numbers of included and excluded articles at each stage are displayed in a flowchart (cf. Fig. A-1).

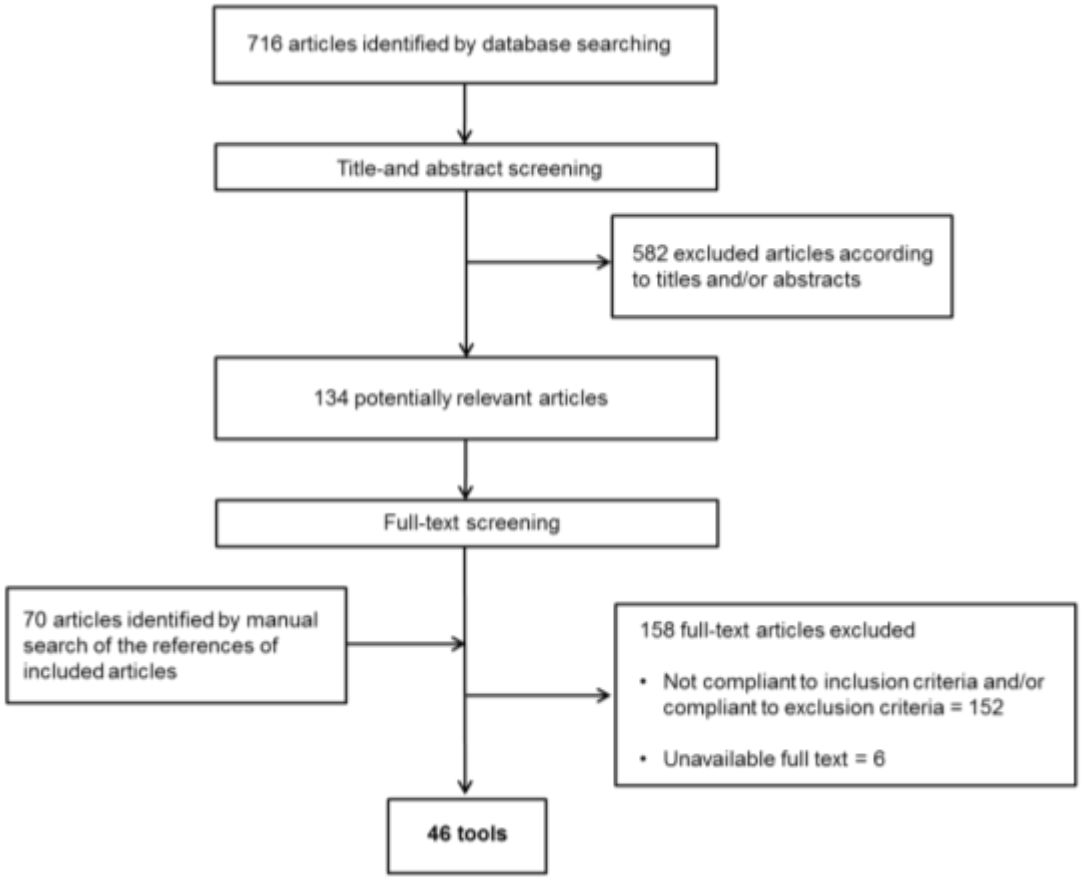

Figure A-1: Flowchart of the literature search

In the end, 46 publications met the inclusion criteria and described 46 different tools. Twenty (43%) of the 46 tools were related to previously published tools (cf. Fig. A-2).

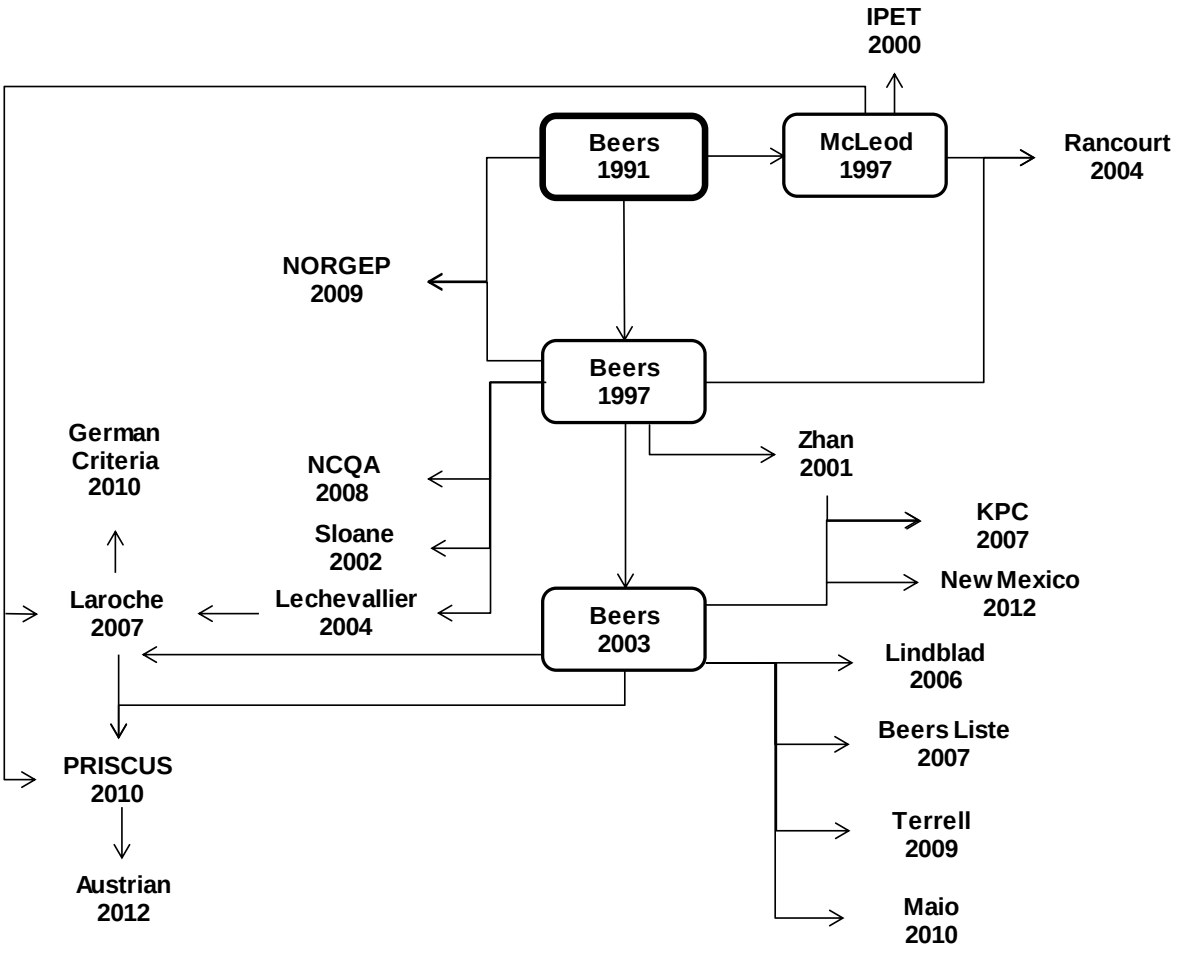

Figure A-2: Relation between different assessment tools. Tools in boxes represent criteria, most frequently used as basis for the development of other tools. (Austrian: Austrian Criteria [82]; Beers: Beers Criteria, different versions [37, 71, 72]; Beers Liste [83]; German Criteria: Unangemessene Arzneistoffe für geriatrische Patienten [84]; IPET: Improving Prescribing in the Elderly Tool [85]; KPC: Kaiser Permanente Colorado Criteria [86]; Laroche: Laroche Criteria [87]; Lechevallier: Lechevallier Criteria [88]; Lindblad: Lindblad's List of Clinically Important Drug-Disease Interactions [89]; Maio: Maio Criteria [90]; McLeod: McLeod Criteria [38]; NCQA: NCQA Criteria – High Risk Medications (DAE-A) and potentially harmful Drug-Disease Interactions (DDE) in the Elderly [91]; New Mexico: New Mexico Criteria [92]; NORGEP: Norwegian General Practice Criteria [93]; PRISCUS: The PRISCUS List [94]; Rancourt: Rancourt Criteria [95]; Sloane: Sloane List of Inappropriate Prescribed Medicines [96]; Terrell: Terrell Computerized Decision Support System to reduce potentially inappropriate prescribing [97]; Zhan: Zhan Criteria [39])

Characteristics (cf. Table A-1, -2 and -3)

Twenty-eight (61%) of 46 tools were explicit, 8 (17%) were implicit and 10 (22%) used a mixed approach. Looking at the patient groups the tools focused on, thirty-six (78 %) tools named older people as target patients and 10 (22%) tools did not specify the target age group. Four (8.5 %) tools were designed to detect inappropriate prescribing in hospitalized patients, 9 (19.5%) focused on patients in ambulatory care and 6 (13%) were developed for use in long-term care. Twenty-seven (59%) tools did not specify the healthcare setting. Consensus methods were applied in the development of 19 tools (41%; RAND 2, Delphi technique 16, Nominal group technique 1), the others were based on either simple expert panels (13, 28%) or on a literature search (11, 24%). For three tools (7%) the development method was not described [98-100]

Aspects of inappropriate prescribing

The aspect of misprescribing was covered to a different extent by each tool. Fourteen (30%) tools focused on overprescribing, 6 (13%) on underprescribing, 8 (17%) mentioned nonadherence and 5 (11%) the cost-effectiveness. Fourteen (30%) tools offered alternative therapies.

Table A-1: Explicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing							Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug Interactions	Drug-Food Interactions					
RD	**<u>ACOVE QIs - Assessing Care of Vulnerable Elders Quality Indicators</u> [101, 102](USA, 1999)** A set of QIs to measure the medical care provided to vulnerable, older persons, created in 1999 and twice updated in 2001 (ACOVE-2, http://www.rand.org/content/dam/rand/www/external/health/projects/acove/docs/acove_qi.pdf) and 2006 (ACOVE-3) [103]. All ACOVE QIs are presented in the following format: IF-THEN-(BECAUSE). Not all QIs measure aspects of inappropriate prescribing but some consider inappropriate prescribing. ACOVE-1 (1999) covers 22 clinical conditions and 236 quality indicators. ACOVE-3 (2006) covers 26 clinical conditions and includes 392 quality indicators .	*ns*	*El*	●				○				○			○
Dp	**<u>Austrian Criteria [82]</u> (Austria, 2012)** A list of 73 drugs to avoid in older patients because of an unfavourable benefit/risk profile and/or unproven effectiveness. A justification for the inappropriateness of a specific drug or drug class is given and for some of the drugs safer alternatives are proposed.	*ns*	*El*	●											○

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-1: Explicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug Interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Dp	**Beers Criteria [71] (USA, 1991)** The Beers Criteria, originally developed for nursing home residents, consists of 19 medications or medications classes to avoid generally in the elderly and 11 criteria describing doses, frequencies, or durations that should not be exceeded. **Update 1997 [72]**: 28 medications or medication classes to avoid generally in the elderly and 15 diseases and conditions and medications to be avoided in these conditions **Update 2003 [37]**: 48 medications or medication classes to avoid generally in the elderly and 20 diseases and conditions and medications to be avoided in these conditions **Update 2012 [73]**: 34 medications or medication classes to avoid in the elderly and 14 diseases and conditions and medications to be avoided in these conditions, and 5 medications to be used with caution in older adults.	*ns*	*El*	●	○	○		○							○
Dp	**Beers-Liste [83] (Germany, 2007)** German adaption of Beers Criteria 2003. Structure and content are similar to the original Beers Criteria, but have been adapted for the German Market.	*ns*	*El*	●	○	○		●							○
Dp	**Laroche Criteria [87] (France, 2007)** Designed for use in the French healthcare system, including 34 medications to be avoided in elderly. Each drug has a declaration for its inappropriateness and safer therapeutic alternatives were recommended for most of the criteria.	*ns*	*El*	●	○		○	○	○						○

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: Dp = Delphi method; NGT = Nominal Group Technique; El=Elderly; ns = not specified

Table A-1: Explicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug Interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Dp	**Lindblad's List of Clinically Important Drug-Disease Interactions [89] (USA, 2006)** A consensus list of 28 clinically important drug-disease interactions ordered by disease.	*A*	*El*	●				●							
Dp	**Malones List of Drug-Drug Interactions [104] (USA, 2004)** A list of 25 potential harmful drug-drug interactions with clinical importance, designed for use in community pharmacies, implemented in a computerized alert system.	*A*	*ns*	●					●						
Dp	**McLeod Criteria [38] (Canada, 1997)** Includes 38 inappropriate prescribing practices to avoid in elderly, focused on four main topics: 1) drugs to treat cardiovascular diseases, 2) non-steroidal anti-inflammatory drugs and other analgesics, 3) psychotropic drugs, and 4) miscellaneous drugs. For each practice, the risk to the patient is specified and an alternative therapy is suggested.	*ns*	*El*	●		○		○	○						●

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-1: Explicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug Interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Dp	**NCQA Criteria - High Risk Medications (DAE-A) and potentially harmful Drug-Disease Interactions (DDE) in the Elderly [91] (USA,2008)** The DAE-A and the DDE lists are part of the Healthcare Effectiveness Data Information Set (HEDIS), a tool to measure performance on important dimensions of care and a service developed by the National Committee for Quality Assurance (NCQA). The DAE-A list includes 17 medication classes, which should be avoided in the elderly, the DDE list shows medication categories affecting the condition of the elderly in a negative way. As a part of HEDIS, the DAE-A and DDE lists are available as interactive, web-based reporting software and receive regular updates.	*ns*	*El*	●				○							
Dp	**NORGEP - Norwegian General Practice Criteria [93] (Norway, 2009)** A list of 21 drugs and drug dosages, as well as 15 drug combinations to be avoided in the elderly in general practice. Each criterion is specified by a comment.	*A*	*El*	●	○				●						
Dp	**Rancourt Criteria [95] (Canada, 2004)** Consists of a list of 111 potentially inappropriate prescriptions categorized as 1) Potentially inappropriate medication, 2) Potentially inappropriate dosage 3) Potentially inappropriate duration and 4) Potentially inappropriate drug-drug interaction.	*L*	*El*	●	○	○			●						

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-1: Explicit tools to assess inappropriate prescribing																	
				Aspects of inappropriateness													
				Misprescribing													
Development method		Healthcare setting	Patient group	Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug Interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Dp	**START - Screening Tool to Alert doctors to the Right Treatment [105] (Ireland, 2007)** A list of 22 prescribing indicators to identify prescribing omissions in older adults. The prescribing indicators are arranged according to the physiological system and present information about disease status for which a drug **should** be prescribed. Combining this tool with STOPP (see directly below) is possible.	*ns*	*El*	●		○									
Dp	**STOPP - Screening Tool of Older Person's Prescriptions [106, 107] (Ireland, 2008)** 65 criteria focusing on prevalent problems associated with commonly prescribed medication, arranged according to physiological systems. Each criterion is accompanied by a short explanation concerning the inappropriateness of its use.	*ns*	*El*	●	○	○	●	○	○						
Dp	**The PRISCUS List [94] (Germany, 2010)** Consists of 83 potentially inappropriate medications in a total of 18 medication classes and is designed for use in the German healthcare system. For each inappropriate medication, the criteria include main concerns, possible therapeutic alternatives and precautions to be taken when these medications are used. The freely available online version[108] additionally focuses on drug-disease interactions.	*ns*	*El*	●	○			●							●

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-1: Explicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug Interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Dp	**Winit-Watjana Criteria [109] (Thailand, 2008)** The list consists of 77 high-risk drugs divided into drugs to be avoided; drugs rarely appropriate; and drugs with some indications for older patients. A practice statement for each drug gives additional information about the inappropriateness.	*ns*	*EI*	●				○	○						
Dp	**Zhan Criteria [39] (USA, 2001)** Includes 33 potentially inappropriate medications divided into the categories: 1) drugs to avoid 2) drugs, appropriate in rare circumstances and 3) drugs with some indications but often misused.	*A*	*EI*	●											
NGT	**Maio Criteria [90] (Italy, 2010)** The Italian adaption of Beers Criteria 2003. The criteria contain 23 potentially inappropriate drugs and divide them into three categories: 1) Drugs to always be avoided, 2) Drugs rarely appropriate, and 3) Drugs with some indications but often misused.	*A*	*EI*	●	○	○									
Ex	**American Medical Directors Association - Top 10 Particularly Dangerous Drug Interactions [110] (USA, cited 2011)** An online list of America's top 10 dangerous drug interactions for patients in long-term care. For each interaction, information about impact, mechanism of interactions, alternatives to patient management, monitoring, precautions and references were provided. The list is based on considerations of drug-drug interactions with clinical significance and a potential to cause harm, the frequency with which these interactions occur and the frequency with which these drugs are prescribed in nursing homes.	*L*	*ns*	●					●						●

●=Aspect totally covered by the criteria, ○=Aspect partially covered by the criteria, Abbreviations: see previous page

Table A-1: Explicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug Interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Ex	**KPC- Kaiser Permanente Colorado Criteria [86] (USA, 2007)** The criteria consist of 11 potentially inappropriate medications for use in elderly and suggestions for alternative therapies. The criteria are incorporated in an electronic pharmacy information management system. Alerts are generated if a drug, included in the Kaiser Permanente Colorado Criteria, should be dispensed. For each medication, a specific intervention guideline and patient counselling script is defined.	*A*	*El*	●											●
Ex	**Lechevallier Criteria [88] (France, 2005)** The French adaption of Beers Criteria 1997 includes 24 inappropriate prescriptions. Drugs mentioned in Beers criteria but not available in France were excluded, drugs available in France belonging to medication classes considered inappropriate in Beers Criteria were included.	*A*	*El*	●			○								
Ex	**New Mexico Criteria [92] (USA, 2012)** The New Mexico Prescription Improvement Coalition (NMPIC) created a list of 72 drugs, based on the Beers criteria [37] and the Zahn criteria, to be used with caution in the elderly. The list uses a color-coded scheme to identify different severity levels and lists concerns and alternative suggestions for each drug.	*ns*	*El*	●	○										●

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-1: Explicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug Interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Ex	**Terrell Computerized Decision Support System to reduce potentially inappropriate prescribing [97] (USA, 2009)** This system was developed for the emergency department and serves as an alert system when using one of nine high-use potentially inappropriate medications. Safer substitute therapies are proposed.	*H*	*El*	●											●
Lit	**CMS - List of unnecessary Medications Used in Residents of Long-Term Care Facilities [111] (USA, 2006)** The Centre of Medicare and Medicaid Services (CMS) list of medications which have the potential to cause clinically significant adverse consequences, that may have limited indications, require specific monitoring, and which warrant careful considerations of relative risk and benefit for use in older adults. All medications are grouped into a total of 24 medication classes/pathophysiological domains. Important information about dosage, adverse consequences, indications, interactions, monitoring and duration of therapy are added. In an additional table drugs with anticholinergic properties that should be avoided in elderly are listed. Beside the medication list, users will find a lot of additional tips how to improve medications management.	*L*	*El*	●	○	○		○	○						
Lit	**IPET - Improving Prescribing in the Elderly Tool [85] (Canada, 2000)** The IPET resulted as a shortened version of the McLeod Criteria and consists of 14 criteria representing potentially inappropriate prescription. Commonly encountered drug-disease interactions and medication classes are discussed, mostly focusing on cardiovascular and psychotropic drugs.	*ns*	*El*	●		○		○							

●=Aspect totally covered by the criteria. ○=Aspect partially covered . Abbrev. Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized

Table A-1: Explicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug Interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Lit	**<u>Matsumura Alert System for Inappropriate Prescriptions [112]</u> (Japan, 2009)** A clinical decision support system combined with a computerised physician order entry system to aid physicians in prescribing medication appropriately. The system focuses on renal disease, liver disease and diabetes mellitus and generates alerts in case of inappropriate dosage or contraindication. The alert system is patient-specific, changes in therapy parameters and clinical laboratory data were automatically updated.	*ns*	*ns*	●	○			●							
Lit	**<u>Sloane List of Inappropriate Prescribed Medicines [96]</u> (USA, 2002)** The Sloane List was developed for identifying inappropriately prescribed medications in older patients in residential care/assisted living facilities. The Beers Criteria served as its basis. Inappropriate medication is presented together with the usual indication, a rationale for being classified as "inappropriate", and possible appropriate alternatives.	*L*	*El*	●											●
Lit	**<u>Unangemessene Arzneistoffe für geriatrische Patienten [84]</u> (DE, 2010)** German adaption of Laroche Criteria. Structure and content are similar to the original Laroche Criteria, but have been adapted to the German market, and new recommendations were added.	*ns*	*El*	●	○		○	○	○						

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-1: Explicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing							Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug Interactions	Drug-Food Interactions					
ns	**<u>FORTA- Fit for the aged criteria [99, 113]</u> (Germany, 2009)** A positive list that grades medications into four groups (A-D), concerning their evidence for use in the elderly. Category A: indispensable, with obvious benefit, B: proven efficacy but limited effects, C: questionable efficacy or safety, should be used carefully; D: no evidence, should be avoided in the elderly. Until now, the FORTA criteria are not yet fully tested in a clinical setting and an overview of recommended drugs is not yet available.	*ns*	*El*	●											

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-2: Implicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Dp	**Cantrill Indicators of Appropriateness of long term prescribing [114] (UK, 1998)** Nine indicators of prescribing appropriateness for assessing the entire drug regimen of patients on long term medication in general practice.	*L*	*ns*	●	●	●			●		●		●		
Ex	**Lipton's Tool to assess the Appropriateness of Physicians' Geriatric Drug Prescribing [115] (USA, 1992)** Evaluation of each drug in the patient's regimen in seven categories of potential drug-therapy problems: 1) Drug allergy, 2) Drug dosage, 3) Drug schedule, 4) Appropriateness of drug therapy, 5) Drug-drug interactions, 6) Therapeutic duplication and 7) Prescribing omission. For all categories, a score is given: 0=no problem, 1=clinically significant but not life-threatening, 2=potentially life threatening or potentially leading to serious injury or hospitalisation; 9=not enough clinical information to make an assessment.	*ns*	*El*	●	●		●		●		●	●			
Ex	**MAI - Medication Appropriateness Index [74] (USA, 1992)** Ten questions used to assess medication appropriateness, which are answered using a three-point Likert scale. For each criterion, a rating of 1 represents appropriate medication use; a rating of 2 represents marginally appropriate medication use; and a rating of 3 represents inappropriate use.	*ns*	*ns*	●	●	●	●	●	●		●		●		

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-2: Implicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Ex	**PMDRP - Pharmacist's Management of Drug-Related Problems [116] (Canada, 1997)** Developed by pharmacists to facilitate learning and the better provision of pharmaceutical care. It requires the pharmacists to collect patients' clinical and medical data and serves as a comprehensive documentation system guiding the pharmacists through the whole pharmaceutical care process.	*ns*	*ns*	●	●			●	●	●	●	●		●	
Lit	**Barenholtz Levy self-administered Medication-Risk Questionnaire [117] (USA, 2003)** Ten-item, self-administered questionnaire for use by elderly patients to identify who is at increased risk of potentially experiencing a medication-related problem.	*ns*	*El*	●							●			●	
Lit	**Hamdy Criteria for Medication Profile Review in Extended Care [118] (USA, 1995)** The criteria were developed with the aim of reducing polypharmacy in patients in long-term care. Five open questions assess the appropriateness of patients' medication focusing on patients taking 10 or more medications.	*L*	*ns*	●	●	●	●	●	●		●				
Lit	**Owens Steps to achieve optimal Pharmacotherapy [119] (USA, 1994)** Consists of five questions: 1) Diagnosis: Is pharmacological intervention necessary? 2) Drug appropriateness? 3) Dose appropriateness? Pharmacokinetic and pharmacodynamic parameters; 4) Reassess: Is medication still needed? 5) Drug-induced disease.	*ns*	*El*	●	●	●		●			●				

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-2: Implicit tools to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
ns	**<u>Robertson's Flow Charts to prevent, identify and resolve Drug Therapy Problems [98]</u> (USA, 1996)** Robertson's Flow Charts were developed to help pharmacy students to focus on drug therapy issues during clinical clerkship rotations. Ten flow charts encourage a uniform approach to preventing, identifying, and correcting drug therapy problems.	*H*	*ns*	●	●			○	●	●	●		○	●	

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-3: Tools with a mixed approach (explicit/implicit) to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
RD	**<u>Australian Prescribing Indicators [120, 121]</u> (Australia, 2008)** A list of 41 indicators is presented based on the medications most frequently prescribed to Australians and the most frequent medical conditions in the elderly. An additional list provides criteria usage information containing necessary medical information for each criterion.	*ns*	*EI*	●	○	○		○	●		○	○			
Ex	**<u>Brown Model for Improving Medication Use in Home Healthcare Patients [122]</u> (USA, 1998)** A list of 15 potential medication problems occurring in patients receiving home healthcare. A structured procedure is described, where home health nurses, in consultation with a drug utilisation review coordinator (e.g. clinical pharmacist), present problems and potential solutions to the patient's physician.	*A*	*EI*	●	●		●	○							○
Ex	**<u>Indicators for Quality Use of Medicines [123]</u> (Australia, 2007)** The New South Wales Advisory Group Quality Indicators were developed for the monitoring of aspects of care in Australian hospitals. Not all of the 30 mentioned indicators consider aspects of prescribing. Each indicator is clearly described and usage information is provided.	*H*	*ns*	○	○										
Ex	**<u>Oborne's Prescribing Indicators [124]</u> (UK, 1997)** A list of 14 prescribing indicators based on the drug charts of 1686 patients. The indicators were presented in the form of algorithms guiding the user through the process of detecting inappropriate prescribing. A version of Prescribing Indicators thought for use in nursing homes is available [125].	*H*	*EI*	●	○		○	○			○	○			

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: see previous page

Table A-3: Tools with a mixed approach (explicit/implicit) to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Ex	**<u>TIMER - Tool to Improve Medications in the Elderly via Review [126]</u> (USA, 2009)** Developed to help pharmacists and pharmacy students identify drug-related problems during patient medication reviews. TIMER addresses four main categories: 1) Cost-effectiveness, 2) Adherence, 3) Medication safety, with methods to assess ADEs and drug-drug interactions 4) Attaining therapeutic goals	*ns*	*El*	●			●	○	●				●	●	
Ex	**<u>The Geriatric Medication Algorithm [127]</u> (USA, 1994)** Designed to educate physicians in reducing inappropriate prescribing, divided into four steps: 1) Obtaining a complete medication list from patient and orthostatic blood pressure; 2) Evaluating each drug regarding indication, high risk medications and dosage; 3) Evaluating the entire drug regimen regarding drug-drug interactions and simplification of drug regimen; 4) Evaluating adherence. Some explicit lists of high risk drugs and drugs requiring dosage reduction in the elderly are also provided.	*ns*	*El*	●	●			●	●		●			●	
Lit	**<u>Kaiser Permanente Model [128]</u> (USA, 1995)** Consists of a pathway for determining high risk patients, then guides the pharmacist with a list through Rx-validation and dispensing, and offers drug grids in order to improve appropriate interventions.	*A*	*ns*	●	●		●	●	●					●	

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-3: Tools with a mixed approach (explicit/implicit) to assess inappropriate prescribing

Development method		Healthcare setting	Patient group	Aspects of inappropriateness											
				Misprescribing											
				Drug choice	Dosage	Duration of therapy	Duplication	Drug-Disease Interactions	Drug-Drug interactions	Drug-Food Interactions	Overprescribing	Underprescribing	Cost effectiveness	Non-Adherence	Alternative therapies
Lit	**Medication Management Outcomes Monitor [129] (USA, 2006)** The criteria focus on reducing inappropriate prescribing (including medication from Beers Criteria 1991), decreasing polypharmacy, avoiding adverse events and maintaining the functional status of older adults. Those four major outcomes serve as an outline and are divided into several specific subgroups, each containing bibliographical references or guidelines on how to assess or intervene. These guidelines are to be used by registered nurses, nurse practitioners, and pharmacists.	*ns*	*El*	●	●		●				●		●	●	
Lit	**POM - Prescribing Optimisation Method for Improving Prescribing in Elderly Patients [130] (Netherlands, 2009)** POM assists physicians to optimise polypharmacy prescribing in the elderly population. This method is based on six open questions, whereby each question in presented with an overview of the most frequent and clinically relevant problems, together with explicit suggestions to improve prescribing.	*ns*	*El*	●	●			●	●	●	●	●		●	○
ns	**ARMOR- A Tool to Evaluate Polypharmacy in Elderly Persons [131] (USA, 2009)** ARMOR is a stepwise approach for the assessment of a geriatric patient who is: (1) receiving nine or more medications; (2) seen for initial assessment; (3) seen for falls and/or changes in behaviour; and/or (4) admitted for rehabilitation. The tool consists of five steps: Assess (medication), Review (e.g. interactions), Minimise (nonessential drugs), Optimise (e.g. Duplication, Dose adjustment) and Reassess (e.g. blood pressure).	*ns*	*El*	●	●		●	●	●		●				

●=Aspect totally covered by the criteria. ○=Aspect partially covered by the criteria. Abbreviations: RD=RAND method; Dp = Delphi method; NGT = Nominal Group Technique; Ex=Expert panel; Lit=based on literature research; El=Elderly; L= Patients in long-term care; H=Hospitalized patients; A=Ambulatory patients; ns = not specified

Table A-4: Correlation of inappropriate prescribing with adverse patient outcomes

Tool	Outcomes	References
Beers Criteria	- higher probability of hospitalization with 2 or more potentially inappropriate medications (PIM) - significantly increased risk for ADRs in elderly with at least one PIM - increased risk of hospitalisation and death with PIM - increased risk of falling when using PIM	Albert 2010 [132], Ruggiero 2010 [133], Passarelli 2005 [70], Dedhiya 2010 [134], Gallagher 2008 [107]
Kaiser Permanente Model	- lower likelihood of hospitalisation in high-risk patients when using the Kaiser Permanent Model of consultation	McCombs 1998 [135]
Lipton Criteria	-association between the prescribing scores and the number of reported adverse effects	Lipton 1993 [136]
STOPP Criteria	- increased risk for ADEs and hospital admission in patients with PIM according to STOPP	Hamilton 2011 [137], Gallagher 2008 [107]
NCQA Criteria	- Increased risk of hospitalisation with medication on the NCQA list	Albert 2010 [132]

Abbreviation: NCQA: National Committee for Quality Assurance

Discussion

The rapidly growing number of publications about inappropriate prescribing demonstrates the increased interest in this topic over the last decade. Many attempts have been made to improve drug prescribing. Tools to achieve this aim are numerous, as we show in this overview, each with a different structure and degree of comprehensiveness and complexity. Many of them might serve as a useful aid to improve prescribing, but each tool has its limitations, strengths and weaknesses. In general, an ideal tool to assess the appropriateness of drug prescriptions should:

- cover all aspects of appropriateness (efficacy, safety, cost-effectiveness and patients' preferences)
- be developed using evidence-based methods
- show significant correlation between the degree of inappropriateness and clinical outcomes
- be applicable not only in research conditions but also in daily healthcare practice

None of the tools we describe in this systematic overview covers all aspects of inappropriate prescribing. In particular, underprescribing is only mentioned in 6 tools, although underprescribing represents an important aspect of inappropriate prescribing and is prevalent particularly in the elderly [138]. Many tools strongly emphasize the choice of a drug that leads to a better compliance with treatment guidelines. But respecting all relevant treatment guidelines without individualisation is in the best case rational prescribing but not necessarily appropriate prescribing [139]. Individualisation is therefore a prerequisite for appropriate prescribing and, thus, the drug–patient interaction is implicitly included in any aspect of appropriate prescribing.

The development methods of the tools we mapped varied a lot and ranged from those which included no information about any aspects of development, to those which used an intensive literature search combined with multiple consensus techniques.

The results obtained from the use of any of the tools represent process measures. Improving the patient's prescription according to such a tool does not necessarily improve outcomes (e.g. mortality, morbidity, adverse drug events, quality of life, etc.). Correlations between process measures and clinical outcomes should be demonstrated in well-designed clinical

trials. For the majority (39/46) of the tools we could not find such clinical validation in the literature.

In a systematic review, Spinewine et al. [32] analysed the correlation between the use of inappropriate medications according to the Beers Criteria [37, 71, 72], the McLeod's Criteria [38], and the Medication Appropriateness Index [74] and patient outcomes. Many studies examined the Beers Criteria and showed a significant correlation of potentially inappropriate medication (PIM) and negative clinical outcomes (e.g., mortality, adverse drug reactions, hospital admission). Additional studies not included in Spinewine's review showed evidence that minimizing inappropriate prescriptions may reduce negative patient outcomes (cf. Table A-4).

Assessment tools are not intended as a substitute for the prescriber's careful clinical decision making, even if they have been perfectly validated. Instead, when implemented in daily practice, they alert healthcare professionals to the likelihood of inappropriate prescribing [79]. Such implementation, however, requires that tools should not only be well designed and comprehensive, but also still practical in daily use. Integration of assessment tools in electronic decision support systems could be a promising approach [97, 104, 112, 140]. One tool, the Barenholtz-Levy Medication Risk Questionnaire [117] is designed for self-assessment by the patient which represents a very different strategy.

A short description of each tool including the number of items, where assessable (cf. Table A-1, 2 and 3), provides some information about the construction and complexity. The number of items per tool varies a lot and ranges from less than ten to more than a hundred items. However a direct relation between the number of items and the complexity of a tool is not clearly given. As an example: the implicit Medication Appropriateness Index (MAI) [74] consists of only 10 questions to patient's medication. But the application of the MAI requires clinical knowledge and is time intensive. On the other hand the explicit Beers Criteria [73], with a high number of items, but arranged in a comprehensive way is easy to handle for a person who is used to it.

Limitations

The literature search was restricted to articles published in English and German; criteria published in other languages were reasonably not included because analysing and mapping the tools required a complete understanding of the text. Literature search, abstract and full text screening were done by only one of the authors (RT). Uncertainties were discussed by all authors. The mapping was developed by one author (RT) and reviewed by a second (CK). Uncertainties about eligibility of a study or classification of the tool were discussed by at least three authors.

Conclusions

Through a systematic literature search, we identified 46 different tools that assessed inappropriate prescribing. They showed a large variety of methodological aspects and validation variability. Not surprisingly with such a variety of tools in such a complex field, this overview could not identify a single ideal tool but may help readers to choose one, either for research purposes or for use in daily practice, according to the situation in which it is intended to be applied. By outlining the characteristics in a highly structured manner, this overview may reveal strengths and weaknesses, and thus, may stimulate further research in this area.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions of authors' statement (with relevance to the ICMJE Guidelines)

C. P. Kaufmann: Contribution to the study design and the analysis and interpretation of data, involvement in the literature search, manuscript writing, final approval of the version to be published.

R. Tremp: Contribution to the study design and the analysis and interpretation of data, conducted the literature search and the mapping of the different tools.

K.E. Hersberger: Manuscript review and final approval of the version to be published.

M.L. Lampert: Contribution to the study design and the analysis and interpretation of data, manuscript review and final approval of the version to be published

PROJECT B: Assessment of patients at risk for drug-related problems

Introduction

Risk factors for DRPs

A preliminary definition of characteristics and conditions is required to enable the identification of a patient as "being at risk".

Clinical pharmacy services for inpatients has been shown to reduce MEs, as well as ADEs and ADRs. However, limited resources make it impossible for clinical pharmacists to comprehensively monitor every patient's therapy. Identifying patients at risk for the development of DRPs may be an efficient approach to target clinical pharmacy resources to those who would benefit the most.

In pharmaceutical research, studies on the evaluation of risk factors (RFs) for DRPs are numerous and are heterogeneous with respect to study design and outcomes. Accordingly, a comparison of study results is difficult.

The most prevalent RF is polypharmacy [16, 141-147], showing the strongest association with adverse outcomes. However the definition of polypharmacy varies between the intake of "more than 4" to "8 drugs and more". Besides polypharmacy, polymorbidity [141, 145], renal impairment [16, 141, 145, 146] and dementia/impaired cognition [141, 147] are prevalent RFs in many studies. Focusing on drugs, most publications highlight oral anticoagulants [16, 141, 143, 146, 148], diuretics [16, 146, 148], non-steroidal anti-rheumatics [141, 148] and antidiabetics [141, 146] as medications with the highest risk of causing harm. A majority of studies focused on a quantitative approach to gather these RFs. Variables were mostly identified by either a retrospective review of literature, medical records and statistical analysis of databases, or a prospective assessment of patient data by the researcher or healthcare professionals. Few studies followed a qualitative approach. Howald et al [148] investigated the causes of preventable drug-related hospitalisations in the UK. Clinical ward pharmacists screened patients admitted to the hospital. Patients with drug-related admissions were included. Following patients' discharge, Howald undertook semi-structured interviews with patients (in their home), their GPs, community pharmacists and, if possible, with other healthcare professionals involved in the care of this patient. All healthcare professionals were independently interviewed at their place of work and answered questions on the patients' medication management and their involvement in their care. The study revealed

communication failures and knowledge gaps, underpinned by a variety of contributing factors, including time and workload pressures and problems with computer system design as major causes for drug-related hospitalisations. Howald et al. explained the reason for using a qualitative approach was the possibility to gathering a more complete picture of the cascade of events leading to drug-related hospitalization by conducting interviews. Problems like missing data, unverifiable data or fragmented records, which may occur in retrospective analyses of data, were therefore overcome. However, the number of cases remained relatively small - a well-known limitation of many qualitative studies.

Data from the literature provided a good basis for the assessment of RFs for DRPs. However, we questioned whether these data fully reflect the real-life situation of practicing healthcare providers, especially when the information comes from another country with a very different healthcare system. In addition, many studies had a narrow focus on specific points in the whole care process of a patient For example, the focus may be restricted to hospital admission or discharge, or to specific patient groups, such as geriatric patients.

With this background, we aimed to start our own research and assess RFs for the development of DRPs with regard to the entire medication process of a patient in the Swiss healthcare system. We followed a triangulation method with a mixed method approach. Triangulation is defined as “the use of multiple methods or perspectives for the collection and interpretation of data on a certain topic, in order to obtain an accurate representation of reality” [149]. To reflect the real-life situation as much as possible we intended to conduct a Nominal Group Technique (NGT) besides the literature search, where a panel of healthcare providers could share their professional experience and knowledge. NGT is defined below. We were aware that qualitative expert interviews were considered as a research method with a low level of evidence. To augment credibility, validity and reliability of our findings, we decided to apply consensus methods.

Consensus methods

Consensus methods are usually applied when there is a lack of scientific evidence, or when there is contradictory evidence on an issue [150]. Consensus methods are group facilitation techniques developed to investigate the level of consensus among a group of experts by synthesizing and clarifying expert opinions [76]. Well-known consensus methods are the Nominal Group Technique (NGT) and the Delphi technique, both of which were used in this thesis (cf. project B1)

NGTs have their use primarily in the generation and prioritisation of ideas [76]. The name of the NGT derives from the fact that the technique is nominally a group which is highly structured. Adequate advance preparation is a prerequisite for the successful identification of the desired information from the panellists [151]. The NGT requires a group facilitator, either one who is an expert on the topic, or a credible non-expert [151]. Unlike the Delphi technique, there is usually no previous review of the current scientific literature. The facilitator however needs to be well informed on the subject to provide panellists with adequate background information so that they gain an insight into the context and aim of the meeting [76]. The NGT only requires a small group. More than ten to twelve panellists are not recommended because it negatively affects the structured discussion and exchange of views. The process of the NGT consists of an introduction on the topic by the facilitator. He formulates the nominal question and the panellists generate ideas in writing. All ideas are collected on a chart, eventually grouped by similar topics and discussed in the group for clarification and evaluation of each idea [152]. Afterwards each panellist, privately and anonymously, rank and prioritize all ideas. The facilitator collects all data and provides feedback to the panellists. Ratings are then discussed and the facilitator might carry out a rerating in order to finalise the results [76]. A NGT leads to more ideas than a conventional, unstructured group discussion. Panellists are actively encouraged to express their personal view to produce explicit outcomes [151]. For data analysis, audiotaping of the NGT is highly recommended and facilitates the generation of a transcript afterwards. When conducting face-to-face meetings, attention should be paid to the risk of psychosocial bias, especially if the group-composition includes very dominant persons or high profile experts. In such cases, some panellists may feel intimidated, and this might affect their statements. On the other hand, face-to face meetings, if well directed by the facilitator, show the benefit of social interaction. The direct social contact of panellists enables an in depth discussion of context and the opportunity to share ideas and experiences

[76]. It is the facilitator's task to create a comfortable atmosphere and to encourage a balanced exchange between all participants.

Like the NGT, the Delphi method is also a decision making process. In contrast to the NGT the Delphi method gathers information through an indirect approach. In principle, panellists do not meet each other, which may inhibit group dynamics but may also prevent social biases [76]. Contact with the participants occurs by questionnaire. The standard process comprises a systematic literature review of current evidence that forms the basis for the development of the questionnaire. The Delphi technique is a flexible method. Numerous modifications of the basic technique have been made [151]. Prior to any ranking process, selected experts may also be asked to generate ideas on the given subject, based on their expertise and knowledge, to generate items for the later questionnaire[76]. The rating of ideas, primarily gathered in a NGT, is also a common approach that we aimed to follow in this thesis. After having received the questionnaire, each participant ranks his agreement with every statement. The rankings are then summarised and redistributed in a repeat version of the questionnaire. Participants rerank, with the opportunity to change their score in view of the group's response. The rerankings are summarised again. If an acceptable degree of consensus is obtained the process ends, with final results fed back to participants; if not, the third round is repeated [150].

For this thesis, we intended to conduct a NGT and let experts generate RFs for the development of DRPs. These findings would then be combined with the findings from a literature search. Summarized RFs will be used in a Delphi questionnaire and let the same panelists who participated in the NGT rank the RFs concerning their relevance for the occurrence of DRPs.

Development of a risk-assessment tool

Once we identified a set of RFs there was the challenge of putting all these RFs in a usable form to identify patients at risk for DRPs in a most efficient way. Several approaches for the patient identification were discussed. The implementation of the RFs in an electronic patient system provides the advantage of a fast, reliable screening without using many human resources. The disadvantage is the exclusion of the patients' opinion who might provide important RFs that are not recorded in the electronic data. In addition, electronic patient data systems are only partially implemented in Swiss hospitals. The clinical pharmacist or other

healthcare providers could assess the patients at risk personally, either by interviewing the patient and/or studying medical data. This approach enables a comprehensive report, including patient opinion when needed, but is very time- and resource-intensive. We intended to create a self-assessment tool, to be filled out by the patient himself. The expert panel supported the idea, pharmacists as well as nurses and physicians emphasized that they do not have enough time to screen every patient by themselves. Instead of thinking of patients in a passive way and treat them as passive recipient of medical care, it can be beneficial to see the hospitalized patient as a valuable source of important information and concede him to play a little more active role in his own care [153].

We encountered different risk assessment instruments in the literature. To gain an overview what has already been done in this field of research we aimed to create a comprehensive and structured overview on all published assessment tools. A mapping, highlighting their properties and development method, should serve as orientation and inspiration for the intention to modify an existing instrument or to create a new one (cf. overview B3). The tools we found where created either for a specific group of patients (e.g. geriatric patients [117, 145, 154], patients prescribed medicines for cardiovascular disease [155]), tools for the use in a special environment (e.g. in an emergency department [147, 156], primary care [154, 157]) or tools which assumed the availability of special resources for their application (e.g. electronic patient files [158]. Some of the tools were very comprehensive [155, 159] or they lacked of information concerning their development or validation [157]. Most of these tools where not developed as self-assessment tools for the patient.

Because we did not find a tool which has met our criteria (patient self-assessment tool, applicable to all patients, not focused on a special setting, availability of electronic data not needed, easy-to-use and validated) we decided to develop a screening tool by ourselves.

We used the following approach:

- In project B1 we identified RFs for the occurrence of DRPs
- With project B2 we aimed to create a self-assessment questionnaire out of the identified RFs from project B1 and to validate the questionnaire regarding feasibility, acceptability, and the reliability of the patients' answers.
- In part B3 we aimed to provide an overview on existing risk assessment tools. Because researchers from all over the world developed new screening tools, while we were developing our own tool, we continued our literature review on risk screening tools and included every newly published tool we found in order to provide a very up-to-date synopsis about what is going on in this topic. As far as we know, there exists no similar overview on risk assessment tools.

PROJECT B1

Determination of risk factors for drug-related problems: a multidisciplinary triangulation process

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BMJ open (2015);5:e006376

DOI:10.1136/bmjopen-2014-006376

ABSTRACT

Introduction and objectives: Drug-related problems (DRPs) constitute a frequent safety issue among hospitalised patients leading to patient harm and increased healthcare costs. Because many DRPs are preventable, the specific risk factors that facilitate their occurrence are of considerable interest. The objective of our study was to assess risk factors for the occurrence of DRPs with the intention to identify patients at risk for DRPs to guide and target preventive measures where they are needed most in patients.

Design: Triangulation process using a mixed method approach.

Methods: We conducted an expert panel, using the nominal group technique (NGT) and a qualitative analysis, to gather risk factors for DRPs. The expert panel consisted of two consultant hospital physicians (internal medicine and geriatrics), one emergency physician, one independent general practitioner, one clinical pharmacologist, one clinical pharmacist, one registered nurse, one home care nurse and two independent community pharmacists. The literature was searched for additional risk factors. Gathered factors from the literature search and the NGT were assemble and validated in a two-round Delphi questionnaire.

Results: The NGT resulted in the identification of 33 items with 13 additional risk factors from the qualitative analysis of the discussion. The literature search delivered another 39 risk factors. The 85 risk factors were refined to produce 42 statements for the Delphi online questionnaire. Of these, 27 risk factors were judged to be ‘important’ or ‘rather important’.

Conclusions: The gathered risk factors may help to characterise and identify patients at risk for DRPs and may enable clinical pharmacists to guide and target preventive measures in order to limit the occurrence of DRPs. As a further step, these risk factors will serve as the basis for a screening tool to identify patients at risk for DRPs.

Strengths and limitations of the study

- This research project followed a comprehensive triangulation method to gather risk factors for drug-related problems (DRPs), integrating expert opinion and literature data, which represents — to the best of our knowledge, a new approach in this topic.
- Participating experts represented a wide variety of settings of patient care and steps in the medication process. This allowed a broad view on the topic of DRPs.
- Inviting actively practising healthcare professionals as experts ensures the practical relevance of gathered risk factors.
- The restricted number of participants in the nominal group technique may have limited the diversity of risk factors.

Introduction

Drug-related problems (DRPs), defined as 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes'[4], constitute a frequent safety issue among hospitalised patients leading to patient harm and increased healthcare costs. The term DRP embraces medication errors (MEs), adverse drug events (ADEs) and adverse drug reactions (ADRs). An ME is 'any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer'[5]. An ADE can be defined as 'an injury—whether or not causally related to the use of a drug'[6]. ADRs include 'any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological functions'[160]. In a systematic review of the years from 1991 to 2001, Krähenbühl-Melcher et al [16] found that approximately 8% of hospitalised patients experience an ADE, and 5–10% of all drug prescriptions or drug applications are erroneous. In general internal medicine, about 15% of hospitalised patients and 12–17% of patients after discharge experience ADEs [17, 161]. In a group of 435 patients with discharge prescriptions from six different European countries, Paulino et al [18] found a DRP in at least 63% of cases. In a Swiss study, 89 of 264 (34%) discharge prescriptions contained qualitative deficiencies and 72 (27%) showed DRPs [20]. Thus, unplanned medication-related readmissions within a short time after discharge are frequent. In a multicenter observational study with a prospective follow-up, 5.6% of 12'793 unplanned admissions were medication related and of these 46.5% were potentially preventable [15].

Because DRPs are an important problem and many of them are preventable, the specific risk factors that facilitate the occurrence of DRPs are of considerable interest. Previous studies have determined numerous risk factors for DRPs. In a literature review, female sex, polypharmacy, administration of drugs with a narrow therapeutic range or renal elimination, age over 65 years, and the use of oral anticoagulants and diuretics, were identified as relevant risk factors for ADEs and ADRs [16]. Leendertse and colleagues considered risk factors, such as four or more comorbidities, polypharmacy, dependent living situation, impaired cognition, impaired renal function and non-adherence to medication regimen, as independent and significant risk factors potentially responsible for preventable hospital admission [15].

These publications mostly rely on retrospective data and often focus on specific points in the whole care process of a patient, for example, hospital admission or discharge. Thus, data from the literature might not fully reflect the current problems of practising healthcare providers, especially when the information comes from another country with a completely different healthcare system. Few studies used a qualitative approach and attempted to reflect real life situations by interviewing patients and healthcare providers. Risk factors reported in such studies differed from those found in quantitative studies. Howard et al [162] conducted qualitative interviews with patients, general practitioners and community pharmacists, and concluded that communication failures and knowledge gaps at multiple stages in the medication process are important risk factors for preventable drug-related admissions. A combination of a qualitative as well as quantitative approach in gathering risk factors for DRPs has not been very prevalent in the current literature.

The aim of our study was to determine the individual risk factors for DRPs by combining current evidence from the literature with the professional experience of healthcare providers throughout the entire medication process. A triangulation process with quantitative and qualitative research methods in combination with consensus techniques served as a comprehensive approach to bridge the gap between research results and professional experience. It is hoped that this will lead to a list of risk factors for DRPs that accurately reflects the reality of daily practice. Risk factors collected will help to characterise and identify patients at risk for DRPs and will enable clinical pharmacists to guide and target preventive measures in order to minimise the occurrence of DRPs.

Methods

Nominal Group technique

We used the nominal group technique (NGT) as a method for eliciting risk factors [76, 151, 152]. We set up an expert panel consisting of two consultant hospital physicians (internal medicine and geriatrics), one emergency physician, one independent general practitioner, one clinical pharmacologist, one clinical pharmacist, one registered nurse, one home care nurse and two independent community pharmacists. The selection was based on the desirability of including a wide variety of experts from different settings, who are all involved in the patients'

medication management. Every expert had at least 5 years of professional experience, held a senior/executive position and was involved in daily patient care.

We set the duration of the NGT to 2 h. The moderator (CK) started the NGT meeting with a short introduction to the topic, with the aim of communicating the goal of the meeting and bringing the entire panel's knowledge about DRPs up to the same level. The participants were then asked to write down as many risk factors for DRPs as they could spontaneously think of. To avoid double-nominations, synonyms and very closely related terms (e.g., 'dementia' and 'cognitive impairment'), two clinical pharmacists (MLL and DS) and a community pharmacist (KEH) grouped the gathered risk factors while retaining each individual factor in the list. This work was done during the NGT. Subsequently, we presented the collected risk factors to the participants and invited them to rank each risk factor by its relevance. Each expert allocated 50 points (1.5 times the number of risk factors (=33)). We determined the amount of points by ourselves. Experts should be able to rank every risk factor, instead of choosing a defined number of most important factors. However, we limited the amount of points to force a consensus finding. Experts could assign as many points to as many of the risk factors as they wanted until all points were used. After the first ranking, we collected the ranking sheets and summarized the points to create a first ranking list. We discussed the ranking list with the expert panel, paying special attention to high and low scoring and discrepancies in the ranking among participants. In the second round of the ranking process, panellists had only as many points as the number of available risk factors, forcing them to fine-tune their previous ranking and to reach a consensus. We collected the rerated lists, created the new ranking, and then returned the resulting ranking list to all participants for final comments. Because we worked neither with patient data nor with patients themselves, we did not need ethical approval.

We audiotaped the entire discussion session of the expert panel and transcribed it into written text for qualitative analysis. One of the authors (DS) split the transcript into fragments and a second author (CPK) checked the splitting. Later the two authors (DS and CPK) together rearranged the fragments into groups treating related subjects. The whole grouping was then discussed by three authors (CPK, DS and MLL). Disagreements were discussed until the three authors reached consensus. We labelled every fragment with a unique index number to assure transparency.

Literature search

We conducted a non-systematic literature search to supplement the findings of the expert panel. Our goal was to gain an impression of the current state of research in the field of risk factors leading to DRPs. We wanted to know which risk factors for DRPs were described in the current literature and which were most mentioned. We conducted our search in PubMed and EMBASE. Language was restricted to German and English. The following search terms wer used in EMBASE: 'drug related problems' AND 'risk'/exp AND factors AND [systematic review]/lim AND ([english]/lim OR [german]/ lim) AND [humans]/lim.; 'Triage'/exp OR 'triage'/syn AND ('risk'/exp OR 'risk'/syn) AND assessment AND ([child]/lim OR [adolescent]/lim OR [adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([meta-analysis]/lim OR [systematic review]/lim) AND ([article]/lim OR [review]/lim).; 'Adverse drug reaction'/exp AND 'screening'/exp AND 'high risk patient'/exp AND [humans]/lim AND [english]/lim

The following search terms were used in PubMed: "Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; "Drug Toxicity"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; (("Drug Toxicity"[Mesh]) OR "Medication Errors"[Mesh]) AND "Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; "Medication Errors"[Mesh] AND "Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; ("Risk Factors"[MeSH Terms]) AND "Hospitalization/statistics and numerical data" [MAJR] "Risk Assessment/methods"[MeSH Terms] AND "Medication Errors"[Mesh]

Titles and abstracts were screened for relevance. Abstracts needed to mention the terms 'risk factors', 'predictors' or 'high risk' in combination with 'drug-related problems' or subterms of its definition.

We checked the reference list of each paper selected for further possible hits. Besides this literature search, we reviewed different tools focusing on the assessment of inappropriate prescribing, which we identified in a previous systematic review [163]. Inappropriate prescribing is a known source of DRPs, ADEs and ADRs. Original publications of these tools were screened for risk factors associated with inappropriate prescribing that are connected with negative outcomes, for example, DRPs, ADEs, ADRs and rehospitalisation. PubMed and

EMBASE were searched for validation studies using the name of the tool and, if necessary, 'outcome' or 'assessment' as MeSH terms or by checking publications that cited the original paper.

Delphi process

We validated the risk factors collected from the literature search and the NGT by using the Delphi technique [164]. Before integrating the risk factors in the questionnaire, we condensed them by using the following exclusion criteria:

- The risk factor is mentioned in only one of the relevant publications.
- The risk factor set in the lowermost quartile of our NGTs ranking list is not mentioned anywhere else.
- The risk factor is categorised as an issue of seamless care (e.g. lack of communication between healthcare professionals, patient information and discharge management).
- The risk factor represents a barely predictable event or circumstance (e.g. unscheduled discharge, confusion of drug names by professionals).

We excluded seamless care issues, because they are not individual risk factors but instead reflect system failures; they are, therefore, not assessable for an individual patient. In addition, we combined synonyms in one term. Any ambiguous risk factors were discussed by experts to decide about their inclusion or exclusion on a case-by-case basis.

In a two-round online Delphi survey (Flexi Form, In 2.0 ed.), following 2 months after the NGT, the NGT participant rated each risk factor on a four-item Likert scale (1='unimportant' 2='rather unimportant', 3='rather important', 4='important') according to its potential to cause DRPs (cf. Annex A1.1).

The questionnaire for the second rating started 2 weeks after the end of the first rating and included the same questions as the first one, but the sequence represented the ranking list of the first round. We presented the median score and the interquartile range (IQR) of each question to the participants to give them the possibility to consider the group's rating for their own re-rating. Below the Likert scale of each question, the number of participants who rated for the respective relevance was shown. After the second rating, the median scores and IQRs were calculated and a final ranking list of risk factors collected was established.

Results

NGT rating and literature search

The ranking process of the NGT resulted in 33 items (figure B1-1). The qualitative analysis of the discussion not only confirmed risk factors identified in the rating process but also revealed 13 additional risk factors. Main topics were high-risk drugs, communication issues between healthcare professionals, patient education and questions of responsibility. The literature search resulted in 39 additional factors that were not mentioned in the NGT.

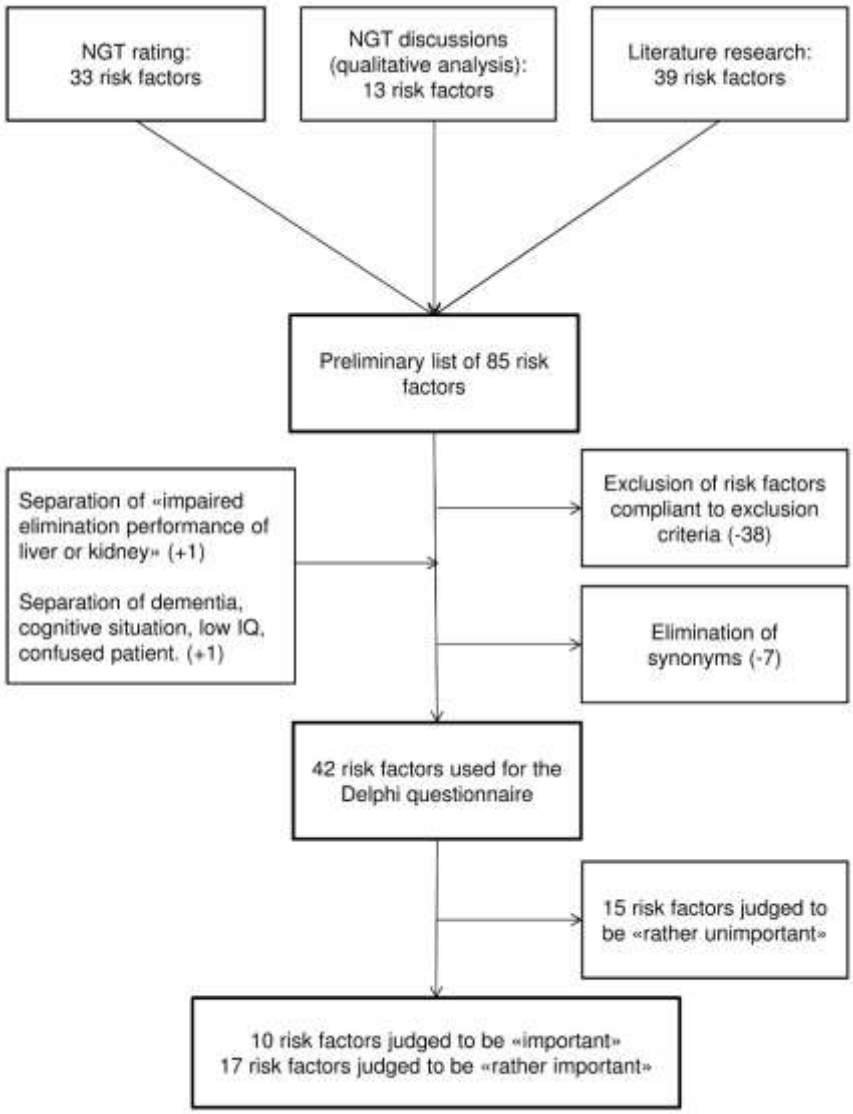

Figure B1-1: Flowchart of eliciting risk factors possibly leading to DRPs (NGT, nominal group technique; DRPs, drug-related problems).

Delphi questionnaire

In total, we gathered a preliminary list of 85 risk factors. Of these, we excluded 38 risk factors because they fulfilled our exclusion criteria (cf. table B1-1). Twice, we split a risk factor into two parts, and we eliminated seven synonyms. Ultimately, we used 42 risk factors in the Delphi questionnaire.

The results of the Delphi technique are shown in tables B1-2 and B1-3. They are arranged by median score of the second round. In the second round, 10 risk factors were judged as 'important' (Likert scale: 4) concerning their contribution to the occurrence of DRPs, 17 risk factors were judged as 'rather important' (Likert scale: 3), 15 risk factors were judged as 'rather unimportant' (Likert scale: 2) and no risk factor was considered as 'unimportant' (Likert scale: 1). The sum of the IQRs changed from 30 in the first round to 20 in the second round, representing a stronger consensus between the participants. Finally, we created a list of 27 risk factors rated as important or rather important for the occurrence of DRPs.

Table B1-1: Risk factors excluded from the Delphi questionnaire, including information to their origin.

Excluded risk factors	
Mentioned in only one of the selected publications	heart failure (L); liver disease (not hepatic impairment) (L); problems with "water works"(L); antidepressant (L); drugs with positive inotrope effects (L), potassium channel activators (L); antibacterial drugs (L); laxatives (L); corticosteroids for inhalation (L), loperamide (L); statins (L); cephalosporins (L); compound analgesics (with opioids)(L); low molecular weight heparins (L); macrolide antibiotics (L); penicillin (L); aspirin (L); salbutamol (L); antihypertensives (L); bladder antimuscarinic drugs (L); cerebral vasodilators (L); nitroglycerine (L); ranitidine (L); 1st generation antihistamines (L)
Lowermost quartile of the NGT ranking list and not mentioned elsewhere	money (N); Morbus Parkinson (N); xerostomia (N); oral bisphosphonate (N)
Seamless care issue or intervention to improve seamless care **OR** **Unpredictable event or circumstance**	unclear prescription/unclear or non-available dosage regimen at discharge (N); multiple treating physicians (L,N); missing instruction of relatives(N); medication-taking gap (N); briefing of the patient (L;Q); confusion of drug names (N); new medication / lots of changes/ alternating dosages (N); changes in therapy: stop due to hospitalisation/discharge/generic medication (N,Q); unscheduled discharge (N)
Synonyms	
- behaviour at home during an ADR (N); earlier experiences with medication (N,Q) → included as: experience with ADR (Q) **- impaired mobility (L,N)** → included as: High risk of falls, motion insecurity (L,N,Q) **- language (Q)** → included as: language issues (N) **- oral corticosteroid (L); systemic corticosteroids (L)** → included as: corticosteroids (L) **- parallel therapy (N)** →incl. as: self-medication with non-prescribed medicines (N,Q)	

Abbreviations: L: Literature search, N: NGT ranking list, Q: Qualitative analysis of the NGT

Table B1-2: Final ranking list of the 27 risk factors contributing to the occurrence of DRPs rated by the expert panel as "important" (Likert scale: 4) or "rather important" (Likert scale: 3).

Risk factor	Delphi		NGT		Literature
	Median	IQR	Ranking list	Qual. anal.	
Dementia, cognitive situation, Low IQ, confused patient	4	4.00 – 4.00	YES		[15], [156], [147], [165], [107]
Polypharmacy (number of drugs >5)	4	4.00 – 4.00	YES	YES	[15], [156], [147], [143], [145], [16]
Antiepileptics	4	4.00 – 4.00		YES	[148, 166], [107], [137]
Anticoagulants	4	4.00 – 4.00		YES	[15], [143], [148], [167], [16]
Combinations of non-steroidal anti-inflammatory drugs (NSAID) and oral anticoagulants	4	4.00 – 4.00		YES	[107]
Insulin	4	4.00 – 4.00	YES		[15], [148, 166]
Missing information, half-knowledge of the patient, the patient does not understand the goal of the therapy	4	4.00 – 3.25	YES		[162]
Medication with a narrow therapeutic window	4	4.00 – 3.25	YES	YES	[16]
Non-adherence	4	4.00 – 3.00	YES		[15]
Polymorbidity	3.5	4.00 – 3.00	YES	YES	[15], [145]
Digoxin	3	4.00 – 3.00			[166], [107], [115]
Renal impairment (eGFR <30 ml/min)	3	4.00 – 3.00	YES		[15], [145], [107]
NSAIDs	3	4.00 – 3.00		YES	[15], [143], [148, 166], [16, 137]
Experience of ADR	3	3.75 – 3.00	YES	YES	[145]
Medication which is difficult to handle	3	3.75 – 3.00	YES		

Risk factor	Delphi		NGT		Literature
	Median	IQR	Ranking list	Qual. anal.	
Language issues (i.e. non-native speakers)	3	3.00 – 3.00	YES	YES	
Diuretics	3	3.00 – 3.00		YES	[15], [148, 166], [167], [165], [137], [16]
Tricyclic antidepressants	3	3.00 – 3.00			[143], [107]
Hepatic impairment	3	3.00 – 3.00	YES		[145], [107]
Self-medication with non-prescribed medicines	3	3.00 – 3.00	YES	YES	
Impaired manual skills (causing handling difficulties)	3	3.00 – 3.00	YES		
Visual impairment	3	3.00 – 3.00	YES	YES	[156]
Anticholinergic drugs	3	3.00 – 3.00			[168]
Benzodiazepines	3	3.00 – 3.00			[143], [107], [168], [137], [169]
Opiates/Opioids	3	3.00 – 3.00			[15], [148], [167], [107], [137]
Corticosteroids	3	3.00 – 2.00			[15], [148, 166]
Oral antidiabetics	3	3.00 – 2.00			[15], [148, 166]

The sequence represents the ratings of the Delphi survey indicating median ratings and IQR, and appearance in the NGT ranking list, the qualitative analysis of the NGT and in the literature. Factors with no reference in the literature section were only mentioned by the experts. IQR, interquartile range; ADR, adverse drug reaction; DRP, drug-related problem; eGFR, estimated glomerular filtration rate; NGT, nominal group technique; NSAID, non-steroidal anti-inflammatory drugs.

Table B1-3 Risk factors contributing to the occurrence of DRPs rated from the expert panel as 'rather unimportant' (Likert scale: 2) or 'unimportant' (Likert scale: 1) and therefore not included in the final list of risk factors

Risk factor	Delphi		NGT		Literature
	Median	IQR	Ranking list	Qual. anal.	
Age	2.5	3.75 – 2.00		YES	[170], [16]
Extreme body weight (too high or too low)	2	3.00 – 2.00	YES		
Antiplatelet drugs	2	3.00 – 2.00			[15], [148, 166]
Drugs affecting the renin-angiotensin-aldosterone-system (RAAS)	2	3.00 – 2.00			[15], [148]
Patient living alone	2	3.00 – 2.00	YES		[147], [165], [171]
Calcium antagonists	2	3.00 – 2.00			[15], [148], [107]
Nitrates	2	3.00 – 2.00			[148, 166]
Patient's education about his therapy	2	2.75 – 2.00		YES	[162]
Beta-blockers	2	2.00 – 2.00			[15], [148, 166], [107], [137]
Antacids	2	2.00 – 2.00			
High risk of falls, motion insecurity	2	2.00 – 2.00	YES	YES	[147], [165], [171], [107], [137], [168], [169]
Previous hospitalisation in the last 30 days	2	2.00 – 2.00			[156], [147], [170]
Need for caregiver at home	2	2.00 – 2.00	YES		[15]
Calcium containing drugs	2	2.00 – 1.00			[115]
Respiratory drugs	2	3.00 – 1.00			[15], [148], [167]

The sequence represents the ratings of the Delphi survey indicating median ratings and IQR, and appearance in the NGT ranking list, the qualitative analysis of the NGT and in the literature. Factors with no reference in the literature section were only mentioned by the experts. IQR, interquartile range; DRP, drug-related problem; NGT, nominal group technique; RAAS, renin-angiotensin-aldosterone system.

Discussion

We were able to determine 27 risk factors that appear to contribute substantially to the occurrence of DRPs. The triangulation, for which we used the NGT with its rating process, the expert panel and a literature search, enhanced the accuracy of our findings and ensured their practical relevance. In agreement with previous quantitative studies, we identified expected and well-known risk factors in our literature search. The inclusion of an expert panel gave us valuable insight into problems healthcare professionals are confronted with and the risk factors they judge as important or not. As we expected, risk factors that were prevalent in the literature were mentioned by the experts as well, for example, some high-risk drugs (such as anticoagulants and insulin), polypharmacy and renal impairment. Apart from that, the expert panellists showed us valuable risk factors often seen in their daily practice and less described in the literature. Insufficient information transfer between the primary and secondary care setting was considered as important handicap in daily practice. Problems are considered to have already begun at hospital admission, where patients often arrive without being able to give information about their current longterm medication. During the hospital stay, the medication of the patient undergoes significant changes. Lack of communication among the different healthcare providers leads to confusion.

Community pharmacists reported about having insufficient access to patients' medical records, which hinders them in advising the patient in a comprehensive way. Panellists from every healthcare area emphasised the importance of patient information. They were aware that patients' knowledge about their medication is often incomplete. Self-medication is rarely mentioned in the dialogue with the healthcare professionals because the patient does not regard their vitamin pills and herbal supplements as real medication.

An increasing number of patients speaks a foreign language, which complicates communication. To improve the education of patients and to guarantee the transfer of information about patients' medication, panellists acknowledged the benefit of appointing an individual who would be responsible for the medication management and education of the patient.

The experts stated that the medication manager would ideally be someone who could walk across all floors of the hospital, meeting with newly admitted patients, compiling a complete

medication history and checking for DRPs. This medication manager would monitor the patient throughout the hospital stay and, at the patient's discharge, he or she would perform the final medication check to identify potential DRPs, and ensure that the patient understands the prescribed therapy and knows how to take the medication. After discharge, the medication manager would ensure that the correct information is shared with the community pharmacy and the general practitioner in order to guarantee seamless care. The medication manager would serve as a consultant and not as a replacement for the prescribing physician. The panellists considered clinical pharmacists or pharmacologists the most appropriate professionals for this task, due to their broad knowledge about medication.

The risk factor 'age' does not belong to the final list of most important risk factors. The experts stated clearly that an 80-year-old patient could be in a much healthier condition than one who is a 60 years old. When talking about geriatric patients, we are aware of risk factors such as polypharmacy, renal impairment, dementia and many more. The expert panel rated these risk factors as more important than the 'age' factor itself.

The composition of the expert panel was multidisciplinary by choice, because we aimed to bring together all stakeholders in the medication process of a patient. By performing an NGT instead of interviews, we gave the panellists the possibility not only to answer our questions, but to discuss their different views with other healthcare professionals. The panellists were highly motivated and discussed in an engaged and informative way. Despite their different professional backgrounds, they agreed on many discussion points. They appreciated the interdisciplinary exchange and found that it would be worthwhile to conduct such discussion rounds more frequently.

The ensuing Delphi process enabled the desired consensus-forming. By conducting the Delphi process with online questionnaires, where the participants were anonymous, we avoided any psychosocial biases. In the first round, the total number of IQRs was 30, whereas it was 20 in the second round. This means that the degree of consensus increased among the participants.

Study limitations

There are some general concerns about the validity and generalisability of information created by qualitative research methods. The Delphi and NGT approaches are both often criticised for showing a lack of research-based evidence concerning diverse feedback methods, and their influence on the validity and reproducibility of the decisions reached by the panel members [151]. Other influences on the whole group dynamic are psychosocial biases, which were described by Pagliari et al [172]. We addressed this by assigning each panellist a place in the NGT in order to avoid grouping of friends or panellists from the same profession. We decided to use a small expert panel with 10 panellists. Although larger groups would provide a more extensive representation, they may be difficult to lead, which may only be resolved by introducing more structure and role definition into the process [172].

A limitation of our Delphi technique after employing NGT is the restricted number of participants. We chose the very same motivated experts for the Delphi and the NGT, because they were already familiar with the topic. In conclusion, the gathered risk factors may help to characterise and identify patients at risk for DRPs, and may enable clinical pharmacists to guide and target preventive measures in order to limit the occurrence of DRPs. In a further step, these risk factors will serve as the basis for a screening tool to identify patients at risk for DRPs.

Acknowledgements: The authors thank the members of the expert panel who contributed to our findings.

Contributors:

CPK contributed to the study design, the analysis and interpretation of the data, manuscript writing, final approval of the version to be published, and was substantially involved in the literature search, and conduction of the nominal group technique (NGT) and the Delphi questionnaire.

DS contributed to the study design, the analysis and interpretation of the data, the literature search, and conduction of the NGT and the Delphi questionnaire.

KEH contributed to manuscript review and final approval of the version to be published.

MLL contributed to the study design and the analysis and interpretation of the data, conduction of the NGT and Delphi survey, and also contributed to the manuscript review and final approval of the version to be published.

Funding: The study is financially supported by an unrestricted research grant from the Swiss Society of Public Health Administration and Hospital Pharmacists (GSASA).

Competing interests: None.

PROJECT B2

The Drug Associated Risk Tool - DART

A new instrument to screen patients at risk for drug-related problems

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ABSTRACT

Background and Objectives: Drug-related problems (DRPs) are a serious concern among hospitalized patients, leading to harm and increased health-care costs. Identifying patients with a high risk for drug-related problems (DRPs) might optimise the allocation of targeted clinical pharmacy activites during the hospital stay and upon discharge. The objective of this study was to develop a self-assessment screening tool to identify patients at risk for DRPs and validate the tool regarding feasibility, acceptability, and the reliability of the patients' answers.

Design and Setting: Prospective validation study in two mid-sized hospitals in Basel-Land, Switzerland.

Methods: Twenty-seven risk factors for the development of DRPs, evaluated in a previous study, provided the basis for the Drug-Associated Risk Tool (DART). Consenting patients filled in the DART, and we compared their answers with objective patient data from medical records and laboratory data. Exclusion criteria were age under 18 years, ambulatory or palliative patients, or a health status not allowing meaningful communication.

Results: One hundred and sixty-four patients (median age: 74 years [age range: 20-95 years], 49% female) filled in the DART in an average time of 7 minutes. The questions of the DART reached an overall specificity of 0.95 (range: 0.82-1), whereas the overall sensitivity was 0.58 (range: 0.21-1).

Conclusions: The new DART self-assessment questionnaire showed a satisfying feasibility and reliability. False positive results can be excluded with a high probability of success due to constantly high specificity values. The sensitivity varied and was higher in statements concerning diseases that require regular disease control and daily attention to self-care and drug management. Drugs requiring a high amount of self-management showed the highest sensitivity. Despite some low sensitivity values, this questionnaire seems to be applicable to patients in a hospital setting. Patients may be a valuable, but often neglected source of information. Asking patients about their conditions, their medications and related concerns and problems can facilitate getting a first, but broad picture of the risk for DRPs and possible pharmaceutical needs. To strengthen the reliability of the DART some questions should be rephrased and risk factors with a very low prevalence should be validated in a more specific population.

Key words: drug-related problems, risk factors, risk screening, self-assessment questionnaire, validation study

Impact of findings on practice statements

- A self-assessment questionnaire as a screening for risk factors that could lead to drug-related problems is a new approach and seems acceptable and feasible
- Patients may be a reliable source for information about drug therapy issues and related risk.

Introduction

Drug-related problems (DRPs) are a frequent issue among hospitalised patients, leading to patient harm and increased healthcare costs [16]. Many unplanned admissions are medication-related [141] and a considerable number could be prevented [10]. Complexity and often poorly designed processes foster the development of drug-related problems inside and outside of the hospital. A study from Switzerland showed that 36% of all discharge prescriptions contained technical DRPs like unreadable prescriptions, missing drug form and package size, and 19.6% showed clinical DRPs like drug-drug interactions, inappropriate drug choice and wrong dosing [20]. Not surprisingly, a remarkable number of patients experience adverse drug events (ADEs) after discharge [161].

Clinical pharmacy services in hospitals have been shown to increase patient safety by reducing medication errors and Adverse Drug Events (ADEs), as well as adverse drug reactions (ADRs). They increase medication appropriateness, improve patients' knowledge about drug therapy and adherence, and finally reduce the length of hospital stays [54]. Limited resources and capacities force clinical pharmacists to target their clinical activities to those patients who are most likely to benefit therefrom, or in other words, to those who are at the highest risk of experiencing DRPs, and in consequence, ADEs. An effective screening tool to identify high-risk patients might prove a successful approach. How do we characterize a patient at risk? The literature provides us with well-known risk factors for the development of DRPs, for example, polypharmacy, renal impairment, or the use of non-steroidal anti-inflammatory drugs (NSAIDs) [141, 143, 148]. There are some available risk assessment tools which focus on various combinations of these risk factors. Most of them are created either for a specific group of patients (e.g. those with renal impairment [173], geriatric patients [145, 154], patients prescribed medication for cardiovascular disease [155]), tools for the use in a special environment (e.g. in an emergency department [174]) or tools which need special resources to be applied in hospital (e.g. computerized patient files [175]). These tools often have the disadvantage of being time and personnel intensive; some are hardly applicable without electronic data or they have not been validated.

Therefore, we decided to develop a new risk assessment tool from the ground up. The "Drug-Associated Risk Tool (DART)" should serve as a reliable, easy-to-use screening instrument to

detect patients at risk for DRPs. To save personal resources and time, we set out to develop a self-assessment questionnaire that can be filled in by the patients themselves.

In a previous study [176], we identified 27 risk factors for the development of DRPs, which provided the basis for the self-assessment questionnaire. We searched for relevant risk factors, not only in literature, but also by using qualitative research. We conducted an expert panel discussion to get a deeper insight into everyday practice, and by doing so, to identify additional risk factors that had been neglected in literature.

The aim of this study was to create a self-assessment questionnaire out of the identified risk factors and to validate the questionnaire regarding feasibility, acceptability, and the reliability of the patients' answers by assessing sensitivity and specificity.

Ethical approval

The local ethics committee (Ethikkommission beider Basel) approved the study (cf. Annex A2.1). All participating patients gave informed consent (cf. Annex A2.2)

Method

Our study was divided in two parts: First the development of the self-assessment questionnaire and second its validation.

Development of the questionnaire

Twenty-seven risk factors for the development of DRPs, collected in a previous study [176], provided the basis for the self-assessment questionnaire. With the intention of creating a questionnaire for patients, we translated each risk factor into statements that could be answerable by medical laypersons (cf. table B2-1).

We covered the risk factor "non-adherence" with a question that we retrieved from a validated questionnaire, the Morisky Medication Adherence Scale MMAS-8 [177], a validated self-report 8-item questionnaire, widely used to measure adherence. Risk factors concerning patients' beliefs about medicines in general were covered by using four questions from the Beliefs about Medicines Questionnaire BMQ [178], a questionnaire that comprised two five-item scales assessing patients' opinions about the necessity of prescribed medication for controlling their illness and their concerns about the potential adverse consequences of taking it.

Amateur test

Prior to the study, we conducted an amateur test and asked ten medical laypersons from the personal environment of the authors (no patients) to fill out the DART. We did not provide any support during its completion. We asked each individual for his/her judgment concerning the comprehensibility of the statements.

Validation of the questionnaire

Study design and Setting

For the prospective validation study, we recruited the patients in two mid-sized hospitals with each 400 beds in Basel-Land, Switzerland. We recruited on the orthopaedic, geriatric, and internal medicine wards.

Patient Selection

Eligibility criteria were age over 18 years, ability to speak German in order to communicate with the investigator, and the patient required hospitalization. We excluded ambulatory patients and patients with a health status not allowing a meaningful communication (e.g. delirium, acute psychosis, advanced dementia, aphasia, clouded consciousness state) as well as palliative or terminally ill patients. We included patients suffering from mild dementia if a meaningful communication was possible (cf. Annex A2.6.).

Study Flow

During a predefined period, the investigators (CK, NM, TS) and three additional trained clinical pharmacists met with every hospitalized patient on the included wards who met the inclusion criteria. They informed each patient orally and with an informational letter about the study. After giving informed consent, the patient received the DART and filled in the questionnaire independently, i.e. the investigator left the room or stayed in the room without giving any assistance in filling out the questionnaire. If a patient showed impaired manual skills, the investigator could assist with the writing. When finished, the investigator asked the patient five questions about the structure and content of the DART in order to see if the questionnaire was easy to understand and not too intrusive (cf. Annex A2.3.). Furthermore, the investigator interviewed the patient in detail with regard to the patient's attitude towards health and medicine. Validated questionnaires were used to investigate compliance (Morisky Medication Adherence Scale – MMAS-8[177]), concerns and beliefs towards medicines (Beliefs about Medicines Questionnaire - BMQ[178]), and mental health (Micro Mental Test - MMT[179]). Participation in the study was voluntary. The patient could terminate the interview at any time without giving a reason.

Pre-test

With a first draft of the DART, we conducted a pre-test with five inpatients. The procedure followed the same study flow we determined for the validation study (see study flow). This pre-test with inpatients served as an opportunity to correct any remaining issues of comprehensibility or ambiguity.

Data Collection and Analysis

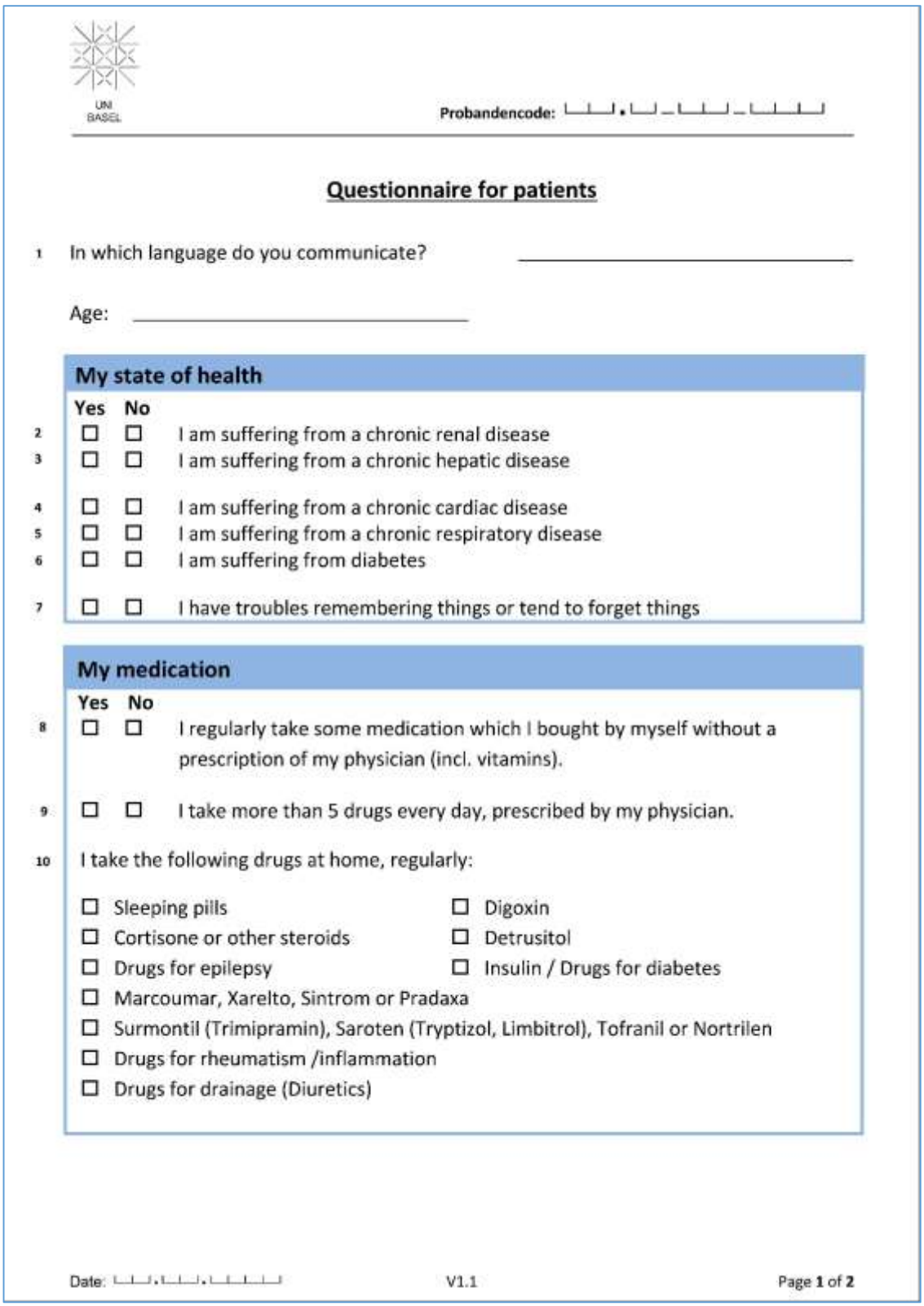
We evaluated all data anonymously. In order to ensure traceability, we assigned each patient a unique identifying number coding for the particular hospital/ward/investigator/patient. All data were entered in a prepared case report form (cf. Annex A2.4.). The investigator CK provided written instructions for the completion of the CRF (cf. Annex A2.5.)

We used the IBM SPSS Statistics Software, V 22 (IBM Corp., Armonk, NY, USA) for data analysis. We transferred all collected data in an SPSS table. A second investigator double-checked all data. In cases of ambiguity, we discussed the affected data with all authors. We evaluated sensitivity and specificity of each question of the DART by comparing the subjective answers in the DART with objective data from medical records (diagnosis, laboratory values, and medicines at entry) and answers from the MMAS-8[177], the BMQ[178] and the MMT[179]. Acceptance criteria for correlation of subjective and objective data were defined a priori (cf. table B2-1). We calculated the sensitivity and specificity for each question of the DART and added the prevalence of each risk factor (except questions number 8, 16, 17 and 18 (cf. figure B2-1). No objective measurement is possible or needed to correlate them). We calculated the chi-square-test or Fisher's Exact Test, when appropriate and the phi-coefficient as a measure for the association of subjective with objective data. A value of $p < 0.05$ was considered statistically significant. For our data sample, the phi-coefficient could range from 0 to +1, where 1 indicates perfect association, and 0 indicates no relationship. Missing data were excluded from analysis.

Results

Development of the questionnaire

The first page of the DART consists of ten items concerning the presence of diseases and high-risk medicines. The second page includes nine items reflecting the patient's attitude towards his/her medicines and statements about medication management and handling difficulties (cf. figure B2-1). The ten non-patient individuals from the amateur test had no difficulties completing the questionnaire, and only minor adjustments in wording were necessary.



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Questionnaire for patients

1 In which language do you communicate? _____

Age: _____

My state of health

	Yes	No	
2	☐	☐	I am suffering from a chronic renal disease
3	☐	☐	I am suffering from a chronic hepatic disease
4	☐	☐	I am suffering from a chronic cardiac disease
5	☐	☐	I am suffering from a chronic respiratory disease
6	☐	☐	I am suffering from diabetes
7	☐	☐	I have troubles remembering things or tend to forget things

My medication

	Yes	No	
8	☐	☐	I regularly take some medication which I bought by myself without a prescription of my physician (incl. vitamins).
9	☐	☐	I take more than 5 drugs every day, prescribed by my physician.

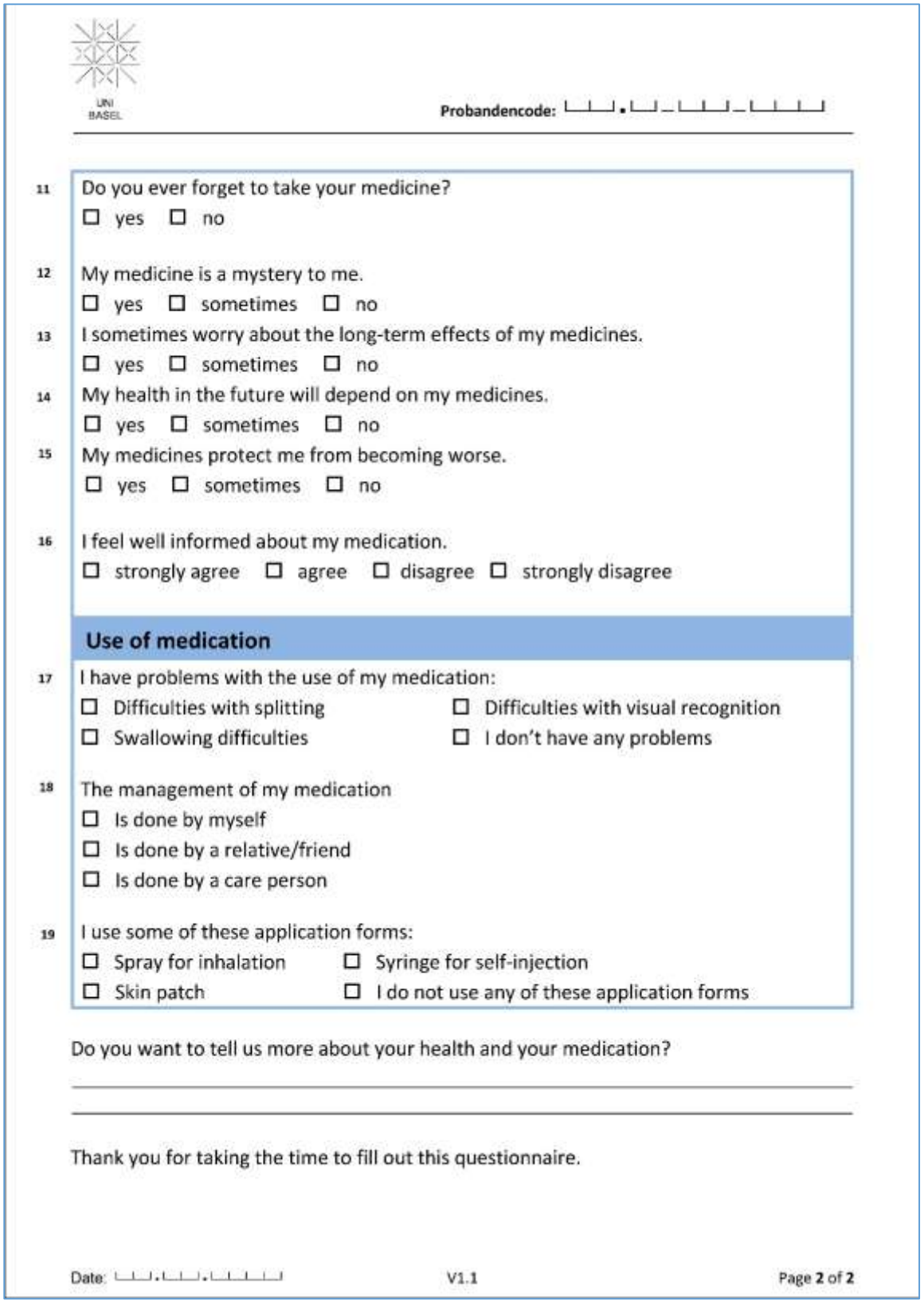
10 I take the following drugs at home, regularly:

- ☐ Sleeping pills
- ☐ Cortisone or other steroids
- ☐ Drugs for epilepsy
- ☐ Digoxin
- ☐ Detrusitol
- ☐ Insulin / Drugs for diabetes
- ☐ Marcoumar, Xarelto, Sintrom or Pradaxa
- ☐ Surmontil (Trimipramin), Saroten (Tryptizol, Limbitrol), Tofranil or Nortrilen
- ☐ Drugs for rheumatism /inflammation
- ☐ Drugs for drainage (Diuretics)

Date: ⌊⌊⌋.⌊⌊⌋.⌊⌊⌋⌊⌊⌋ V1.1 Page **1** of **2**

Figure B2-1: Drug Associated Risk Tool (DART), page 1of 2

Legend: Detrusitol = Tolterodine (most used anticholinergic drug in Switzerland), Tryptizol & Limbitrol = Amitriptyline, Tofranil = Imipramine



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11 Do you ever forget to take your medicine?
☐ yes ☐ no

12 My medicine is a mystery to me.
☐ yes ☐ sometimes ☐ no

13 I sometimes worry about the long-term effects of my medicines.
☐ yes ☐ sometimes ☐ no

14 My health in the future will depend on my medicines.
☐ yes ☐ sometimes ☐ no

15 My medicines protect me from becoming worse.
☐ yes ☐ sometimes ☐ no

16 I feel well informed about my medication.
☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree

Use of medication

17 I have problems with the use of my medication:
☐ Difficulties with splitting ☐ Difficulties with visual recognition
☐ Swallowing difficulties ☐ I don't have any problems

18 The management of my medication
☐ Is done by myself
☐ Is done by a relative/friend
☐ Is done by a care person

19 I use some of these application forms:
☐ Spray for inhalation ☐ Syringe for self-injection
☐ Skin patch ☐ I do not use any of these application forms

Do you want to tell us more about your health and your medication?

Thank you for taking the time to fill out this questionnaire.

Date: ⌊⌊⌋.⌊⌊⌋.⌊⌊⌊⌋⌋ V1.1 Page **2** of **2**

Figure B2-1: Drug Associated Risk Tool (DART), page 2 of 2

Validation of the questionnaire

The pre-test with five inpatients did not reveal any additional issues, and we decided to start the validation study without major changes.

During ward visits, we approached 208 eligible patients. Out of them 165 (79.3%) consented to participate, and we were able to complete 164 patient interviews (cf. figure B2-2).

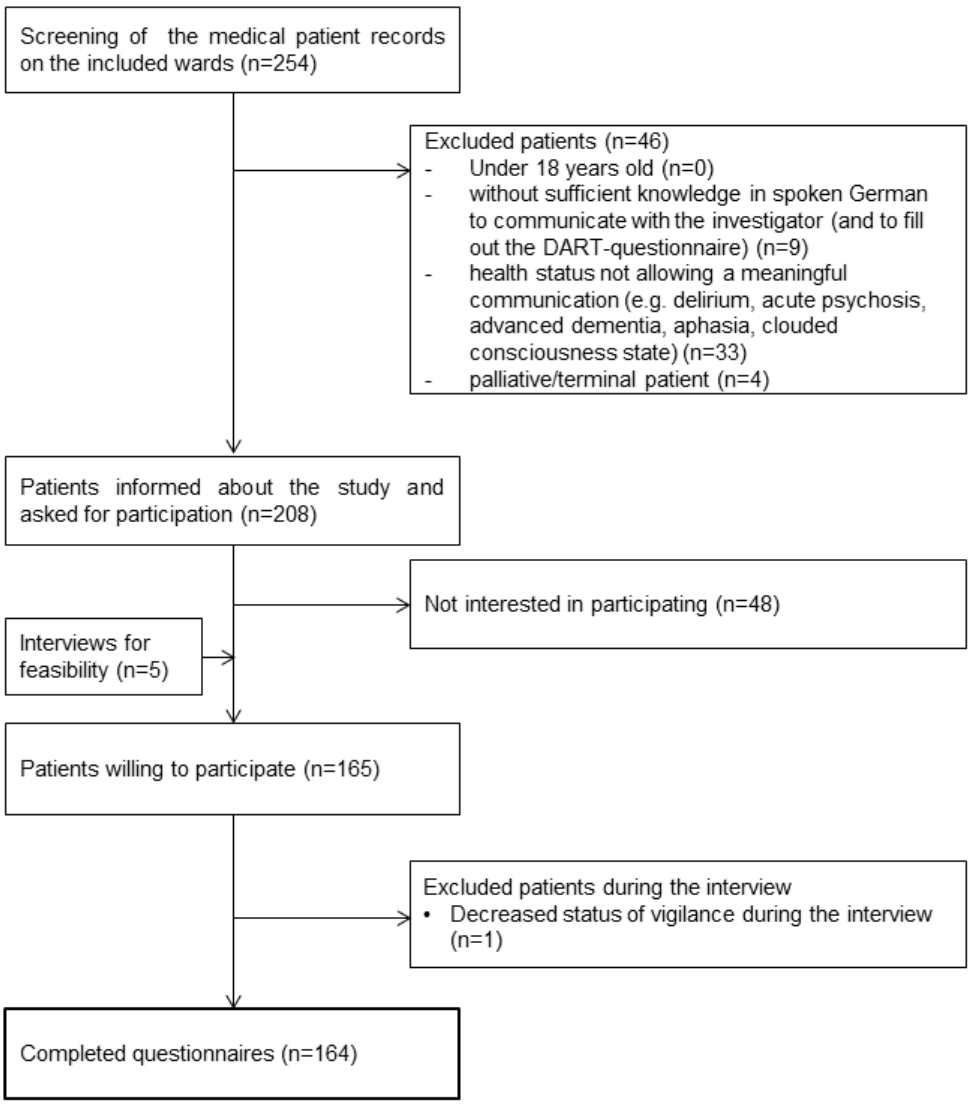

Figure B2-2: Flow chart of the validation study

The median age of 164 patients entering the validation study was 74 years with a minimum age of 20 and a maximum age of 95. Forty-nine percent of participants were female. The mean number of drugs per patient at time of admission was 4 and ranged from 0 to 19. Fifty-six (34%) patients came from the geriatric ward with a mean age of 81 (40-95) years and a mean number of drugs of 5 (0-19). Sixty-eight (42%) patients were from the medical ward with a mean age of 65 (20-91) years and a mean number of drugs of 3 (0-15) and 40 (24%) patients were orthopaedic patients with a median age of 67.5 (20-91) years and a mean number of drugs of 4 (0-10).

After 51 interviews, we reduced the number of questions. We eliminated the questions about feasibility and understandability of the DART, because we had enough meaningful data with a clear conclusion. For the same reason, we stopped answering the Morisky and the BMQ questionnaire that we used for comparison with the answers from the DART. This allowed us to shorten the duration of the patient interview.

On average, it took patients 7 minutes to complete the DART by themselves. None of the patients found any of the statements bothersome or too intrusive on his privacy. Ten out of 51 patients showed some difficulties in completing the questionnaire, seven did not understand the wording of a statement and in three cases, data are missing. The DART questions reached an overall specificity of 0.95 (range: 0.82-1), whereas the overall sensitivity was 0.58 (range: 0.21-1). All questions (except statement number 9 about polypharmacy, the statements concerning the intake of Digoxin or anticholinergic drugs and statements 12-15 about the BMQ) showed a significant correlation between the patient's answers and the objective data. The extent of correlation varied a lot, the φ -coefficient showed a range from 0.29 – 0.88. More details are shown in table B2-2. Regarding the intake of OTC drugs, eighty-five patients (35%) affirmed, 103 (63%) patients denied, and three patients (2%) gave no answer. On the question "I feel well informed about my medication", 85 patients (52%) answered with "strongly agree", 45 (27%) agreed, 18 (11%) disagreed, three (2%) strongly disagreed and 13 patients (8%) gave no answer. Ten (6%) patients named difficulties with tablet-splitting, 17 (10%) mentioned swallowing difficulties, 5 (3%) patients affirmed difficulties with visual recognition and 122 (74%) said that they have no such problems. Fifteen (9%) answers were missing. One hundred and twenty five patients (74%) managed their

medication by themselves, 12 (7%) had a relative or a friend who did the management, 15 (9%) patients named a home care person as their medication manager and 16 (10%) patients gave no answer. Sixteen (10%) of the patients indicated that they use an inhaler, 15 (9%) a transdermal therapeutic system, 18 (12%) a syringe for self-injection, 101 (62%) did not use any of these application forms and 20 (12%) gave no answer.

Table B2-1: Risk factors, their corresponding statement in the Drug Associated Risk Tool (DART) and criteria to evaluate correlation between the answers in the DART and objective data

Risk factor	Corresponding statement DART	Acceptance criteria for correlation
Language issues (e.g. migration background)	1	No comparison with objective data
Polymorbidity: divided in subcategories		
- **Renal impairment**	2	- Diagnosis of renal impairment AND/OR GRF<60ml/min for at least 3 months [180].
- **Hepatic impairment**	3	- Diagnosis of hepatic impairment AND/OR chronic hepatitis AND/OR hepatic cirrhosis
- **Chronic cardiac disease**	4	- Diagnosis of chronic cardiac disease (heart failure, coronary heart disease, arrhythmias)
- **Chronic respiratory disease**	5	- Diagnosis of asthma or chronic obstructive pulmonary disease
- **Diabetes**	6	- Diagnosis of diabetes mellitus type 1 or 2 or diabetes caused by steroids
- **Cognitive impairment/dementia**	7	- Diagnosis of cognitive impairment or dementia OR 25/30 points in the mini mental state examination (MMSE) [181] OR < 14/20 points in the Micro-Mental-Test (MMT) [179]
The patient takes medication(s) besides the prescribed ones (e.g. over-the-counter, vitamin supplementation)	8	No comparison with objective data possible
Polypharmacy	9	The patient takes more than five medicines when admitted to the hospital
Antiepileptic, anticoagulants, NSAIDs, non-steroidal antirheumatics, comb. of NSAID and anticoagulants, digoxin, corticosteroids, diuretics, tricyclic antidepressants, anticholinergic drugs, benzodiazepines, opiates/opioids, oral antidiabetics/insulin, medication with a narrow therapeutic range	10	The drug is present on patients medication list at hospital admission
Non-Adherence	11	< 8 points in the MMAS-8 questionnaire
Earlier experience of ADRs	12-15	Negative total score in both - the statements 12-15 AND the BMQ OR a positive total score in both – the statements 12-15 AND the BMQ
Missing information, partial knowledge of the patient, the patient does not understand the goal of the therapy	16	No comparison with objective data needed.
Impaired manual skills - causing handling difficulties	17	No comparison with objective data needed.
Visual impairment / impaired eye-sight	17	No comparison with objective data needed.
Difficult to handle medication	19	Medicines for parenteral, transdermal or inhalative application at time of hospital admission

Table B2-2: Calculated sensitivity and specificity of the single statements of the DART

Statements or questions of the DART	Number of answers [n]	Missing data	True pos.	False pos.	True neg.	False neg.	Prevalence of the RF (%)	Sensitivity	Specificity	χ^2 [*P*]	φ (*P*)
I am suffering from a chronic renal disease	162	2	9	3	127	23	20	0.28	0.98	< 0.001	0.39 (<0.001)
I am suffering from a chronic hepatic disease	161	3	4	1	148	8	07	0.33	0.99	< 0.001	0.50 (< 0.001)
I am suffering from a chronic cardiac disease	159	5	26	3	96	34	38	0.43	0.96	< 0.001	0.51 (< 0.001)
I am suffering from a chronic respiratory disease	157	7	14	1	129	13	17	0.52	0.99	< 0.001	0.72 (< 0.001)
I am suffering from diabetes	158	6	23	0	129	6	18	0.79	1.00	< 0.001	0.87 (< 0.001)
I have troubles remembering things or tend to forget things	157	7	9	26	116	6	10	0.60	0.82	< 0.001	0.29 (< 0.001)
I take more than 5 drugs every day, prescribed by my physician	144	20	10	12	84	38	33	0.21	0.88	0.190	0.11 (0.190)
Sleeping pills	147	17	15	10	121	1	11	0.93	0.92	< 0.001	0.71 (<0.001)
Cortisone or other steroids	149	15	11	2	129	7	12	0.61	0.98	< 0.001	0.69 (<0.001)
Antiepileptic drugs	149	15	0	0	149	0	00	n.a.	1.00	n.a.	n.a.
Oral anticoagulants	149	15	21	5	123	0	14	1.00	0.96	< 0.001	0.88 (< 0.001)
Tricyclic antidepressants	149	15	2	2	145	0	01	1.00	0.99	0.001	0.70 (< 0.001)
Drugs for rheumatism/inflammation	149	15	7	18	120	4	07	0.64	0.87	< 0.001	0.35 (< 0.001)
Drugs for drainage (diuretics)	149	15	26	9	89	25	34	0.51	0.91	< 0.001	0.47 (< 0.001)
Digoxin	149	15	1	0	147	1	01	0.50	1.00	0.013	0.71 (<0.001)
Anticholinergic drugs	149	15	1	0	146	2	02	0.33	1.00	0.020	0.57 (<0.001)
Insulin/drugs used in diabetes	148	16	16	2	127	3	13	0.84	0.98	< 0.001	0.85 (< 0.001)
Do you ever forget to take your medicine?	61	103	11	0	28	22	54	0.33	1.00	< 0.001	0.61 (< 0.001)
BMQ	54	110	39	8	3	4	20	0.27	0.91	0.036	0.69 (0.036)
I use some of these application forms: spray for inhalation, skin patch, syringe for self-injection	129	35	27	12	84	6	26	0.82	0.88	< 0.001	0.66 (<0.001)
Mean value								**0.58**	**0.95**		
Range								**0.21-1**	**0.82-1**		

Legend: n.a. = not applicable; RF = risk factor, χ2: chi-square, φ: phi-coefficient

Discussion

With the present study, we intended to create an easy-to-use and reliable screening tool to identify patients who are at increased risk for DRPs. The application of such a tool has the potential to support the healthcare professionals in choosing the patients who would benefit the most of intensified pharmaceutical care. In our opinion, a patient-self-assessment tool is not only a time- and resource-saving approach for healthcare professionals, but also allows by the involvement of the patient, to assess risks for DRPs in a more comprehensive way.

As a basis for the tool, we used risk factors for the development of DRPs evaluated in a former project where we combined a literature search with the statements of an expert panel [176]. As far as we know, this approach has not been adopted previously in this area of research.

The Drug Associated Risk Tool (DART) showed a good acceptability and feasibility. The patients completed the self-assessment quickly and indicated no major difficulties with understanding the content of the questionnaire. The 48 patients (23%) who refused to participate were either not interested in participating or felt too tired to follow an interview.

All statements of the DART showed a high specificity (mean value: 0.95, range 0.82 – 1.00). Thus, we can exclude false positive cases with a high probability. The sensitivity of the statements, however, was lower and showed more variability (mean value: 0.58, range 0.21 – 1.00). In general, the sensitivity turned out to be higher in statements addressing conditions that require regular disease control and daily attention to self-care and drug management. Drugs requiring a high level of self-management showed the highest sensitivity (e.g. oral anticoagulants, insulin and oral antidiabetics). We assume the more symptoms they suffer from, the higher is the patients' awareness about their disease(s).

Several factors might have influenced the sensitivity and the correlation. First, the defined criteria for correlation (cf. table B2-1) served as a basis for the validation of the questionnaire. Depending on how we defined the criteria, we reached a certain degree of correlation between patients' answers and the objective data. After a first validation of the DART, a revision of certain criteria could be useful. As an example: the sensitivity for the question on adherence was low. The original MMAS-8 [177] questionnaire defines high adherence with a score of 8 on the scale, moderate adherence with a score of 6 to < 8 and low adherence with a score of < 6. In our acceptance criteria, we defined a score beyond eight points as "non-

adherent". If we were to change our criteria and define only a score beyond 6 as "non-adherent", our sensitivity would increase from 0.33 to 0.42, but the specificity would decrease from 1 to 0.88. Second, we evaluated the sensitivity and specificity of each question by comparing the subjective answers in the DART with objective data from medical records. Literature shows that medication histories at the time of hospital admission are often erroneous or incomplete [182], which might have influenced our results. Especially the statement "I take more than 5 drugs every day, prescribed by my physician", showed surprisingly weak correlation between subjective patient answers and objective medical data. Lau et al. [183] stated that regarding at the medication history in the hospital medical record, 25% of the prescription drugs in use are not recorded and 61% of all patients have one or more drugs not registered. Bedell et al. [184] evaluated the discrepancies between what physicians prescribe and what patients report they actually take. They showed, that discrepancies between recorded and reported medication are common. Half of the discrepancies (51%) result from patients taking medications that were not recorded. One third of the discrepancies involved over-the-counter drugs or herbal therapies. A more reliable medical record including an accurate medication list will be necessary for further research in order to avoid conclusions derived from incomplete medical data. Thirdly, patients stated that they had no problems with filling in the DART; however, we noticed some problems with their understanding of the word "chronic". Some rephrasing will be necessary in order to clarify statements about chronic conditions.

Finally, the low prevalence of some risk factors is a limitation of our results. Some risk factors showed such a low prevalence (e.g. antiepileptic drugs, tricyclic antidepressants, digoxin and anticholinergic drugs) that a clear conclusion concerning the validity of these questions in the DART is not possible. Larger studies will be necessary to strengthen our findings. A potential limitation to our study might also be the patient selection. Patients who refused to participate may have been individuals with less knowledge about their illness and therapy.

Conclusion

The new DART self-assessment questionnaire showed a satisfying feasibility and reliability. Despite some low sensitivity values, this questionnaire seems to be applicable to patients in a hospital setting. Patients may be a valuable, but often neglected source of information. Asking them about their conditions, their medications and related concerns and problems can facilitate getting a first, but broad picture of the risk for DRPs and possible pharmaceutical needs. Compared to gathering all the relevant data from case notes, electronic patient files and other sources, a self-assessment questionnaire seems to be a quick and easy method. To strengthen the reliability of the DART some questions should be rephrased and risk factors with a very low prevalence should be validated in a more specific population.

Acknowledgments: The authors thank the clinical pharmacists Christina Ernstberger, Dominik Staempfli and Balbina Preston who helped with conducting the patient interviews and Michael Mittag for his statistical expertise. We also acknowledge the support by the medical staff on the study wards.

Funding: The study is financially supported by an unrestricted research grant from the Swiss Society of Public Health Administration and Hospital Pharmacists (GSASA).

Conflict of interest: None

B3

How to detect patients at risk for drug-related problems: a structured overview of assessment tools

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ABSTRACT

Background: Clinical pharmacy services in hospitals have been shown to increase patient safety by reducing drug-related problems (DRPs). However, restricted resources and capacities limit pharmacists' activities. A tool to assess patients at risk from DRPs may serve as a successful approach to target pharmaceutical activities for those patients who benefit the most. Despite development of numerous risk assessment tools, a comprehensive overview is missing.

Objective: To create a structured overview of existing tools for the assessment of a patients' risk of experiencing DRPs.

Methods: We conducted a non-systematic literature search with a clear search strategy using Pubmed. The tools were sorted by year and the following properties were extracted and mapped in a structured way: information on the content, development method, and extent of validation.

Results: The literature search resulted in 15 risk assessment tools. Seven tools (47%) focused on elderly patients and eight tools (53%) included adult patients in general. Nine tools (60%) were developed for use in primary care and six (40%) for use in secondary care. Seven tools (47%) were designed for self-assessment. The development of the tools varied significantly. One tool (7%) was developed by using a literature search, three tools (20%) based on a statistical analysis and other 3 tools (20%) used an orientation on existing tools who served as basis for the development of the new tool. Three tools (20%) combined a literature search with the consultation of healthcare experts, 1 tool (7%) combined the literature search and the orientation on unpublished screening tools, 1 tool (7%) used a statistical analysis of variables and supplemented it with data from the literature and one tool (7%) combined statistical analysis with expert opinions. Two tools (13%) provided no clear information on their development.

Discussion: This overview revealed an increased level of activity in the field of risk-assessment during the last few years. Published assessment tools are very heterogeneous and differ in structure, content, targeted patient group, setting for application, selected outcomes and extent of validation. Our comprehensive mapping may serve as a summary to assist readers in choosing a tool, either for research purposes or for use in daily practice.

INTRODUCTION

Drug-related problems (DRPs), which have been defined as “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes”[4], include medication errors (MEs), adverse drug events (ADEs) and adverse drug reactions (ADRs). An ME is “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer”[5]. An ADE can be defined as “an injury—whether or not causally related to the use of a drug”[6]. ADRs include “any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological functions”[7]. DRPs are very common in primary and secondary care leading to patient harm and increased healthcare costs [16, 18, 185, 186].

Clinical pharmacy services in hospitals have been shown to increase patient safety by reducing MEs, ADEs and ADRs. They increase medication appropriateness, improve patients’ knowledge about drug therapy and adherence, and reduce the length of hospital stay [54]. However, with pharmacists’ limited resources and capacities, it is important to identify which patients would benefit the most from clinical pharmacists’ activities. An obvious approach is to focus on the patients who are at the highest risk of experiencing DRPs.

During recent years, attempts have been made to determine risk factors (RFs), which may determine the occurrence of DRPs. The most prevalent RF is polypharmacy [16, 141-147], showing the strongest association with adverse outcomes, whereby the definition of polypharmacy varies between the intake of “more than 4” to “8 drugs and more”. Besides polypharmacy, polymorbidity [141, 145], renal impairment [16, 141, 145, 146] and dementia/impaired cognition [141, 147] are prevalent RFs in many studies. Focusing on drugs, most publications highlight oral anticoagulants [16, 141, 143, 146, 148], diuretics [16, 146, 148], non-steroidal anti-rheumatics [141, 148] and antidiabetics [141, 146] as medication with the highest risk of causing harm. Research following a qualitative approach revealed communication failures and knowledge gaps, underpinned by a variety of contributing factors, including time and workload pressures and problems with computer system design, as major causes for drug-related hospitalisations [148].

A tool for a fast and reliable identification of patients, showing such RFs, may be a successful approach to target clinical pharmacy activities and therefore save resources and increase efficiency. Different tools to assess patients at risk for DRPs have already been developed and published. These instruments differ widely from each other depending on the outcomes they focus on (e.g. DRPs, ADRs), the setting for which they were developed (e.g. primary or secondary care), the patient group they target (e.g. elderly patients, all age groups) and their method of application (e.g. self-assessment). A comprehensive overview has been missing. The objective of this study was to provide a literature search to create a comprehensive and structured overview of existing risk assessments. A mapping exercise was undertaken to give an orientation on content, development method and potential validation of the tools.

METHODS

Literature search and mapping

We conducted a non-systematic literature search with a clear search strategy on Pubmed by using the following MeSH terms: “Drug-related side effects and adverse reactions”, “medication errors”, “risk”, “risk assessment” and the following search terms: “risk score”, “patient safety”, “risk management”, “pharmacist”, “tool”. The absence of a MeSH term for DRPS limited a precise search strategy. “Drug-related side effects and adverse reactions” served as the closest possible approach, including ADRs and ADEs. The database search was completed with a manual search from the reference list of included articles. We limited our search to studies in adults. Articles must have been published in English or German.

Title and abstracts were screened for relevance. They needed to contain the term “tool” or similar terms with similar meanings like “instrument”, “assessment”, “questionnaire” AND “drug-related problems” or similar terms like “medication-related problems”, “adverse drug events”, “adverse drug reactions”. Studies which focused on RFs for the occurrence of DRPs without the description of a screening instrument where excluded, as well as tools targeting children, medication review techniques which did not use a tool, risk screening which did not focus on DRPs/circumstances and general guidelines/recommendations or educational interventions to assess patients at risk for DRPs.

The reviewer (CPK) screened articles for eligibility. Each article showing uncertainty regarding inclusion or exclusion criteria was discussed with two of the authors (CPK, MLL). We mapped the tools in a structured way by describing briefly their content, development method and validation steps. We sorted the tools by year to show the progress in the topic of risk assessment.

RESULTS

The literature search resulted in 15 risk assessment tools (cf. table B3-1). Eight tools (53%) were developed for the detection of risk for DRPs (also named by researchers as medication-related problems), 3 tools (20%) screened for ADRs and other tools named other outcomes similar to DRPs, such as “drug therapy problems”, “medication misadventure”, “difficulties in managing medication” and “risk for rehospitalisation”. The term “risk for rehospitalisation” seemed unsuitable for our inclusion criteria. However, the focus on patient’s drug therapy was described in the abstract of the tool, which justified its inclusion. Seven tools (47%) focused on elderly patients and eight tools (53%) included adult patients in general. Nine tools (60%) were developed for use in primary care and six (40%) for use in secondary care. Seven tools (47%) were designed as self-assessment. The development of the tools varied significantly and included a literature search (1 tool, 7%), statistical analysis of variables (3 tools, 20%), or the orientation on existing tools who served as basis for the development of the new tool (3 tools, 20%). Three tools (20%) combined a literature search with the consultation of healthcare experts, 1 tool (7%) based its development on data from literature and unpublished screening tools, 1 tool (7%) used a statistical analysis of variables and supplemented it with data from the literature and one tool (7%) combined statistical analysis with expert opinions. Two tools (13%) provided no clear information on their development.

DISSCUSSION

Our overview showed an increasing activity in the field of risk-assessments for DRPs. Seven of 15 tools had been published in the last two years. Canada and the UK were pioneers, with different European countries following. Pharmacists have been actively involved in the development of every tool, what shows their increasing presence and importance as one of the stakeholders in the area of medication safety. Almost half of the tools focused on elderly

patients because geriatric patients usually present with multiple morbidities and complex pharmacotherapy which makes them susceptible for adverse outcomes. The usability of tools for the identification of patients at risk for ADRs seemed questionable, as ADRs are, according to our definition, not preventable. Sometimes the definition for an ADR corresponded more to an ADE, which in some cases led us to believe that researchers may have mixed up ADRs with ADEs.

Compared to older tools, recently published instruments were often designed for the implementation in an electronic system in order to screen electronic patient records for the presence of RFs. Very comprehensive questionnaires like the tool from Pit et al. [159] may be less applicable nowadays due to the presence of limited resources. An electronic tool has the advantage of fast and easy screening, reducing healthcare professional time expenditure.

Many tools lack proper validation. They have been validated regarding feasibility and acceptability, but a proven association with clinical outcomes is often missing. This may be because of the effort in time and resources needed to conduct a proper validation study.

Limitations

The literature search was restricted to articles published in English and German; criteria published in other languages were not included because analysing and mapping the tools required a complete understanding of the text. We did not conduct a fully systematic literature search. Keywords used in title and abstracts, were heterogeneous what made the development of a comprehensive search strategy difficult.

CONCLUSION

The literature search revealed 15 screening tools for the assessment of patients at risk for DRPs. All tools focus on the occurrence of problems with patient's medication but are very heterogeneous with respect to content and selected outcomes. Most of the tools showed no complete validation. Comprehensive, but user-friendly tools with a proven association with well-selected outcomes are needed to enable pharmacists to target their clinical activities in the most efficient way.

Table B3-1: Tools for the assessment of patients at risk for DRPS (last updated: 08/2015)

Author [Year]	*Country*	*Title of the publication/ Description of the tool*	*Development*	*Validation*
Barenholtz Levy et al. [2003] [117]	Canada	**Self-Administered Medication-Risk Questionnaire in an Elderly Population** A 10-item self-administered questionnaire for the use by elderly patients (≥60 years) to identify who is at increased risk of potentially experiencing a medication-related problem (MRP).	The 10 items selected for inclusion in the questionnaire were based on published literature [128, 187] and unpublished screening tools obtained through colleagues of the researchers. Clarity of the questionnaire was pilot-tested in 10 patients, with wording adjusted for the final version.	Validated concerning acceptability, feasibility, inter-rater and test-retest reliability, internal consistency, verification of the accuracy of the patient self-reports, applicability of the tool (prospective validity)
Fuller et al. [2005] [154]	UK	**Validating a self-medication risk assessment instrument** A 7-item self-medication risk assessment who should allow nurses, pharmacists and physicians to screen elderly people, who live alone, for difficulties in the management of their medication.	No detailed explanation concerning the development of the tool available.	Validated concerning internal consistency, intra-and interrater reliability
Gordon et al. [2005] [155]	UK	**The development and validation of a screening tool for the identification of patients experiencing medication-related problems** A patient interview, divided into five sections with questions regarding their use of medicines and medical services and focused on patients in a primary care setting, using drugs for cardiovascular diseases.	The tool was developed based on a literature review. No further details on the development were described.	Partially validated by assessing the practicability and sensitivity of the tool.

Author [Year]	*Country*	*Title of the publication/ Description of the tool*	*Development*	*Validation*
Langford et al. [2006] [188]	Canada	**Implementation of a Self-Administered Questionnaire to Identify Patients at Risk for Medication-Related Problems in a Family Health Center** A 5 item self-administered questionnaire to identify patients at risk for medication-related problems in primary care.	The questionnaire was developed out of the already existing and validated questionnaire from Barenholtz Levy [117].	Validated concerning feasibility. A lager validation study is planned.
Pit et al. [2008] [159]	Australia	**Prevalence of self-reported risk factors for medication misadventure among older people in general practice** A 31-item medication risk self-assessment form in order to find patients in primary care who may benefit from a medication review.	The risk assessment is based on a list of "triggers" identifying patients for whom a medication review might be beneficial, published by the National Prescribing Service [189]. A first draft of the tool was discussed with an expert panel, followed by two pre-tests and a pilot test with patients and healthcare professional in the primary care area.	Only validated for acceptability and feasibility
Roten et al. [2010] [158]	CH	**An electronic screening of medical records to detect inpatients at risk of drug-related problems** An electronic screening tool for clinical pharmacists, which screens the medical records of inpatients and helps detecting patients at risk for DRPs in preparation for the ward round.	Electronical queries as basis for the tool were formulated based on a literature review, experience of clinical pharmacists, a list of queries used at a hospital in Boston USA (personal contact), and the programming feasibility.	Prospectively validated against standard of care (CP doing medication review on the ward). Calculation of sensitivity and specificity of the tool
Onder et al. [2010] [145]	Italy	**Development and Validation of a Score to Assess Risk of Adverse Drug Reactions Among In-Hospital Patients 65 Years or Older** A nine-item GerontoNet ADR Score	A physician collected all baseline characteristics of the patients (age, gender, diagnosis, drug history,…) by questionnaire. In a prospective study all ADRs where documented. All patient variables where statistically compared according to the presence of ADRs. Variables with a strong association with an ADR where included in the final risk score. The study was supplemented with data from medical literature.	Validated concerning the predictive validity of the score

Author [Year]	*Country*	*Title of the publication/ Description of the tool*	*Development*	*Validation*
Rovers et al. [2012] [157]	USA	**Self-assessment tool for screening patients at risk for drug therapy problems.** A 12-item tool for the application in the primary care setting.	Development method not provided	No clear information provided.
Dimitrov et al. [2014] [190]	Finland	**Content validation of a tool for assessing risks for DRPs to be used by practical nurses caring for home-dwelling clients aged ≥ 65 years: a Delphi survey** 18-item tool for assessing risks for DRPs	The tool was developed based on two systematic literature reviews and the clinical expertise of the research group. Content validity was determined by a three-round Delphi survey involving a panel of 18 experts in geriatric care and pharmacotherapy.	Validated concerning content validity and feasibility. Pending predictive validity
Makowsky et al[2014] [191]	Canada	**Feasibility of a self-administered survey to identify primary care patients at risk of medication-related problems** A 10-item self-administered survey	The paper survey was developed out of two already existing and validated questionnaires: the 10-item MRP questionnaire by Barenholtz Levy [117], and the modified five-item questionnaire by Langford et al [188].	Only validated concerning feasibility
Sharif et al. [2014] [173]	United Arab. Emirates	**Development of an Adverse Drug Reaction Risk Assessment Score among Hospitalized Patients with Chronic Kidney Disease** An assessment score, using 7 evaluated RFs to predict the risk for an ADR in hospitalized patients with chronic kidney disease	Development of an electronic prediction model, based on statistic evaluations of associations between prospectively collected patient characteristics with the occurrence of an ADR.	Only validated concerning the reliability of the electronic generation of risk scores
Tangiisuran et al. [2014] [192]	UK	**Development and Validation of a Risk Model for Predicting ADRs in Older People during Hospital Stay: Brighton Adverse Drug Reactions Risk (BADRI) Model** A risk model, based on 5 clinical variables.	A prospective study where collected patient data were statistically correlated with assessed ADRs. Variables that were identified in other studies as being important predictors of ADR were also included in the statistical analysis. The five final variables were chosen using a stepwise statistic selection procedure.	Externally validated concerning predictive validity (sensitivity and specificity)

Author [Year]	*Country*	*Title of the publication/ Description of the tool*	*Development*	*Validation*
Urbina et al. [2014] [175]	Spain	**Design of a score to identify hospitalized patients at risk of drug-related problems** A score to identify hospitalized patients at risk of DRPs.	A prospective observational study. Patients' baseline characteristics and data on diagnosis and drug history were gathered at time of admission. A statistical analysis of the data was performed to confirm or disconfirm the association between the presence of DRPs at admission with respect to each of the patient variables analysed. Variables with the highest sensitivity and specificity were selected for the score, according to the method of Onder et al. [145]	Prospectively validated in a cohort of patients at the time of admission.
Alassaad et al. [2015] [193]	Sweden	**A tool for prediction of risk of rehospitalisation and mortality in the hospitalised elderly: secondary analysis of clinical trial data.** A 7 item score, the "80+ score", for the prediction of the risk of rehospitalisation and mortality in the hospitalized elderly, aged 80 years and older	Patient baseline characteristics were used from a randomised controlled trial (RCT) investigating the effects of a comprehensive clinical pharmacist intervention. Potential risk factors were selected based on a combination of clinical judgement and statistical properties of the variables. Selected data where statistically analysed for association with the defined outcomes "time to rehospitalisation" or "death".	Only internally validated, pending validation in an independent cohort
Snyder et al. [2015] [194]	USA	**Utility of a brief screening tool for medication-related problems** A 9-item screening tool for medication-related problems	The questionnaire was developed out of items from an already existing questionnaire the" Blalock's Drug Therapy Concerns Questionnaire (DTC)" [195] found by the authors in an earlier literature search. .	Validated concerning reliability and predictive validity (sensitivity and specificity)

General discussion and conclusions

The nature of DRPs has been investigated in numerous research projects over the last thirty years. DRPs are prevalent and a major problem for in-and hospital outpatients. Various attempts, like the implementation of clinical pharmacists for intensified patient care, have been described as effective in reducing DRPs and in consequences adverse health outcomes. Criteria to assess the appropriateness of prescriptions can serve as a helpful guideline to improve a patient's pharmacotherapy in daily practice. This thesis developed a structured compilation of published criteria (project A) with the aim of assisting physicians and pharmacists to choose the most suitable tool. Restricted resources limit an extended implementation of clinical pharmacy services. Identifying those patients who show the highest risk for developing of DRPs would allow clinical pharmacists to increase their efficiency and save resources by targeting their activities. To realize this idea we identified in the second part of this thesis (project B) risk factors (RFs) for the occurrence of DRPs, translated them into a self-assessment tool for the identification of patients at risk for DRPs and validated the tool for its usability in daily practice.

In **project A** we provided a comprehensive overview of published criteria for the assessment of inappropriate prescribing (IP). IP is a significant public health problem, especially in the elderly, resulting in increased morbidity, mortality and use of healthcare resources [32]. As the name indicates, IP mainly results from poor choice of medication by the prescriber. A tool, supporting the prescriber's clinical judgement in drug selection should theoretically reduce IP [196].

In our systematic literature research, we found 46 assessment tools, which indicated that the topic of IP is of great interest. The question arises as to which tool should be preferred? As we concluded, the ideal tool to assess the appropriateness of drug prescriptions should:

- cover all aspects of appropriateness (efficacy, safety, cost-effectiveness and patients' preferences)
- be developed using evidence-based methods
- show significant correlation between the degree of inappropriateness and clinical outcomes
- be applicable not only in research conditions but also in daily healthcare practice

Mahony and Gallagher [196] further proposed that there should be:

- generalizability for the global community of physicians and pharmacists
- quick application and a clear organization on the basis of physiological systems
- the ability to interface with electronic patient records

None of the listed tools fulfilled all of the abovementioned requirements. The mapped tools differed widely from each other concerning structure, complexity and degree of comprehensiveness. Our mapping enabled an overview and orientation and may help as a decision aid, but does not provide an answer as to which tool might be “the best one”.

When thinking about choosing a tool, users should be aware that the recommendations for IP vary depending upon the targeted patient group and the country in which the tool has been developed. It might be advisable for prescribers to choose a tool, developed in their own country, as these tools are usually adapted for nationally approved medicines and prescribing standards. The selection of a tool, which is regularly updated is preferred. The comprehensiveness, especially of explicit tools is a limitation of their use in daily practice. Implementing an explicit tool in an electronic system might be beneficial in terms of time, but poses a risk of excessively alerting physicians, who may ignore them. Further, when using these tools, it is important to keep in mind that “inappropriate” is not “contraindicated”. A drug, which is inappropriate for a patient may still be the best available option.

Prescribers have to keep in mind that the degree of comprehensiveness and complexity gives no information about the extent of its association with positive or negative outcomes. There is a need for well-structured case-control studies to demonstrate that the application of IP-assessment tools improves clinical outcomes. Existing indicators of preventable drug-related morbidity (e.g. [197], [198]) should be considered when conducting validation studies. Examples for such indicators are hyper - or hypokalemia, fall or fracture, gastrointestinal bleeding and digoxin toxicity. Of course there are many more. As we described in our project, the effect of the application of assessment criteria on health outcomes and healthcare costs still remains unclear and needs to be evaluated for most of the described tools.

The topic of appropriate prescribing remains complex, time-consuming and requires clinical expertise. It is advisable that the responsibility for appropriate prescribing no longer falls solely on the shoulders of physician-prescribers. Rather the responsibility should be shared with all healthcare professionals in order to provide the most appropriate care to patients [46].

In **project B** we developed an tool to assess patients at risk for the development of DRPs in order to target clinical pharmacy activities. We evaluated risk factors (RFs) for the occurrence of DRPs (project B1), compiled and validated a risk assessment questionnaire, the Drug Associated Risk Tool (DART) out of these RFs (project B2) and conducted an literature search to identify current efforts in the field of risk assessment for DRPs (overview B3).

For the assessment of RFs in **project B1** we combined professional experience and knowledge of healthcare providers with a systematic literature search. This may serve as a valuable method to obtain an accurate representation of the real-life situation in the Swiss healthcare setting.

We used the NGT as a method for eliciting RFs for the occurrence of DRPs. The systematic approach of this consensus technique provides more evidence based results than an unstructured expert meeting [151]. The involvement of all relevant stakeholders of the entire medication process in the expert panel enabled us to cover a great area of knowledge and expertise. We chose experts carefully to minimize psychosocial biases as described by Pagliari et al [172]. We followed recommendations from the literature [172] and tried to control these psychosocial influences as follows:

- We selected a small sample size of ten experts, as endorsed by the literature. Larger groups may lack cohesiveness and be difficult for the investigator to lead.
- We invited at least two stakeholders of the same working field.
- We invited, where possible, experts from different geographic areas with no or only few direct professional contact. Therefore, the different hierarchical levels were within different institutions and the participants were not directly dependent from each other.
- We assigned each expert a place in order to avoid grouping of friends or panelists of the same profession.

- We started with an introduction in the topic with the aim to bring the entire panels' knowledge about DRPs to the same level.
- We tried to ensure the participation of every expert in the discussion and that the contributions were equal.
- We placed the first discussion round after the first rating of the collected RFs in order to avoid panelists being influenced before their rating occured.

The NGT proved to be successful. The panellists were highly motivated and discussed in an engaging and informative way. They appreciated the interdisciplinary exchange and found that it would be worthwhile to conduct such discussion rounds more frequently.

The literature search supported the findings from the NGT. Most of the RFs that were prevalent in the literature were mentioned by experts. This fact confirmed the ability to reproduce evidence based information with a carefully planned NGT. In addition, the literature revealed specific high-risk drugs. In the NGT we might have set the focus inadvertently on patient-specific RFs, which probably turned the focus away from single high risk drugs. The experts focused on patient characteristics and named only a few drugs, but important ones, like "anticoagluants", "diuretics", "Non-steroidal antirheumatics" and "anticholinergics" which are known for their high potential to cause harm. Depending on the accuracy of the literature search, one can find almost every drug associated with the risk for the occurrence of DRPs. Not all of them seem to be clinically relevant, not surprisingly that experts did not mention every drug. In contrast, experts mentioned many process-associated RFs rarely described in the literature. They highlighted the important role of seamless care issues for the occurrence of DRPs in their daily life. Therefore, the use of a NGT proved a valuable source of information for us by providing a considerable number of RFs rarely mentioned in the literature, but important for healthcare providers in their daily practice. The fact that we needed to exclude seamless care issues is a pity because the panelists attributed them with a high importance. We considered seamless care issues not to be individual risk factors but instead reflect system failures; they are, therefore, not assessable for an individual patient. However, we recognized them as important RFs for the occurrence of DRPs in general and concluded that there is a need for improvement in this area.

We finally conducted the Delphi technique with 42 RFs with the aim of letting experts reassess the importance of every RFs concerning the occurrence of DRPs, including RFs from the literature search. We chose the same ten experts for the Delphi questionnaire that took part in the NGT because they were already familiar with the topic. We conducted only two Delphi rounds. We could see the consensus-forming processes by summing up the IQRs that we calculated for both rounds. As our Delphi technique took part in the form of an online questionnaire, we had no problems with the occurrence of psychosocial biases. Participants could fill in the survey anonymously and in an environment where they feel comfortable

A lot of RFs mentioned by the experts were also mentioned in scientific publications. As an example, Gordon et al. developed their risk assessment tool based “only” on a literature review [155] and showed similar RFs to us.

Inclusion of an expert panel in the process of identification of RFs was beneficial because:

- The experts identified RFs that were relevant in the Swiss health system, as most studies on the topic of risk assessment were conducted outside Switzerland.
- The experts assessed the relevance of each of the identified RF with respect to their experiences in daily practice.
- The experts mentioned very patient specific RFs like impaired manual skills, visual impairment and missing information/understanding of the therapy. These RFs were not or less prevalent in our results of the literature search which could lead to the assumption that they were also less relevant for the occurrence of DRPs. The fact, that the experts highlighted their relevance showed their importance in daily practice.
- The expert gave valuable inputs concerning application of the tool (patient self-assessment)

With the Delphi questionnaire, following the NGT and the literature search, we were able to focus on 27 RFs judged by the experts as very important or important for the occurrence of DRPs, which we could use as basis for the development of our risk assessment tool.

In **project B2** we developed a risk assessment tool and validated it concerning feasibility, acceptability and reliability of patients answers. RFs from project B1 served as a basis for the questionnaire. To see what already has been done in the field of DRP risk assessment, we searched literature and created an overview of already published risk assessment tools **(overview B3).**

We developed the Drug Associated Risk Tool (DART) in the form of a self-assessment to be filled out by the patient himself. A patient-self-assessment tool is not only a time - and resource-saving approach for healthcare professionals but also allows, by the involvement of the patient, an assessment of risks for DRPs in a more comprehensive way. Vincent et al. [153] supported healthcare providers to recognize and encourage the active role of the patient in their care and not to think of them in a passive way. Our final list of RFs contained factors like "Missing information, half-knowledge of the patient, the patient does not understand the goal of the therapy", "Self-medication with non-prescribed medicines", "Impaired manual skills" and "Visual impairment", judged by the experts as "very important" or "important" for the occurrence of DRPs. It is obvious that we received the most accurate answers to these questions by asking the patients themselves.

We did not limit the application of the DART to specific adults. With the patient recruitment on different hospital wards, we were able to cover a broad, representative sample of patients. The orthopedic ward served as a source for younger patients generally with no chronic conditions and therefore no or only few RFs. These patients were suitable for the evaluation of the specificity of our statements. In contrast, geriatric and medical patients tended to have different diseases and treatments and were important for the evaluation of the sensitivity of the DART. With this approach, we reached a population that was very heterogeneous varying in age (range: 20-89 years) as well as the number of medications at admission (range: 0-1). All chronic diseases we asked for in the DART were prevalent among our patients. The prevalence of swallowing difficulties was similar to findings from another Swiss study (10%) [199]. The prevalence of patients showing problems with the splitting of their tablets was unexpectedly low at 7%. Data from a German study showed much higher values [200]. An explanation could be the inclusion of many younger patients with no or only few medicines. On the other hand, the geriatric patients frequently indicated that their relatives or a care person prepare their drug therapy and do split the tablets for the patients.

We found the DART to be acceptable to the participants and feasible for self-administration. The DART showed an overall sensitivity of 58% and an overall specificity of 95%. In comparison with risk assessment tools from our literature search (overview B3), indicating sensitivity and specificity values, the DART reached a satisfying high specificity and a slightly lower sensitivity. Gordons screening tool [155] showed a sensitivity of 81% and a specificity of 87%. Onder et al. [145] evaluated a sensitivity of 68% and a specificity of 65% for their tool and Roten et al. [158] achieved a sensitivity of 85% and a specificity of 60%. The DART is the only self-assessment in this list, which might have contributed to its lower sensitivity. Roten et al. [158] developed an electronic screening, whereby he formulated the aim to reach a sensitivity of at least 80%. He then used statistic calculations to develop a risk score that met this condition. This different approach might be a reason why electronic screenings often showed higher sensitivity values. The threshold when a sensitivity value is seen as sufficient or good has not been clearly determined in literature and depends on the subject of investigation. A screening tool for diagnostic use should show higher sensitivity and specificity values than a prognostic tool like the DART, which is intended to forecast the beneficial effect of targeted pharmaceutical activities.

The following steps might have influenced our sensitivity and specificity values and have been examined more detailed in the discussion part of project B2:

First the *comprehensibility of the DART questions*: Despite the fact that patients stated they understood the meaning of all questions in the DART, we discovered some problems with the understanding of the word “chronic”. In order not to bias our results we did not gave further explanations to the patient if we noticed some uncertainties. Some rephrasing of this word is recommended in order to clarify our statements.

Second, the *reliability of medical records and medication lists* was sometimes questionable. Inaccurate medication lists could have been responsible for lower sensitivities when patients indicated the intake of different drugs, which were nonexistent in their patient charts. Data from the literature confirm the frequent incompleteness of medication histories in the hospital medical records [182, 183]. More reliable medication reconciliation will be necessary for further research, in order to avoid conclusions derived from incomplete medication data.

And third, successful implementation of patient self-assessment tools presumed *reliable answers of the patients* according to their illnesses and drug therapies. We observed that many patients showed poor knowledge about their disease state and they did not understand their drug therapy. Few patients wrongly confirmed the presence of a disease, whereas many patients erroneously denied any illnesses. These findings are consistent with an example from an Australian study [201] which did research on patients newly referred to a renal outpatient department and reported that these patients mostly received little or no education from their primary care physician and had poor or no knowledge about their kidney disease. A Danish study [202] evaluated the medication knowledge of elderly patients and revealed that only 60% of the subjects knew the purpose of their medication. A small study from Norway [203] interviewed 58 patients from all age groups. Seven percent of the patients could not recall why their drugs had originally be prescribed. There is a need for a better patient education by all healthcare providers in primary and secondary care.

In comparison with other self-assessment tools that we collected in the overview B3 [117, 157, 159, 188, 191], the DART showed similar complexity regarding number of items with the advantage of an appealing and clearly structured design. The content of the tools appeared to be quite similar. The DART seemed to be very comprehensive and covered many RFs by asking patients about the presence of chronic diseases and polypharmacy, but also about physical disabilities, patient knowledge, adherence, as well as beliefs and concerns towards their medicines. Compared to Levy et al. [117] and Pit et al. [159] the DART did not target a specific patient group. Compared to the tools of Makowsky et al.[191], Rovers et al. [157] and Langford et al. [188] who focussed on primary care patients, the DART did not focus on a specific setting but has been developed in a secondary care setting. Together with the risk-assessment of Levy et al. [117], the DART tool appeared to be one of the best validated tool. However, a prospective validation regarding clinical outcomes is missing in the DART, as well as in all other self-assessment tools.

In this thesis, we developed a first draft of the DART and proved its feasibility and acceptability. The validation of the reliability of patients' answers resulted in a satisfactory specificity but a slightly low sensitivity. A rephrasing of some questions in the DART might enhance better understandability. A second validation with an accurate medication list and reliable medical data will be necessary to reevaluate sensitivity and specificity of the DART. The future aim of

our screening tool is the creation of a scoring system, in order to assign every patient a total score that identifies him for being a patient “at high risk” or “at low risk” for the development of DRPs. Then, a validation regarding the association between the DART score and the occurrence of DRPs is essential to prove the concept of our risk assessment.

Limitations

Project A: A limitation of project A was the applied search strategy. Different efforts to develop a systematic search strategy were undertaken. Unfortunately, the MESH term “Inappropriate prescribing” was introduced only in 2011 and prior to this included in the broadly defined MESH term “Drug therapy”. Using this MeSH-term revealed a large number of very diverse articles in the higher four-digit spectrum and made it impossible to screen and evaluate all titles and abstracts within the time scheduled for this work. However, despite the fact, that our search strategy did not fully correspond to a systematic review, we feel that our review has been the most comprehensive review on tools for the assessment of IP that has ever been published.

Project B1: There were some general concerns about the validity and generalisability of information created by qualitative research methods. We discussed this fact in detail in the general introduction of project B and project B1. Results of the NGT could have been tampered by psychosocial influence of the NGT panellists as described by Pagliari et al [172]. The measures we initiated to keep these biases as small as possible were discussed in the general introduction of project B, in project B1 and in the final general discussion. A limitation of our Delphi technique might be the restricted number of participants, even if optimal size of panellists has not been established. Research has been published based on samples ranging from 4 to 3000 [76]. In addition, the results of the NGT, especially the discussion rounds, were confined to the Swiss health system and cannot be generalized to other countries.

Project B2: A limitation of project B2 was the small patient sample. Precise conclusions to certain sensitivity and specificity values were sometimes not possible because of the very low prevalence of risk factors. For the selection of patients for the interviews, we screened patient charts for inclusion and exclusion criteria which could be assumed to have influenced our results (selection bias). In addition, the patients who agreed to the interview might have been those who generally show better knowledge of their disease and medicines. The patient

interview for the DART-validation were conducted by multiple investigators, resulting in a potential performance bias, despite a prior briefing of the investigators. The investigator (CK) who filled in the case report forms was not blinded to the patient answers in the DART, which could have potentially led to reader bias.

Overview B3: The conducted literature search was not a systematic review, which could have led to the missing risk screening tool data.

Conclusions

From the results and experiences of this thesis the following conclusions could be drawn:

- Inappropriate prescribing (IP) is a major risk for the occurrence of DRPs. The avoidance of IP should not only be the task of the physician but shared between different healthcare providers in order to guarantee the most appropriate therapy. Tools for the assessment of IP can provide a useful aid to evaluate the appropriateness of a therapy, during a medication review, or during the process of prescribing itself.
- Inappropriate prescribing assessment tools are numerous. They show a large variety in structure, degree of comprehensiveness and extend of validation. By providing an overview of published assessment tools, this thesis may assist healthcare providers to choose a tool, either for research purposes or for use in daily practice, according to the situation in which it is intended to be applied.
- The Drug Associated Risk Tool (DART) is a promising approach for clinical pharmacists to assess patients at risk for the development of DRPs and thereby target their clinical pharmacy activities to those patients who benefit the most thereof.
- The DART is based on a combination of a systematic literature search, with the professional experience and knowledge of a multidisciplinary expert panel, which enabled the comprehensive finding of risk factors for DRPs representing the real-life situation in the Swiss healthcare setting.
- A first technical validation of the DART was successful and supported the concept of a patient self-assessment. Compared to similar self-assessment tools, the DART has comparable complexity and comprehensiveness, has an appealing design and shows a satisfactory validation concerning feasibility, acceptability and reliability of patients' answers.

Outlook

A first successful draft of the Drug Associated Risk Tool (DART) has been developed and validated. We saw a lower sensitivity of the DART compared to similar risk self-assessments. We proposed potential issues that might have affected the sensitivity of our tool: The understandability of the questions, the accuracy of medical histories and medical data and the reliability of patient answers.

The following steps are recommended:

1. A rephrasing of the statements with very low sensitivity values with the aim of improving the understanding of the question.
2. A validation of the improved version of the DART concerning feasibility, acceptability and reliability of patients' answers
3. A validation in a more specific population could be considered in order to increase the prevalence of the risk factors.
4. An accurate medication list is essential to avoid a falsification of validation results.
5. After a second validation , there is a need for the development of a scoring system, in order to assign each patient a total score that characterizes him for being " at high risk" or "at low risk" for the occurrence of DRPs
6. A validation with clinical outcomes is crucial to prove the concept of the risk assessment. An association between a higher risk score and the occurrence of DRPs and adverse outcomes will be needed to justify the broad implementation of the DART.

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Annex

Index

A1.1 Delphi questionnaire

Arzneimittelbezogene Probleme: Risikofaktoren

Willkommen bei der Delphi-Befragung!

(Sollten Sie auf Fehler stossen, vergewissern Sie sich, dass Javascript in Ihrem Browser aktiviert ist.)

Bitte nehmen Sie sich einen Moment Zeit für die sorgfältige Beantwortung. Wir bitten Sie, für jeden Faktor auf einer vorgegebenen Skala dessen Relevanz in Bezug auf das Auftreten eines arzneimittelbezogenen Problems zu bewerten. **Die Skala reicht von 1 bis 4: 1 = „nicht wichtig", 2 = „eher unwichtig", 3 = „eher wichtig", 4 = „wichtig".**

Beispiel: Wenn Sie finden, dass Polymedikation häufig zu arzneimittelbezogenen Probleme führt, so klicken Sie auf der Skala die 4 an.

Bitte wählen Sie die Antwort ganz nach Ihrer persönlichen Einschätzung und im Hinblick auf die Ausarbeitung eines konkreten Screening-Tools aus. Wir möchten, dass Sie zu jedem aufgelisteten Risikofaktor möglichst klar Stellung beziehen.

Da die Rangliste aus der Expertenrunde als eine der Grundlagen diente, ist es gut möglich, dass Sie einige Faktoren wiedererkennen werden – bitte nehmen Sie aber auch zu diesen erneut Stellung. Andererseits fehlen auch ein paar Faktoren aus der Expertenrunde. Dies liegt daran, dass wir viele der Schnittstellenproblematik und allfälligen Interventionen zugeordnet haben, welche in einem Screening Tool schwierig erfassbar wären.

Fragen mit einem Ausrufezeichen dahinter sind obligatorisch: Ohne die Beantwortung der Frage können Sie den Fragebogen nicht abschliessen. Dies gilt auch für das erste Feld „Name". Ihr Name wird nicht in die Analyse miteinbezogen und nicht mit Ihren Antworten in Verbindung gebracht. Er dient nur der Erfassung derer, welche den Fragebogen bereits abgeschlossen haben.

Vielen Dank für Ihre Teilnahme!

Name ⓘ

Als wie wichtig schätzen Sie die Relevanz der folgenden Risikofaktoren für das Auftreten eines Arzneimittel-assoziierten Problems ein (1 = „nicht wichtig", 2 = „eher unwichtig", 3 = „eher wichtig", 4 = „wichtig")?

Der Patient ist kognitiv eingeschränkt oder ist dement. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Der Patient war in den letzten 30 Tagen bereits schon einmal im Spital. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Der Patient nimmt nebst den ärztlich verordneten Medikamenten noch andere Präparate zu sich (OTC, Vitaminpräparate). ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Fehlende/mangelnde Information, Halbwissen des Patienten, Patient versteht Therapieziel nicht. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Die manuellen Fertigkeiten des Patienten sind eingeschränkt, er hat Handhabungsschwierigkeiten. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Der Patient besitzt eine eingeschränkte Nierenfunktion. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Wenn mit 3 oder 4 bewertet: Unter welcher Kreatinin-Clearance?

○ < 60 ml/Minute
○ < 30 ml/Minute
○ < 15 ml/Minute

Kommentar

Der Patient besitzt eine eingeschränkte Leberfunktion. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Das Vorhandensein von Polymorbiditäten, beziehungsweise das Vorhandensein von Grundkrankheiten. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Der Patient hat sprachliche Schwierigkeiten (z.B. bedingt durch einen Migrationshintergrund). ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Das Vorhandensein von Visusproblemen/das Besitzen einer eingeschränkten Sehkraft. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Polypharmazie. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Wenn mit 3 oder 4 bewertet: Ab wievielen Medikamenten?

○ Mindestens 5
○ Mindestens 7
○ Mindestens 10

Kommentar

Non-Compliance. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Vom Patienten erlebte Nebenwirkungen. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Das Einnehmen von Medikamenten mit engem therapeutischem Bereich. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Therapie mit einem schwierig zu handhabenden Medikament (z.B. Tablette muss halbiert werden). ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Das Benötigen von Hilfe zuhause (Pflegepersonal, Spitex, Betreuung durch Angehörige). ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Extremes Körpergewicht (Sowohl Übergewicht als auch Unterernährung). ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Der Patient ist sturzgefährdet/leidet an einer Gangunsicherheit. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Der Patient lebt alleine. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Alter. ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Wenn mit 3 oder 4 bewertet: Ab welchem Alter?

○ > 65 Jahre
○ > 75 Jahre
○ > 85 Jahre

Kommentar

Die Ausbildung des Patienten (z.B. Hochschulabschluss versus Realschulabschluss). ⓘ

○ 1 ○ 2 ○ 3 ○ 4

Kommentar

Im folgenden Matrixfeld geben Sie bitte an, als wie kritisch Sie die Therapie mit folgenden Medikamenten in Bezug auf Arzneimittel-assoziierte Probleme einschätzen. (1 = 'unwichtig', 2 = 'eher unwichtig', 3 = 'eher wichtig', 4 = 'wichtig') ⓘ

	1	2	3	4
Antacida	○	○	○	○
Anticholinerge Substanzen	○	○	○	○
Antiepileptika	○	○	○	○
Antikoagulantien	○	○	○	○
Benzodiazepine	○	○	○	○
Calciumantagonisten	○	○	○	○
Calciumpräparate	○	○	○	○
Corticosteroide	○	○	○	○
Diuretika	○	○	○	○
Medikamente zur Inhalation (Atemwegserkrankungen)	○	○	○	○
Insulin	○	○	○	○
Kombinationen von Nicht-steroidalen Schmerzmitteln (NSAR) und oralen Antikoagulantien	○	○	○	○
Nicht-steroidale Schmerzmittel (NSAR)	○	○	○	○
Opiate/Opioide	○	○	○	○
Orale Antidiabetika	○	○	○	○
Thrombozytenaggregationshemmer	○	○	○	○
ß-Blocker	○	○	○	○
Trizyklische Antidepressiva	○	○	○	○
Digoxin	○	○	○	○
Substanzen, welche das Renin-Angiotensin-Aldosteron-System (RAAS) beeinflussen.	○	○	○	○
Nitrate	○	○	○	○

Kommentare zum Matrixfeld. Wenn Sie Bezug auf eine spezifische Medikamentenklasse nehmen, erwähnen Sie diese bitte deutlich. Hier dürfen Sie auch weitere Vorschläge einbringen.

Allgemeine Kommentare und Ergänzungen

A2.1. Final board decision of the Ethikkommission beider Basel for the DART patient interviews

Beschlussmitteilung der Ethikkommission beider Basel

Die Ethikkommission beider Basel hat an ihrer Sitzung vom 28. Februar 2013 (in der Zusammensetzung, wie sie auf Seite 2 wiedergegeben ist) das nachstehende Forschungsprojekt eingehend begutachtet.

Titel **des Forschungsprojektes** Ref.Nr. EK: **44/13**

DART - Drug Associated Risk Tool: Validierung eines Fragebogens

Prüfer/in

Name, Vorname, Titel:	Lampert, Markus L., Dr. phil. nat.
Funktion:	Studienleitung
Adresse:	Kantonsspital BL, 4101 Bruderholz

Die Ethikkommission stützt ihre Beurteilung auf die Unterlagen, wie sie im beiliegenden "Antrag auf Begutachtung" vom 08. Februar 2013 abschliessend aufgezählt sind.

X normales Verfahren ☐ vereinfachtes Verfahren ☐ Nachbegutachtung

Die Ethikkommission kommt zu folgendem **Beschluss**:

X **A positiv**
☐ **B positiv mit Bemerkungen** (siehe Seite 2ff)
☐ **C mit Auflage** (siehe Seite 2ff)
Nachbegutachtung durch Ethikkommission notwendig ☐
schriftliche Mitteilung an Ethikkommission ausreichend ☐
☐ **D negativ (mit Begründung und Erläuterung für die Neubeurteilung)** (siehe Seite 2ff)
☐ **E Nicht-Eintreten (mit Begründung)** (siehe Seite 2ff)

Der Beschluss gilt auch für die im "Antrag auf Begutachtung" gemeldeten weiteren Prüfer/innen im Zuständigkeitsbereich der Ethikkommission.

Pro Memoria: **Pflichten des/der verantwortlichen Prüfers/in**

- Geprüfte Produkte und Vergleichsprodukte (Arzneimittel und Medizinalprodukte) müssen - zur Sicherstellung der Qualität und der Sicherheit - fachgerecht hergestellt, evaluiert und eingesetzt werden.
- Meldepflicht bei:
  a) schwerwiegenden unerwünschten Ereignissen (serious adverse events) unverzüglich
  b) neuen Erkenntnissen, die während des Versuchs verfügbar werden und die Sicherheit der Versuchspersonen sowie die Weiterführung des Versuchs beeinflussen können
  c) Änderung des Protokolls (Versuchsplans)
  d) Ende oder Abbruch der Studie
- Zwischenbericht: einmal pro Jahr
- Meldungs- oder Bewilligungspflicht von Studien bei Swissmedic bzw. anderen Bundes- oder kantonalen Behörden - sofern erforderlich (bei sponsorisierten Studien ist dies die Pflicht des Sponsors)
- Schlussbericht

Für die Ethikkommission:

Ort, Datum: Basel, 10. April 2013 Name(n): Prof. T. Kühne
Prof. A. P. Perruchoud

Unterschrift(en):

A2.2. Informed consent for the participating patients

UNI BASEL

Carole Kaufmann, Studienkoordinatorin
Tel. +41 61 436 23 54
E-Mail: carole.kaufmann@unibas.ch

Schriftliche Einverständniserklärung des Probanden zur Teilnahme an einer klinischen Studie

- Bitte lesen Sie dieses Formular sorgfältig durch.
- Bitte fragen Sie, wenn Sie etwas nicht verstehen oder wissen möchten.

Titel der Studie	„Drug associated risks: Development of an assessment tool"
Prüfer: Name und Vorname	
Probandin/Proband: Name und Vorname	
Geburtsdatum: ⌊⌊⌋⌊⌋.⌊⌊⌋⌊⌋.⌊⌊⌋⌊⌋⌊⌋⌊⌋	Geschlecht: □ F □ M

Ich wurde vom unterzeichnenden Prüfer mündlich und schriftlich über die Ziele, den Ablauf der Studie, sowie über mögliche Vor- und Nachteile informiert.

Ich habe die zur oben genannten Studie abgegebene schriftliche Probandeninformation gelesen und verstanden. Meine Fragen im Zusammenhang mit der Teilnahme an dieser Studie sind mir zufriedenstellend beantwortet worden. Ich kann die schriftliche Probandeninformation behalten und erhalte eine Kopie meiner schriftlichen Einverständniserklärung.

Ich hatte genügend Zeit, um meine Entscheidung zu treffen.

Ich weiss, dass meine persönlichen Daten nur in anonymisierter Form an aussenstehende Institutionen zu Forschungszwecken weitergegeben werden. Ich bin einverstanden, dass die zuständigen Fachleute der Kantonalen Ethikkommission zu Prüf- und Kontrollzwecken in meine Originaldaten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.

Ich nehme an dieser Studie freiwillig teil. Ich kann jederzeit und ohne Angabe von Gründen meine Zustimmung zur Teilnahme widerrufen, ohne dass mir deswegen Nachteile bei der weiteren medizinischen Betreuung entstehen.

Im Interesse meiner Gesundheit kann mich der Prüfer jederzeit von der Studie ausschliessen. Zudem orientiere ich den Prüfer über die Behandlung bei einem anderen Arzt sowie über die Einnahme von Medikamenten (vom Arzt verordnete oder selbständig gekaufte).

Ort, Datum	Unterschrift der Probandin/des Probanden

Bestätigung des Prüfers: Hiermit bestätige ich, dass ich diesem Probanden/dieser Probandin Wesen, Bedeutung und Tragweite der Studie erläutert habe. Ich versichere, alle im Zusammenhang mit dieser Studie stehenden Verpflichtungen zu erfüllen. Sollte ich zu irgendeinem Zeitpunkt während der Durchführung der Studie von Aspekten erfahren, welche die Bereitschaft des Probanden/der Probandin zur Teilnahme an der Studie beeinflussen könnten, werde ich ihn/sie umgehend darüber informieren

Ort, Datum	Unterschrift des Prüfers

Patientencode: ⌊⌊⌋⌊⌋_⌊⌊⌋⌊⌋_⌊⌊⌋⌊⌋⌊⌋⌊⌋

V1.0, 7.2.2013

A2.3. Patient Questionnaire to evaluate the feasibility and acceptability of the DART

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: └┴┘.└┘_└┴┴┘_└┴┴┴┘

Schlussbefragung
(vom Studienapotheker durchgeführt)

Befragung des Probanden zum Fragebogen

- Wie lange benötigten Sie ungefähr zum Ausfüllen des Fragebogens? └┴┘ min
- War der Zeitaufwand angemessen? Ja ☐ / Nein ☐

- Hatten Sie Schwierigkeiten beim Ausfüllen? Ja ☐ / Nein ☐

  ➢ Falls ja, warum? (Mehrfachantworten sind möglich)
  - ☐ Hatten Sie Schwierigkeiten aufgrund der deutschen Sprache?
  - ☐ Lag es an der Formulierung der Fragen?
  - ☐ War die Schriftgrösse zu klein?
  - ☐ Andere Schwierigkeiten (In Stichworten notieren)

  _____

  ➢ Falls ja, bei welchen Fragen hatten Sie besonders Mühe? (Nummer der betreffenden Frage/n notieren (Siehe codierter Probandenfragebogen, welcher in der Studienmappe enthalten ist.))

  _____

- Waren Ihnen gewisse Fragen unangenehm / zu persönlich? Ja ☐ / Nein ☐ (Nummer der betreffenden Frage/n notieren (Siehe codierter Probandenfragebogen, welcher in der Studienmappe enthalten ist.))

  _____

- Haben Sie gewisse Fragen nicht beantwortet? Ja ☐ / Nein ☐
  ➢ Falls ja, Nummer der betreffenden Frage/n notieren (Siehe codierter Probandenfragebogen, welcher in der Studienmappe enthalten ist.)

  _____

Seite **1** von **4**

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: ⌊⌊⌋•⌊⌋_⌊⌊⌋_⌊⌊⌋⌊⌋

- Warum haben Sie gewisse Fragen nicht beantwortet?
  (Mehrfachantworten sind möglich)
  - □ Haben Sie die Frage übersehen?
  - □ Hatten Sie Schwierigkeiten aufgrund der deutschen Sprache?
  - □ Lag es an der Formulierung der Fragen?
  - □ War die Schriftgrösse zu klein?
  - □ War Ihnen die Frage zu persönlich?
  - □ Ich weiss nicht mehr, warum ich die Frage nicht beantwortet habe.
  - □ Andere Schwierigkeiten (In Stichworten notieren)

Seite **2** von **4**

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: ⌊⌊⌋⌊⌋ . ⌊⌋ _ ⌊⌊⌋⌊⌋ _ ⌊⌊⌋⌊⌋

Weitere Befragung des Probanden

- Hatten Sie bereits einmal Probleme mit Ihren Medikamenten?
  - □ Ja
  - □ Nein
  - ➢ Falls ja, wissen Sie noch, welche Medikamente Ihnen Probleme bereitet haben?
    (Den Medikamentennamen und das Problem kurz notieren)

_____

_____

_____

_____

_____

- Haben Sie Bedenken bei der Einnahme Ihrer Medikamente?
  - □ Ja
  - □ Nein
  - ➢ Falls ja, um welche Medikamente handelt es sich und was für Bedenken haben Sie?
    (Den Medikamentennamen und die Bedenken kurz notieren)

_____

_____

_____

_____

_____

- Wo beziehen Sie in der Regel Ihre Medikamente?
  (Mehrfachantworten sind möglich)
  - □ Beim Arzt
  - □ In der Apotheke
  - □ Über die Versandapotheke
  - □ Andere Bezugsorte

Seite **3** von **4**

UNI
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DART: Validierung eines Fragebogens

Probandencode: ⌊⌊⌋⌊⌋.⌊⌋⌊⌋⌊⌋_⌊⌋⌊⌋⌊⌋

Ausfüllen der folgenden 4 Fragebogen zusammen mit dem Probanden:

- Ausfüllen des BMQ-Fragebogens (zu finden im CRF)
- Ausfüllen des Morisky-Fragebogens (zu finden im CRF)
- Ausfüllen des Mikro-Mental-Tests (zu finden im CRF)
- Ausfüllen des SF-12v2 Fragebogens (zu finden im CRF)

Seite **4** von **4**

A2.4. Case Report Form (CRF)

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DART: Validierung eines Fragebogens

Probandencode: └┘└┘.└┘_└┘└┘└┘_└┘└┘└┘└┘

Datenerfassung (CRF)

Probandencode: └┘└┘.└┘_└┘└┘└┘_└┘└┘└┘└┘

Datum des Interviews: └┘└┘.└┘└┘.└┘└┘└┘└┘

Geschlecht: ☐ F ☐ M

Höchster Bildungsabschluss:
☐ Grundschule
☐ Berufslehre
☐ Hochschulabschluss
☐ keine Angaben

Hospitalisationsgrund:

☐ keine Angaben

Hinweis auf adverse drug events (ADE) bei Spitaleintritt:

Ja ☐ / Nein ☐

Bemerkungen: (wörtlich übertragen)

☐ keine Angaben

Gewicht: └┘└┘└┘ kg ☐ keine Angaben

Grösse: └┘└┘└┘ cm ☐ keine Angaben

Jahrgang: └┘└┘└┘└┘ ☐ keine Angaben

Datum: └┘└┘.└┘└┘.└┘└┘└┘└┘ Unterschrift:_____

V1.1

Seite **1** von **13**

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: ⌊⌊⌋.⌊⌋_⌊⌊⌋_⌊⌊⌋⌊⌋

Chronische Nierenerkrankung:

- Diagnose in der Diagnoseliste: Ja ☐ / Nein ☐
  (wörtlich übertragen)

  _____

  _____

  _____

- GFR in der Diagnoseliste: ⌊⌊⌋⌊⌋ ml/min ☐ keine Angaben

  Erfassungsdatum: ⌊⌊⌋.⌊⌊⌋.⌊⌊⌋⌊⌋ ☐ keine Angaben

Datum	Kreatinin [µmol/l] (gemessen)	GFR [ml/min] (berechnet)	Proteinurie

- Labor > 3 Monate: Ja ☐ / Nein ☐

Chronische Lebererkrankung:

- In der Diagnoseliste aufgeführt: Ja ☐ / Nein ☐

  ☐ Leberzirrhose: Child score ☐ A ☐ B ☐ C ☐ keine Angaben
  ☐ chron. Hepatitis
  ☐ andere Hepatopathien (wörtlich übertragen):

  _____

  ☐ keine Angaben

V1.1

Datum: ⌊⌊⌋.⌊⌊⌋.⌊⌊⌋⌊⌋ Unterschrift:_____ Seite **2** von **13**

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: └┴┘.└┘_└┴┴┘_└┴┴┴┘

Polymorbidität:

Chronische kardiovaskuläre Erkrankungen:

- Diagnose in der Diagnoseliste: Ja ☐ / Nein ☐

Bemerkungen: (wörtlich übertragen)

Chronische Atemwegserkrankungen:

- Diagnose in der Diagnoseliste: Ja ☐ / Nein ☐

Bemerkungen: (wörtlich übertragen)

Diabetes mellitus:

- Diagnose in der Diagnoseliste: Ja ☐ / Nein ☐

☐ Typ I ☐ andere Diabetesformen (Steroiddiabetes)
☐ Typ II ☐ keine Angaben

Demenzerkrankung:

- Diagnose in der Diagnoseliste: Ja ☐ / Nein ☐
- Falls vorhanden MMSE (aus KG): └┴┘ von 30 Punkten ☐ keine Angaben
- Uhrentest (aus KG): └┴┘ von 7 Punkten ☐ keine Angaben

  Erfassungsdatum: └┴┘.└┴┘.└┴┴┴┘ ☐ keine Angaben
- Ansonsten MMT: └┴┘ von 20 Punkten ☐ keine Angaben

Datum: └┴┘.└┴┘.└┴┴┴┘ Unterschrift:_____

V1.1

Seite **3** von **13**

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DART: Validierung eines Fragebogens

Probandencode: └─┘└─┘.└─┘_└─┘└─┘_└─┘└─┘└─┘

Medikamente: (bei Spitaleintritt)

Medikament	Galenische Form	Dosis	Verabreichungsschema

Datum: └─┘.└─┘.└─┘└─┘ Unterschrift:_____

V1.1
Seite **4** von **13**

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: └─┘└─┘.└─┘_└─┘└─┘_└─┘└─┘└─┘

MMAS-8 D – Morisky Medication Adherence Scale Deutsche Version:

Score: └─┘ von 8 Punkten

BMQ-Fragebogen:

Score: └─┘ └─┘└─┘ von -20 bis 20 Punkten

SF-12:
Score: └─┘ von Punkten

Datum: └─┘.└─┘.└─┘└─┘ Unterschrift:_____

V1.1
Seite **5** von **13**

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: └┴┘.└┘_└┴┴┘_└┴┴┴┘

Mikro-Mental-Test #1

Version 2

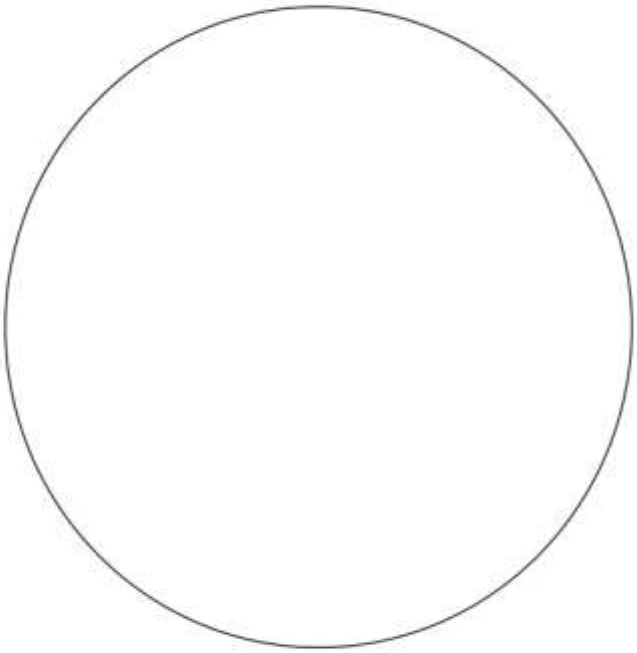
Maximale Punktzahl	Punktzahl	
5	( )	**WIEDERHOLUNG** Nennen Sie fünf Begriffe: (Bild, Garten, Fabrik, Sänger, Heim). Nehmen Sie sich für jeden Begriff eine Sekunde Zeit. Bitten Sie den Patienten, alle fünf Begriffe zu wiederholen, nachdem Sie sie genannt haben. Geben Sie einen Punkt für jede richtige Antwort. Wiederholen Sie dann die Begriffe, bis der Patient alle fünf gelernt hat. Informieren Sie den Patienten, daß diese Begriffe später nochmals erfragt werden.
2	( )	**BENENNEN** FRAGEN SIE: "Was ist das?" , und zeigen Sie (einen Bleistift) _____ (1) "Was ist das?" , und zeigen Sie (eine Uhr) _____ (1)
5	( )	**ZEITLICHE ORIENTIERUNG** FRAGEN SIE: "Welches Jahr haben wir _____(1), welche Jahreszeit _____(1), welchen Monat _____(1), welches Datum _____(1), welchen Wochentag _____(1)?"
3	( )	**KONSTRUKTION** Bitten Sie den Patienten, ein Bild einer Uhr mit Ziffern und Zeigern zu zeichnen, die die Zeit zehn Minuten nach elf anzeigt. Geben Sie einen Punkt für die Ziffern 1 bis 12, einen Punkt für die korrekte Position der Ziffern, und einen Punkt für die korrekte Stellung der Zeiger.

Datum: └┴┘.└┴┘.└┴┴┴┘ Unterschrift:_____ V1.1 Seite **6** von **13**

UNI
BASEL

DART: Validierung eines Fragebogens

Probandencode: └┴┘•└┘_└┴┴┘_└┴┴┴┘



WIEDERGABE

5 ( )

Fragen Sie nach den fünf Begriffen, die zu Beginn wiederholtwurden. Geben Sie einen Punkt für jede korrekte Antwort.

Gesamtpunktzahl: _____

Datum: └┴┘.└┴┘.└┴┴┴┘ Unterschrift:_____ V1.1 Seite **7** von **13**

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: ⌊⌊⌋⌊⌋.⌊⌋⌊⌋_⌊⌋⌊⌋⌊⌋_⌊⌋⌊⌋⌊⌋⌊⌋

BMQ-Fragebogen

Gerne würden wir Ihre **persönliche Überzeugung** in Bezug auf Medikamente, die Sie aufgrund Ihrer Krankheit einnehmen, wissen.
Dabei präsentieren wir Ihnen **10 Meinungsäusserungen** von verschiedenen Patienten. Bitte kreuzen Sie jenes Kästchen an, welches Ihrer Meinung am ehesten entspricht.
Es existieren keine richtigen/falschen Antworten.
Nur Ihre persönliche Sicht interessiert uns.

		5 ++	4 +	3 +-	2 -	1 --
1.	Meine derzeitige Gesundheit hängt von meinen Medikamenten ab.	☐	☐	☐	☐	☐
2.	Es bereitet mir Sorgen, Medikamente nehmen zu müssen.	☐	☐	☐	☐	☐
3.	Mein Leben, so wie ich es jetzt führe, wäre ohne meine Medikamente nicht möglich.	☐	☐	☐	☐	☐
4.	Ohne meine Medikamente wäre ich sehr krank.	☐	☐	☐	☐	☐
5.	Manchmal mache ich mir Sorgen wegen der langfristigen Auswirkungen meiner Medikamente.	☐	☐	☐	☐	☐
6.	Meine Medikamente sind mir ein Rätsel.	☐	☐	☐	☐	☐
7.	Meine zukünftige Gesundheit hängt von meinen Medikamenten ab.	☐	☐	☐	☐	☐
8.	Meine Medikamente stören mein Leben.	☐	☐	☐	☐	☐
9.	Manchmal mache ich mir Sorgen, zu abhängig zu werden von meinen Medikamenten.	☐	☐	☐	☐	☐
10	Meine Medikamente schützen mich davor, dass es mir schlechter geht.	☐	☐	☐	☐	☐

Legende:
5: Stimme **voll und ganz** zu
4: Stimme eher zu
3: Weder noch
2: Stimme eher nicht zu
1: Stimme **überhaupt nicht** zu

V1.1

Datum: ⌊⌊⌋.⌊⌊⌋.⌊⌋⌊⌋⌊⌋⌊⌋ Unterschrift:_____ Seite **8** von **13**

UNI
BASEL

DART: Validierung eines Fragebogens

Probandencode: ⌊⌊⌋⌊⌋.⌊⌋⌊⌋⌊⌋_⌊⌋⌊⌋⌊⌋⌊⌋

Zusätzliche wichtige Bemerkungen des Probanden während dem Ausfüllen des BMQ-Fragebogens:

Datum: ⌊⌊⌋.⌊⌊⌋.⌊⌊⌋⌊⌋⌊⌋⌊⌋ Unterschrift:_____

V1.1

Seite **9** von **13**

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: └─┘└─┘.└─┘_└─┘└─┘_└─┘└─┘└─┘

MMAS-8 D – Morisky Medication Adherence Scale Deutsche Version

Leute, die Medikamente einnehmen müssen, haben verschiedene Aspekte ihres Einnahmeverhaltens aufgedeckt und wir möchten gerne wissen, welche Erfahrungen Sie gemacht haben. Es gibt keine richtige oder falsche Antwort. Bitte beantworten Sie jede Frage nach Ihrer persönlichen Erfahrung in Bezug auf Ihre Krankheit.		
1. Vergessen Sie manchmal, Ihre Medikamente einzunehmen?	ja	nein
2. Manchmal wird ein Medikament nicht eingenommen, und zwar aus einem anderen Grund, als Vergesslichkeit. Wenn Sie an die letzten 2 Wochen denken, gab es Tage, an welchen Sie Ihre Medikamente nicht eingenommen haben?	ja	nein
3. Haben Sie jemals die Einnahme Ihrer Medikamente verringert oder gestoppt ohne Ihren Arzt/Ihre Ärztin zu informieren, weil Sie sich schlechter fühlten nach der Einnahme?	ja	nein
4. Wenn Sie reisen oder Ihr Zuhause verlassen, vergessen Sie manchmal Ihre Medikamente mitzunehmen?	ja	nein
5. Haben Sie Ihre Medikamente gestern genommen?	ja	nein
6. Wenn Sie das Gefühl haben, dass Ihre Krankheit unter Kontrolle ist, hören Sie manchmal mit der Einnahme Ihre Medikamente auf?	ja	nein
7. Jeden Tag Medikamente zu nehmen empfinden viele Personen als lästig. Fühlen Sie sich manchmal schikaniert und/oder eingeschränkt wenn Sie den Therapieplan für Ihre Krankheit genauestens einhalten müssen?	ja	nein

8. Wie oft haben Sie Mühe, sich an die Einnahme aller Ihrer Medikamente zu erinnern?

Nie/selten	Hin und wieder	Manchmal	Fast immer	Immer

V1.1

Datum: └─┘.└─┘.└─┘└─┘ Unterschrift:_____ Seite **10** von **13**

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: └─┘└─┘.└─┘_└─┘└─┘_└─┘└─┘└─┘

SF-12v2 Fragebogen

Ihre Gesundheit und Ihr Wohlbefinden

In diesem Fragebogen geht es um die Beurteilung Ihres Gesundheitszustandes. Der Bogen ermöglicht es, im Zeitverlauf nachzuvollziehen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen. ***Vielen Dank für die Beantwortung dieses Fragebogens!***

Bitte kreuzen Sie für jede der folgenden Fragen das Kästchen ☒ der Antwortmöglichkeit an, die am besten auf Sie zutrifft.

1. **Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben?**

Ausgezeichnet	Sehr gut	Gut	Weniger gut	Schlecht
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Die folgenden Fragen beschreiben Tätigkeiten, die Sie vielleicht an einem normalen Tag ausüben. Sind Sie durch Ihren derzeitigen Gesundheitszustand bei diesen Tätigkeiten eingeschränkt? Wenn ja, wie stark?**

	Ja, stark eingeschränkt	Ja, etwas eingeschränkt	Nein, überhaupt nicht eingeschränkt
a. Mittelschwere Tätigkeiten, z. B. einen Tisch verschieben, staubsaugen, kegeln, Golf spielen	☐ 1	☐ 2	☐ 3
b. Mehrere Treppenabsätze steigen	☐ 1	☐ 2	☐ 3

V1.1

Datum: └─┘.└─┘.└─┘└─┘ Unterschrift:_____ Seite **11** von **13**

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: └─┘└─┘.└─┘_└─┘└─┘_└─┘└─┘└─┘

3. Wie oft hatten Sie in den vergangenen 4 Wochen aufgrund Ihrer körperlichen Gesundheit folgende Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause?

	Immer	Meistens	Manchmal	Selten	Nie
	▼	▼	▼	▼	▼
• Ich habe weniger geschafft als ich wollte	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
• Ich konnte nur bestimmte Dinge tun	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. Wie oft hatten Sie in den vergangenen 4 Wochen aufgrund seelischer Probleme folgende Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z. B. weil Sie sich niedergeschlagen oder ängstlich fühlten)?

	Immer	Meistens	Manchmal	Selten	Nie
	▼	▼	▼	▼	▼
• Ich habe weniger geschafft als ich wollte	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
• Ich konnte Dinge nicht so sorgfältig wie üblich tun	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. Inwieweit haben Schmerzen Sie in den vergangenen 4 Wochen bei der Ausübung Ihrer Alltagstätigkeiten zu Hause oder im Beruf behindert?

Überhaupt nicht	Etwas	Mäßig	Ziemlich	Sehr
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

V1.1

Datum: └─┘.└─┘.└─┘└─┘ Unterschrift:_____ Seite **12** von **13**

UNI BASEL

DART: Validierung eines Fragebogens

Probandencode: ⌊⌊⌋⌊⌋.⌊⌋_⌊⌊⌋_⌊⌊⌋⌊⌋

6. In diesen Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen in den vergangenen 4 Wochen gegangen ist. Bitte kreuzen Sie in jeder Zeile die Zahl an, die Ihrem Befinden am ehesten entspricht. Wie oft waren Sie in den vergangenen 4 Wochen…

	Immer	Meistens	Manchmal	Selten	Nie
a. ruhig und gelassen?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. voller Energie?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. entmutigt und traurig?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in den vergangenen 4 Wochen Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt?

Immer	Meistens	Manchmal	Selten	Nie
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Vielen Dank für die Beantwortung dieser Fragen!

Datum: ⌊⌊⌋.⌊⌊⌋.⌊⌊⌋⌊⌋ Unterschrift:_____

V1.1

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A2.5. Instructions for the completion of the CRF

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Anweisung zum Ausfüllen der Case Report Form (CRF)

- Probandencode siehe Einverständniserklärung
- Datum des Interviews siehe Einverständniserklärung
- Geschlecht siehe Einverständniserklärung
- Zeit zum Ausfüllen des Fragebogens siehe Schlussbefragung
  (jeweils auf 5, 10, 15,… Minuten runden)
- Hinweise auf ADE evtl. bei Anamnesegrund zu finden
- Gewicht, sowie die Körpergrösse werden auf ganze Zahlen gerundet:
  ≥0.5 wird aufgerundet, < 0.5 wird abgerundet
- „GFR (berechnet)" bedeutet nicht, dass die jeweiligen Studienapotheker diese berechnen müssen. Die GFR wird allenfalls von Nadine Mory aus dem gemessenen Kreatininwert berechnet.
- Bei chronischer kardiovaskulärer Erkrankung Screening auf Begriffe wie:
  Koronare Herzkrankheit, Herzinsuffizienz, Herzrhythmus-störungen (Vorhofflimmern), etc.
- Bei chronischer Atemwegserkrankung Screening auf Begriffe wie:
  COPD, Asthma, obstruktive Atemwegserkrankung, etc.
- Punkte für Mikro-Mental-Test (MMT), aus dem Fragebogen, welcher mit dem Probanden zusammen ausgefüllt wurde, berechnen und eintragen.
  - MMT:
    Wie die Punkte vergeben werden, ist auf dem Mikro-Mental-Test selbst beschrieben.
- Im Spital neu verordnete Medikamente werden im CRF nicht erfasst!
- Punkte für BMQ und Morisky aus den jeweiligen Fragebögen, welche mit dem Probanden zusammen ausgefüllt wurden, berechnen und eintragen.
  - BMQ:
    - Alle Punkte zu den Fragen für „Necessities" (Frage 1, 3, 4, 7 und 10) zusammen zählen (Ist das Feld 1 angekreuzt, ergibt dies einen Punkt; ist das Feld 2 angekreuzte, ergibt dies 2 Punkte, usw.).
    - Alle Punkte zu den Fragen für „Concerns" (Frage 2, 5, 6, 8 und 9) zusammen zählen (Ist das Feld 1 angekreuzt, ergibt dies einen Punkt; ist das Feld 2 angekreuzte, ergibt dies 2 Punkte, usw.).
    - Punkte für „Necessities" – Punkte für „Concerns"
    - Die Punktzahl kann somit zwischen -20 und 20 Punkten liegen.
  - Morisky:
    - Die Fragen 1, 2, 3, 4, 6 und 7 ergeben einen Punkt falls nein angekreuzt ist.
    - Die Frage 5 ergibt einen Punkt falls ja angekreuzt ist.
    - Die Frage 8 ergibt einen Punkt falls Nie/selten angekreuzt ist. Ansonsten ergibt die 8. Frage null Punkte.

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B 2.6. Protocol for the selection of patients

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DART: Validierung eines Fragebogens

Probandencode: ⌊⌊⌋⌊⌋.⌊⌋_⌊⌊⌋_⌊⌊⌋⌊⌋

Protokoll Patientenselektion

Datum des Screenings:	⌊⌊⌋⌊⌋.⌊⌊⌋⌊⌋.⌊⌊⌋⌊⌋⌊⌋⌊⌋
Einschlusskriterien: - >18 Jahre alt - ausreichenden Sprachkenntnisse deutsch in Wort und Schrift - Stationärer Patient	☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein
Ausschlusskriterien: - < 18 Jahre alt - Keine ausreichenden Sprachkenntnisse deutsch in Wort und Schrift - ambulanter Patient - Gesundheitszustand, welcher eine sinnhafte Unterhaltung nicht zulässt (d.h. Delir, akute Psychose, fortgeschrittene Demenz, Aphasie, getrübter Bewusstseinszustand) - Palliativer oder terminaler Patient	☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein 1x Ja = Ausschluss
Der Patient ist geeignet.	☐ **Ja** ☐ **Nein**

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Curriculum vitae

- On request -