Drug-Related Problems: Assessments of Risk and Relevance

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Dominik Stämpfli aus Moosseedorf (BE)

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auf Antrag von

Prof. Dr. Kurt E. Hersberger

PD Dr. med. Balthasar Hug

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Prof. Dr. Martin Spiess
Dekan

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AuROC	Area under the Receiver Operating Characteristic Curve
BMQ	Beliefs about Medicines Questionnaire
CI	Confidence Interval
DART	Drug-Associated Risk Tool
DRM	Drug-Related Morbidity
DRP	Drug-Related Problem
FIP	International Pharmaceutical Federation
ICC	Intra-Class Correlation

MAI	Medication Appropriateness Index
MR	Medication Review
OTC	Over-the-Counter Medication
PIM	Potentially Inappropriate Medication
PMC	Polymedication Check
WHO	World Health Organization

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SUMMARY

Pharmacotherapy is the most frequently used form of treatment intervention. The benefits of the therapy need to be weighed carefully against its risks, as drugs also cause up to 25% of all emergency department visits. Preventable inappropriate prescribing and medication errors, including the patient's own mishandling, manifest in drug therapy failures and adverse drug events, which subsequently may generate costly hospitalisations. Of the adult Swiss population aged over 65 years, 21% are prescribed a potentially inappropriate medication. Within this setting, medication reviews are a method of assessing the patient's drug regimen regarding its appropriateness and the patient's preferences in order to address inappropriate prescribing and prevent medication errors. Medication reviews reduce the number of drug-re-

lated problems (DRPs) and decrease drug-related emergency department visits as well as hospital length of stay. But medication reviews are a time-consuming intervention. In a country like Switzerland, where 35.9 full-time equivalents of clinical pharmacists should promote safe, economic, and appropriate medicinal therapies for 1.4 million hospitalisations per year, there is a demand for risk stratification and patient prioritisation. Newly developed algorithms that generate alerts for clinical pharmacists on pooled electronic data, however, do not take into account the patient-centred causes of DRPs. The Drug-Associated Risk Tool (DART) was developed to identify hospitalised patients at greater risk of DRPs and in need of clinical pharmacy services, i.e. medication reviews. As a self-administered questionnaire for patients, the screening tool assesses items concerning the patients' medical information in combination with their opinions and concerns about the pharmacotherapy whilst not increasing the workload of any caregiver.

In this thesis, the DART was validated regarding its ability to discriminate between patients with lower and higher numbers of DRPs. Issues concerning the patients' current pharmacotherapy were identified with a medication review with pooled data on drug regimens, diagnoses, laboratory values, and structured patient interviews. The medication reviews combined implicit and explicit criteria of inappropriate prescribing to balance the benefits and drawbacks of each approach. This thesis looked into the performance of the criteria used and reports on the number of DRPs identified with each method. The structured patient interview was newly developed by combining a remunerated public pharmacy interview on adherence with questions on concerns about the medication. This thesis describes the benefits of the patient interview by presenting the type of DRPs identified and weighs it against the additional clinical pharmacy resource require-

ments. The DART validation study also necessitated the use of a tool to estimate the potential relevance of pharmacists' interventions. With the translation and subsequent reliability testing of the French tool CLEO, this thesis reports on the performance of a validated German version. $CLEO_{de}$ may help German-speaking pharmacists to estimate the potential relevance of their own interventions in three distinct dimensions: Patient-centred clinical, cost-focusing economic, and institution-based organisational. The study focused on interrater and test–retest reliability of $CLEO_{de}$ and presented an overview of clinical pharmacists' activity within three Swiss-German hospitals. This thesis also critically evaluated the performance of another tool for risk stratification and patient prioritisation concerning one specific drug-related problem: The RISQ-PATH score and its ability to predict drug-induced QT-prolongation and heart arrhythmias.

The thesis encompassed the execution of medication reviews, including patient interviews, for 110 geriatric patients within a study period of 10 months, identifying 595 DRPs estimated to be of minor to lifesaving relevance. The performed patient interviews identified over one third of all DRPs with insufficient patient knowledge and incomplete patient documentation as most the prominent and not otherwise identifiable causes. This thesis reports an average time of 16.6 minutes needed for the individual structured patient interviews. The ability of the DART to distinguish between patients with low and high numbers of current DRPs was demonstrated: Cluster analysis and subsequent discriminant function analysis allowed for an item reduction to five questions associated with the number of DRPs. These questions allow targeting patients who would benefit most from direct engagement and bedside interventions. $CLEO_{de}$ was used by 10 clinical pharmacists working in three hospitals during 13 days of routine clinical pharmacy services to estimate the relevance of 324

performed pharmacists' interventions. The use of $CLEO_{de}$ was seen as appropriate, acceptable, feasible, and precise. Statistical analysis showed good interrater reliability and excellent test–retest reliability for the clinical and economic dimension, whereas the organisational dimension achieved poor interrater and fair test–retest reliability. By critically examining the association between the RISQ-PATH scores and the measured QT_c intervals, we identified an already previously present prolonged QT_c interval as moderating variable, necessitating subgroup generation for score interpretation. These results also allowed this thesis to articulate a simple code of practice when handling drugs with the potential to prolong the QT_c interval.

This thesis, entitled "Drug-Related Problems: Assessments of Risk and Relevance," presents a validated self-administered patient questionnaire to stratify for drug-related risk, a validated assessment to estimate the relevance of drug-related problems, a structured patient interview to identify issues on drug-related adherence, handling, and concerns, and a valid score to detect patients at risk of drug-induced QT-prolongation.

GENERAL INTRODUCTION

I. Medicines Use and Patients on Polypharmacy

"Medicinal therapy is the most frequently used form of treatment intervention in any health practice setting. Its use has grown dramatically as the population has aged, the prevalence of chronic disease has increased, new infectious diseases have emerged and the range of effective medications has broadened." – WHO & FIP 2006,[1]

A proportion of 41.2% of Swiss men and women aged over 65 years is prescribed five or more medicines.[2] The current life expectancy of 80.7 years of age for men and 84.9 for women leaves this population stratum with more than 15 years of polypharmacy.[3] The demographic shift, in which the proportion of men and women over 65 years of age will increase from 18.0% in 2014 to 26.4% in 2045,[4] will further enlarge the number of patients on polypharmacy. This shift towards polypharmacy has been shown in Scotland: Within a time span of 15 years, the proportion of adults in Tayside which got dispensed ≥ 5 drugs increased two-fold, and the proportion receiving ≥ 10 increased three-fold, doubling the number of potentially serious drug–drug interactions.[5] As polypharmacy is an independent predictor of hospitalisation and

re-hospitalisation,[6] the current Swiss hospitalisation rate of 121.7 per 1000 inhabitants may be expected to further increase.[3] This development is relevant to the Swiss health care system in general.

II. Drug-Related Problems

"An undesirable event, a patient experience that involves, or is suspected to involve drug therapy, and that manifestly or potentially, interferes with a desired patient outcome" – Cipolle & Strand 1998,[7]

Drug-related problems (DRPs) – also described as medicine-related problems in American lierature[8] – are distinguished by their preventability, their presence, and their cause:[9] (1) They are preventable or not, (2) they are potential or present and manifest, and (3) they are caused by an error, a deviation from accepted medical practice, or an unpredictable reaction towards an appropriately selected drug. As the term DRP includes all aspects of drug therapy, DRPs are present in up to 81% of all hospitalised patients as they include, but are not restricted to, dosing issues, missing laboratory data, wrong drug selection, untreated indications, and medical chart errors.[10] Within the terminology of DRPs, adverse drug reactions (ADRs) may be described as unpreventable, manifest, and often unpredictable DRPs: ADRs are noxious and unintended reactions occurring at labelled doses normally used in humans, more commonly described as side-effects.[11] One example is the capability of some drugs to potentially influence repolarisation of the heart, prolonging the QT_c interval measured in ECG measurements. Prescribing multiple QT-prolonging drugs puts patients at risk of potentially lethal arrhythmias.[12] [13] Adverse drug events (ADEs), on the other hand, are an undesired medical occurrence during a drug treatment with a questionable causal relationship,[8] an example being falls during drug treatment. Failures by health care providers or patients themselves in prescribing, dispensing, storing, preparation, and administration represent preventable DRPs and define medication errors – one being the previously described prescription of multiple QT interval-prolonging drugs for a high-risk patient.[14] Similarly, unintentional non-adherence – the extent to which a patient's behaviour does not correspond with agreed recommendations from a health care provider[15] – can be described as medication error and hence marks a preventable and manifest DRP.[9] The relationship of all the terms to DRPs is visualised in Figure 1. The definition of a DRP in the broadest sense of the term also embraces medication errors and ADRs that may remain potential and do not manifest in symptoms, hence remain potential DRPs without consequences. Figure 1 highlights this circumstance with all areas not intersecting the area of ADEs. The area of ADEs marks symptoms of manifest medical situations.

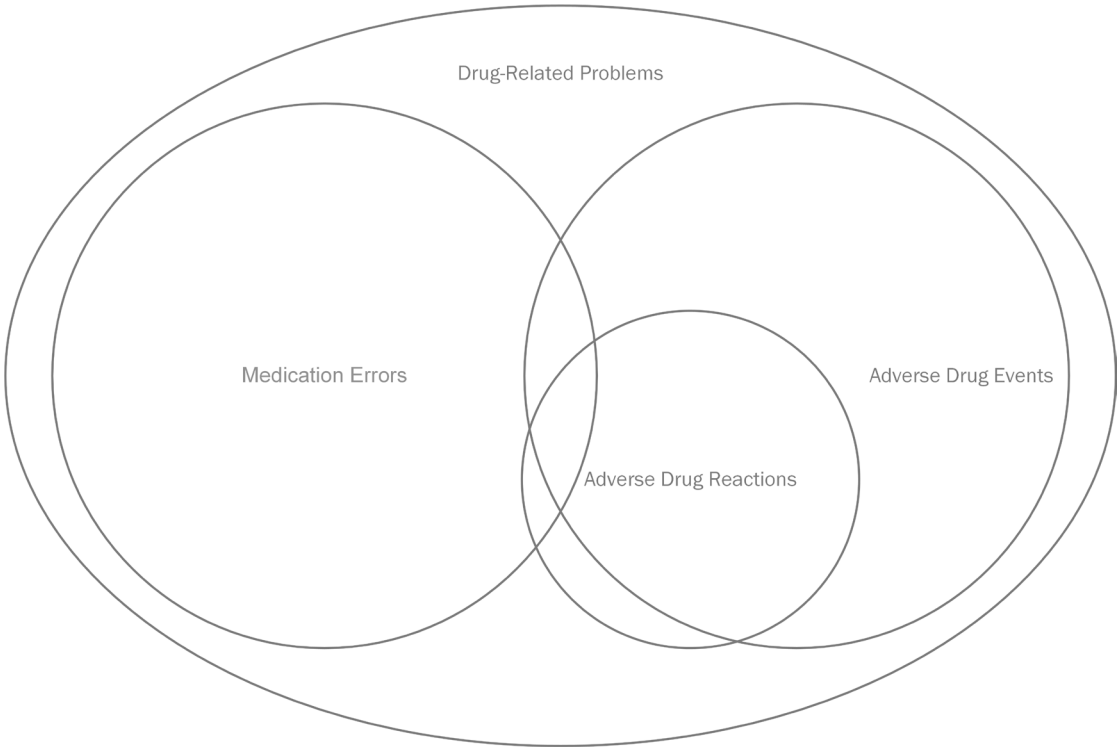


Figure 1 Relationship of drug-related problems, medication errors, adverse drug reactions, and adverse drug events. The areas of medication errors and adverse drug reactions not intersecting adverse events display errors and potential sideeffects that do not manifest in symptoms and remain without consequences. Drug-related problems, being the broadest sense of the term, also include physical or psychological dependence, ineffectiveness and interactions, as well as potential issues. Size is not representative of prevalence. Visualisation inspired by Anita Maria Krähenbühl-Melcher.[16]

Undetected and therefore unresolved potential or manifest DRPs place the patient at risk for drug-related morbidity (DRM), where the patient suffers from an injury causally originating from the treatment or lack thereof.[17] Subsequently, DRPs may lead to results diametrically opposed to the intentions for using pharmacotherapy in the first place: The modification of pathological states for the benefits of the patients places them at risk of injuries.[11] DRM is estimated to be the cause of 8.6– 24.2% of all emergency department visits.[18] Of these visits, where over a fifth result in a subsequent hospital admission as an inpatient, 70% would be preventable. It is the DRPs drug therapy failure, ADRs, and overdoses that most prominently result in a hospital admission.[19]

During the subsequent hospitalisation, patients may experience additional DRPs: About 5% of all drug applications within the hospital are accompanied by a medication error. Given the number of 5–10 drugs per day for a patient treated on a medical ward, the probability of an erroneous drug application is increased with each day spent in

the hospital.[20] In 2000, the publication „To Err is Human" was a major landmark in medication-error awareness:[21] The report referred to 44,000 extrapolated deaths due to medication errors in a total of 33.6 million hospital admissions. Put into perspective, this number presented medication errors as one of the 10 leading causes of deaths in the United States of America. Besides causing patient harm, the errors also incur additional costs for the health care system: Preventable adverse drug events add $4,700 per admission.[22] „To Err is Human" underpinned its goal of improving patient safety with the words: „The status quo is not acceptable and cannot be tolerated any longer. Despite the cost pressures, liability constraints, resistance to change and other seemingly insurmountable barriers, it is simply not acceptable for patients to be harmed by the same health care system that is supposed to offer healing and comfort."

III. Inappropriate Prescribing

Pharmacotherapy is considered to be appropriate when there is an evident indication, the therapy is tolerated by most patients within the same population, and the treatment is cost-effective.[24] Inappropriate prescribing as a whole encompasses misprescribing, overprescribing, and underprescribing, and may be regarded as a DRP in the realm of medication errors. Misprescribing describes the selection of a drug that increases the risk for ADEs for the treated population. It also describes choosing the wrong dose, frequency, modality, or duration for an otherwise appropriate pharmacotherapy. Overprescribing is used for when there is no evident indication apparent for the drug. Underprescribing is the omission of a drug, which would be indicated for the treatment or prevention of a disease.[24] In addition, the tolerance for many drugs changes in the elderly: The patients are at higher risk for ADRs as the pharmacologic effects increase or decrease.[25] For this reason, a drug for which there is a safer or more effective alternative for the treatment of the elderly is considered a potentially inappropriate medication (PIM).[25]

"The rational use of drugs requires that patients receive medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community." – WHO 1985,[23]

"However, rational use of medicines remains the exception rather than the rule. For those people who do receive medicines, more than half of all prescriptions are incorrect and more than half of the people involved fail to take them correctly." – WHO 2004,[1]

Patients exposed to PIMs use more health care services and incur higher costs as the association between PIM use and ADEs has shown.[24,26] The number of concurrent PIMs correlates with hospitalisation rates for the Swiss population aged more than 65 years:

In the study of Blozik and colleagues, the adjusted hazard ratio for hospitalisation was 1.13 (95%-confidence interval [CI] 1.07–1.19) for 1 PIM, 1.27 (95%-CI 1.19–1.35) for 2 PIMs, 1.35 (95%-CI 1.22–1.50) for 3 PIMs, and 1.63 (95%-CI 1.40– 1.90) for more than 3 PIMs compared to no PIM use.[27] Of the population stratum, 21.1% of the patients received at least one PIM.[2] The prevalence of PIM prescribing increased with a positive correlation to age. Putting the financial burden into perspective, Blozik and colleagues showed that the costs for the 15 most prevalent PIMs affect the Swiss health care and insurance systems, with 145.9 million Swiss francs in direct costs – while not further assessing the additional indirect costs for subsequent hospitalisations and management of ADRs associated with PIM use.

Inappropriate prescribing can be measured and approached by using explicit and implicit criteria for prescribing appropriateness.[24] Explicit criteria are rigid lists of drugs and recommendations, usually based on expert opinions and literature reviews.[24 28] Examples of explicit criteria are the Beers' List,[29] the PRISCUS List,[30] and the STOPP criteria.[31] Explicit criteria allow for a quick evaluation of prescribing appropriateness as they do not require clinical judgement and may be implemented in automated algorithms.[28] As rigid lists, these criteria need to be updated regularly in vast validation processes.[31] As the answers to the incorporated items are dichotomous, explicit criteria do not allow for patient tailoring or involvement:[28] Patients either receive a drug that is listed as a PIM, or they do not. The use of the STOPP criteria, which target misprescribing and overprescribing in the elderly, is shown to improve medication appropriateness and to reduce the prevalence of ADRs, as the items are associated with ADEs.[31] Contrarily to explicit criteria, implicit criteria are tools filled with information based on clinical judgement. An example of an implicit tool is the Medication Appropriateness Index (MAI).[32] The results of such an assessment are unique to the affected patient, but depend on the user's knowledge and capabilities. For each medicine, 10 items are judged to be "appropriate", "marginally appropriate", or "not appropriate". A weighted score is applied for the judgements "partially appropriate" and "marginally appropriate".[33] The total score of a medication indicates the appropriateness while each contributing item indicates an opportunity for optimisation. For the MAI, feasibility, content validity, predictive validity, and reliability have been shown.[34] Improvements in drug therapy are reflected in a better (i.e. decreased) total MAI score.[35] As the assessments are performed per patient or even per drug, implicit criteria are time-consuming.[28] Explicit and implicit criteria are best used in conjunction as their benefits may be combined whilst minimising their drawbacks.[28]

IV. Medication Reviews

"Medication review is, at heart, a diagnostic intervention which aims to identify problems for action by the prescriber, patient, or both but can also be regarded as an educational intervention to support patient knowledge and adherence." – Blenkinsopp 2012,[36]

Medication review (MRs) is a process in which health care professionals assess the appropriateness of a drug therapy in regard to the patient's illnesses and in respect of the patient's own preferences. MRs involve evaluating therapeutic efficacy, adherence, manifest and potential DRPs, interactions, and the patient's understanding of the condition and its treatment. MRs may include explicit and implicit criteria of inappropriate prescribing if suitable for the specific patient population. After an MR, a decision is made on changes to the drug treatment in order to improve its appropriateness.[36 37] The quality of an MR is affected by the amount of information available to the assessor and the relationship to the prescriber.[36]

MRs are categorised into three distinctive categories with varying degrees of clinical data and patient involvement.[38] A *Simple Medication Review (MR Type 1)* is based solely on the available patient medication history. MRs Type 1 may reveal interactions, treated ADRs, inappropriate prescribing, and adherence issues. An *Intermediate Medication Review (Type 2A and Type 2B)* is additionally based either on information about the patient being present for an interview or on clinical information. Compared to MRs Type 1, MRs Type 2A additionally reveal drug–food interactions, drug effectiveness issues, insufficient understanding by the patient, and problems with over-the-counter medicines. MRs Type 2B replace the additional information gained from the patient interview with the possibility of detecting overprescribing and underprescribing, as laboratory values and diagnoses are available. Finally, an *Advanced Medication Review (MR Type 3)* is based on all data, hence consisting of drug treatment information, patient interviews, and clinical data. MRs Type 3 are best suited to identifying the previously described vast diversity of possible DRPs.

MRs are shown to improve the quality of prescribing.[39] They reduce the total MAI score of the patient's drug treatment and lower the numbers of present PIMs.[35] MRs that involve patient counselling also positively affect adherence.[6 40] Outpatient MRs seem to reduce emergency department visits and early in-hospital MRs positively influence hospital length of stay;[41] however, evidence on reduced mortality or hospital readmissions is still sparse.[42]

V. Pharmaceutical Care and Clinical Pharmacy

"Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life"– Hepler & Strand 1990,[43]

The pharmacy profession is shifting away from its traditional role as compounders and medicine suppliers. Pharmacists are becoming providers of services, information and, ultimately, of care.[1] By optimising their patients' medicines use, pharmacists contribute to the overall care of a patient and get involved in the improvement of health outcomes.[44] Pharmaceutical care includes liable decisions on the drug needs of a patient and provides services surrounding these drugs to assure a safe and effective medicines therapy, e.g. MRs. In order to establish a continuity of care, the provided services require a feedback mechanism.[45] For this reason, patient-centred care is a collaborative service.[46] More recently, the lead for providing pharmaceutical care was attributed to the pharmacist: "Pharmaceutical Care is the pharmacist's contribution to the care of individuals in order to optimise medicines use and improve health outcomes."[44] This definition respects the circumstances that pharmacists should be involved in the care of their patients and that other health care professionals can provide medicines-related services.[44] In order to establish pharmaceutical care, pharmacists may apply clinical pharmacy techniques as a continuous and recurring service.

"Clinical pharmacists work in collaboration with other providers to deliver comprehensive medication management that optimizes patient outcomes." – American College of Clinical Pharmacy 2014,[47]

Clinical pharmacists are responsible for the development and promotion of a safe, appropriate, and economic use of medicines. They are collaborators in care with a patient-centred approach towards drug treatment.[48] Clinical pharmacists optimise medication therapy by applying in-depth pharmacologic knowledge and evidence-based therapeutic guidelines. As primary source for advice on objective therapeutic drug information, clinical pharmacists are accountable for advancing rational drug use and averting inappropriate prescribing.[49]

Pharmacists' interventions aim at improving the use of medicines to address manifest or potential DRPs.[50] Such interventions may be defined as "any action that directly results in a change in patient management or therapy."[51] Documenting these interventions demonstrates accountability for the actions taken and helps in facilitating pharmaceutical care research.[1 50 51] More importantly, the documentation improves the patient's quality of care as it is a way of communicating with other health care providers – a necessity for the continuous provision of pharmaceutical care, as described.[51] Hence it is important that the relevance of a pharmacist's intervention is assessed in addition to its documenta-

tion.[52] Examples of pharmacists‘ interventions include adaptions of the application form from tablets to granulate according to the patient's preference, identifying an untreated atrial fibrillation, or asking nurses to wear protective masks while crushing tablets containing cancerogenic drugs. The impact of pharmacists' interventions varies in affected processes and outcomes.[52] Therefore, the impact and relevance of an intervention depends on the measured traits: Focusing on the effect for the patient's quality of life will trivialise the relevance of reducing the nurses' exposure to a cancerogenic drug. The variety of methods to assess the relevance of the interventions reflects this diversity: Studies may use (1) small expert panels who decide on the relevance of the interventions and often have to reduce the amount of interventions by sampling,[53] (2) specific tools for self-assessment,[54] or (3) pairs of pharmacists and physicians using scales.[55] Consensus-finding processes in teams or expert panels are possible in study settings, but are too resource-exhaustive for daily practice. However, tools to assess the relevance of pharmacists' interventions mainly focus on clinical impacts and neglect effects on hospital costs or workplace safety. Additionally, only sparse information on reliability and validity is available.[52]

Casting aside issues on measuring the relevance of the interventions, pharmacists' participation on ward rounds, provision of medication reconciliation, and delivery of drug-specific services are shown to reduce the occurrence of ADRs and medication errors. They also improve medication adherence, knowledge, and appropriateness and shorten hospital length of stay.[56] In a sample of over one fifth of all US hospital admissions (22.4%, 7,892,430), pharmacy services were found to reduce mortality rates.[57] A pooled median benefit-to-risk ratio across 15 studies of 4.81 to 1 was calculated, showing $4.81 in reduced costs or other economic benefits for every $1 spent on clinical pharmacy services.[58] However, clinical pharmacy is not common in Switzerland:[59] From a total of 239.2 full-time equivalents of Swiss hospital pharmacists, only 15% were assigned to clinical pharmacy in 2013. This put 35.9 full-time equivalents of clinical pharmacists in stark contrast to 1.4 million hospitalisations. Weekly performed treatment recommendations during ward rounds are restricted to selected wards only and direct patient engagement is especially rare, leaving the general patient unapproached and with unresolved DRPs. Current resources are not sufficient to provide pharmaceutical care through Swiss clinical pharmacists and necessitate patient prioritisation.

VI. Assessment of Risk for Drug-Related Problems

Prioritising patients in order to structure the daily workload is an accepted requirement to maintain effective clinical pharmacy services with finite resources.[60] [61] However, recommendations from official guidelines on patient prioritisation remain vague regarding risk factors:[60] “High risk disease states”, “difficulty with managing own medici-

nes", or "complex medication regimens" depend on a subjective risk stratification or previously completed additional assessments. Hence, tools to assess the risk for DRPs have been developed – some as algorithms, some as paper-based questionnaires. An overview of popular tools is presented in Table 1.

Table 1 Overview of tools to assess the risk for drug-related problems (DRPs).

The GerontoNet ADR risk score[62 63]	
The GerontoNet ADR risk score allows prioritisation of patients according to their likelihood of developing ADRs.	
Variables	
Comorbid conditions (≥ 4); Heart failure; Liver disease; Number of drugs (≤ 5; 5 – 7; ≥ 8); Previous ADR; Renal failure (< 60 mL/min)	
Population Inpatients > 65 years of age	**Validation Status** Validated
Comment: The score focuses on clinical data with number of drugs (> 5) and previously experienced ADRs as strongest predictors. There was no association between age and increased risk for an ADR.	

The Brighton Adverse Drug Reactions Risk Model (BADRI)[64]	
The Brighton Adverse Drug Reactions Risk Model (BADRI) is another tool to predict ADRs and is aimed at a population of patients older than 85 years of age.	
Variables	
Hyperlipidaemia; Number of drugs (> 8); Hospital length of stay (≥ 12 days); Use of anti-diabetics; High white cell count on admission	
Population Inpatients > 85 years of age	**Validation Status** Validated
Comment: Out-performing all other models, this score has been described as fairly discriminative and sufficiently validated by the systematic review of Falconer and colleagues.[61]	

The Self-Administered Medication-Risk Questionnaire[65]

Barenholtz Levy developed the Self-Administered Medication-Risk Questionnaire containing questions on risk factors for DRPs. This questionnaire was designed to be completed by patients while they are waiting to be seen by their physician or pharmacist.

Variables

Number of drugs (> 5); Number of doses (≥ 12 /day); Certain drugs (carbamazepine, lithium, phenytoin, quinidine, warfarin, digoxin, phenobarbital, procainamide, theophylline); Number of prescribers (> 1); Comorbid conditions (≥ 3); Number of pharmacies (> 1); Third-party medication preparation; Adherence; Number of changes to the drug therapy regimen (≥ 4/ year); Medication literacy

Population	**Validation Status**
Outpatients > 60 years of age	Reliability; Correlation with Drug Regimen Review Scores

Comment: The association with the Drug Regimen Review scores, which was additionally developed, was only present for the five items on number of drugs (> 5), number of doses (≥ 12 /day), certain drugs (carbamazepine, lithium, phenytoin, quinidine, warfarin, digoxin, phenobarbital, procainamide, theophylline), comorbid conditions (≥ 3), and number of changes to the drug therapy regimen (≥ 4/ year).

The Medication Risk Assessment Questionnaire[66]

This questionnaire is an excerpt of Barenholtz Levy's questionnaire. The authors used the five items of the original questionnaire that showed a statistically significant correlation and added a threshold of three "Yes"-answers as a definition of risk patients.

Variables

Number of drugs (> 5); Number of doses (≥ 12 /day); Certain drugs (carbamazepine, lithium, phenytoin, quinidine, warfarin, digoxin, phenobarbital, procainamide, theophylline); Comorbid conditions (≥ 3); Number of changes to the drug therapy regimen (≥ 4/ year)

Population	**Validation Status**
Ambulatory patients > 18 years of age	Not validated

Comment: Questionable performance analysis. The study only compared referral rates to a specialised pharmacist between a control group and an intervention group: Within the control group, the referral was prescribed by a physician; within the intervention group, the referral was performed by three "Yes"-answers on the questionnaire. The questionnaire was described as a capable identification tool due to a significant proportion of patients within the control group who were not referred but also ticked three "Yes"-answers on the questionnaire.

The University of Alberta Hospital Family Medicine Clinic's Medication Risk Assessment Questionnaire[67]

This questionnaire is reported to be the combination of Barenholtz Levy's questionnaire and The Medication Risk Assessment Questionnaire, although the latter is manifestly an excerpt from the former. The study assessed the number of patients presenting three "Yes"-answers as in the study of The Medication Risk Assessment Questionnaire, but missed validating the questionnaire regarding identifying patients with high numbers of DRPs.

The Assessment of Risk Tool[68 69]	
The Assessment of Risk Tool is an application that monitors clinical data on specified medication and other risk factors. The risk factors are grouped into five categories: Patient profile (e.g. age), patient encounter (e.g. mental health history), clinical profile (e.g. co-morbidity COPD), high-risk medications (e.g. anti-diabetic medication), and laboratory values (e.g. renal function < 30 mL/min). Each trigger has a weighted score assigned and helps in prioritising patients into low, medium, and high risk for ADEs. The score also recommends pharmacists' interventions.	
Variables	
The application is triggered by a total of 38 risk factors on patient traits, recent hospitalisation, chronic conditions, certain drugs, and exceeding laboratory values	
Population	**Validation Status**
Inpatients with mean age 66 ± 19 years (SD)	Validated
Comment: The ART score is validated in regard to identifying patients with a higher risk for unintentional medication discrepancies as recognised in a medication reconciliation process. Some of the risk factors need clinical pharmacy processes in order to be evaluated, e.g. "Admitted patients identified via medication reconciliation process as having comprehension difficulties or as poorly compliant with medications." The category of risk factors on laboratory values was excluded from the validation study as there were technical difficulties, which reduced the ART score to 25 items.	

The Drug-Related Problem Risk Assessment Tool[70]	
Dimitrow and colleagues introduced a questionnaire completed by nurses to assess the risk for DRPs of patients older than 65 years of age in homecare.	
Variables	
Number of drugs (> 7); Number of doses (≥ 12 /day); Comorbid conditions (≥ 3); Number of changes to the drug therapy regimen (≥ 1/ 4 weeks); Certain drugs (non-steroidal antirheumatics drugs, diuretics, statins, amiodarone, carbamazepine, digoxin, fluoxetine, lithium, methotrexate, theophylline, warfarin); Use of over-the-counter (OTC) drugs; Previous ADR; Number of prescribers (> 1); Adherence; Recent hospitalisation; Certain symptoms; Third-party medication preparation	
Population	**Validation Status**
Homecare patients > 65 years of age	Content validity
Comment: Content validity of the tool was evaluated by Delphi surveys with members of geriatric care, where an agreement of ≥ 80 % for an item had to be reached. Feasibility was assessed by distributing the questionnaire to nurses and collecting feedback.	

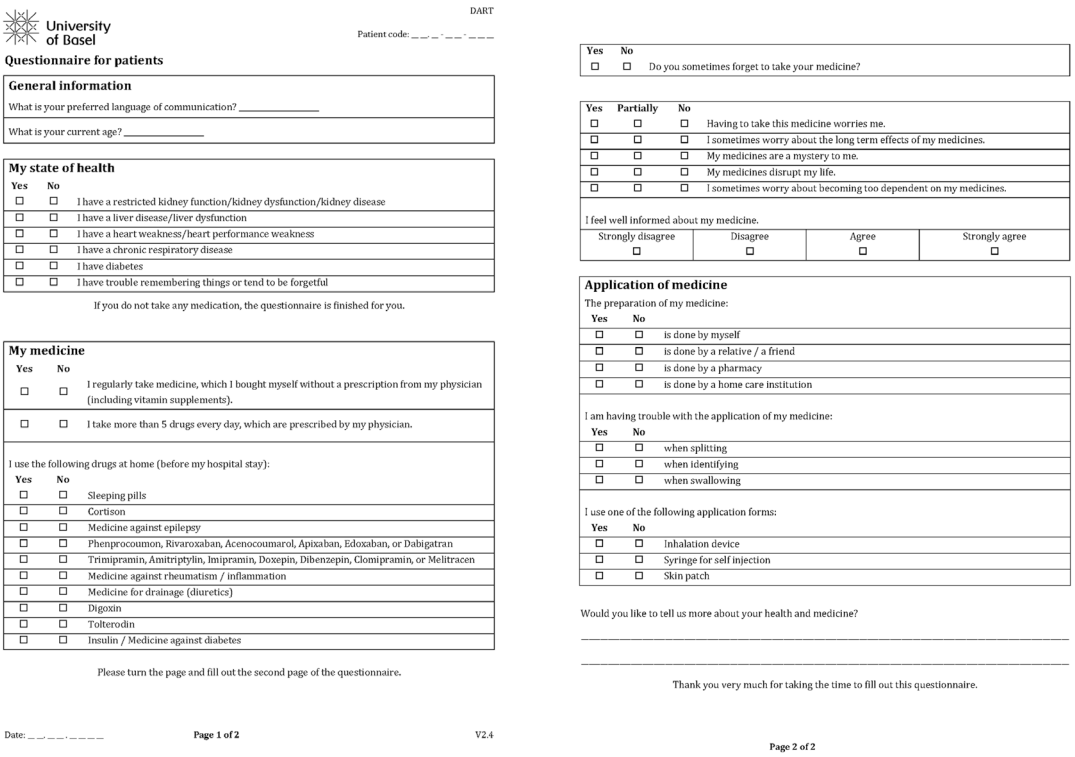
Tools such as those described in Table 1 were comprehensively evaluated by Falconer and colleagues.[61] For this systematic analysis, Falconer included studies where the primary outcome measures were ADRs, DRPs, and medication errors. Hence, this review

delivers a critical appraisal of the published tools to prioritise patients according to their risk for DRPs in general. Studies were, however, only included if they used multivariable logistic regression for model development, which excluded questionnaires like the one of Barenholtz-Levy (Table 1) or even their own model, which was based on clinical experience. Of the 11 models in their final assessment, only the Brighton Adverse Drug Reactions Risk (BADRI) model by Tangiisuran and colleagues remained as a tool with fair discrimination, sufficient validation, and reasonable performance. As outlined in Table 1, the BADRI score focuses on the five clinical variables hyperlipidaemia, number of drugs (> 8), length of hospital stay (≥ 12 days), use of anti-diabetics, and high white cell count on admission, and is validated for an inpatient population with a median age of 85 years. With its variables, the score is able to be implemented into automated screening algorithms, but requires laboratory measurements involving further effort by a health care profession.

Contrary to a model based on clinical data, a well-developed paper-based questionnaire can be distributed to patients while they are waiting to be seen by their physician or pharmacist.[65] Patient-completed questionnaires also help in identifying additional patient-centred DRPs, e.g. low adherence and poor medication literacy. But, as pointed out in Table 1, patient-completed questionnaires are rarely sufficiently validated. The Self-Administered Medication-Risk Questionnaire by Barenholtz-Levy is validated, but was developed by one researcher on basis of an unsystematic literature review.[65]

VII. Rationale and Project Description

With the Drug-Associated Risk Tool (DART), we aimed to develop a valid tool to screen for patients at higher risk of DRPs. As other tools, the DART should help clinical pharmacists in prioritising their patients and in tailoring specific clinical pharmacy services in order to ameliorate efficiency and effectiveness. Given the already finite resources at hand, we also aimed for a tool that does not increase the workload of any health care professional. The DART was designed to be a patient self-administered questionnaire to be distributed to patients at the time of hospitalisation. The questionnaire is displayed in Figure 2.



DART

University of Basel

Patient code: __ __ . __ __ . __ __ __

Questionnaire for patients

General information

What is your preferred language of communication? _____

What is your current age? _____

My state of health

Yes	No	
☐	☐	I have a restricted kidney function/kidney dysfunction/kidney disease
☐	☐	I have a liver disease/liver dysfunction
☐	☐	I have a heart weakness/heart performance weakness
☐	☐	I have a chronic respiratory disease
☐	☐	I have diabetes
☐	☐	I have trouble remembering things or tend to be forgetful

If you do not take any medication, the questionnaire is finished for you.

My medicine

Yes	No	
☐	☐	I regularly take medicine, which I bought myself without a prescription from my physician (including vitamin supplements).
☐	☐	I take more than 5 drugs every day, which are prescribed by my physician.

I use the following drugs at home (before my hospital stay):

Yes	No	
☐	☐	Sleeping pills
☐	☐	Cortison
☐	☐	Medicine against epilepsy
☐	☐	Phenprocoumon, Rivaroxaban, Acenocoumarol, Apixaban, Edoxaban, or Dabigatran
☐	☐	Trimipramin, Amitriptylin, Imipramin, Doxepin, Dibenzepin, Clomipramin, or Melitracen
☐	☐	Medicine against rheumatism / inflammation
☐	☐	Medicine for drainage (diuretics)
☐	☐	Digoxin
☐	☐	Tolterodin
☐	☐	Insulin / Medicine against diabetes

Please turn the page and fill out the second page of the questionnaire.

Date: __ __ . __ __ . __ __ __ __ **Page 1 of 2** V2.4

Yes	No	
☐	☐	Do you sometimes forget to take your medicine?

Yes	Partially	No	
☐	☐	☐	Having to take this medicine worries me.
☐	☐	☐	I sometimes worry about the long term effects of my medicines.
☐	☐	☐	My medicines are a mystery to me.
☐	☐	☐	My medicines disrupt my life.
☐	☐	☐	I sometimes worry about becoming too dependent on my medicines.

I feel well informed about my medicine.

Strongly disagree	Disagree	Agree	Strongly agree
☐	☐	☐	☐

Application of medicine

The preparation of my medicine:

Yes	No	
☐	☐	is done by myself
☐	☐	is done by a relative / a friend
☐	☐	is done by a pharmacy
☐	☐	is done by a home care institution

I am having trouble with the application of my medicine:

Yes	No	
☐	☐	when splitting
☐	☐	when identifying
☐	☐	when swallowing

I use one of the following application forms:

Yes	No	
☐	☐	Inhalation device
☐	☐	Syringe for self injection
☐	☐	Skin patch

Would you like to tell us more about your health and medicine?

_____

_____

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

Page 2 of 2

Figure 2 The Drug-Associated Risk Tool (DART).

The 35-items questionnaire was generated on the results of a triangulation process including the opinions of experts (structured by the Nominal Group Technique[71]), a literature search as enrichment, and two Delphi-Rounds[72 73] as prioritisation. The expert panel consisted of representatives of patient care: Family physicians, emergency physicians, geriatricians, pharmacologists, homecare nurses, community pharmacists, and clinical pharmacists. The transition of the gathered risk factors into a self-administered questionnaire and the first reliability tests were performed by Dr. Carole Kaufmann.[74] The questionnaire is divided into six sections on two pages: Health, polypharmacy, medication, adherence, concerns, and handling. The health section covers illnesses associated with an increased risk of DRPs, i.e. renal insufficiency, hepatic insufficiency, asthma/COPD, diabetes, and heart insufficiency. The polypharmacy section asks about the intake of more than five medicines and use of OTC drugs. The medication section focuses on specific drugs and drug classes deemed to be associated with an increased risk for DRPs and DRM. The adherence section consists of one question asking the patient about compliance with the medication regimen. The concerns section consists of the five questions from the Beliefs about Medicines Questionnaire (BMQ) focusing on concerns about the drug treatment negatively affecting knowledge and adherence.[75] The handling section is aimed at detecting difficulties in splitting, recognising, and swallo-

wing the medicines. All original questions were designed as being dichotomous "Yes" and "No" answers. Those from the BMQ kept their Likert scale. Reliability testing focused on patients' ability to reproduce their own medical information as compared to clinical information, i.e. medication charts and diagnoses.[76]

The difference between the DART and the aforementioned tools is its ability to combine clinical information and patient opinions within one self-administered questionnaire. Contrary to other published tools we also aimed for a full evaluation including all seven criteria for patient-based measures:[77] (1) Appropriateness: Are the items of the questionnaire appropriate for the identification of DRPs? (2) Acceptability: Is the questionnaire acceptable to the patients? (3) Feasibility: Is the questionnaire easy to use? (4) Interpretability: How well can the answers be interpreted? (5) Reliability: Does the tool generate answers that are reproducible? (6) Validity: Does the tool measure what it claims to measure? (7) Responsiveness: Is the questionnaire responsive to changes over time? We were able to incorporate appropriateness and responsiveness by design: The items of the questionnaire represent risk factors assimilated by expert opinion and studies on DRPs. The dichotomous and ordinal answers are able to reflect change in the patient's health, medicinal treatment, or handling of medicines. Acceptability, feasibility, and reliability testing are described in the project "Drug Associated Risk Tool – Development and Validation of a Self-Assessment Questionnaire to Screen for Hospitalised Patients at Risk for Drug-Related Problems", where hospitalised patients were given the questionnaire to complete themselves and their answers were compared to their clinical records.

The questionnaire's ability to distinguish patients into low and high levels of risk, its true validity, remained to be proven – as for many of the questionnaires previously described (Table 1). The DART validation study, with its linkage between a subset of items and specific clinical pharmacy services, is described in the project 'Assessing the ability of the Drug-Associated Risk Tool (DART) questionnaire to stratify patients according to their risk of Drug-Related Problems.'

Not all pharmacists' interventions and underlying DRPs have the same relevance. It was therefore necessary to have a tool at hand that enables the estimation of relevance. CLEO respects the variety of pharmacists' interventions in the perceived impacts on processes, outcomes, and probability. The tool is based on a systematic review on measures of relevance and combines humanistic, ecologic, and process-related outcomes. Translation and reliability testing of $CLEO_{de}$ are described in the project "Translation and Validation of a Tool to Assess the Impact of Clinical Pharmacists' Interventions." The German version of the tool, $CLEO_{de}$, gave us the opportunity to make statements on the relevance of the DRPs that the DART is able to detect.

The validation study of the DART encompassed patient interviews. With the data we collected we had the opportunity to demonstrate the value of direct patient contact in detecting DRPs in Swiss hospitalised patients. This analysis is described in "Patient Interviews as Part of a Comprehensive Approach Contribute to the Identification of Drug-Related Problems on Geriatric Wards."

Lessons learned from the validation study of the DART were transposed into an additional dataset on one specific DRP: Drug-induced QT_c interval prolongation, previously described as an example for ADRs. The RISQ-PATH score is an assessment of risk much like the DART, but focuses only on the specific DRP of QT-prolongation. Vandael and colleagues investigated identified risk factors and a baseline ECG as predictors for a follow-up ECG when a new QT_c-prolonging drug was started. With their results, they developed the RISQ-PATH score, which aims to rule out low-risk patients from further ECG measurements when starting QT_c-prolonging drugs. The project entitled 'Risk of Drug-Induced QT_c Interval Prolongation – A Step Closer to a Clinical Risk Management' aimed to investigate the performance of the RISQ-PATH score in a geriatric, hospitalised patient population and is presented in this thesis.

VIII. Goal and Aims

The goals of this thesis were (1) the validation of a self-administered patient questionnaire as a risk stratification tool on DRPs and (2) the external validation of the RISQ-PATH score. Aims to achieve these goals were (1) establish an evaluation tool to estimate the relevance of DRPs, (2) develop a structured patient interview as an information source for MR Type 3s, (3) validate the DART by correlation with MR Type 3s including patient interviews, and (4) validate the RISQ-PATH score by correlation with measured QTc intervals.

THESIS OVERVIEW

Project	Description
Translation and Validation of a Tool to Assess the Impact of Clinical Pharmacists' Interventions [Manuscript ready for submission]	The French evaluation tool CLEO helps pharmacists to assess the relevance of their own interventions in the view of the patients, the hospital, and the staff. It was the first tool concerning clinical relevance to be developed according to the findings of a systematic literature review. We translated this tool into German following accepted principles and tested its interrater and test–retest reliability.
Drug Associated Risk Tool – Development and Validation of a Self-Assessment Questionnaire to Screen for Hospitalised Patients at Risk for Drug-Related Problems [Published in BMJ Open]	In this shared first-authorship article we describe in detail the development of the Drug-Associated Risk Tool (DART). The DART is a patient self-administered questionnaire which aims to help pharmacists tailor their services according to the patient's risk of drug-related problems We also report the results of two tests on the patients' ability to use the questionnaire as a self-administered questionnaire and our subsequent changes to the item formulation.

Project	Description
Assessing the ability of the Drug-Associated Risk Tool (DART) questionnaire to stratify patients according to their risk of Drug-Related Problems [Published in BMJ Open]	In this main project we validated the DART by correlating its score to DRPs identified in MRs Type 3. Cluster analysis and discriminatory function analysis reduced the questionnaire to a set of five items for its main purpose.
Patient Interviews as Part of a Comprehensive Approach Contribute to the Identification of Drug-Related Problems on Geriatric Wards [Published in Drugs & Aging]	MRs Type 3 involve the patients' opinion, their attributes and their knowledge. Based on established tools, we developed a structured interview and highlighted its capabilities to identify DRPs.
Risk of Drug-Induced QTc Interval Prolongation – A Step Closer to a Clinical Risk Management [Draft]	The RISQ-PATH score aims to deliver guidance on when to order an ECG measurement when a new QT_c-interval prolonging drug is started. We externally validated the score for geriatric, hospitalised patients and identified a moderation effect by one of the risk factors. The results restricted the score's generalisability, but provided a simple code of practice for starting a new QT_c-interval prolonging drug.

PROJECTS

I. Translation and Validation of a Tool to Assess the Impact of Clinical Pharmacists' Interventions

To appropriately research and report DRPs, data on their relevance is necessary.[78] This relevance comprises the evaluation of actual negative consequences of an unresolved DRP, the evaluation of actual positive consequences of a resolved DRP, or the estimation of potential risk for the patient.[52] As the assessment of actual consequences is often hindered by difficulties in follow-up, lack of resources, or the determination of causality, the estimation of potential risks is used to report the relevance of DRPs or pharmacists' interventions. To reduce the subjectivity and simultaneously increase the reliability of this estimation, expert panels may be consulted; however they often only evaluate subsets of the data, as focus groups are a resource-intensive method.[79-81] A different method of estimating the potential risks for a patient without introducing issues about subjectivity and reliability is the use of an appropriate tool.[52] Such a tool was developed and validated in Grenoble: CLEO lets pharmacists rate the impact of their interventions in three proposed dimensions.

Focusing on methodological aspects, CLEO was translated and culturally adapted into $CLEO_{de}$ in a process proposed by the ISPOR Task Force for Translation and Cultural Adaptation for Patient-Reported Outcome Measures.[82] This process consists of 10 steps: (1) Preparation, (2) Forward Translation, (3) Reconciliation, (4) Back Translation, (5) Back Translation Review, (6) Harmonisation, (7) Cognitive Debriefing, (8) Review of Cognitive Debriefing Results and Finalisation, (9) Proofreading, and (10) Final Report. As recommended, the translation steps were conducted with the help of two professional translators. The cognitive debriefing, where comprehensiveness and linguistic style are measured, included clinical pharmacy experts from all native German-speaking countries. Interrater and test–retest reliability of $CLEO_{de}$ were assessed in order to be able to report comparability across different raters and consistency in coding. As recommended by Hallgren,[83] the intra-class correlation (ICC) was used to calculate the interrater reliability instead of the often-used methods Cohen's kappa or percentage of agreement. Cohen's kappa is only suitable for up to two coders and percentage of agreement has been rejected as an adequate measure of interrater reliability. To report the potential clinical implications of $CLEO_{de}$, the tool was distributed to 10 clinical pharmacists to be used in their daily clinical pharmacy practice. The collected data were supplemented with subjective feedback on appropriateness, acceptability, feasibility, and precision of $CLEO_{de}$.

Translation and Validation of a Tool to Assess the Impact of Clinical Pharmacists' Interventions

Dominik Stämpfli (1), Pascal Baumgartner (1), Fabienne Boeni (1), Pierrick Bedouch (2), Kurt E. Hersberger (1), Markus L. Lampert (1)

Manuscript prepared for submission and reviewed by all co-authors
(awaiting publication of the original tool)

(1) Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; (2) Department of Clinical Pharmacy, Faculty of Pharmacy TIMC-IMAG/CNRS (UMR5525), University Grenoble Alpes, Grenoble, France

Abstract

Background

The tool CLEO in French language is designed for estimating the potential relevance of pharmacists' interventions (PIs) in three independent dimensions with regard to process-related, clinical, economic, and humanistic impact. We aimed to translate CLEO into German ($CLEO_{de}$), to demonstrate its feasibility in daily practice and to validate the German version.

Methods

We initially translated CLEO according to the ISPOR Principles of Good Practice. The potential relevance of PIs performed within a 13-day period of routine clinical pharmacy services of three Swiss hospitals was then estimated with $CLEO_{de}$. Ten clinical pharmacists experienced with $CLEO_{de}$ subsequently completed a 19-item questionnaire to assess user's agreement on appropriateness, acceptability, feasibility, and precision of the tool. To test for interrater and test-retest reliability, each pharmacist evaluated 10 model cases with $CLEO_{de}$.

Results

$CLEO_{de}$ was used to estimate the potential relevance of 324 PIs. The reported time needed to complete a single estimation was less than one minute. The use of $CLEO_{de}$ was seen as appropriate, acceptable, feasible, and precise. Interrater reliability was good for the clinical and economic dimensions and was poor for the organisational dimension; test-retest correlation was strong for all three dimensions with excellent to fair reliability.

Conclusion

We present $CLEO_{de}$ as a validated tool in German language suitable to estimate the potential relevance of PIs. After further refinement of the organisational dimension, $CLEO_{de}$ could provide a qualitative value to quantitative information on PIs.

Background

A drug-related problem (DRP) is defined as “an event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care [1].” DRPs are multidimensional in that they may be preventable or not; potential or actual; and be caused by a medication error, by a deviation from current guidelines, or by an unpredictable reaction to an appropriate pharmacological treatment [2]. DRPs are frequent in hospitalised patients [3]. Approximately 5% of all drug applications in hospitals are medication errors that may lead to DRPs [3]. These occur during drug prescription, dispensing, or administration. Due to the high number of drug applications on medical wards, medication errors are expected to affect most hospitalised patients. Approximately 6% of all hospitalised patients experience an adverse drug reaction, which is judged to be preventable in 59% of the cases, suspecting medication errors as underlying reason [3].

A pharmacist’s task in a health care team is to promote drug therapies that are appropriately indicated, effective, and safe [4], hence averting medication errors and consequentially preventing adverse drug reactions. In this role, pharmacists are engaged in interprofessional collaborations with other health care professionals to improve health outcomes to the optimum of medical care for patients [5]. Pharmacists’ interventions (PIs), defined as discrete activities by pharmacists related to patient care [6], are shown to improve health outcomes when carried out on ward rounds, in patient interviews, medication reconciliation, and patient counselling [7]. However, pharmacists often fail to take responsibility for their interventions and tend to not adequately document, monitor, and review their services [4]. In Switzerland, the Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA) promotes the use of the GSASA classification system [8] for clinical pharmacists to appropriately report their identified DRPs and proposed PIs. This system classifies DRPs in five categories: problem (5 subcategories), type of problem (2 subcategories), cause of intervention (18 subcategories), intervention (11 subcategories), and outcome of intervention (5 subcategories).

Such classification of DRPs and their corresponding intervention ensures that the services of clinical pharmacists are adequately documented, but fails to report their impact. Data on the relevance of PIs is necessary to publicise the value pharmacists add to health care [9]. There are three distinct approaches to

assess the relevance of PIs: 1) The evaluation of actual consequences of an unresolved DRP; 2) The evaluation of actual consequences of a resolved DRP by follow-up; or 3) The estimation of potential relevance of a PI or the estimation of possible risk of a DRP for the patient [10]. The assessment of actual clinical outcomes (approaches 1 and 2) is often hindered by difficulties in follow-up, lack of resources, or the determination of causality. The estimation of potential relevance of PIs (approach 3) does not suffer from these drawbacks, but is prone to issues on subjectivity, reliability, and validity. To address some of these issues, expert panels could be consulted to report on the potential relevance of the PIs being investigated [11-13], which is a resource intensive method only feasible in study settings.

Vo et al. [10] identified and reviewed 46 tools that estimate the potential relevance of PIs. They concluded that the majority of tools primarily focus on the clinical aspect of PIs and fail to evaluate their potential relevance more comprehensively, such as when information to other health care professionals is provided. As stated, DRPs may be multidimensional, and the PIs provided to resolve them will follow this structure. Vo and colleagues developed a new tool named CLEO to estimate the potential relevance of PIs within its three dimensions CLinical, Economic, and Organisational. The clinical dimension focuses on impact related to the patient's well-being from the patient's perspective: Averted damages, improved quality of life, and improved adherence. The economic dimension assesses the immediate impact of the PI on the current costs of therapy from the institution's perspective. The organisational dimension evaluates the impact on the process of care, focusing on the view of the health care professionals: reduced time expenditures, decreased work load, improved work place safety, and simplified collaborations. The French version of CLEO has since been validated within the hospital setting [14].

Aim of the study

Our aims were 1) to translate the French version of CLEO into German (termed $CLEO_{de}$); 2) to demonstrate feasibility in daily practice; 3) and to validate the German version.

Methods

Translation

We asked the original developers of CLEO for permission to translate their work. The translation into German was performed according to the ten steps of the ISPOR Principles of Good Practice for the Translation and Cultural Adaption Process for Patient-Reported Outcome Measures [15]. Two independent translators with knowledge of pharmaceutical terminology simultaneously translated the original French version with focus on equality of sense/analogous meaning. We merged the two translations into a single German version with the aid of one of the translators. Discrepancies were discussed in a reconciliation meeting to ensure that semantic and conceptual equivalence between source and target language versions was achieved. We sought the second translator's approval for all changes made. Back-translation from German into French was done by a third translator unfamiliar with the original version with focus on equality of words. We sought agreement on the back-translated version from the developers of the original tool. The adapted target language version was sent to six native German-speaking and experienced clinical pharmacists, each two from Austria, Germany, and Switzerland for cognitive debriefing using a modified evaluation sheet of Breuer et al. [16]. We asked for their ratings (Likert scale; 1: poor, 6: very good) on each item of the tool with regard to comprehensiveness and linguistic style using an online questionnaire form (Flexiform© version 2.7.1g, IT-services University of Basel). The threshold of acceptance was pre-defined to sufficient (4) for the standard deviations. All suggestions in the comments section were evaluated after categorisation into technical (orthographic, grammatical and stylistic remarks), conceptual (substantial discrepancies), and questions/uncertainties. We added a final back-translation as an 11th step to the ISPOR Principles of Good Practice for agreement with the original developers to possible changes due to feedback from the cognitive debriefing.

Validation

We validated the $CLEO_{de}$ version according to Fitzpatrick's criteria [17] appropriateness, acceptability, feasibility, interpretability, precision, and reliability. We did not test for the remaining two criteria responsiveness and validity as the tool does not measure changes in health status and validity was already tested for the original French version. The validation process is visualised in Figure 1.

	Part 1: Translation	**Part 2**: Validation		
		Interpretability	Appropriateness, Acceptability, Precision, Feasability	Interrater reliability, test-retest reliability
Methods	ISPOR Principles of Good Practice for the Translation and Cultural Adaption Process for Patient Reported Outcome Measures	Performed pharmacists' interventions during 13 days in three Swiss hospitals Classification with GSASA Evaluation with $CLEO_{de}$	User's agreement - 10 clinical pharmacists - 19-items questionnaire - 7-point Likert scale	10 model cases 10 clinical pharmacists Wash-out: 7 days

Figure 1 Translation and validation process.

Data collection and interpretability

We asked for a convenience sample of three Swiss hospitals (capacities of 679, 337, and 290 beds) to collect performed PIs during routine clinical pharmacy services. All PIs were classified with the GSASA classification system [8] according to common practice in these hospitals. Additionally, the participating clinical pharmacists estimated the potential relevance of their PIs with $CLEO_{de}$, which was integrated into their own electronic adaption of the GSASA classification system (either Microsoft® Excel® spreadsheet or Microsoft® Access® database). Training prior to data collection consisted of written instructions on the use of $CLEO_{de}$ and two instructional videos including general information and two model cases. To demonstrate interpretability and future applications, we performed descriptive statistics on the data set obtained.

Appropriateness, acceptability, feasibility, and precision

In a second step of the validation, we tested for appropriateness, acceptability, feasibility, and precision of $CLEO_{de}$ with an adapted questionnaire of AbuRuz et al. [18], which has been used in earlier studies [8, 19]. The questionnaire was sent as an online form to the clinical pharmacists who had been involved in the 13-day data collection. The questionnaire consisted of 19 items with a 7-point Likert scale to assess the extent of their agreement (1: entirely disagree, 4: neutral, 7: entirely agree).

Reliability

The clinical pharmacists previously involved in data collection classified 10 model cases and estimated the potential relevance of the PIs described with $CLEO_{de}$ (see Box 1 for an example). The model cases consisted of five validated cases from literature [20] which have been used previously [8], and five descriptive cases

from the validation studies of the original French version of CLEO. Drug names and therapy costs were adapted to the local situation. All clinical pharmacists received the model cases in a randomized order. We distributed the link to an online questionnaire form with restricted access via e-mail for data collection (Flexiform©). There was a wash-out phase of seven days prior to the test-retest reliability evaluation.

> «Mrs. A., 81 years, 167 cm, 59 kg is hospitalised because of her derailed Diabetes mellitus type 2. Due to an episode of depression, she is treated with Seropram (Citalopram) 20 mg tablets 0-0-1 (Fr. 1.10 / day). Since her arrival, Mrs. A. complains about insomnia. You ask her why the drug was prescribed to be taken in the evening. There was no plausible reason for the evening dose. Therefore, you propose a morning dose. Your intervention will be implemented.»

Box 1 Example of a model case used to assess interrater and test-retest reliability.

We used a two-way mixed, agreement, single-measures intra-class correlation ($ICC_{A,1}$) to assess the inter-rater reliability of each dimension [21]. For reasons of comparability to other studies, we additionally calculated weighted (squared) Kappa values (κ_w) [22] of each rater pair, reporting the arithmetic mean as proposed for multiple rater [23]. To assess test-retest reliability, we compared both ratings of each rater individually and calculated $ICC_{A,1}$ means ($\overline{ICC}_{A,1}$) and Spearman's rank correlation coefficient means ($\bar{\rho}$) [24]. We performed all calculations using RStudio [25] (version 0.99.903) running R version 3.3.1 [26] with the package irr [27] (version 0.84). We interpreted the $ICC_{A,1}$ and $\overline{ICC}_{A,1}$ results according to Cicchetti [28]: $ICC_{A,1}$ < .40 as poor, .40 to .59 as fair, .60 to .74 as good, and .75 to 1.0 as excellent. κ_w were interpreted according to Landis and Koch [29]: κ_w .00 to .20 as slight agreement, .21 to .40 as fair agreement, .41 to .60 as moderate agreement, .61 to .80 as substantial agreement, and .81 to 1.00 as almost perfect or perfect agreement. $\bar{\rho}$ values were interpreted as follows: $\bar{\rho}$ = .1 as weak, .3 as intermediate, and .5 as strong.

Ethics

According to the requirements of the Swiss federal law on human research this study did not need an ethics approval.

Results

Translation

We received permission from the original developers to translate the CLEO tool into German. The translation process was completed within 10 weeks and produced 10 different German versions. The two initial independent forward translations had 20 linguistic discrepancies between each other which were resolved at the reconciliation meeting with one of the translators. We received approval for the merged version by the second translator. The original developers identified two discrepancies in our back-translated version when compared with their original version. Additionally, the developers proposed the use a slightly modified version of the definition of the organisational dimension, which was introduced into the original tool after the start of our translation process. We were able to address the discrepancies and to introduce the new definition as part of the back-translation review process. For the cognitive debriefing, we received responses from five of six clinical pharmacy experts (Austria: 1, Germany: 2, Switzerland: 2). The means of each of the 21 items were at least sufficient (4) for both, linguistic style and comprehensiveness. The standard deviations of 11 items exceeded our threshold of sufficient (4) in comprehensiveness or linguistic style. We reviewed all 11 items and changed 12 words according to the suggestions in the comments section of the questionnaire. The changes focused on the cultural adaption process (e.g., “Medikamententreue” was changed to “Therapietreue [Adhärenz]”). The five clinical pharmacists provided 60 suggestions, which were categorised into technical (n = 23), conceptual (n = 19), and questions/uncertainties (n = 18). Proofreading of the final version resulted in one last change of wording in the organisational dimension. Our final back-translated version was accepted by the original developers. The finalised German version $CLEO_{de}$ is shown in Figure 2.

Evaluation der Auswirkung einer pharmazeutischen Intervention (PI) durch die CLEO$_{de}$ Skala

Klinische Auswirkung

Grundsatz: Die klinische Auswirkung wird nach einem wahrscheinlichem Szenario und nicht nach schlimmstem/bestem Szenario bewertet.
Die klinische Auswirkung wird aus Sicht des Patienten bewertet

Erläuterung:
Schaden: Körperlicher Schaden - Beeinträchtigung der physischen und/oder psychischen Fähigkeiten des Patienten.
Lebensqualität: Physische Aspekte (Autonomie, körperliche Fähigkeiten, Fähigkeit tägliche Aufgaben zu erledigen, etc.), psychologische Aspekte (Ängste, Depression, Emotionalität, etc.), soziale Aspekte (bezogen auf das familiäre oder professionelle Umfeld, Freundeskreis, Pflege persönlicher Beziehungen, Teilnahme an Sozial- und Freizeitaktivitäten, etc.) und somatische Aspekte (Symptome der Krankheit).
Überwachung: Nachkontrollen, labormedizinische Kontrollen.
Behandlung: Änderung der Therapie oder zusätzliche medizinische/chirurgische Behandlung.

Score	Auswirkung	Definition
-1C	schädlich/ negativ	Die pharmazeutische Intervention (PI) kann zu negativen Ergebnissen hinsichtlich des klinischen Zustandes, des Wissenstandes, der Zufriedenheit, der Therapietreue (Adhärenz) und/oder der Lebensqualität des Patienten führen.
0C	ohne	Die PI hat keine Auswirkung auf den Patienten hinsichtlich des klinischen Zustandes, des Wissenstandes, der Zufriedenheit, der Therapietreue (Adhärenz) und/oder der Lebensqualität des Patienten.
1C	gering	Die PI kann den Wissensstand, die Zufriedenheit, die Therapietreue (Adhärenz) und/oder die Lebensqualität des Patienten verbessern. ODER Die PI kann einen Schaden beim Patienten verhindern, der keine Überwachung/Behandlung erfordert.
2C	mittel	Die PI kann einen Schaden beim Patienten verhindern, der eine Überwachung oder Behandlung erfordert, aber keine Hospitalisierung herbeiführt oder einen bestehenden Spitalaufenthalt verlängert.
3C	erheblich	Die PI kann einen Schaden verhindern, welcher einen Spitalaufenthalt des Patienten verursacht oder verlängert. ODER Die PI kann einen Schaden beim Patienten verhindern, der eine dauerhafte Invalidität oder Beeinträchtigung verursacht.
4C	lebensnotwendig	Die PI kann einen Schaden beim Patienten verhindern, der eine intensiv-medizinische Behandlung nach sich zieht oder zum Tod des Patienten führt.
NB	nicht beurteilbar	Die verfügbaren Informationen erlauben es nicht, die klinische Auswirkung zu beurteilen.

Wirtschaftliche Auswirkung

Grundsatz: Die Kosten der medikamentösen Behandlung beziehen sich auf die finanziellen Kosten des Krankenhauses.

Erläuterung:
Die Kosten der **medikamentösen Behandlung** beinhalten zwei prinzipielle Aspekte:
- Arzneimittelkosten
- Die Kosten der Überwachung der medikamentösen Behandlung (z.B. Folgeuntersuchungen, Labor, etc)

Score	Auswirkung	Definition
-1E	höhere Kosten	Die PI erhöht die Kosten der medikamentösen Behandlung des Patienten.
0E	keine Veränderung	Die PI verändert die Kosten der medikamentösen Behandlung nicht.
1E	geringere Kosten	Die PI reduziert Kosten bei der medikamentösen Behandlung des Patienten.
NB	nicht beurteilbar	Die verfügbaren Informationen erlauben es nicht, die wirtschaftliche Auswirkung zu beurteilen.

Organisatorische Auswirkung

Grundsatz: Die organisatorische Auswirkung beschreibt den Einfluss auf die Qualität des Behandlungsprozesses aus Sicht des medizinischen Personals.

Erläuterung:
Folgende **Aspekte** sind insbesondere zu berücksichtigen:
- Zeitersparnis
- Vereinfachung der professionellen Tätigkeit
- Erhöhte Sicherheit für das Personal
- Verbesserte Kenntnisse
- Vereinfachte Zusammenarbeit
- Kontinuität der Behandlung

Score	Auswirkung	Definition
-1O	verringert	Die PI reduziert die Qualität des Behandlungsprozesses.
0O	ohne	Die PI hat keinen Einfluss auf die Qualität des Behandlungsprozesses.
1O	erhöht	Die PI erhöht die Qualität des Behandlungsprozesses.
NB	nicht beurteilbar	Die verfügbaren Informationen erlauben es nicht, die organisatorische Auswirkung zu beurteilen.

Figure 2 CLEO$_{de}$

Validation

Data collection, interpretability

$CLEO_{de}$ was used for 13 working days within routine clinical pharmacy practice in April and May 2016 in three Swiss hospitals. A total of 324 PIs were performed by ten clinical pharmacists. They were classified with the GSASA classification tool and evaluated with $CLEO_{de}$. Twenty-one PIs (6.5%) were evaluated as 'not determined' in all three dimensions. Frequencies of all PI evaluations by $CLEO_{de}$ are presented in Figure 3. Most PIs (n = 138, 42.7%) were evaluated to have a minor clinical relevance (starting/restarting or stopping a therapy, 37.0%; dose adjustment, 21.7%; optimisation of dosing modalities, 15.2%; substitution/replacement, 9.4%; others, 16.7%), whereas 9.9% were evaluated to have a major or vital clinical relevance. PIs which were evaluated to decrease costs (n = 116, 36.0%) were classified as stopping a therapy (44.0%), dose adjustment (25.9%), substitution/replacement (10.3%), optimisation of dosing modalities (7.8%), or others (12.1%). Almost half of the PIs that were evaluated to increase costs (n = 66, 20.5%) were starting/restarting a therapy (48.5%), followed by therapy monitoring (15.0%), dose adjustment (12.2 %), information to health care professionals (10.6%), and others (13.6%). The PIs were judged to have a positive (39.4%), a negative (16.0%) or no relevance (35.7%) within the organisational dimension of $CLEO_{de}$. The underlying interventions were present in all three levels of the organisational dimension. Examples of PIs for all possible evaluations with $CLEO_{de}$ are presented in Table 1.

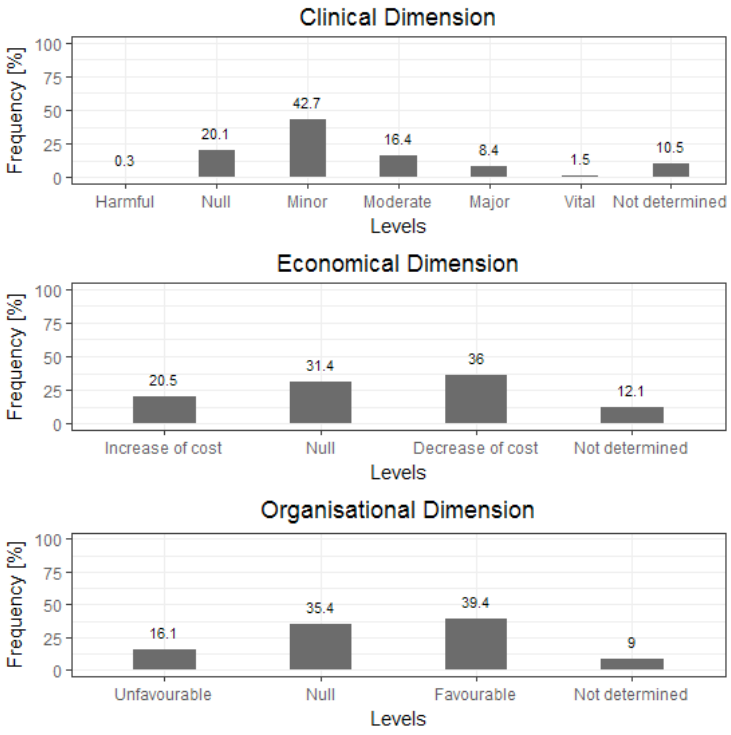


Figure 3 Estimated potential relevance of pharmacists' interventions during 13 days in three Swiss German hospitals, sorted according to the dimensions of CLEO$_{de}$ (n = 324).

Table 1 Examples of PIs documented with the GSASA classification and evaluated with CLEO$_{de}$.

Description	GSASA Problem	GSASA Reason	GSASA Intervention	CLEO$_{de}$ Clinical	CLEO$_{de}$ Economic	CLEO$_{de}$ Organisational
Anticoagulation is currently paused because patient is awaiting pericard puction. Preventive therapy with heparin is recommended for short hospital leave	Untreated indication	Treatment not received	Therapy started/restarted	Major	Increase of cost	Favourable
Information to the health care team: SGLT2-inhibitors may cause urinary tract infections	Safety of treatment	Adverse effect	Information to care givers	Null	Null	Favourable
Amlodipin 5 mg twice a day replaced with 10 mg once a day	Patient dissatisfaction	Inappropriate timing or frequency of administration	Optimisation of administration	Minor	Decrease of cost	Favourable
Taking of thyroid hormone changed to 30 minutes before a meal	Treatment effectiveness	Inappropriate timing or frequency of administration	Optimisation of administration	Medium	Null	Unfavourable
Treatment of atrial fibrilation has been forgotten when the patient changed wards	Untreated indication	Treatment not received	Therapy started/restarted	Vital	Increase of cost	Favourable
Metamizol prescribed twice as reserve in case of pain	Safety of treatment	Drug not indicated or duplication	Clarification in the case notes	Not determined	Not determined	Not determined
Pharmacist proposed alternative first-line treatment for hypertension (currently: Beta-blocker). Patient informed care providers about his history of tachycardia	Safety of treatment	No concordance with guidelines or contraindication	Substitution	Harmful	Null	Null

Appropriateness, acceptability, feasibility, and precision

All ten clinical pharmacists completed our 19-items questionnaire on user's agreement. $CLEO_{de}$ was seen as appropriate (mean = 5.45; SD = 0.76), acceptable (4.43; 1.28), feasible (5.27; 1.44), and precise (5.90; 1.16) to evaluate the potential relevance of PIs. One item received a mean rating of below neutral (3.70; 1.3): Six out of ten clinical pharmacists stated that they had issues to estimate the potential relevance of PIs with $CLEO_{de}$. The results are reported in Figure 4. Five clinical pharmacists reported an evaluation time of 'less than 30 seconds' per PI; none reported an evaluation time of 'more than one minute'.

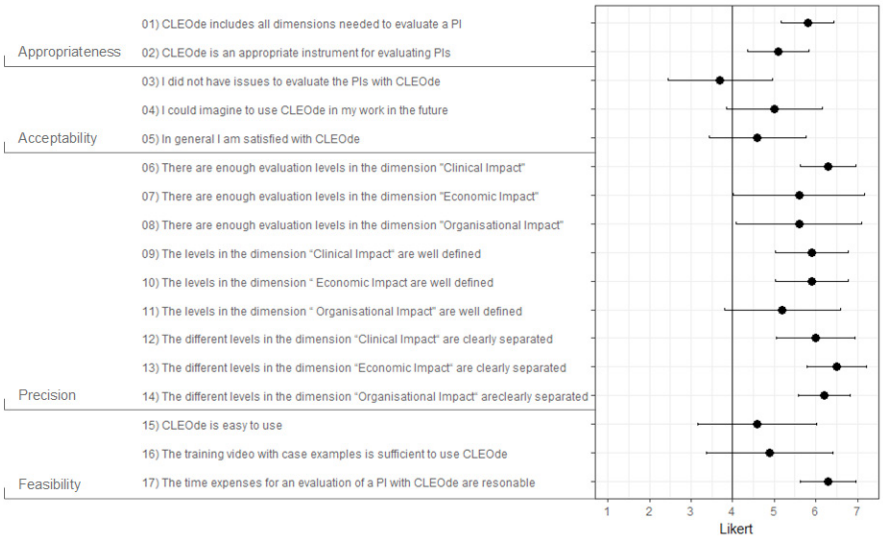


Figure 4 User's agreement on appropriateness, acceptability, precision, and feasibility of the tool. 7-point Likert scale; 1: entirely disagree, 4: neutral, 7: entirely agree (mean ± SD).

Reliability

Each of the ten clinical pharmacists classified all ten model cases and estimated the potential relevance of the PIs twice with a washout phase of seven days in between. Clinical experience of the participating pharmacists ranged from < 6 months (n = 3) to > 5 years (n = 1); the median was one year of clinical experience.

The interrater reliability for $CLEO_{de}$ was good for the dimensions clinical (intra-class correlation $ICC_{A,1}$ = .63) and economic ($ICC_{A,1}$ = .65) and poor for organisational ($ICC_{A,1}$ = .30). Mean weighted Kappa values obtained were: Substantial for the dimensions clinical (mean weighted Kappa $\bar{\kappa}_w$ = .62) and economic ($\bar{\kappa}_w$ = .61), fair for organisational ($\bar{\kappa}_w$ = .23). Test-retest correlation was strong for all three dimensions (clinical: mean Spearman's rank correlation coefficient $\bar{\rho}$ = .77; economic: $\bar{\rho}$ = .85; organisational: $\bar{\rho}$ = .58), yielding in

excellent test-retest reliability for the dimensions clinical (mean intra-class correlation $\overline{ICC}_{A,1}$ = .76) and economic ($\overline{ICC}_{A,1}$ = .85) and fair for organisational ($\overline{ICC}_{A,1}$ = .53).

Discussion

We successfully translated the French evaluation system for PIs CLEO into German by following the ten steps of the ISPOR Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes Measurement. In a time period of 13 days we collected 324 PIs routinely performed by 10 clinical pharmacists at three Swiss hospitals. The participating pharmacists classified their PIs with the GSASA classification system and estimated the potential relevance with $CLEO_{de}$.

Data collection, interpretability

The 324 PIs were estimated to mainly (42.7%) have a minor clinical relevance. This low level of clinical relevance describes improvements in humanistic outcomes (better knowledge, satisfaction, adherence, quality of life) or avoided potential physical or psychological damages which would not require additional surveillance or treatments. The clinical pharmacists may have evaluated their PI as minor instead of the next higher level (i.e. moderate) because the (laboratory) measurements were routinely planned and easily feasible in the hospital setting anyway, skewing the data on clinical relevance. The levels ‘moderate’, ‘major’ and ‘vital’ all describe the avoidance of potential damages, which at least need an additional test or treatment to be resolved, i.e., they describe actions needed to be taken to prevent patient harm. Levels moderate to vital combined amounted to 26.3% of all 324 evaluated PIs. Dean et al. [13] collected data on 538 prescribing errors identified by clinical pharmacists within four weeks, and similarly detected 26% (n=142) potentially serious errors (“likely to cause patient harm”) rated by one researcher and one clinical pharmacologist.

The allocation of PIs that were evaluated to increase (20.5%) or decrease (36.0%) the costs corresponds to the categorisation of the proposed PI: Approximately 76% of the PIs evaluated as cost-raising were categorised as starts or restarts of therapies, dose increases, or recommended therapy monitoring, all of which generate immediate costs; Approximately 80% of the PIs evaluated as cost-lowering were categorised as termination of therapies, dose decreases, or substitutions, all of which decrease the immediate costs. This congruence of evaluation and categorisation of PIs suggests validity of the economic dimension. Furthermore, the proportion of PIs evaluated to decrease the costs (36.0%) is consistent with a peer-review team’s evaluation on the

economic relevance of 1027 PIs who indicated the interventions as improvement of cost in 41.7% of the cases [30]. In contrast to CLEO, they also took avoidable costs due to toxic effects and reduction of days spent in hospital as savings into account. With the use of $CLEO_{de}$ in common clinical practice, regular reviewing of the cost generating interventions might help to identify potentially unnecessary recommendations and save costs.

The evaluation of the organisational impact was inconsistent: The ten clinical pharmacists rated the same interventions (e.g. 'starting/restarting a therapy', 'terminating a therapy'' substitution/replacement') as having a positive, having a negative, or having no impact on organisational aspects, thus preventing a clear interpretation of the findings. The evaluation of the organisational impact hence seems heavily dependent on the point of view: The same intervention may cause additional work load for nurses, but improves the indicator 'workplace safety'. The current version of CLEO leaves the decision up to the rater on which indicators they focus to estimate the organisational impact of their PI.

In our study, only 21 PIs (6.5%) were evaluated as 'not determined' in all three dimensions, confirming appropriateness of $CLEO_{de}$. As these 21 PIs were heterogeneous in their underlying DRP, we were not able to define a certain intervention as not determinable by $CLEO_{de}$.

Appropriateness, acceptability, feasibility, and precision

Clinical pharmacists familiar with the tool rated $CLEO_{de}$ as appropriate, acceptable, feasible, and precise. In addition, they reported 'less than one minute' needed for the estimation of the potential relevance of one PI. As time expenditure is an essential element for the acceptance of a new tool, this result removes a hurdle for future implementation. However, the standard deviations on individual questions in the evaluation exceeding 4 on the Likert scale (see Figure 4) highlight issues that need to be addressed prior to implementation: These evaluation issues, especially within the organisational dimension, were reported by the users in the comments section and affected user satisfaction. Each clinical pharmacy team may discuss their most common PIs and agree on a uniform evaluation for all three dimensions. With guidance established by using typical examples from daily practice, a greater degree of consistency could be achieved. Some clinical pharmacists also stated that the training video with two sample cases was insufficient as preparation. We suggest an intensified training process addressing the identified issues.

Reliability

$CLEO_{de}$ achieved good ($ICC_{A,1}$) and substantial ($\bar{\kappa}_w$) interrater and excellent ($\overline{ICC}_{A,1}$) test-retest reliability for the dimensions clinical and economic in a sample of 10 selected clinical pharmacists, working in three different hospitals and having different levels of clinical experience. The obtained interrater reliabilities (weighted Kappa) are in line with the results of Vo and colleagues: They reported moderate (clinical), substantial (economic) and fair (organisational) interrater reliability between a sample of pharmacists working at a centralised chemotherapy preparation unit and peer reviewing pharmacists [14].

The interrater reliability can only be compared to few other tools and only for the clinical dimension of $CLEO_{de}$ because the majority of published tools primarily focus on the clinical aspect of PIs [10]. Interrater reliability data from specifically tools designed for the estimation of potential relevance of a PI are sparse. Rupp reported a Kappa (κ) value of .68 for a four item questionnaire which assesses the potential for patient harm [31]. Chua and colleagues used Stubbs' four categories of clinical significance [32] in their study and calculated a Kappa (κ) value of .73 [33]. Similar to the clinical dimension of $CLEO_{de}$, both of these values may be interpreted as substantial according to Landis and Koch [29]. A high degree of reliability is a key factor when considering a specific tool for the estimation of the potential relevance of a PI [10]. This aim is met for CLEO and $CLEO_{de}$ for the clinical and economic dimensions, similar to the above mentioned tools.

Similar to the interpretability and user's agreement results, we identified issues in the reliability of the organisational relevance evaluation: This dimension achieved poor ($ICC_{A,1}$) and fair ($\bar{\kappa}_w$) interrater and fair ($\overline{ICC}_{A,1}$) test-retest reliability. These issues have already been identified for the French version of CLEO: Vo et al. [14] reported fair interrater reliability. Our results again highlight the necessity to facilitate the evaluation in this dimension by reducing the number of indicators to choose from and by intensifying the training process, as proposed above. It may be argued that in contrast to the other two dimensions, clinical pharmacists might not be familiar with judging their PIs from the perspective of the process of care. When proposing a PI, they may not account for/focus on the impact on time expenditure, work load, work place safety, and collaborations. Combined with the many organisational indicators to choose from in this dimension, the evaluation of the organisational impact with CLEO becomes difficult.

Clinical implications

We defined PIs as discrete activities by pharmacists related to patient care. These activities and their underlying causes should be documented for the development of pharmaceutical care practice and for future research [34]. $CLEO_{de}$ is a reliable and user-friendly approach to the estimation of the potential relevance of PIs whilst respecting the multidimensionality and diversity of the service. With less than one minute per PI evaluation, $CLEO_{de}$ is suitable for implementation in daily practice. Evaluated PIs will help in generating and ameliorating clinical services, decreasing costs, identifying current issues in medication safety, and portraying the relevance of clinical pharmacy services.

Strengths and limitations

The strengths of the work presented here lie in the structured methodological approach of the translation process and the consecutive validation of the translated version: We minimised the risk of mistranslating or inserting our own interpretations by closely following the steps of the ISPOR Principles [15]. Cognitive debriefing with native speaking clinical pharmacy experts from all three German speaking countries ensures comprehensibility and correct linguistic style for the targeted users. We tested for appropriateness, acceptability, feasibility, interpretability, precision, and reliability, covering all criteria which might be influenced by the quality of a translation. Each of the tests presented its own value by either confirming previously identified issues or highlighting new aspects to consider. Simultaneously we were able to demonstrate feasibility for implementation and possibilities for evaluation in daily routine clinical pharmacy services.

One limitation of this study is that only ten clinical pharmacists were involved in the validation process of $CLEO_{de}$, of which five had a clinical working experience of less than one year. This imposes selection bias that potentially affected our data collection and our assessment of Fitzpatrick's criteria. However, the composition of clinical pharmacists represents the current situation in the involved hospitals, i.e., Junior clinical pharmacists are responsible for the documentation of PIs which were previously discussed with their experienced supervisors.

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Conclusion

We present $CLEO_{de}$ as a correctly translated and culturally adapted tool, validated with regard to reported acceptability, appropriateness, feasibility, and precision, as well as interpretability and reliability. $CLEO_{de}$ is a promising tool for both, research and practice, which may in combination with existing classification systems for drug-related problems add qualitative value to quantitative information on PIs. With less than one minute per evaluated PI, $CLEO_{de}$ enables quick grading of data collection on interventions and allows reviewing pharmacy services.

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II. Drug Associated Risk Tool – Development and Validation of a Self-Assessment Questionnaire to Screen for Hospitalised Patients at Risk for Drug-Related Problems

In this joint first-authorship article we describe the development of the DART from items deemed to be associated with a higher risk of DRPs into a patient-completed questionnaire. The questionnaire was assessed by Dr. Carole Kaufmann regarding feasibility, acceptability, and the ability of the patients to reproduce medical information in reference to medical charts.

Items with an unsatisfactory performance regarding patient understanding were re-worded as part of this thesis. The revised items included disease descriptions from Swiss patient information leaflets. These patient information leaflets are contained in the official packages of the medicines and are bound by Swiss legal requirements concerning readability and understandability, as they directly address the patients. This approach ensured the use of wording that patients should be most familiar with. The thesis re-checked the ability of the patients to reproduce the presence of a certain disease in reference to their medical charts, this time focusing on patients presenting with one or more of the re-worded diseases.

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Drug-Associated Risk Tool: development and validation of a self-assessment questionnaire to screen for hospitalised patients at risk for drug-related problems

Carole P Kaufmann,[1] Dominik Stämpfli,[1] Nadine Mory,[1] Kurt E Hersberger,[1] Markus L Lampert[1,2]

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CPK and DS contributed equally.

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[1]Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland
[2]Institute of Hospital Pharmacy, Solothurner Spitäler, Olten, Switzerland

Correspondence to
Dr Markus L Lampert;
markus.lampert@unibas.ch

ABSTRACT

Introduction Identifying patients with a high risk for drug-related problems (DRPs) might optimise the allocation of targeted pharmaceutical care during the hospital stay and on discharge.

Objective 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 Prospective validation study.

Setting Two mid-sized hospitals (300–400 beds).

Participants 195 patients, exclusion criteria: under 18 years old, patients with a health status not allowing a meaningful communication (eg, delirium, acute psychosis, advanced dementia, aphasia, clouded consciousness state), palliative or terminally ill patients.

Methods Twenty-seven risk factors for the development of DRPs, identified in a previous study, provided the basis of the self-assessment questionnaire, the Drug-Associated Risk Tool (DART). Consenting patients filled in DART, and we compared their answers with objective patient data from medical records and laboratory data.

Results One hundred and sixty-four patients filled in DART V.1.0 in an average time of 7 min. After a first validation, we identified statements with a low sensitivity and revised the wording of the questions related to heart insufficiency, renal impairment or liver impairment. The revised DART (V.2.0) was validated in 31 patients presenting heart insufficiency, renal impairment or liver impairment as comorbidity and reached an average specificity of 88% (range 27–100) and an average sensitivity of 67% (range 21–100).

Conclusions DART showed a satisfying feasibility and reliability. The specificity of the statements was mostly high. The sensitivity varied and was higher in statements concerning diseases that require regular disease control and attention to self-care and drug management. Asking patients about their conditions, medications and related problems can facilitate getting a first, broad picture of the risk for DRPs and possible pharmaceutical needs.

Strengths and limitations of this study

- ► The Drug-Associated Risk Tool (DART) is a patient self-assessment risk screening tool, based on a selection of risk factors for the development of drug-related problems (DRPs), previously identified in a combination of literature search and the opinion of a multidisciplinary expert panel.
- ► DART should enable clinical pharmacists to identify patients at risk for DRPs and target their clinical pharmacy activities to patients who benefit the most thereof.
- ► A first validation of DART showed good acceptability and feasibility and a satisfactory reliability of patient's answers.
- ► The low prevalence of some risk factors hinders clear conclusions about the validity of the respective statements in DART.

INTRODUCTION

Drug-related problems (DRPs) are defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.[1] The term 'DRPs' has mostly taken hold in European countries where English is not the native language, while pharmacists in the USA tend to use the term 'medicine-related problems' or 'drug-therapy problems' instead of DRPs.[2] DRPs are a frequent issue among hospitalised patients, leading to patient harm and increased healthcare costs.[3] Many unplanned admissions are medication related[4] and a considerable number could be prevented.[5] Complexity and often poorly designed processes foster the development of DRPs inside and outside of the hospital. Unsurprisingly, a remarkable number of patients experience adverse drug events after discharge.[6] 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.[7]

Clinical pharmacy services in hospitals have been shown to increase patient safety by reducing medication errors and adverse drug events, as well as adverse drug reactions. They increase medication appropriateness, improve patients' knowledge about drug therapy and adherence, and finally reduce the length of hospital stays.[8] 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 patients who are at the highest risk of experiencing DRPs, and in consequence, adverse drug events. An effective screening tool to identify high-risk patients might prove a successful approach. The literature provides risk factors for the development of DRPs such as polypharmacy, renal impairment or the use of non-steroidal anti-inflammatory drugs .[4 9 10] The literature is replete with assessment tools, which focus on various combinations of risk factors for DRPs. They may be created either for a specific group of patients (eg, those with renal impairment,[11] geriatric patients,[12–16] patients with prescribed medication for cardiovascular disease[17]) or for a special environment (eg, in an emergency department,[18] primary care[19 20]). The tools may also need special resources to be applied in the hospital (eg, computerised patient files[21]). Screening tools often have the disadvantage of being time and personnel intensive; some are hardly applicable without electronic data. Many have not been validated.[22]

Therefore, we decided to develop a new risk assessment tool. The 'Drug-Associated Risk Tool (DART)' should serve as a reliable, easy-to-use screening instrument to detect patients at risk for DRPs. Developed as a self-assessment questionnaire for the patients, DART should save personnel resources and time.

In a previous study,[23] we identified 27 risk factors for the development of DRPs, which provided the basis of the self-assessment questionnaire. Risk factors identified in relevant literature were supplemented with results from qualitative research methods: We conducted a Nominal Group Technique with practitioners to ensure relevance in everyday practice and to identify risk factors possibly neglected in quantitative research methods.

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 comparing them to reference information retrieved from medical charts.

METHODS

Development of the questionnaire

Figure 1 shows the development process of the questionnaire.

Twenty-seven risk factors for the development of DRPs, identified in a previous study,[23] provided the basis of the self-assessment questionnaire, DART. With the intention of creating a questionnaire for patients, we formulated a statement for each risk factor that could be answered by medical laypersons (cf. table 1).

We covered the risk factor 'non-adherence' with an adapted question retrieved from the adherence risk prediction tool of Krousel-Wood,[24] a validated self-report 4-item questionnaire used to measure adherence. A validated self-report four-item questionnaire used to measure adherence. Risk factors with regard to patients' concerns about medicines were covered by using five questions from the Beliefs about Medicines Questionnaire (BMQ),[25] a questionnaire that comprises 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 10 medical laypersons from the personal environment of the authors (no patients) to fill out DART. We did not provide any support during its completion. We asked the participants for their judgement concerning the comprehensibility of the statements and edited issues that arose within the statements. In cases of ambiguity, the study investigators (CPK, MLL, NM, DS) discussed and clarified the unclear statements.

Validation of the questionnaire

Study design and setting

For the prospective validation study, we recruited patients in two mid-sized hospitals with 300–400 beds each. We recruited on orthopaedic, geriatric and internal

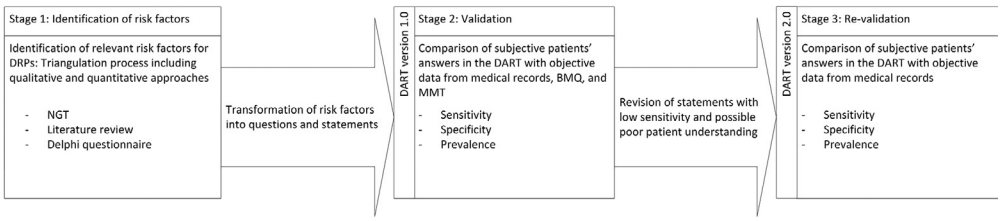


Figure 1 Development process of the questionnaire. BMQ, Beliefs about Medicines Questionnaire; DART, Drug-Associated Risk Tool; DRP, drug-related problem; MMT, Micro-Mental Test; NGT, nominal group technique.

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

Risk factor	Corresponding statement in DART	Acceptance criteria for correlation
Language issues (eg, migration background)	1	No comparison with objective data
Polymorbidity: divided in subcategories		
Renal impairment	2	Diagnosis of renal impairment *and*/*or* GFR <60 mL/min for at least 3 months[33]
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[34] *or* <14/20 points in the Micro-Mental Test[26]
The patient takes medication(s) besides the prescribed ones (eg, 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, non-steroidal anti-inflammatory drugs (NSAIDs), combination of NSAIDs 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	No comparison with objective data[24]
Earlier experience of adverse drug reactions	12–16	Negative total score in both—the statements 12–16 *and* the Beliefs about Medicines Questionnaire (BMQ)[25] *or* a positive total score in both—the statements 12–16 *and* the BMQ[25]
Missing information, partial knowledge of the patient, the patient does not understand the goal of the therapy	17	No comparison with objective data
Impaired manual skills—causing handling difficulties	18	No comparison with objective data
Visual impairment/impaired eyesight	18	No comparison with objective data
Difficult to handle medication	19	Medicines for parenteral, transdermal or inhalative application at time of hospital admission

GFR, glomerular filtration rate.

medicine wards in order to validate the questionnaire in very diverse patients.

Patient selection

Eligibility criteria were stationary hospitalisation, age over 18 years and ability to speak German in order to communicate with the investigator. We excluded patients with a health status not allowing a meaningful communication (eg, delirium, acute psychosis, advanced dementia, aphasia, clouded consciousness state) as well as palliative or terminally ill patients. We included patients suffering from mild dementia in case a meaningful communication was possible.

Study flow

During a predefined period, the investigators (CPK, DS, NM) and two additional trained clinical pharmacists met with every hospitalised 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 DART and filled in the questionnaire independently, that is, the investigator gave no assistance in filling in the questionnaire. If a patient had impaired manual skills, the investigator was only allowed to assist with writing. When finished, the investigator asked the patient five questions about the structure and content

of DART in order to see if the questionnaire was easy to understand and not too intrusive. 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 concerns and beliefs towards medicines (BMQ[25]) and mental health (Micro-Mental Test (MMT)[26]). Participation in the study was voluntary, the investigators offered no inducement or payment for subjects to participate. The patient was allowed to terminate the interview at any time without stating a reason.

Pretest

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

Data collection and analysis

All data were processed anonymously. In order to ensure traceability, we assigned each patient a unique identifying number coding for the particular hospital/ward/investigator/patient.

We used IBM SPSS Statistics Software, V.22 for data analysis. We evaluated sensitivity, specificity and prevalence of each question of DART by comparing the subjective answers in DART with objective data from medical records (diagnosis, laboratory values and medicines at entry) and answers from the BMQ[25] and the MMT.[26] Acceptance criteria for correlation of subjective and objective data were defined a priori (cf. table 1). In addition we calculated the negative and positive predictive values for each question in DART. Missing data were excluded from analysis.

Revision of statements

Statements with an unsatisfactory performance within reliability testing of the questionnaire (ie, sensitivity <0.5 and possible poor patient understanding) were revised in their wording. In order to find a terminology patients may be familiar with, we used official patient information leaflets (PILs) of selected drugs, which are either contraindicated or in need of a dose adaptation in presence of the risk factor assessed by the statement under revision. These PILs are contained in the official packages of the medicines, are created by the manufacturer and are bound to the Swiss legal requirements concerning readability and understandability. We extracted and analysed the wording from these PILs which is used to describe the risk factor to patients and phrased new statements. We retested the new statements with the same study flow. In this cycle, we only recruited patients presenting one or more of the risk factors assessed by the statements under revision.

RESULTS

Development of the questionnaire

The first page of DART consists of items concerning the presence of diseases and high-risk medicines. The second page includes items reflecting the patient's attitude towards his/her medicines and statements about medication management and handling difficulties. The 10 non-patient participants from the amateur test had no difficulties completing the questionnaire, and only minor adjustments in wording were necessary.

Validation of the questionnaire

The pretest with five inpatients did not reveal any additional issues.

During ward visits, we approached 208 eligible patients. One hundred and sixty-five (79.3%) consented to participate, and we were able to complete 164 patient interviews (cf. figure 2). The median age was 74 years (range 20–95) and 49% of participants were women. The mean number of drugs per patient at time of admission was 4 and ranged from 0 to 19. Fifty-six patients (34%) 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 patients (42%) 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 patients (24%) 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 DART, because we had enough meaningful data with a clear conclusion. For the same reason, we stopped answering the BMQ questionnaire that we used for comparison with the answers from DART. This allowed us to shorten the duration of the patient interview.

On average, it took patients 7 min to complete DART by themselves. None of the patients experienced any of the statements as bothersome or too intrusive on his privacy. Ten out of 51 patients (19.6%) showed some difficulties in completing the questionnaire, 7 (13.7%) did not understand the wording of a statement and in three cases we had no clear statements what the difficulties were.

DART questions of the version V.1.0 reached specificity values from 27% to 100% and sensitivity values from 21% to 100%. Positive predictive values varied between 26% and 100% and negative predictive value varied between 20% and 100%. Regarding the intake of over-the-counter (OTC) drugs, 85 patients (35%) affirmed, 103 patients (63%) denied and 3 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, 3 (2%) strongly disagreed and 13 patients (8%) gave no answer. Ten patients (6%) named difficulties with tablet splitting, 17 (10%) mentioned swallowing difficulties, 5 patients (3%) affirmed difficulties with visual recognition and 122

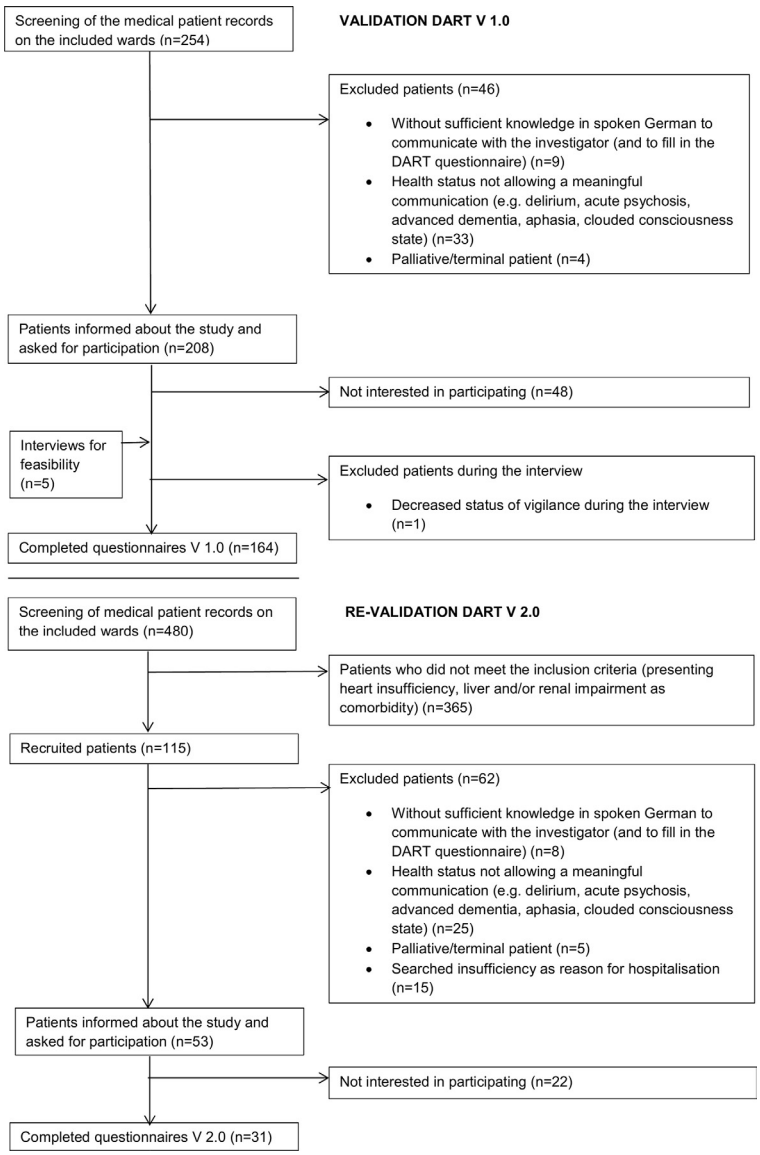
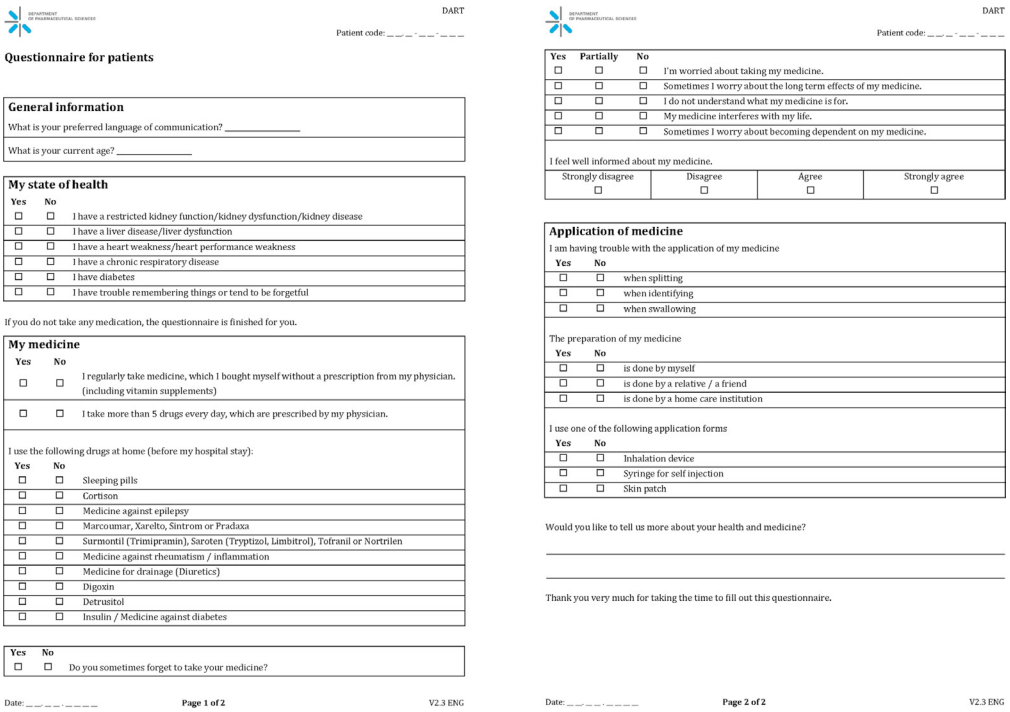


Figure 2 Flow chart of the validation study. DART, Drug-Associated Risk Tool.

(74%) stated no such difficulties. Fifteen answers (9%) 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 patients (9%) named a home care person as their medication manager and 16 patients (10%) gave no answer. Sixteen patients (10%) indicated the use of an inhaler, 15 (9%) the use of a transdermal therapeutic system and 18 (12%) the use of a syringe for self-injection. One hundred and one patients (62%) did not use any of these application forms and 20 (12%) gave no answer.



DART

Patient code: _ _ _ - _ _ - _ _ _

Questionnaire for patients

General information

What is your preferred language of communication? _____

What is your current age? _____

My state of health

Yes	No	
☐	☐	I have a restricted kidney function/kidney dysfunction/kidney disease
☐	☐	I have a liver disease/liver dysfunction
☐	☐	I have a heart weakness/heart performance weakness
☐	☐	I have a chronic respiratory disease
☐	☐	I have diabetes
☐	☐	I have trouble remembering things or tend to be forgetful

If you do not take any medication, the questionnaire is finished for you.

My medicine

Yes	No	
☐	☐	I regularly take medicine, which I bought myself without a prescription from my physician. (including vitamin supplements)
☐	☐	I take more than 5 drugs every day, which are prescribed by my physician.

I use the following drugs at home (before my hospital stay):

Yes	No	
☐	☐	Sleeping pills
☐	☐	Cortison
☐	☐	Medicine against epilepsy
☐	☐	Marcoumar, Xarelto, Sintrom or Pradaxa
☐	☐	Surmontil (Trimipramin), Saroten (Tryptizol, Limbitrol), Tofranil or Nortrilen
☐	☐	Medicine against rheumatism / inflammation
☐	☐	Medicine for drainage (Diuretics)
☐	☐	Digoxin
☐	☐	Detrusitol
☐	☐	Insulin / Medicine against diabetes

Yes	No	
☐	☐	Do you sometimes forget to take your medicine?

Date: _ _ _ _ - _ _ - _ _

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V2.3 ENG

DART

Patient code: _ _ _ - _ _ - _ _ _

Yes	Partially	No	
☐	☐	☐	I'm worried about taking my medicine.
☐	☐	☐	Sometimes I worry about the long term effects of my medicine.
☐	☐	☐	I do not understand what my medicine is for.
☐	☐	☐	My medicine interferes with my life.
☐	☐	☐	Sometimes I worry about becoming dependent on my medicine.

I feel well informed about my medicine.

Strongly disagree	Disagree	Agree	Strongly agree
☐	☐	☐	☐

Application of medicine

I am having trouble with the application of my medicine

Yes	No	
☐	☐	when splitting
☐	☐	when identifying
☐	☐	when swallowing

The preparation of my medicine

Yes	No	
☐	☐	is done by myself
☐	☐	is done by a relative / a friend
☐	☐	is done by a home care institution

I use one of the following application forms

Yes	No	
☐	☐	Inhalation device
☐	☐	Syringe for self injection
☐	☐	Skin patch

Would you like to tell us more about your health and medicine?

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

Date: _ _ _ _ - _ _ - _ _

Page 2 of 2

V2.3 ENG

Figure 3 Drug-Associated Risk Tool (DART). Drug names mentioned in the section 'My medicine' correspond to the most commonly used medicines in the respective therapeutic class from the Swiss market.

Revision of statements

Initially, statements about heart insufficiency, renal impairment and liver impairment showed low sensitivity (0.43, 0.28 and 0.33, respectively) due to possibly poor patient understanding. The PILs of in total 134 medicines, either contraindicated or in need of dose adaptation in presence of heart insufficiency, renal impairment or liver impairment, were used to identify expressions most frequently used to describe these conditions to patients. For DART V.2.0, the statements were changed accordingly: 'I am suffering from a chronic renal disease' was changed to 'I have a restricted kidney function/kidney dysfunction/kidney disease', 'I am suffering from a chronic cardiac disease' was changed to 'I have a heart weakness/heart performance weakness' and 'I am suffering from a chronic hepatic disease' was changed to 'I have a liver disease/liver dysfunction' (cf. figure 3). These expressions were directly translated from German to English and may be written differently in English-speaking countries.

A total of 31 patients (median age: 82 years (range 59–96 years), 61% women), each presenting heart insufficiency, renal impairment or liver impairment as comorbidity, filled out the revised questionnaire (cf. figure 2).

After the second comparison to medical records, the sensitivity of the reworded item 'heart failure' improved from 0.43 to 0.80, while the specificity dropped from 0.96 to 0.60. Similarly, the sensitivity for 'renal insufficiency' ameliorated from 0.28 to 0.38, while the specificity was lowered from 0.98 to 0.80. The small sample size combined with the low prevalence of liver insufficiency prohibited the evaluation of the refined statement covering liver insufficiency. With these modifications DART V.2.0 reached an overall sensitivity of 67% with an overall specificity of 88% (cf. table 2).

DISCUSSION

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 patients who benefit the most of intensified pharmaceutical care. A patient self-assessment tool may save time and resources of caregivers, but also allows the better involvement of the patient. Assessing DRPs with such involvement of the patient may reveal more issues.[27]

Table 2 Sensitivity and specificity of the single statements of DART V.2.0

Statements or questions of DART	Number of answers (n)	Missing data	True positive	False positive	True negative	False negative	Prevalence of the Rf (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
I have a restricted kidney function/kidney dysfunction/ kidney disease	31*	0	10	1	4	16	84	38	80	90	20
I have a liver disease/liver dysfunction	NA*	NA	NA	NA	NA	NA	Na	Na	NA	NA	Na
I have a heart weakness/heart performance weakness	30*	1	8	8	12	2	33	80	60	50	86
I am suffering from a chronic respiratory disease	157	7	14	1	129	13	17	52	99	93	91
I am suffering from diabetes	158	6	23	0	129	6	18	79	100	100	96
I have troubles remembering things or tend to forget things	157	7	9	26	116	6	10	60	82	26	95
I take more than five drugs every day, prescribed by my physician	144	20	10	12	84	38	33	21	88	46	69
Sleeping pills	147	17	15	10	121	1	11	93	92	60	99
Cortisone or other steroids	149	15	11	2	129	7	12	61	98	85	95
Antiepileptic drugs	149	15	0	0	149	0	00	NA	100	NA	NA
Oral anticoagulants	149	15	21	5	123	0	14	100	96	81	100
Tricyclic antidepressants	149	15	2	2	145	0	01	100	99	50	100
Drugs for rheumatism/inflammation	149	15	7	18	120	4	07	64	87	28	97
Drugs for drainage (diuretics)	149	15	26	9	89	25	34	51	91	74	78
Digoxin	149	15	1	0	147	1	01	50	100	100	99
Anticholinergic drugs	149	15	1	0	146	2	02	33	100	100	99
Insulin/drugs used in diabetes	148	16	16	2	127	3	13	84	98	89	98
Do you sometimes forget to take your medicine?											
BMQ	54	110	39	8	3	4	20	91	27	83	43
I use some of these application forms: spray for inhalation, skin patch, syringe for self-injection	129	35	27	12	84	6	26	82	88	96	93
Mean value								67	88	74	86
Range								21–100	27–100	26–100	20–100

*Rephrased statements for DART V.2.0, revalidated with 31 patients.
BMQ, Beliefs about Medicines Questionnaire; DART, Drug-Associated Risk Tool; NA, not applicable; Rf, risk factor.

We used risk factors for the development of DART, previously identified in a combination of a literature search and an expert panel.[23] To our knowledge, this approach has not been adopted previously in this area of research.

DART V.1.0 showed good acceptability and feasibility. The patients were able to complete the self-assessment within on average 7 min 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.

After the validation of the first version of DART (V.1.0), we engaged three statements with an identified low sensitivity and possible poor patient understanding and aimed to improve their wording by implementing expressions into our questionnaire which are frequently used in PILs. We were able to include a statement covering heart failure with an acceptable sensitivity, while observing some more false positive answers. The reliability of patients to answer questions about renal insufficiency remains a challenge: Disease awareness among patients with chronic kidney disease is generally low,[24 28 29] hence making it difficult to retrieve information on from a self-assessment questionnaire. The low knowledge of chronic comorbidities like chronic kidney disease may show a lack of patient education within counselling and may therefore pose an additional task for pharmaceutical care.

Finally, after the validation of the revised questionnaire, most statements of DART V.2.0 showed high specificity (mean value 88%, range 27%–100%) preventing false positive answers with a high probability. The sensitivity of the statements was lower and showed higher variability (mean value 67%, range 21%–100%). 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 (eg, oral anticoagulants, insulin and oral antidiabetics).

Several factors may have influenced the sensitivity values. First, the defined criteria for correlation (cf. table 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. Second, we evaluated the sensitivity and specificity of each question by comparing the subjective answers in DART with objective data from medical records. Literature shows that medication histories at the time of admission are often erroneous and incomplete,[30] 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*[31] 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*[32] 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 OTC drugs or herbal therapies. We used medical records as reference for testing our statements' and the patients' reliability to provide correct answers in our self-assessment questionnaire. Errors within the medical histories as described above would carry over to our findings about the statements. Third, patients stated that they had no problems with filling in DART; however, we noticed some problems with their understanding of the word 'chronic'. And we were aware of the possible existence of a social desirability bias when we directly asked patients for their opinion about the questionnaire.

Finally, the low prevalence of some risk factors (eg, antiepileptic drugs, tricyclic antidepressants, digoxin and anticholinergic drugs) hinders clear conclusions about the validity of the respective statements in DART.

CONCLUSIONS

The self-assessment questionnaire 'DART' 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 medicines and related concerns and problems may facilitate getting a first, but broad picture of the risk for DRPs and possible pharmaceutical needs. Compared with 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 identify patients in need for intensified pharmaceutical care.

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Competing interests None declared.

Patient consent Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

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Drug-Associated Risk Tool: development and validation of a self-assessment questionnaire to screen for hospitalised patients at risk for drug-related problems

Carole P Kaufmann, Dominik Stämpfli, Nadine Mory, Kurt E Hersberger and Markus L Lampert

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III. Assessing the ability of the Drug-Associated Risk Tool (DART) questionnaire to stratify patients according to their risk of Drug-Related Problems

As the association between DRPs and negative outcomes such as DRM and subsequently, hospitalisation, had already been shown, it was adequate to demonstrate the validity of the DART as a screening tool for DRP risk by demonstrating its ability to discriminate between patients in populations with low and high numbers of present manifest or potential DRPs – its concurrent criterion validity. DRPs were to be detected by MRs Type 3 as they pose the most advanced assessment of drug treatment appropriateness. A patient interview had to be an integral part of the assessment as patient interviews are (1) a required information for a MR Type 3 definition-wise and (2) the DART poses questions on information only accessible via direct patient contact, i.e. OTC medication, adherence, concerns, and handling. The screening for DRPs consisted of the recommended combination of implicit and explicit criteria of prescribing appropriateness. The validation process is displayed in Figure 3.

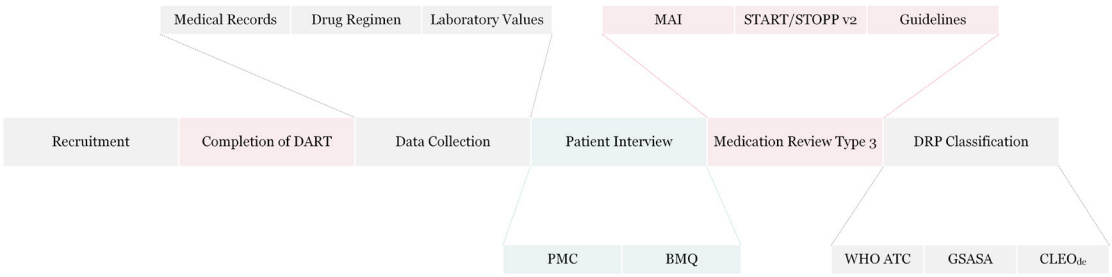

Figure 3 Study design of the DART validation. PMC = Polymedication Check; BMQ = Beliefs about Medicines Quesiotnnaire; MAI = Medication Appropriateness Index; START = Screening Tool to Alert doctors to the Right Treatment; STOPP = Screening Tool of Older Persons' potentially inappropriate Prescriptions; ATC = Anatomical Therapeutic Chemical classificaiton; GSASA = Society of Swiss administrative and hospital pharmacists' classification.

To study the concurrent criterion validity of the DART, statistical analyses beyond scale correlations (i.e. score of the DART with numbers of identified DRPs) were desirable as we aimed to investigate in detail the possible associations between the items and the identified DRPs in order to draw conclusions on item reduction and clinical pharmacy services linking. As studies reported means of eight to ten identified DRPs per patient,[79] [84] our dependent variable (i.e. numbers of DRPs) was expected to lack a predefined cut-off value, i.e. low risk patients having zero DRPs. Instead of defining an artificial cut-off for a tolerable number of DRPs (e.g. low risk patients having four DRPs), a cluster analysis was used. Cluster analyses group observations into collectives with respect to all defined variables without necessitating previous categorisation:[85] The analyses were

hence expected to form patient clusters with high DART scores and high numbers of DRPs and low DART scores and low numbers of DRPs in the absence of an artificial definition of high and low. Figure 4 visualises the cluster formation.

Figure 4 Cluster formation. Cluster analyses group observations into collectives with respect to all defined variables without necessitating previous categorisation.[85] The cluster analysis was expected to group patients with a higher DART score (+) and higher numbers of identified DRPs (+) together in one cluster.

To investigate a statistical procedure that is used to form groups of observations, a structural assessment such as the discriminant function analysis may be used. Using both procedures in conjunction is recommended.[85] The discriminant function analysis in the validation study focused on the discriminatory potential of subsets of items of the questionnaire and hence identified the possibility of reducing the number of items in the questionnaire. In the study presented in this thesis, the subset of items identified by the discriminatory function analysis also enhanced the association between the independent predictor variable (i.e. score) and the dependent outcome variable (i.e. number of DRPs), further advising on the reduction of items.

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Assessing the ability of the Drug-Associated Risk Tool (DART) questionnaire to stratify hospitalised older patients according to their risk of drug-related problems: a cross-sectional validation study

Dominik Stämpfli,[1] Fabienne Boeni,[1,2] Andy Gerber,[3] Victor A D Bättig,[1] Rebekka Weidmann,[4] Kurt E Hersberger,[1] Markus L Lampert[1,2]

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[1]Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland
[2]Clinical Pharmacy, Solothurner Spitaler AG, Olten, Switzerland
[3]Gerontopharmakologie, Felix Platter-Hospital, Basel, Switzerland
[4]Department of Psychology, University of Basel, Basel, Switzerland

Correspondence to
Dr Dominik Stämpfli;
dominik.staempfli@unibas.ch

ABSTRACT

Objectives The Drug-Associated Risk Tool (DART) has been developed as a self-administered questionnaire for patients with the aim of stratifying patients according to their risk of drug-related problems (DRPs). We aimed to validate the ability of the questionnaire to distinguish between hospitalised patients showing lower and higher numbers of DRPs.

Design Cross-sectional study assessing the questionnaire's concurrent criterion validity.

Setting Five geriatric and the associated physical and neurological rehabilitation wards of a Swiss regional secondary care hospital with 617 beds.

Participants We recruited 110 patients from a total of 437 admissions. Exclusion criteria were insufficient knowledge in spoken or written German, medical conditions preventing meaningful conversations and already receiving pharmacy services.

Interventions Comprehensive pharmacist-led clinical medication reviews were performed, including patient interviews, to identify potential and manifest DRPs. A cluster analysis was conducted to assess the discriminatory potential of the DART to group patients according to number (low and high) of identified DRPs. A subsequent discriminatory function analysis was performed to reduce the number of items. We determined which DART items may be used to trigger what type of medication review.

Results Recruited patients had a median age of 79 years and were prescribed a median of 11 drugs. Patients with a median DART score of 10 and a median of 3 DRPs represented one cluster, whereas patients with a median DART score of 15 and a median of 8 DRPs represented another cluster. Discriminatory function analysis reduced the questionnaire to five items with a moderate to strong correlation with the number of DRPs per patient (Spearman's rank correlation ρ=0.44). Additional items were associated with patients benefiting from interviews.

Conclusions As a self-administered questionnaire for patients, the DART may be used to stratify hospitalised non-acute older patients in groups of having low and high likelihood of DRPs. The analyses showed that a short form of the DART can be used instead of the full tool to identify older inpatients at risk for DRPs. Additional eight items from the DART may be used to initiate additional clinical pharmacy services. The linkage between certain DART questions and type of medication review enables pharmacist resource allocation.

Strengths and limitations of this study

- ► The performed comprehensive clinical medication reviews were performed by one pharmacist to ensure consistency and repeated by a second pharmacist to ensure their validity.
- ► Item reduction was possible following a cluster analysis and a subsequent discriminant function analysis making the Drug-Associated Risk Tool less time consuming.
- ► However, the questionnaire is currently only validated in older non-acute patients with the ability to engage in conversation hospitalised on geriatric and associated rehabilitation wards.
- ► Patients with cognitive impairments (eg, dementia) had to be excluded, which further restricts the generalisability of the results.

BACKGROUND

When pharmacists take responsibility for the optimisation of medicines use, they are practising pharmaceutical care.[1] This care includes the prevention, identification and resolution of drug-related problems (DRPs).[2] DRPs are defined as 'events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes' and are distinguished by preventability, presence and cause.[3] The DRPs that pharmacists are able to avert are preventable potential or

manifest DRPs, which are erroneously caused by deviations from accepted guidelines or by patients' behaviour. Within hospitals, clinical pharmacists practise pharmaceutical care and advise on appropriate, safe and economic use of medicines.[4] Hospitals are a point of care where new medicines are introduced to treat acute illnesses in addition to existing treatment for chronic conditions—a process growing more complex with each added medicine.[5] Besides focusing on newly introduced medicines, hospitalisation can be an opportunity for clinical pharmacists to perform medication reviews on the patient's whole drug therapy while having access to the vast amount of information provided by medical records, laboratory measurements and patients' opinions and experiences.[5 6] Drug therapy evaluations including this information are classified as Medication Reviews Type 3 (MRT3).[7] MRT3s take into account the circumstances in which patient interviews are necessary for the identification of the majority of DRPs. Whereas Medication Reviews Type 2a (MRT2a) rely on information from medication histories and patient interviews, MRT3s also take clinical data and laboratory measurements into consideration.[6] They are conducted using a combination of methods for DRP identification, are structured and multifaceted and therefore yield optimal results.[5 6 8] The combination of methods needs to include explicit as well as implicit criteria of inappropriate prescribing to balance the benefits and drawbacks of each method.[9] Explicit criteria are rigid statements that enable quick evaluation of the therapy appropriateness with little clinical judgement but do not allow for individual patient tailoring. Implicit criteria are individual assessments that enable a patient-specific evaluation of complex drug therapy regimens but require clinical knowledge and time.[9] Such comprehensive drug therapy evaluations can reduce the number of days spent in hospital for selected patients[10] but require human resources currently not available in Swiss hospitals: the 35.9 full-time equivalent clinical pharmacist positions stand in strong contrast to 1.4 million hospitalisations per year.[11]

Prioritising patients in order to structure the daily workload is an accepted requirement to maintain effective clinical pharmacy services with finite resources.[12 13] The systematic review of Falconer and colleagues comprehensively evaluated published algorithms to prioritise patients according to their risk for DRPs.[13] Of the 11 models in their final assessment, only the Brighton Adverse Drug Reactions Risk model by Tangiisuran and colleagues[14] remained as tool with fair discrimination, sufficient validation and reasonable performance. The score requires laboratory measurements further necessitating effort by a healthcare professional (ie, high white cell count on admission). Contrary to a model based on clinical data, a well-developed paper-based questionnaire may be distributed to the patients while they are waiting to be seen by their physician or pharmacist.[15] Patient-filled questionnaires also help in identifying additional patient-centred DRPs, for example, low adherence and poor health literacy.

The Drug-Associated Risk Tool (DART) is a 35-item questionnaire about risk factors deemed to be associated with DRPs.[16] The DART was developed to assist clinical pharmacists in stratifying their patients for medication reviews and to tailor clinical pharmacy services according to available resources. The items of the questionnaire were identified by triangulation, including quantitative and qualitative methods, described elsewhere.[17] The tool is designed to be a self-administered questionnaire for patients in order not to increase the workload of either clinical pharmacists or other healthcare professionals. The applicability of the DART used as a self-administered questionnaire has been shown for hospitalised patients; compared with documented medical records, patients from geriatric, medical and orthopaedic wards with a median age of 81, 65 and 67.5 years, respectively, were able to adequately reproduce their medical information, limitations being renal and hepatic insufficiency.[16]

In order to evaluate the DART as a risk stratification tool, the goal of the present study was to validate its ability to distinguish between hospitalised patients showing lower and higher numbers of currently present potential and manifest DRPs.

METHODS

Setting and study design

Prospective patient enrolment and data collection were conducted in a Swiss regional secondary care hospital with 617 beds from February to November 2016. The hospital administration gave permission to recruit patients for 10 months; we aimed to recruit at least 100 study participants, as discussed for self-administered questionnaires by Barenholtz Levy.[15] We chose to prove the concurrent criterion validity for the DART,[18] as there is currently no gold standard for the risk assessment of DRPs. The concurrent criterion validity assessment correlates a new tool with another measure of the trait under study, both administered at the same time.

Recruitment

We recruited patients from five geriatric and the associated physical and neurological rehabilitation wards with approximately 60 beds and a reported mean hospital stay of 17 days.[19] In this hospital, patients get transmitted from other wards to the rehabilitation wards after acute care and generally mark less acutely ill patients. Patients were included in the study when admitted to one of the participating wards and were approached within 72 hours of admission. Exclusion criteria were insufficient knowledge in spoken or written German, medical conditions preventing meaningful conversations (eg, deliria, acute psychosis, dementia, aphasia and cognitive impairment), patients treated within palliative care and patients who were already subject to other clinical pharmacy services (ie, ward rounds and phone consultation). Ethical considerations required the approval of the ward physician or responsible caregiver before patient contact.

Data collection

After giving informed consent, the patients received the DART questionnaire to complete in self-admission. The DART consists of 29 questions with dichotomous answers and 6 questions with Likert scale answers. The questionnaire is divided in sections on health, polypharmacy, self-medication, specific drugs, adherence, concerns over the medication, medication literacy and medication application. The study pharmacist collected clinical data on medical conditions, drug treatment (inpatient medication list) and laboratory values (ie, renal and hepatic function, nutritional state, health and disease markers and drug-monitoring values) from the electronic patient charts. The completed questionnaires were collected and stored separately without evaluation. The collected clinical data were entered on a case report form.

Tools and measures

As criterion measure we chose MRT3s[7] to identify DRPs, using the implicit criteria on potentially inappropriate medications (PIMs) 'Medication Appropriateness Index' (MAI)[20] and current Swiss treatment guidelines,[21] and the explicit criteria on PIMs 'STOPP/START criteria version 2' (STOPP, Screening Tool of Older People's Prescriptions; START, Screening Tool to Alert to Right Treatment)[22] as part of the review. Feasibility, content validity, predictive validity and reliability have all been demonstrated for the MAI.[23] Improvements in drug therapy appropriateness have been shown to decrease the total MAI score.[8] For each medicine, 10 criteria are judged to be 'appropriate', 'marginally appropriate' or 'not appropriate'. A weighted score is applied for evaluations deemed to be 'partially appropriate' or 'marginally appropriate'.[24] The medicine's total score indicates its appropriateness, whereas each contributing criterion indicates an opportunity for optimisation. The STOPP/START criteria are shown to improve medication appropriateness and to reduce adverse drug reactions, whereas the STOPP statements are associated with adverse drug events.[22] The drug regimens were screened for drug–drug interactions by the commercial online database mediQ.[25] A structured interview for detection of patient-centred DRPs was newly developed as part of the MRT3s; the interview was based on the Polymedication Check (PMC),[26] a reimbursed cognitive service provided by Swiss community pharmacists that focuses on adherence problems, patients' knowledge and handling problems. We supplemented the PMC with items from the Beliefs about Medicines Questionnaire in order to identify drug-related concerns.[27] The interviews took place within 24 hours of study inclusion. Thus, the assessments took place within 4 days of ward admission. All answers to the interview questions were dichotomous. The study pharmacist performed the patient interviews with each patient using an iPad Air, V.2 (Apple, Cupertino, California, USA), where interview guide and data entry were combined within the online questionnaire form Flexiform, V.2.7.1 g (IT-services University of Basel).

Data classification

We coded the medication using the anatomical therapeutic chemical (ATC) classification.[28] DRPs were documented with the GSASA (Swiss Association of Public Health Administration and Hospital Pharmacists) classification system for DRPs, for which inter-rater reliability has been shown.[29] We assessed the potential clinical relevance of the DRPs by using a German version of CLEO, $CLEO_{dc}$, which was tested for inter-rater and test–retest reliability.[30] CLEO assists pharmacists in assessing the potential relevance of their own interventions and the underlying DRPs identified in the three distinct dimensions: clinical/patient, economic/hospital and organisational/staff. For our research, we focused on the clinical dimension, with its six levels: 'harmful', 'null', 'minor', 'moderate', 'major' and 'lifesaving,' which achieved good inter-rater (intraclass correlation ICC=0.63) and excellent test–retest reliability (mean ICC=0.76). Levels equal to or higher than moderate describe interventions that prohibit potential damage requiring additional treatment or that recommend further surveillance.

Based on all collected data, the study pharmacist performed MRT3s and then a second clinical pharmacist repeated the medication reviews independently. Identified potential and manifest DRPs and their estimated relevance were compared; divergence was resolved by discussion until consensus was reached.

Patient and public involvement

Patients were not involved in the development of the research question or the execution of the study. The interview was pilot tested with two inpatients to sort out any issues regarding its understandability. Study participants were encouraged to contact the study pharmacist in case they wanted to be informed on the results. Contact information was available on the study information.

Statistical analysis

The total DART risk score was calculated by assigning points to each answer. Dichotomous answers were assigned a risk score with one (1) point being assigned to each 'Yes' answer and zero (0) points given to each 'No' answer. Ordinal answers were assigned a corresponding dummy variable. As studies reported means of 8–10 identified DRPs per patient,[31 32] the dependent variable (ie, numbers of DRPs) was expected to lack a predefined cut-off value, that is, low-risk patients having zero DRPs. Instead of defining an artificial cut-off for a tolerable number of DRPs (eg, low-risk patients having four DRPs), we used a cluster analysis. Cluster analyses group observations into collectives with respect to all defined variables (ie, DART score and number of DRPs) without necessitating previous categorisation: the analysis was expected to form patient clusters with high DART scores and high numbers of DRPs and low DART scores and low numbers of DRPs in the absence of an artificial definition of high and low. We performed a Ward's hierarchical cluster analysis with squared Euclidian distance

using the variables DART score and number of DRPs. This analysis necessitated the elimination of statistical outliers in order to be performed. For this reason, Backhaus and colleagues recommend a preceding single linkage hierarchical cluster analysis with squared Euclidian distance. Statistical outliers can be objectively identified from the resulting dendrogram.[33] We assessed the appropriateness of the clusters generated by the Ward's hierarchical cluster analysis by homogeneity and calculated the *F*-values for each cluster and variable (ie, DART total risk-score and number of DRPs). *F*-values of below 1 represent a homogeneity that is lower within the proposed cluster than within all observations.[33] We performed effect size calculations using Pearson's correlation coefficient *r*, which were interpreted according to Gignac: *r*=0.1 as small,. 0.2 as medium and 0.3 as large.[34] We compared the obtained clusters concerning their total number of identified DRPs and their total DART risk score by a Mann-Whitney U test.[35] Furthermore, we performed a stepwise discriminant function analysis in order to investigate the discriminatory potential of subsets of items of the questionnaire for the generated clusters and hence to identify possibilities to reduce the number of items in the questionnaire. We calculated Wilks' lambda (λ) for the whole DART questionnaire and the subsets of items ('reduced items') to report on discriminatory values. Lower Wilk's λ values indicate a higher differential potential.[33] For scale correlations, we used Spearman's rank correlation coefficient ρ, which we interpreted as follows: ρ=0.1 as weak, 0.3 as moderate and 0.5 as strong.[36] An area under the receiver operating characteristic curve (AUROC) analysis for the reduced items was performed.

As described above, cluster analysis and subsequent discriminant factor analysis were again used to additionally determine discriminatory DART items concerning DRPs identified within the patient interviews only.

Additionally, we calculated Spearman's rank correlation coefficient ρ to assess the correlation between the score of the reduced items and the potential relevance of the detected DRPs. For the single items, we used a Mann-Whitney U test. These additional tests were used to assign the necessary type of medication review (ie, MRT3 or MRT2a) to certain items of the DART.

We defined statistical significance as p values <0.05. The statistical analysis was performed using IBM SPSS Statistics for Windows, V.24.0. Interview data preparation was performed using RStudio, V.1.0.136 (RStudio, Boston, Massachusetts, USA) and running R, V.3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Dataset

We recruited 110 patients from a total of 437 admissions to the five wards during the enrolment period from February to November 2016. Figure 1 summarises the recruitment flow. Study population characteristics are presented in table 1.

We identified a total of 595 DRPs, averaging 5.4 DRPs per patient (range: 0–17). One hundred and eight patients had at least one DRP (98.2%). Thirty-four DRPs were deemed to be manifest, that is, patients showing signs of adverse drug events. Identified DRPs are presented in table 2. The most frequent causes of DRPs were 'Insufficient knowledge of the patient' (n=138, 23.2%; for example, not knowing the indication of the drug) and 'Incomplete patient documentation' (n=118, 19.8%; for example, missing diagnoses or treatments), summating in the most frequent problems 'Safety of treatment' (n=182, 30.6%) and 'Patient dissatisfaction' (n=154, 25.9%) as classified by the GSASA documentation tool. Analgesics were the drug class linked to most DRPs (71 DRPs, 13.7%), with acetaminophen causing most of the potential issues within this class (26 DRPs). On a drug level, pantoprazole was accountable for most DRPs (35 DRPs, 6.3%), followed by acetaminophen (26 DRPs, 4.7%) and then calcium and cholecalciferol (19 DRPs, 3.4%). With the help of the $CLEO_{dc}$ tool, we estimated the potential clinical relevance of the DRPs to be 'null' (n=47, 7.9%), 'minor' (n=399, 67.1%), 'moderate' (n=106, 17.8%), 'major' (n=40, 6.7%) and 'lifesaving' (n=3, 0.5%).

Validation of the DART

We analysed the datasets for correlation of risk factors identified by the DART questionnaire with the number of DRPs. Seven datasets were excluded from this analysis: two patient cases had incomplete data and another five cases were identified as statistical outliers by the single-linkage cluster analysis. Two of these five patients had a DART score of 16 and 15 and a number of DRPs of 13 and 17, respectively; two patients had a low DART score (0 and 3) and a high number of DRPs (9 and 8); one patient had a high DART score (21) and a low number of DRPs (2). These preliminary steps reduced the analysed dataset to a total of 103 patients.

The DART total risk score showed a weak to moderate correlation with the number of DRPs identified (Spearman's rank correlation ρ=0.27, p<0.01). Using the cluster analysis, we were able to identify two clusters with 61 and 42 observations, respectively. The two clusters may be regarded as completely homogeneous, as all *F*-values are below 1 ($F_{\text{Cluster1, DART risk-score}}$=0.51; $F_{\text{Cluster1, identified DRPs}}$=0.21; $F_{\text{Cluster2, DART risk-score}}$=0.97; and $F_{\text{Cluster2, identified DRPs}}$=0.72). The effect sizes were large for both variables (DART risk-score Pearson's: *r*=0.54; identified DRPs: *r*=0.79). Comparing the two clusters, a Mann-Whitney U test revealed a statistically significant tendency for the DART total risk-score (*U*=476.5, p<0.001) and number of identified DRPs (*U*=100.0, p<0.001). Cluster 1 represented patients with a median of 10 risk factors (range: 3–16) and three identified DRPs (range: 1–6) and cluster 2 represented patients with a median of 15 risk factors (range: 9–23) and 8 DRPs (range: 4–15). The clusters also presented a difference in summated MAI scores per patients: clusters 1 and 2 contained patients averaging at an MAI score of 5.6 and

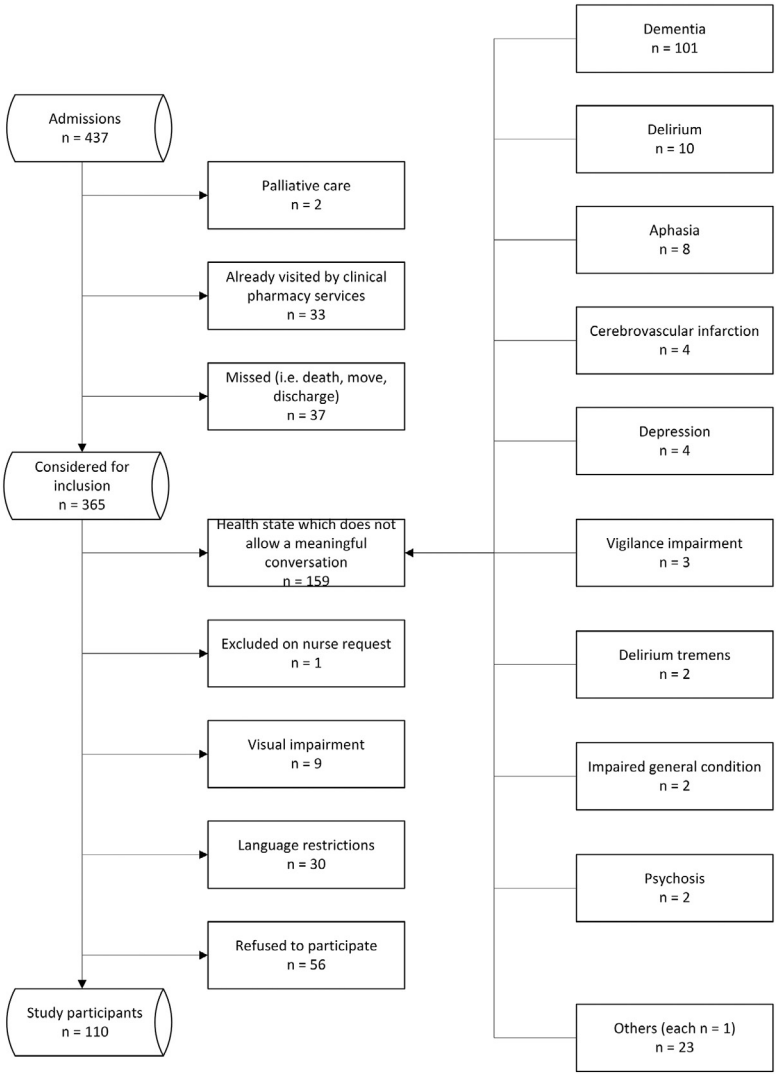

Figure 1 Recruitment flow.

13.2, respectively. In the discriminant function analysis, the DART total risk score achieved a Wilks' λ of 0.69 (p<0.001). Stepwise discriminant function analysis identified the DART items on diabetes, polypharmacy (>5 medicines), missing doses, concerns on dependency and heart failure as important discriminators between the two clusters. These items achieved a combined Wilks' λ of 0.57 (p<0.001), indicating a higher differential potential than the total DART risk score itself. The score of the five items alone showed a moderate to strong correlation with the number of DRPs identified (Spearman's rank correlation ρ=0.44, p<0.01) and a strong correlation with the original total risk score (ρ=0.714, p<0.01). The AUROC was 0.865 (SE=0.035, p<0.001, 95% CI 0.797 to 0.932), further displaying the discriminatory potential of the summated five items. The r eceiver o perating c haracteristic (ROC) curve is shown in figure 2. The coordinates of the ROC curve presented in table 3 show cut-offs at either one (1)

Table 1 Dataset characteristics

Characteristic	Value
Demographic (n=110)	
Age, median (IQR) (years)	79.0 (15.0)
Female, n (%)	76 (69.1)
Clinical status	
Glomerular filtration rate* (CKD-EPI), mean±SD (mL/min)	70.5±20.5
Patients with moderate renal insufficiency up to renal failure, n (%)	29 (27.7)
Diagnosed heart failure, n (%)	4 (3.6)
Diagnosed liver insufficiency, n (%)	0 (0.0)
Diagnosed COPD, n (%)	10 (9.1)
Diagnosed diabetes, n (%)	24 (21.8)
Medication	
Prescribed drugs†, median (IQR)	11.0 (6.0)

*Missing values n=5.
†As reported on the inpatient medication list, including already used as needed medications.
CKD-EPI, chronic kidney disease epidemiology collaboration; COPD, chronic obstructive pulmonary disease.

or two (2) 'Yes' answers with decreasing sensitivity but increasing specificity.

Concerning the DRPs identified within the patient interviews only, Spearman's rank correlation showed a moderate correlation between the score of the reduced five items and the number of DRPs identified (ρ=0.45, p<0.01). Cluster analysis and subsequent discriminant factor analysis on the whole questionnaire classified the DART items on the use of drugs (non-steroidal antirheumatics, antidiabetics and digoxin), restricted kidney function, concerns about dependency, concerns at having to use medicines, use of therapeutic skin patches, preparation of medicines by home care and polypharmacy as predictors of DRPs identified during patient interviews.

The score of the reduced items showed a statistically significant correlation with DRPs estimated to be of moderate (ρ=0.40, p<0.001) and minor (ρ=0.23, p=0.02) clinical relevance. In the evaluation tool CLEO, patient-centred DRPs are estimated to be of minor relevance; these include restricted knowledge of medicines, restricted satisfaction, compliance or quality of life and damage that does not require monitoring or treatment. Mann-Whitney U tests showed a statistically significant correlation between DRPs with high clinical relevance (ie, CLEO 'major', 'lifesaving') and the DART items on issues such as tablet-splitting (U=419.5, p=0.020), heart failure (U=590.0, p=0.018) and use of oral anticoagulants (U=696.5, p=0.004). Use of steroids (U=182.5, p=0.010) was associated with DRPs with moderate clinical relevance. Table 4 presents the synopsis of the statistical results, combining single DART items with two types of medication review.

Table 2 Identified drug-related problems (DRPs) as classified by the GSASA classification system[29]

Description	Total=595, n (%)
Detected problem	
Safety of treatment	182 (30.6)
Patient dissatisfaction	154 (25.9)
Treatment effectiveness	107 (18.0)
Untreated indication	52 (8.7)
Treatment costs	7 (1.2)
Classification not possible	93 (15.6)
Cause of problem	
Insufficient knowledge of the patient	138 (23.2)
Incomplete patient documentation	118 (19.8)
No concordance with guidelines or contraindication	60 (10.1)
Drug not indicated or duplication	46 (7.7)
Treatment not received	46 (7.7)
Interaction	36 (6.1)
Overdose	29 (4.9)
Underdose	25 (4.2)
Inappropriate therapy duration	20 (3.4)
Insufficient adherence	19 (3.2)
Inappropriate timing or frequency of administration	14 (2.4)
Adverse effect	12 (2.0)
Dose not adjusted to organ function	9 (1.5)
Inappropriate dosage form	7 (1.2)
Error in medication process	3 (0.5)
Insufficient knowledge of healthcare professionals	2 (0.3)
Prescribed drug not available	1 (0.2)
Classification not possible	10 (1.7)
Manifest	34 (5.7)
Potential	561 (94.3)

GSASA, Swiss Association of Public Health Administration and Hospital Pharmacists.

DISCUSSION

The goal of the present study was to validate the ability of the DART questionnaire to distinguish between hospitalised patients showing lower and higher numbers of currently present potential and manifest DRPs. With a weak to moderate correlation (ρ=0.27, p<0.01), the total risk score of the DART allowed for the discrimination of two patient groups as a result of a cluster analysis: patients with a median DART score of 10 presented a median of 3 identified DRPs and an average MAI score of 5.6, whereas patients with a median DART score of 15 presented a median of 8 DRPs and an average MAI score of 13.2, supporting the validity of the generated clusters. We identified the five items, diabetes, polypharmacy (>5

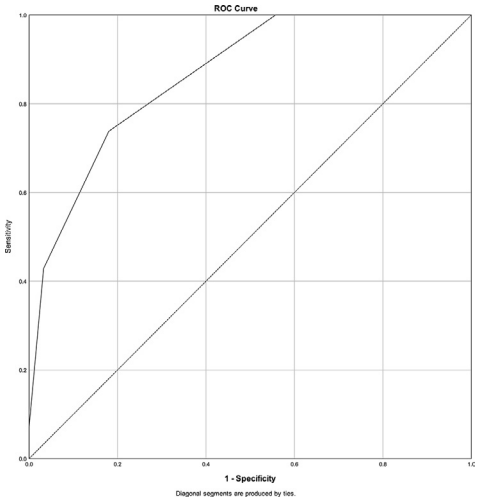

Figure 2 Receiver operating characteristic (ROC) curve of the five DART items on diabetes, polypharmacy (>5 medicines), missing doses, concerns on dependency and heart failure. DART, Drug-Associated Risk Tool.

medicines), missed doses, concerns about dependency and heart failure, as important discriminators between these two patient collectives. The weak to moderate correlation between the DART total score and identified DRPs increased when only these five items of the DART were taken into account, resulting in a moderate to strong correlation (ρ=0.44, p<0.01). Reducing the DART items represents a less time-consuming and more valid measure of identifying DRPs compared with the total DART scale. Because we indicated the source of identification in our dataset, we were able to show that the risk score of the reduced items correlated moderately with the number of DRPs identified only in direct patient interviews (ρ=0.45). With a second cluster analysis and subsequent discriminatory function analysis, we identified additional DART items that were of discriminatory value for patients who specifically benefited from the interviews. Furthermore, stated tablet-splitting issues, heart failure and use of steroids or oral anticoagulants showed a statistically significant correlation to DRPs with moderate to high clinical relevance. Table 4 combines these findings into a repository of patient questions that may be used by practitioners with limited resources to tailor two types of medication reviews.

Table 3 Coordinates of the receiver operating characteristic (ROC) curve

Positive if greater than or equal to	Sensitivity	Specificity
0.5	1.000	0.443
1.5	0.738	0.820
2.5	0.429	0.967
3.5	0.071	1.000
5	0.000	1.000

The items identified as being of discriminatory value for the DART questionnaire and the overall number of DRPs are well in line with previous research on DRPs. The symptoms of heart failure may worsen when drugs are not taken as prescribed,[37] patients with diabetes mellitus who are non-adherent to their medication regimen are especially prone to hospitalisation,[38] polypharmacy and non-adherence in general are established risk factors for medication-related hospitalisations,[39] steroids[40 41] and anticoagulants[41–44] are drugs frequently associated with re-hospitalisation or adverse drug events; tablet-splitting is a known safety issue, as problems with handling and adherence are associated with it.[45] As many as 52.5% of Swedish patients with prescriptions for split-tablets stated a preference and wished for whole tablets instead.[46]

The risk score of the reduced items was associated with DRPs estimated to be of minor and moderate clinical relevance by the CLEO evaluation tool. CLEO associates the level 'minor' with problems being mainly patient centred and without the potential to produce harm that needs further monitoring or treatment.[30] These patient-centred problems include restricted knowledge about the medicines and restricted satisfaction, compliance and quality of life, for example, swallowing difficulties. The assignment of patient-centred DRPs like these to a minor clinical relevance is bound to the use of CLEO in estimating the potential clinical relevance of our identified DRPs and might be argued otherwise: health illiteracy and swallowing difficulties are risk factors for DRPs and non-adherence[47 48] and may cause patient harm. We identified four items of the DART that had a statistically significant correlation with problems deemed to cause patient harm: tablet-splitting issues, heart failure and the use of steroids or use of oral anticoagulants.

As part of ongoing processes to shift medical documentation to electronic datasets, risk stratification tools are currently being developed as automated algorithms.[22 49] Tools that take advantage of computer-based algorithms allow for the surveillance of the whole hospital, showing a clear advantage over paper-based questionnaires such as the DART. In our analysis, we also identified 11 items of the DART that could seamlessly be integrated into an automated algorithm (see table 4); however, we also present five items that necessitate direct patient contact. The WHO expects 'seven-star pharmacists' (caregiver, communicator, decision maker, teacher, life-long learner, leader and manager) to focus on patient-centred care (ie, respect the patients' opinions and concerns).[50] Patients' opinions and sorrows cannot be assessed with automated algorithms processing electronic documentation. With the DART, we present a questionnaire that asks the patients about their medicine use and is intended to be completed by the patient

Table 4 Combination of DART items and possible triggered type of medication review

DART item (translated from German)	Outcome in statistical analysis	Possible triggered clinical pharmacy service
I have a heart weakness/heart performance weakness.	Correlated with DRPs with high clinical relevance.	Consider immediate MRT3 inclusive of a patient interview.
I have trouble taking my medicine because of splitting tablets.	Correlated with DRPs with high clinical relevance.	Consider immediate MRT3 inclusive of a patient interview.
I use Marcoumar (phenprocoumon), Xarelto (rivaroxaban), Sintrom (acenocoumarol), Eliquis (apixaban), Lixiana (edoxaban) or Pradaxa (dabigatran) at home.	Correlated with DRPs with high clinical relevance.	Consider immediate MRT3 inclusive of a patient interview.
I use cortisone at home.	Correlated with DRPs with moderate clinical relevance.	Consider immediate MRT3 inclusive of a patient interview.
I have diabetes.	Discriminated for cluster of patients with a high number of DRPs.	Consider MRT3 inclusive of a patient interview.
I take more than five drugs every day, which are prescribed by my physician.	Discriminated for cluster of patients with a high number of DRPs.	Consider MRT3 inclusive of a patient interview.
Do you sometimes forget to take your medicine?	Discriminated for cluster of patients with a high number of DRPs.	Consider MRT3 inclusive of a patient interview.
I sometimes worry about becoming too dependent on my medicines.	Discriminated for cluster of patients with a high number of DRPs.	Consider MRT3 inclusive of a patient interview.
I use medicines against rheumatism/ inflammation at home.	Discriminated for cluster of patients with DRPs only identified in patient interview.	Consider patient interview (MRT2a).
I use insulin/medicines against diabetes at home.	Discriminated for cluster of patients with DRPs only identified in patient interview.	Consider patient interview (MRT2a).
I use digoxin at home.	Discriminated for cluster of patients with DRPs only identified in patient interview.	Consider patient interview (MRT2a).
I sometimes worry about the long-term effects of my medicines.	Discriminated for cluster of patients with DRPs only identified in patient interview.	Consider patient interview (MRT2a).
Having to take this medicine worries me.	Discriminated for cluster of patients with DRPs only identified in patient interview.	Consider patient interview (MRT2a).
I apply my medication in the form of skin patches.	Discriminated for cluster of patients with DRPs only identified in patient interview.	Consider patient interview (MRT2a).
I have a restricted kidney function/kidney dysfunction/kidney disease.	Discriminated for cluster of patients with DRPs only identified in patient interview.	Consider patient interview (MRT2a).
The preparation of my medicine is done by a homecare institution.	Discriminated for cluster of patients with DRPs only identified in patient interview.	Consider patient interview (MRT2a).

MRT3, Medication Review Type 3; drug therapy evaluations using medical records, laboratory measurements, and the patient's opinions and experiences. MRT2a, Medication Review Type 2a; drug therapy evaluations using medication history and the patient's opinions and experiences.[7]
DART, Drug-Associated Risk Tool; DRPs, drug-related problems.

to trigger clinical pharmacy services promoting tailored patient care.

Strengths and limitations

A strength of the study presented here is the validation procedure: (1) the completed questionnaires were not evaluated until after the MRT3; (2) MRT3 were performed by one pharmacist to ensure consistency and repeated by a second pharmacist to ensure their validity; and (3) the cluster analysis with subsequent discriminant factor analysis showed its additional value over a simple scale correlation by highlighting items for item reduction. Our results contribute to the growing evidence on risk factors associated with DRPs. The items we identified as being valuable within our questionnaire are risk factors that have been judged to be potentially harmful elsewhere.[37–45] Past research has been able to show that these risk factors negatively influenced rehospitalisation and occurrence of adverse drug reaction rates,[37–45] and we showed that they should be used to trigger clinical pharmacy services that include patient interviews.

The limitations of this work constitute the generalisability of the results. The 110 medication reviews of the dataset were performed with older patients hospitalised

on geriatric and the associated physical and neurological rehabilitation wards, having a median age of 79 years and a median of 11 prescribed drugs. This represents an elderly, highly polymedicated population. Additionally, we included patients from rehabilitation wards, who generally mark less acutely ill inpatients. Furthermore, the exclusion criterion 'medical conditions preventing meaningful conversations' was a necessity for patient interviews but excluded patients vulnerable to DRPs, especially cognitively impaired patients that have an independent risk for medication-related hospitalisation.[39] Since the DART was developed as a self-administered questionnaire, cognitive impairment is inherently a limitation of this tool. Combining these limitations, the DART currently proved to be suitable for older non-acute patients with the ability to engage in conversation. Furthermore, the use of a Ward's hierarchical cluster analysis necessitated the exclusion of five statistical outliers as identified by a preceding single linkage hierarchical cluster analysis, which impeded a desirable intention-to-treat analysis. However, the exclusion of two patients who later would have fallen within the cluster of high DART risk score and high number of DRPs demonstrates the objectivity of this outlier identification. The additional three excluded outliers having contradictory DART risk score and numbers of DRPs show that the DART does not perform well for all patients but may be regarded in the lights of restricted specificity and sensitivity of the tool, which are present in any risk assessment. An additional limitation is that we did not correlate the DART with clinical outcomes (ie, rehospitalisation rates). This is because the DART is a screening tool pointing at patients at risk. Identifying risks as such cannot improve outcomes; it has to be followed by appropriate interventions. The DART, however, may help to direct interventions to patients in need of optimising pharmacotherapy and by this improve clinical outcomes.

Implication for practice

The implication of our research for practice is the addition of a self-administered questionnaire to the list of available tools that may be used for risk stratification. Distributed at the beginning of a hospitalisation, the DART may be completed by the patients themselves without increasing the workload for healthcare providers. The results can be used to tailor clinical pharmacy services and to allocate available resources to older non-acute patients who most need them. We suggest as triggers for MRT3 within a hospitalised older population the eight items of the DART on heart insufficiency, tablet-splitting issues, use of anticoagulants or steroids, diabetes, polypharmacy (>5 medicines), adherence and concerns about dependency. If resources permit, the additional eight items on the use of non-steroidal antirheumatic drugs, antidiabetics, digoxin, and restricted kidney function, concerns on dependency, concerns at having to use medicines, use of therapeutic skin patches and preparation of medicines by home care services may be used as indicators for patients who benefit from a patient interview focusing on adherence problems, patients' knowledge and handling problems (ie, MRT2a). As the items of the original DART were carefully selected by a triangulation process, the remaining items may still be used to shape the contents of an MRT3 or a patient interview.

CONCLUSION

We present the DART as a validated self-administered questionnaire that may be used to identify a high risk of DRPs in hospitalised older non-acute patients able to engage in a conversation. Subsets of the items may trigger different clinical pharmacy services for patients in need and allow for rational allocation of work resources.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The regional ethics committee (Ethikkommission Nordwest- und Zentralschweiz (EKNZ)) approved the study (number 44/13). All participating patients gave informed consent. Identified DRPs were reported to the ward staff when deemed ethically necessary (ie, expected patient harm) by an independent clinical pharmacist.

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IV. Patient Interviews as Part of a Comprehensive Approach Contribute to the Identification of Drug-Related Problems on Geriatric Wards

The dataset generated in the validation study of the DART, with its 110 patient cases and 595 documented DRPs, was an opportunity to further evaluate the capabilities of the deployed MRs Type 3. The MRs Type 3 consisted of different measures of inappropriate prescribing and a patient interview. As the sources of DRP identification were documented in the dataset, this newly developed patient interview could be evaluated in light of additional information gained from it. Furthermore, the use of $CLEO_{de}$ allowed for a listing of potential relevance by identification source. And most importantly, performing analyses on the dataset – besides the validation of the DART – permitted the identification of currently present DRPs in a population of Swiss geriatric inpatients.

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ORIGINAL RESEARCH ARTICLE

Contribution of Patient Interviews as Part of a Comprehensive Approach to the Identification of Drug-Related Problems on Geriatric Wards

Dominik Stämpfli[1] · Fabienne Boeni[1,2] · Andy Gerber[3] · Victor A. D. Bättig[1] · Kurt E. Hersberger[1] · Markus L. Lampert[1,2]

Abstract

Background Inappropriate prescribing is linked to increased risks for adverse drug reactions and hospitalisation. Combining explicit and implicit criteria of inappropriate prescribing with the information obtained in patient interviews seems beneficial with regard to the identification of drug-related problems (DRPs) in hospitalised patients.

Objective We aimed to investigate the inclusion of pharmacist interviews as part of medication reviews (including the use of explicit and implicit criteria of inappropriate prescribing) to identify DRPs in older inpatients.

Methods Clinical medication reviews were performed on geriatric and associated physical and neurological rehabilitation wards in a regional secondary care hospital. Data from electronic medical records, laboratory data, and current treatment regimens were complemented with a novel structured patient interview performed by a clinical pharmacist. The structured interview questioned patients on administration issues, prescribed medication, self-medication, and allergies. The reviews included the use of current treatment guidelines, the Medication Appropriateness Index, the Screening Tool of Older People's Prescriptions (STOPP, v2), and the Screening Tool to Alert to Right Treatment (START, v2). The potential relevance of the DRPs was estimated using the German version of the CLEO tool.

Results In 110 patients, 595 DRPs were identified, averaging 5.4 per patient (range 0–17). The structured interviews identified 249 DRPs (41.8%), of which 227 were not identified by any other source of information. The majority of DRPs (213/249, i.e. 85.5%) identified by patient interview were estimated to be of minor clinical relevance (i.e. limited adherence, knowledge, quality of life, or satisfaction).

Conclusion We demonstrated that structured patient interviews identified additional DRPs that other sources did not identify. Embedded within a comprehensive approach, the structured patient interviews were needed as data resource for over one-third of all DRPs.

Key Points

This observational study highlights the benefits of structured patient interviews as part of comprehensive clinical medication reviews within a geriatric ward setting.

The medication reviews included the use of implicit and explicit criteria and allowed for their critical appraisal.

The interviews were needed to identify over one-third of all causes for potential drug-related problems, most prominently due to insufficient patient knowledge and incomplete patient documentation.

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✉ Dominik Stämpfli
dominik.staempfli@unibas.ch

[1] Department of Pharmaceutical Sciences, University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland

[2] Solothurner Spitaeler AG, Olten, Switzerland

[3] Felix Platter-Hospital, Basel, Switzerland

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1 Background

Inappropriate prescribing is common throughout Europe and is estimated to affect almost one-quarter of elderly patients (22.5%) in Switzerland, leading to increased morbidity and mortality [1, 2]. Patients experiencing potentially inappropriate prescribing either receive potentially inappropriate medications (PIMs), are over- or underdosed, or experience potential prescribing omissions [3]. As the use of PIMs is associated with a higher risk for adverse drug reactions (ADRs), their use causes hospitalisations [4–6]: the management of ADRs is estimated to account for 5–10% of all hospital admissions [7]. A drug-related problem (DRP) is defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" [8]. DRPs are estimated to account for 10–30% of all hospital admissions in the elderly population [9]. Moreover, hospitalised patients are prone to additional DRPs as potentially inappropriate prescribing is higher in inpatients and medication errors are assumed to affect most hospitalised patients [3, 10]. Potentially inappropriate prescribing as a cause for potential DRPs needs to be addressed in order to reduce drug-associated morbidity and mortality in the older population. This challenge may be approached by implementing national guidelines and detecting DRPs early [2, 4].

Identifying and resolving DRPs is best approached in a structured and comprehensive manner: diverse interventions need to be combined into a multifaceted, complete, and global assessment of pharmacotherapy [11]. An approach tested in Belgium, where pharmacotherapy optimisation strategies were identified by a clinical pharmacist present on the ward, showed a significant reduction of misprescribing, overprescribing, and underprescribing [9, 12]. The clinical pharmacist used implicit and explicit criteria of potentially inappropriate prescribing to identify potential prescribing optimisation opportunities. Implicit and explicit tools to assess potentially inappropriate prescribing are means to lower the risk of hospitalisation due to DRPs [6]. Resolving DRPs identified by these tools is shown to decrease ADRs and to improve medication appropriateness [5, 6]. Explicit tools are rigid, criterion-based rules that may be applied with little or no clinical judgement, but fail to address individual differences in patients. Implicit tools are adaptive to the individual patient and may integrate patient preferences, but are time-consuming and depend on the user's judgement. As done by clinical pharmacists in Belgium, including both types of tools in a structured assessment provides an efficient method to assess the appropriateness of a prescription as it combines the advantages of both approaches [6]. Although a ward-based intervention with different tools is comprehensive with regard to the systematic analysis of medical and clinical data, relevant problems may be missed; patient interviews have been shown to identify DRPs with a high clinical significance in home-dwelling patients, as well as in hospitalised patients [13, 14]. Hence, combining explicit and implicit criteria of inappropriate prescribing with the information obtained in patient interviews seems beneficial with regard to the identification of DRPs in hospitalised patients.

1.1 Objective

We aimed to investigate the inclusion of pharmacist interviews as part of medication reviews (including the use of explicit and implicit criteria of inappropriate prescribing) to identify DRPs in older inpatients.

2 Methods

2.1 Study Design and Compliance with Ethical Standards

This was an observational study conducted over a 10-month period from February to November 2016. The regional Ethics Committee 'Ethikkommission Nordwest- und Zentralschweiz' (EKNZ) approved the study under number 44/13. All participating patients provided written informed consent.

2.2 Setting and Patients

We recruited patients from five geriatric and associated physical and neurological rehabilitation wards with access to clinical pharmacy services in a Swiss regional secondary care hospital with 617 beds [15]. Patients were eligible for study inclusion if they were admitted to a participating ward and if they had sufficient knowledge in written and spoken German. We excluded patients with medical conditions preventing meaningful conversations (e.g. delirium, acute psychosis, severe dementia, aphasia, and cognitive impairment), patients treated as part of palliative or terminal care, and patients who had already benefited from other clinical pharmacy services. Clinical pharmacy services are already present on these wards, comprised of irregular ward rounds and phone consultations.

2.3 Recruitment and Interviews

We consecutively screened patients admitted to the participating wards, for inclusion and exclusion criteria. The resident physician or nurse responsible was required to give

permission to visit the patient prior to the first interaction of patient and researcher in order to respect acute deteriorations that were not yet documented in the electronic patient documentation (i.e. delirium, acute psychosis, acute cognitive impairment). Patients were approached within 72 h of admission to the ward. Following patients' consent at the initial visit, their medical records were retrieved from the wards as preparation for the structured patient interview. At the second visit, taking place within 24 h of the initial visit, the interview was conducted and answers were recorded into an electronic protocol. We noted the time taken for the interview.

The structured interview combined a modified Swiss Polymedication Check (PMC) questionnaire [16] with the Beliefs about Medicines Questionnaire [17]. The Swiss PMC questionnaire focuses on medication adherence, patient knowledge, and handling of medicines, and has been shown to identify a significant number of DRPs [16, 18]. With the modified PMC, we questioned patients on administration issues (splitting, swallowing, and confusing their tablets), prescribed medication (regimen, knowledge, adherence, concerns, and ADRs), self-medication (reason, satisfaction, and frequency), and allergies. The structured patient interviews followed a strict protocol (see electronic supplementary Appendix S1). The exact number of questions depended on the number of the patient's medications as most questions were tailored to the individual medication regimen. Because this was an observational study, immediate interventions were only performed if deemed ethically necessary (i.e. giving advice, encouraging adherence).

2.4 Data Collection

In addition to the interview data, we collected data from electronic medical records, laboratory data, and handwritten case notes for the current treatment regimens for all included patients. Electronic medical records contained documented diagnoses, current health status, and vital parameters (i.e. blood pressure, heart rate, stool frequency, and blood glucose levels). Primary data collection was performed on a handwritten case report form (CRF), and the ad hoc data entry of the structured patient interview was performed by using the online questionnaire form Flexiform, version 2.7.1 g (IT services University of Basel), on iPads, version Air 2 (Apple Inc., Cupertino, CA, USA). This procedure was piloted with inpatients to sort out any technical difficulties.

2.5 Medication Reviews

With the collected data, type 3 medication reviews (according to Pharmaceutical Care Network Europe [PCNE] nomenclature [19]) were performed, which involves the analysis of medication appropriateness with the help of medication information, clinical data, and patient statements. The reviews were performed by one board-certified clinical pharmacist (DS) using implicit and explicit criteria on medication appropriateness. Implicit criteria consisted of current treatment guidelines (i.e. SURF-med©: Guidelines Medizin der Schweiz [20]) and use of the Medication Appropriateness Index (MAI) [21]. The MAI consists of a set of 10 criteria, which a reviewer uses to rate each medication taken by a patient using the levels 'appropriate', 'marginally appropriate' or 'not appropriate'. For ratings deemed to be 'marginally appropriate' or 'not appropriate', a weighted score is applied [22]. Medications with a higher MAI overall sum are less appropriate. The criteria judged 'marginally appropriate' or 'not appropriate' indicate possible DRPs for the medication in question. Interrater reliability for the MAI has been shown [23]. Screenings on the criterion drug–drug interaction were performed using the mediQ online database [24]. As explicit criteria, we chose the Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria, versions 2 [5]. The application of the STOPP/START criteria have been shown to detect adverse drug events, improve medication appropriateness, and reduce ADRs [5]. We used the explicit statements exclusively and disregarded the implicit section A of the STOPP criteria.

Every medication review was repeated independently by a second board-certified clinical pharmacist working in a specialised geriatric hospital (AG) to reduce subjectivity potentially introduced by implicit criteria for medication appropriateness [6]. Discrepancies between medication reviews on the presence and type of a DRP were resolved by discussion between both clinical pharmacists until consensus was reached. As this was an observational study, the identified DRPs were only communicated to the resident physician responsible when ethical considerations regarding patient harm were present.

The potential relevance of the DRPs was assessed using the German version of CLEO ($CLEO_{de}$) [25]. CLEO allows clinicians to assess the potential relevance of DRPs in three separate dimensions: 'clinical' (perspective of the patient), 'economic' (perspective of the institution), and 'organisational' (perspective of the care team). Clinical relevance is estimated by assigning different levels of potential harm to an unresolved DRP by the identifiers themselves. $CLEO_{de}$ was tested for reliability in another study, showing good interrater reliability and excellent test–retest reliability among 10 clinical pharmacy raters [26].

2.6 Data Classification

We classified the medication using the Anatomical Therapeutic Chemical (ATC) classification [27]. DRPs and their causes were classified using the GSASA (Swiss Association of Public Health Administration and Hospital Pharmacists) classification system for the documentation of DRPs [28]. The GSASA classification system adapted the PCNE classification system v6.2 to Swiss needs and aimed to improve application in daily practice. It consists of five categories: 'detected problem', 'type of problem', 'cause of intervention', 'intervention', and 'outcome of intervention'. Interrater reliability has been shown [28].

2.7 Statistical Analysis

We analysed the dataset using IBM SPSS Statistics for Windows, version 24.0 (IBM Corporation, Armonk, NY, USA). The dichotomous and qualitative answers to the structured interviews were preprocessed using RStudio, version 1.0.136 (RStudio Inc., Boston, MA, USA) running R, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). We used descriptive statistics for the main analysis. Correlations were examined using Spearman's rank correlation coefficient (ρ), and values were interpreted as follows: $\rho = 0.1$, weak correlation; 0.3, intermediate correlation; and 0.5, strong correlation.

3 Results

3.1 Recruitment

During the enrolment period from February to November 2016, we recruited 110 patients from a total of 437 admissions to the five wards. Figure 1 summarises the recruitment flow.

3.2 Patient Characteristics

The mean age was 76.9 years (standard deviation [SD] 10.3), the percentage of females was 69.1%, and the mean number of prescribed drugs was 11.0 (SD 4.2), including drugs prescribed as needed and used within the last 72 h. Further characteristics of the study population are presented in Table 1.

3.3 Prevalence of Drug-Related Problems (DRPs)

We identified a total of 595 DRPs with our medication reviews, averaging 5.4 DRPs per patient (range 0–17). Overall, 108 patients had at least one DRP (98.2%). Of the 595 DRPs, 34 (5.7%) were evaluated as being 'manifest', i.e. the patient showed signs or symptoms of an adverse drug event, therapy failure, or non-treatment. A total of 299 DRPs (50.3%) were due to medication that was prescribed prior to admission.

3.4 Identification of DRPs by Patient Interviews

From the interview data, we identified 227 DRPs (38.2%) that were not detected by any other information source. 'Insufficient patient knowledge' (e.g. the patient not knowing the indication of the drug) and 'incomplete patient documentation' (e.g. missing diagnoses or treatments) caused the majority of these DRPs, i.e. 137 (56.6%) and 42 (18.5%), respectively. In 78 cases (56.9%) of 'insufficient patient knowledge', the affected medication was prescribed prior to admission, suggesting that the lack of knowledge about the medication was present prior to hospitalisation.

Swallowing, splitting, and confusing their tablets were mentioned by 8.2, 5.5, and 1.8% of patients, respectively. Reasons for the swallowing difficulties were general aversion towards the medication, or being related to specific drugs, i.e. acetaminophen, atorvastatin, metformin, and calcium + cholecalciferol. Splitting issues were mentioned for levetiracetam, metformin, and pravastatin.

The mean time needed for the interviews was 16.6 min (SD 6.5) [range 5–40 min].

3.5 Identification of DRPs Using Implicit and Explicit Criteria

Implicit and explicit criteria contributed differently to the detection of DRPs (see Table 2). A total of 84 DRPs (14.1%) were identified by using the treatment guidelines and clinical experience. We detected 59 DRPs with two or more identification sources.

A total of 100 patients (90.9%) had an MAI > 0, meaning that at least one medication was judged as 'marginally appropriate' or 'not appropriate'. The mean MAI value of the study population was 9.0 (SD 9.1) [range 0–52], and the MAI score strongly correlated with the number of identified DRPs (Spearman's rank correlation coefficient ρ 0.65, $p < 0.05$).

3.6 Characterisation of DRPs and Potential Relevance

Classification of the detected DRPs is presented in Table 2. The various identification sources detected different types of DRPs. On the drug-class level, analgesics were accountable for most DRPs (71 DRPs, 13.7%), with acetaminophen being the most frequent cause in this class (26 DRPs). On the individual drug level, pantoprazole had the highest number of DRPs (35 DRPs, 6.3%), followed by

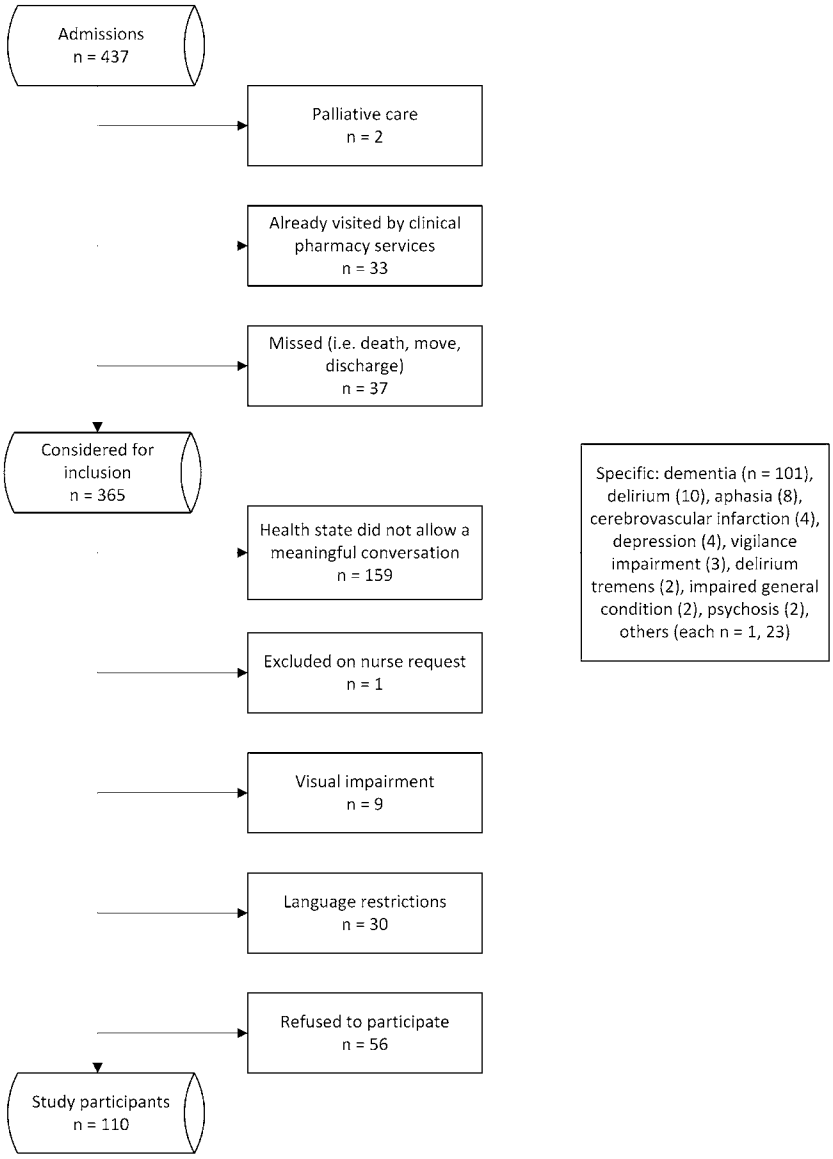

Fig. 1 Study recruitment process

Table 1 Study population characteristics

Characteristic	Value
Demographics [n = 110]	
Age, years [mean ± SD]	76.9 ± 10.3
Female	76 (69.1)
Clinical status	
Glomerular filtration rate[a] [CKD-EPI], mL/min [mean ± SD]	70.5 ± 20.5
Calculated moderate renal insufficiency to renal failure, < 60 mL/min	29 (27.7)
Diagnosed heart insufficiency	4 (3.6)
Diagnosed liver insufficiency	0 (0.0)
Diagnosed COPD	10 (9.1)
Diagnosed diabetes	24 (21.8)
Medication	
Prescribed drugs, including used reserve[b] [mean ± SD]	11.0 ± 4.2
Most prescribed drug groups [ATC 4 digits]	
Antithrombotic agents [B01A]	143 (11.8)
Other analgesics and antipyretics [N02B]	131 (10.8)
Opioids [N02A]	83 (6.8)
Drugs for peptic ulcer and gastro-oesophageal reflux disease [A02B]	70 (5.8)
Drugs for constipation [A06A]	60 (4.9)
Lipid-modifying agents, plain [C10A]	44 (3.6)
Antidepressants [N06A]	39 (3.2)
Antiepileptics [N03A]	37 (3.0)
Antipsychotics [N05A]	33 (2.7)
Blood glucose-lowering drugs, excluding insulins [A10B]	32 (2.6)
Calcium [A12A]	32 (2.6)
Selective calcium channel blockers with mainly vascular effects [C08C]	32 (2.6)
High-ceiling diuretics [C03C]	27 (2.2)
β-Blocking agents [C07A]	27 (2.2)
ACE inhibitors, plain [C09A]	24 (2.0)
Hypnotics and sedatives [N05C]	22 (1.8)
Adrenergics, inhalants [R03A]	22 (1.8)
Vitamin A and D, including combinations of the two [A11C]	20 (1.6)
Other mineral supplements [A12C]	19 (1.6)
Angiotensin II antagonists, combinations [C09D]	18 (1.5)
Insulin and analogues [A10A]	17 (1.4)
Vitamin B12 and folic acid [B03B]	17 (1.4)
Anti-inflammatory and antirheumatic products, non-steroids [M01A]	15 (1.2)
Anxiolytics [N05B]	15 (1.2)
Angiotensin II antagonists, plain [C09C]	13 (1.1)

Data are expressed as n (%) unless otherwise specified

SD standard deviation, *ATC* Anatomical Therapeutic Chemical classification system, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *COPD* chronic obstructive pulmonary disease, *ACE* angiotensin-converting-enzyme

[a]Missing values n = 5

[b]Used within the last 72 h

acetaminophen (26 DRPs, 4.7%) and calcium + cholecalciferol (19, 3.4%). Drug classes and the frequency of DRPs are shown in Fig. 2.

The potential relevance of the DRPs by identification source, as evaluated using $CLEO_{de}$, is shown in Table 3. The clinical dimension of $CLEO_{de}$ estimated the potential relevance of the DRPs to be 'null' (47 DRPs, 7.9%), 'minor' (399, 67.1%), 'moderate' (106, 17.8%), 'major' (40, 6.7%), and 'life-saving' (3, 0.5%).

Table 2 Identified DRPs, as classified by the GSASA classification system [28], and their identification sources

Description	General	Interviews	MAI	START	STOPP
Detected problem					
Safety of treatment	182 (30.6)	19 (7.6)	145 (55.6)	2 (14.3)	44 (93.6)
Patient dissatisfaction	154 (25.9)	151 (60.6)	6 (2.3)	0 (0.0)	0 (0.0)
Treatment effectiveness	107 (18.0)	32 (12.9)	54 (20.7)	2 (14.3)	0 (0.0)
Untreated indication	52 (8.7)	9 (3.6)	1 (0.4)	10 (71.4)	0 (0.0)
Treatment costs	7 (1.2)	0 (0.0)	7 (2.7)	0 (0.0)	2 (4.3)
Classification not possible	93 (15.6)	38 (15.3)	48 (18.4)	0 (0.0)	1 (2.1)
Cause of intervention					
Insufficient patient knowledge	138 (23.2)	138 (55.4)	5 (1.9)	0 (0.0)	1 (2.1)
Incomplete patient documentation	118 (19.8)	45 (18.1)	62 (23.8)	0 (0.0)	3 (6.4)
No concordance with guidelines or contraindication	60 (10.1)	0 (0.0)	27 (10.3)	4 (28.6)	15 (31.9)
Drug not indicated, or duplication	46 (7.7)	4 (1.6)	40 (15.3)	0 (0.0)	21 (44.7)
Treatment not received	46 (7.7)	7 (2.8)	1 (0.4)	10 (71.4)	0 (0.0)
Interaction	36 (6.1)	0 (0.0)	35 (13.4)	0 (0.0)	2 (4.3)
Overdose	29 (4.9)	3 (1.2)	25 (9.6)	0 (0.0)	0 (0.0)
Underdose	25 (4.2)	4 (1.6)	21 (8.0)	0 (0.0)	0 (0.0)
Inappropriate therapy duration	20 (3.4)	3 (1.2)	18 (6.9)	0 (0.0)	4 (8.5)
Insufficient compliance	19 (3.2)	19 (7.6)	1 (0.4)	0 (0.0)	0 (0.0)
Inappropriate timing or frequency of administration	14 (2.4)	3 (1.2)	14 (5.4)	0 (0.0)	0 (0.0)
Adverse effect	12 (2.0)	6 (2.4)	1 (0.4)	0 (0.0)	1 (2.1)
Dose not adjusted to organ function	9 (1.5)	2 (0.8)	7 (2.7)	0 (0.0)	0 (0.0)
Inappropriate dosage form	7 (1.2)	6 (2.4)	2 (0.8)	0 (0.0)	0 (0.0)
Error in the medication process	3 (0.5)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Insufficient knowledge of caregivers	2 (0.3)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Prescribed drug not available	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Classification not possible	10 (1.7)	5 (2.0)	1 (0.4)	0 (0.0)	0 (0.0)
Total	595	249	261	14	47

Data are expressed as *n* (%). Some DRPs were identified by multiple sources. Percentages relate to column data for each detected problem or cause of intervention

MAI Medication Appropriateness Index, *STOPP* Screening Tool of Older People's Prescriptions, *START* Screening Tool to Alert to Right Treatment, *DRP* drug-related problem, *GSASA* Swiss Association of Public Health Administration and Hospital Pharmacists

4 Discussion

We performed 110 type 3 medication reviews for consenting patients on geriatric and associated physical and neurological rehabilitation wards, and identified 595 manifest and potential DRPs, averaging 5.4 per patient. This average was lower than in similar studies, where means of approximately 10 DRPs per patient were reported [12, 13], a discrepancy that may be explained by clinical pharmacy services already being established prior to our observation period, leading to an educational bias [9]. The structured interviews identified 249 DRPs, of which 227 were not identified by any other information source. Although most of the DRPs identified by the interviews were estimated to be of 'minor' clinical relevance, the results suggest a contribution of the interviews to the data completion necessary for DRP identification. The most prominent causes for potential DRPs were insufficient patient knowledge and incomplete patient documentation (i.e. missing medication, missing diagnoses). Questioning patients on the indication for the medications accounted for most DRPs identified during the interviews, even for medication prescribed prior to admission. The proportion of 299 DRPs (50.3%) due to medication that was prescribed prior to admission suggests that these issues could have already been addressed in the primary care setting prior to hospital admission. Insufficient knowledge on the medication regimen may be a sign of health illiteracy, which is linked to reduced health outcomes [29]. As pharmacotherapy is individualised to account for diverse patient goals, patients need to be

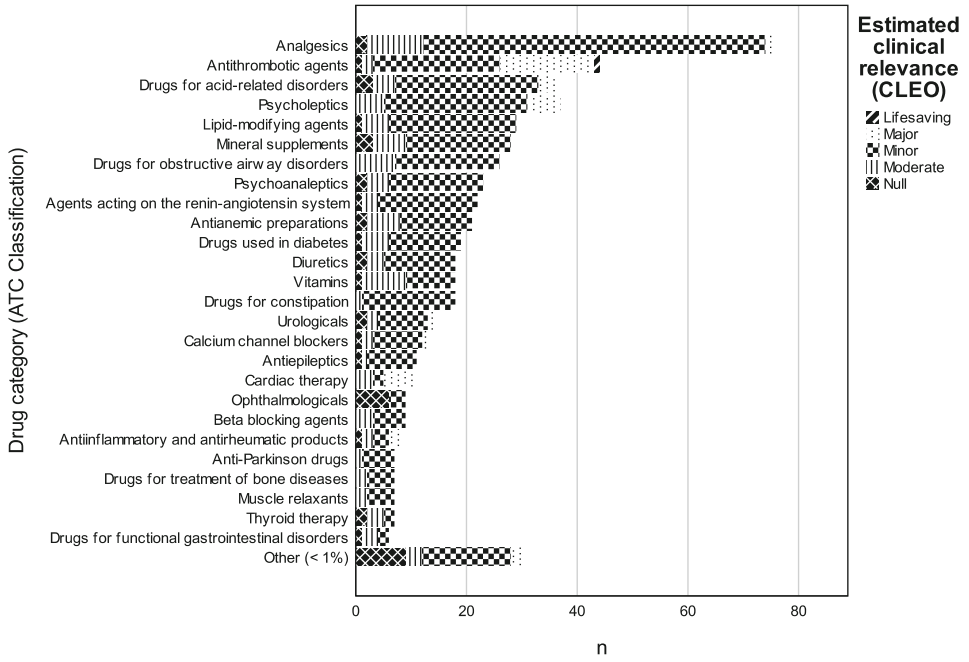

Fig. 2 Number of drug-related problems within drug classes (ATC codes) [27], aggregated in terms of estimated clinical relevance according to $CLEO_{de}$ [26]. *ATC* Anatomical Therapeutic Chemical classification system, *CLEO* CLinical, Economic, and Organizational, $CLEO_{de}$ German version of CLEO

Table 3 Potential relevance of the DRPs by identification source, as evaluated using $CLEO_{de}$

Potential clinical relevance[a]	General	Interviews	MAI	START	STOPP
Null	47	16	30	0	4
Minor	399	213	153	9	32
Moderate	106	17	47	2	7
Major	40	3	31	0	4
Life-saving	3	0	0	3	0

DRPs may have been identified by multiples sources or by application of guidelines only. Null: no effect on the patient in regard to clinical situation, knowledge, satisfaction, adherence or quality of life. Minor: effect on patient in regard to clinical situation, knowledge, satisfaction, adherence or quality of life OR damage that does not necessitate surveillance or treatment. Moderate: damage that necessitates surveillance or treatment but does not lead to hospitalisation or prolongation thereof. Major: damage that leads to hospitalisation or prolongation thereof OR damage that leads to disablement or impairment. Life-saving: damage that leads to intensive care treatment or death

MAI Medication Appropriateness Index, *STOPP* Screening Tool of Older People's Prescriptions, *START* Screening Tool to Alert to Right Treatment, *DRP* drug-related problem

[a]Levels (translated from German)

educated on its specific rationale to improve adherence [30]. Complete patient documentation (e.g. medication histories) is especially important to prevent harm in older patients taking a large number of medications [31]. Our results support previous research on the necessity of bedside interventions and patient counselling by clinical

pharmacists; Viktil et al. detected 39.9% of all 421 DRPs within the hospital setting through interviews performed by clinical pharmacists [14]. Similar to our results, their study found missing medication, medical chart errors, and the need for patient education, to be more frequently identified through interviews [14]. However, individual patient interviews as a source of information are time-consuming; the interview times in our study ranged from 5 to 40 min, averaging 16.6 min per interview. Similarly, the clinical pharmacists in the study by Viktil et al. spent 20.3 min (range 5–60 min) for their interviews. Nonetheless, in their meta-analysis of clinical pharmacy services, Perez and colleagues calculated a pooled median benefit-to-risk ratio of 4.81–1 across 15 studies, showing $4.81 in reduced costs or other economic benefits for every $1 spent on clinical pharmacy services [32], thereby justifying expenditures by the hospital due to clinical pharmacists performing medication reviews inclusive of patient interviews.

Use of the MAI identified 43.9% of all DRPs and the patient's score strongly correlated with the patient's number of DRPs, which highlights the benefits of using a structured and implicit approach towards the assessment of prescribing appropriateness. This correlation may also be used to measure the effect of interventions that target suboptimal prescribing [33]. Hence, we support the suggestion that the MAI should be part of routine practice in drug regimen reviews [9]. However, it must be taken into consideration that patient statements are indispensable for certain MAI criteria (i.e. 'Is the medication effective for the condition?'; 'Are the directions practical?'). Thus, the combination of MAI together with patient interviews, as shown here, seems beneficial. The STOPP and START criteria identified 7.9 and 2.4% of DRPs, respectively. A study on DRPs of community-dwelling older patients concluded that 81% were not represented in either the STOPP or START criteria [34]. However, the low proportion in our results might be associated with our decision to use the explicit criteria only and to exclude all implicit criteria. In other studies, the implicit criterion 'no indication present' was one of the most identified DRPs [34]. We covered this criterion by using the MAI. Additionally, the START criterion 'Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation' was responsible for the identification of the three DRPs estimated to be of 'life-saving' clinical relevance (Table 3). Although all three prescribing omissions were also identified by the application of current treatment guidelines, this circumstance allows for a positive appraisal of the START criteria.

We identified analgesics as the main drug class associated with the identified DRPs. Similar results were obtained in studies conducted on internal medicine and rheumatology wards: opioids, non-steroidal antirheumatic drugs, antithrombotic agents, and agents acting on the renin–angiotensin system were the main contributors [35]. On a drug level, we found pantoprazole to be associated with most DRPs. Proton-pump inhibitors (PPIs) are known to be associated with overprescribing, and it is estimated that 25–70% of patients with PPIs have no appropriate indication [36]. Our population consisted of geriatric patients, of whom 11.8% received an antithrombotic agent. Prevention of upper gastrointestinal bleeding was a possible, but not mandatory, indication for PPIs in Switzerland.

The clinical dimension assessed by $CLEO_{de}$ estimated the potential relevance of DRPs to be 'minor' for 67.1% of cases (n = 399). Furthermore, of the 249 DRPs identified only by patient interviews, 85.5% were estimated to be of 'minor' clinical relevance (n = 219). This stands in contrast to other research where approximately 66% of DRPs found during the interviews were assessed by the interviewers to be of 'major' or 'extremely important' clinical relevance. $CLEO_{de}$ assigns patient-level interventions (i.e. improved adherence, knowledge, quality of life, or satisfaction) to its 'minor' level. The assignment of patient-centred DRPs such as these to minor clinical relevance is related to the use of $CLEO_{de}$ to estimate potential clinical relevance, as $CLEO_{de}$ focuses on direct and prompt consequences. However, this is debatable, since health illiteracy and swallowing difficulties are risk factors for DRPs and non-adherence, and may cause patient harm over the long-term [37, 38].

4.1 Strengths and Limitations

To our knowledge, this is the first study that highlights the information gained by structured patient interviews within a hospital setting as part of type 3 medication reviews, which involved implicit and explicit criteria for medication appropriateness. Described as a necessity for optimising geriatric pharmacotherapy, we display the potential of an approach, which was multifaceted with regard to the assessment of medication appropriateness (implicit and explicit criteria), complete with regard to the performed medication review, and global with regard to the involvement of the patients [11]. In addition, the medication reviews were performed by one clinical pharmacist, which ensured consistency in assessment and coding [39], and were independently repeated by a second clinical pharmacist, which improved validity by reducing subjectivity.

As we were limited to an observational study, the identified DRPs were not resolved (e.g. by suggesting PPI deprescription) unless ethically necessary. Hence, we could not report clinical outcomes or acceptance rates. However, we know from previous studies that interventions based on patient interviews are of high relevance in two-thirds of DRPs assessed [14]. Generalisation of our results to other

areas of clinical practice is limited as the study was conducted on specific wards and the exclusion criteria were restrictive; 'state which does not allow a meaningful conversation' prevented the enrolment of 159 patients (43.6%). Verbal communication is a necessity for structured interviews and was also respected by Viktil et al. Similar reasons led to the exclusion of 84 patients (46.7%) in the corresponding study [21]. The implementation of structured patient interviews in routine clinical practice, as described in this study, does not seem probable as both the interviews and the use of implicit criteria of potentially inappropriate prescribing were time-consuming. However, countries such as Denmark already compel their hospitals to perform regular patient interviews as part of medication reconciliation processes, displaying awareness of both the necessity and feasibility of these strategies [40].

5 Conclusions

We were able to demonstrate that structured patient interviews contribute to the identification of DRPs within a comprehensive approach. The interviews exposed DRPs that are only accessible in dialogue with patients, such as limited adherence, patient knowledge, quality of life, or satisfaction. Structured patient interviews should mainly focus on the patient's knowledge of the indication of the medication, and on the integrity of the patient documentation. An approach including implicit and explicit PIM tools seems mandatory to enable the identification of DRPs with various causes.

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Compliance with Ethical Standards

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Conflict of interest Dominik Stämpfli, Fabienne Boeni, Andy Gerber, Victor Bättig, Kurt Hersberger and Markus Lampert declare that they have no conflicts of interest relevant to the content of this study.

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V. Risk of Drug-Induced QT_c Interval Prolongation – A Step Closer to a Clinical Risk Management

In order to investigate the RISQ-PATH score's ability to predict QT_c intervals, a moderated hierarchical regression analysis was performed on the 156 observed patient cases. Regression analyses are used to analyse associations between a dependent variable and numerous independent variables. They may be used to describe an association (e.g. between proposed scores and measured traits) or to predict the value of the dependent value (e.g. measured QT_c interval). Hierarchical regression analyses – also described as step-wise regression analyses – allow for the identification of statistically significant models that describe an association between the dependent and the independent variables. The independent variables are entered in blocks and only kept if they improve the model. Besides generating a model, this process also displays a hierarchy of statistically significant associations with the most important variable being on top. These identified associations may be moderated by a third variable, which partitions the independent variable (i.e. RISQ-PATH score) into subgroups and influences the strength of the relation to the dependent variable (i.e. measured QT_c interval). These moderators need to be identified in order to understand the model's restrictions.

For the evaluation of the RISQ-PATH score's performance in a population of Swiss geriatric inpatients, this thesis provided the statistical procedures (hierarchical and moderated hierarchical regression analyses) to the draft presented here. These analyses permitted simultaneous investigation of the association between the score and the measured QT_c intervals and the identification of possible moderators affecting this association.

Risk of Drug-Induced QTc Interval Prolongation – A Step Closer to a Clinical Risk Management

Hanh Pham (1), Dominik Stämpfli (2), Markus L. Lampert (2,3)

Draft

(1) Kantonsspital Baselland, Switzerland (2) Department of Pharmaceutical Sciences, University of Basel, Switzerland; (3) Solothurner Spitaeler AG, Switzerland

Background

Numerous drugs are known to evoke a QT-interval prolongation by affecting the cardiac repolarization. The prolongation of the corrected QT interval (QTc) is assessed by electrocardiogram (ECG) and can be used as a surrogate marker of impending ventricular arrhythmia such as torsade de pointes (TdP). TdP is life threatening as it may lead to sudden cardiac death due to ventricular fibrillation [1]–[3].

Over the last few years progress has been made in the understanding of the mechanism of the drug-induced QTc interval prolongation and the knowledge about its risk factors has become more accurate [4]–[7]. The University of Arizona's Center for Education and Research on Therapeutics (Arizona CERT) has ranked over 220 drugs that induce QTc prolongation (QTDrugs) into four distinct lists: Drugs with known risk for TdP (QTDrug list 1), drugs with possible risk for TdP (QTDrug list 2), drugs with conditional risk for TdP (QTDrug list 3), and drugs to avoided by patients with congenital long QT syndrome (LQTS) [8].

Although there are known associations between QTDrugs and the combination with risk factors for increasing the QTc interval prolongation, precise prediction of the risk for a QT-interval prolongation and TdP remains difficult [9], [10]. Hence, prescribers need to carefully balance the possible risks against the therapeutic benefits of a QTDrug. Dhanani and colleagues mentioned the importance of clinical pharmacists in a clinical healthcare team when prescriptions are reviewed and balanced [11]. This is particularly apparent in a multimorbid geriatric population, which combines the presence of several risk factors with being exposed to numerous QTc-prolonging drugs [4]. Daily clinical risk management is especially difficult, as no guidelines on reducing QTc prolongation risk exist.

To date, two research groups (Tisdale et al. and Vandael et al.) each have developed a risk score to predict the potential for QTc interval prolongation. Based on their observational studies they weighed identified risk factors. With a summated risk score Tisdale et al. divided patients into low, moderate, and high risk patients for QTc prolongation [12]. Vandael et al. developed a preliminary risk score, the RISQ-PATH score, which includes concomitant risk factors based on a systematic review of observational studies. The score should guide clinical decision making by estimating the risk of QTc interval prolongation for individual patients and should therefore facilitate the prescribing process of QTDrugs. The RISQ-PATH score was validated with a patient population starting Haloperidol or a QTc prolonging antibiotic or antimycotic [6], [13].

This retrospective study aimed to determine the prevalence of administered QTDrugs and present risk factors in a large hospital-based geriatric cohort. The magnitude of the combined risk factors for QTc interval prolongation should be qualified. This provided an opportunity to investigate and externally validate the RISQ-PATH score within a clinical setting.

Methods

Patient selection, study design

This observational, cross-sectional study was performed on rehabilitation, acute geriatric wards, and internal medicine wards of a Swiss regional secondary care hospital. For six weeks (December 2016 to January 2017), every other day (Monday, Wednesday and Friday) newly admitted inpatients were recruited from the wards when the inclusion criteria ≥ 18 years and ≥ one drug with risk for QTc prolongation as listed on crediblemed.org were present [8]. Demographic and medication data of the inpatients were gathered from the electronic patient file of the hospital.

Study procedure, RISQ-PATH score

On the index day (Monday, Wednesday or Friday), the RISQ-PATH score was calculated for each patient with clinical diagnoses, inpatient medication list, and laboratory data according to the following criteria [13]:

- Medication of the inpatient: all actual medications were recorded on the index day. The ATC-Code of the World Health Organization [14] was allocated to all drugs of the inpatient. All drugs with a potential risk for QTc interval prolongation were categorised according to crediblemeds.org into QTDrug list 1: known, list 2: possible and list 3: conditional risk for QTc interval prolongation.
- Demographical values: Age, sex, weight, height, body mass index (BMI), and smoking habit
- Diagnoses of hypertension, cardiomyopathy, arrhythmia, thyroid disturbance, liver failure, and diabetes
- Laboratory results recorded on the sample day or newest result (max. 1 week old) of serum potassium, calcium, C-reactive protein (CRP) and estimated glomerular filtration rate based on Cockcroft-Gault equation (GFR)

- QTc time (corrected according to Bazett's formula[15]) collected from performed ECG during hospitalization under a treatment with a QTDrug.

As defined by Vandael et al. [13], points were given for each risk factor based on their evidence level. The RISQ-PATH score was summated as follows:

- Very high evidence: 6 points for prolonged QTc [≥450(m)/470(f) ms] and potassium ≤ 3.5 mmol/l;
- High evidence: 3 points for age ≥ 65 years, female gender, smoker, (ischemic) cardiomyopathy, arrhythmia, thyroid disturbances, calcium < 2.15 mmol/l;
- Moderate evidence: 1 point for BMI ≥ 30 kg/m^2, liver failure and CRP > 5 mg/l;
- Low evidence: 0.5 point for positive diabetes anamneses and GFR < 30 ml/min;
- QTDrug list 1: 3 points, QTDrug list 2: 0.5 points, and QTDrug list 3: 0.25 points.

The risk factor "neurological disorder" was not included in this study as it was considered to be too subjective due to its unclear definition. The points of the RISQ-PATH score were summed up for each patient.

Statistical analysis

The dataset of patient cases was analysed for association of the RISQ-PATH score with the measured QTc intervals. Cases were excluded when data was missing, i.e. ECG measurements were not available. Outlier identification was performed by using z-scores checking for normal distribution (variables: RISQ-PATH score, measured QT_c intervals).

Simple scale correlations between the calculated RISQ-PATH score and the measured QTc interval were assessed by Spearman's rank correlation coefficient rho (ρ),[1] which we interpreted as: ρ=.1 as weak, .3 as moderate, and .5 as strong [16]. Moreover, the results were divided in 4 percentiles according to the ascending RISQ-PATH score to investigate the distribution per quantile.

A hierarchical regression analysis was performed to identify risk factors of the RISQ-PATH score significantly contributing to the prediction of the measured QTc intervals. To assess whether these identified risk factors acted as moderators of the associations, we performed moderated hierarchical regression analyses following the procedure described by Aiken, West, and Reno [17]. All other risk factors of the RISQ-PATH

score were entered in a first block. The risk factors identified by the hierarchical regression analysis were then entered in the next block. Finally, the interaction terms between the identified risk factors and the RISQ-PATH score were entered in the last block. When an interaction was found to be significant, which highlighted a significant moderation effect, the measured QTc interval by the RISQ-PATH score were graphed separately with the moderator used as categorical variable. Separate multiple regression analyses were used to evaluate whether the slopes in the graphs were significantly different from zero [17].

We defined statistical significance as *p*-values <.05. The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.), and Microsoft Excel, Version 1712 (2016).

Results

Study population

Figure 1 shows the flow chart of the inclusion process. During the enrolment period, 248 inpatient entries were scanned. 202 (81.5%) patients were included in the study from the internal medicine (N=73 (36.1%)), rehabilitation (N=86 (42.6%)), and acute geriatric (N=43 (21.3%)) units. The study population consisted of 77 male (38.1%) and 125 female (61.9%) inpatients. The detailed demographical data is presented in Table 1. Within the enrolment period, 794 QTDrugs were registered. Thereof, 460 QTDrugs were prescribed as a fix medication as shown in Figure 2 with their corresponding ATC Code [14]. Resulting in 81.5% of all screened patients receiving at least one QTDrug after the hospital admission (Table 1). One-third of all patients (33.7%, N=68) was exposed to at least one QTDrug list 1.

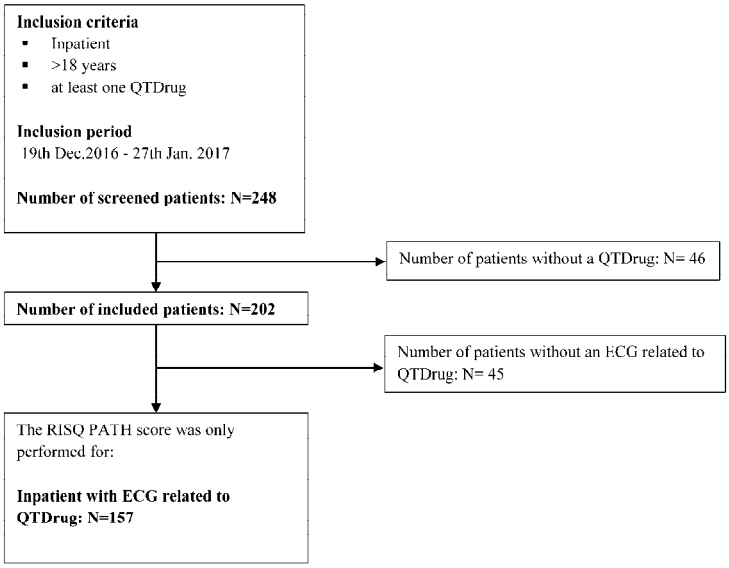

Figure 1 Flow chart of data collection.

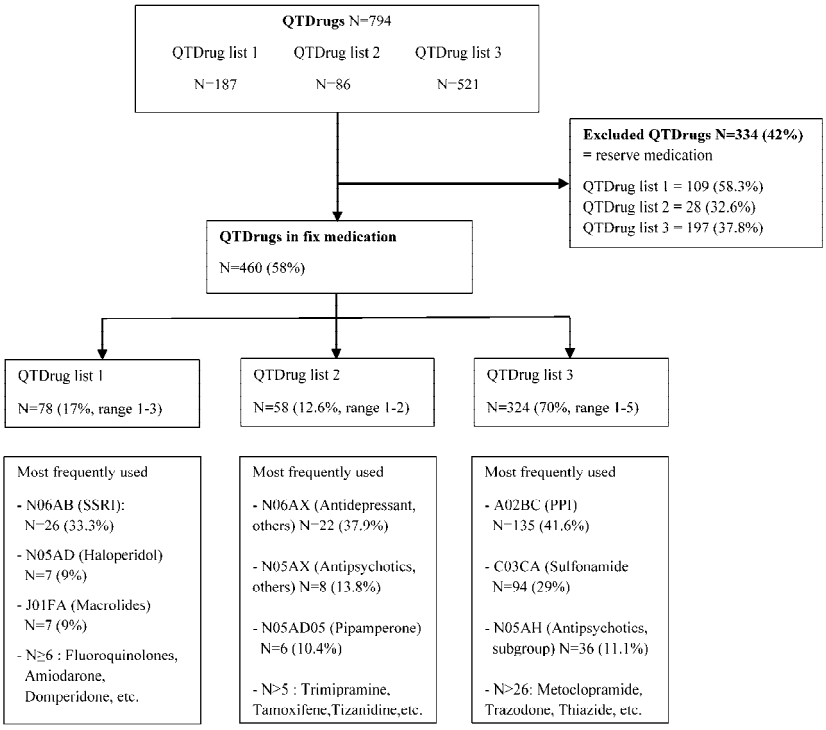

Figure 2 Flow chart of QTDrug in the baseline therapy and the most frequently used three of each category in accordance to their ATC-Code.

Table 1 Demographical data of the inpatients.

Characteristic	Total patient population (N=202) in [number] (%)
Age [median, range]	83 [44-99]
Gender	
Female	125 (61.9)
Male	77 (38.1)
Unit	
Internal Medicine	73 (36.1)
Rehabilitation	86 (42.6)
Acute Geriatric	43 (21.3)
Number of patients with a QTDrug	202
≥1 QTDrug list 1	68 (33.7)
≥1 QTDrug list 2	52 (25.7)
≥1 QTDrug list 3	182 (90.1)

QTDrug lists: crediblemeds.org; QTDrug list 1 = known, list 2 = possible, list 3 = conditional risk for QTc interval prolongation

The antidepressants citalopram (N=5) and its enantiomer escitalopram (N=26) accounted for 39.7 % of CredibleMeds list 1 QTDrugs. 14 antibiotics (chinolone N=7, clarithromycin N=7) and 2 antimycotic (fluconazol) with known risk for QTc prolongation were prescribed during the hospitalisation. The most frequently used medication was pantoprazole (QTDrug list 3) which was found on 130 medication lists. The most popular diuretic of the QTDrug list 3 used in this population was torasemide (N=94).

RISQ-PATH score

The RISQ-PATH score was determined for 156 patients for whom a recent ECG was available. The calculated preliminary RISQ-PATH score for each inpatient ranged from 4 to 30 points, with a median of 14.6 points. Of the available ECGs, 20.6% (N=20 of 97) women and 61% (N=36 of 59) men had a prolonged QTc. The RISQ-PATH score of each patient divided into four quartiles is shown in Table 2. A total of 76.8% of QTc prolongation occurred in the 3rd and 4th quartiles.

Table 2 Results of the study population (N= 156) with an ECG related to a QTDrug treatment divided into 4 quartiles according to the points of the RISQ PATH score.

RISQ PATH risk factor	Total patient population (N=156) in number (%)	1st quartile: RISQ PATH score 0-11.25 points (N=39)	2nd quartile: RISQ PATH score 11.5-14.5 points (N=39)	3rd quartile: RISQ PATH score 14.75-19.25 points (N=39)	4th quartile: RISQ PATH score 19.25-30 points (N=39)
RISQ PATH score [median (range)]	14.625 (4-30)	8.75 (4-11.25)	13.25 (11.25-14.5)	16.75(14.75-19.25)	22.5 (19.5-30)
Age ≥ 65 years	137 (87.8%)	29	35	36	37
Female sex	97 (62.2%)	27	23	19	28
Smoker	28 (17.9%)	5	7	7	9
BMI ≥30 kg/m^2	16 (10.3%)	4	4	3	5
(ischemic) cardiomyopathy	16 (10.3%)	2	4	5	5
Hypertension	102 (65.4%)	20	20	28	34
Arrhythmia	59 (37.8%)	1	12	19	27
ECG					
- prolonged QTc ≥450 ms (m)	36 (23.1%)	1	11	16	8
- prolonged QTc ≥470 ms (f)	20 (12.8%)	0	1	6	13
Thyroid disturbances	19 (12.2%)	0	3	4	12
Liver failure	27 (17.3%)	7	7	5	8
Diabetes	37 (23.7%)	3	9	11	14
Potassium ≤3.5 mmol/L	11 (7.1%)	0	0	3	8
Calcium <2.15 mmol/L	62 (39.7%)	6	14	18	24
CRP >5 mg/L	97 (62.2%)	26	21	23	27
Estimated GFR (Cockroft-Gault) ≤30 mL/min	32 (20.5%)	2	12	6	12
CredibleMeds QTDrug list 1	50 (32.1%)	5	8	12	25
CredibleMeds QTDrug list 2	41 (26.3%)	11	12	6	12
CredibleMeds QTDrug list 3	142 (91.1%)	35	34	37	35

Statistical analysis

Preliminary steps with case exclusions due to missing ECG measurements reduced the analysed dataset to a total of 156 observations, consisting of 97 female and 59 male patients. No outliers were identified.

The RISQ-PATH score showed a moderate correlation with the measured QTc interval (Spearman's rank correlation $\rho = .39$, $p < .01$). Hierarchical regression analysis was first calculated for the whole dataset. Identified significant contributors to the prediction of measured QTc intervals were the risk factors 'Prolonged

QTc' (β = 0.76, $p < .001$) and 'QTDrug list 3' (β = -0.11, $p = .03$). Moderated hierarchical regression analyses were performed with the interaction terms between these two predictors (i.e. 'Prolonged QTc' and 'QTDrug list 3') and the RISQ-PATH score, controlling for all risk factors not significantly contributing to the prediction (i.e. all other risk factors of the RISQ-PATH score). These analyses showed one significant interaction term (see Table 3): 'Prolonged QTc' (β = 0.49, $p = .03$) moderated the association between RISQ-PATH score and measured QTc interval. The interaction term between 'QTDrug list 3' and RISQ-PATH score was not found to improve the model significantly if 'Prolonged QTc' was present as control variable within the model. As shown in Figure 3, the RISQ-PATH score was significantly associated with measured QTc intervals (β = 0.31, $p = .02$) for inpatients with a prolonged QTc interval, such that higher RISQ-PATH scores were related to longer QTc intervals, whereas in patients without a pre-existing prolonged QTc interval there was no significant association between the RISQ-PATH score and measured QTc intervals (β = -0.06, $p = .52$).

Table 3 Moderated Hierarchical regression analysis.

		Value
Step 1	R^2 of total model	0.17
Step 2a	Prolonged QTc on a baseline ECG	0.78**
	RISK-PATH score x 'Prolonged QTc on a baseline ECG'	0.49*
	ΔR^2 of interaction	0.01*
	R^2 of total model	0.65*
Step 2b	List 3 QT-drug CredibleMeds	-0.12*
	RISK-PATH score x 'List 3 QT-drug CredibleMeds'	-0.08
	Delta R^2 of interaction	0.0*
	ΔR^2 of total model	0.64*

Coefficients are standardised regression coefficients if not otherwise indicated. Step 1: Model with all risk factors except 'Prolonged QTc on a baseline ECG' and 'List 3 QT-drug CredibleMeds,' i.e. Age ≥65 years, female sex, smoking, BMI ≥30 kg/m^2, (ischemic) cardiomyopathy, hypertension, arrhythmia, thyroid disturbances, liver failure, neurological disorders, diabetes, potassium ≤3.5 mmol/L, calcium <2.15 mmol/L, CRP >5 mg/L, estimated glomular filtration rate ≤30 mL/min, for each list 1 QT-drug CredibleMeds, for each list 2 QT-drug CredibleMeds. Step 2a: Model with 'Prolonged QTc on a baseline ECG' and the interaction term RISQ-PATH score x 'Prolonged QTc on a baseline ECG' as predictors for measured QT interval, controlled for risk factors entered in step 1. Step 2b: List 3 QT-drug CredibleMeds and the interaction term RISQ-PATH score x 'List 3 QT-drug CredibleMeds' interaction terms as predictors for measured QT interval, controlled for risk factors entered in step 1.
* $p < .05$
** $p < .001$

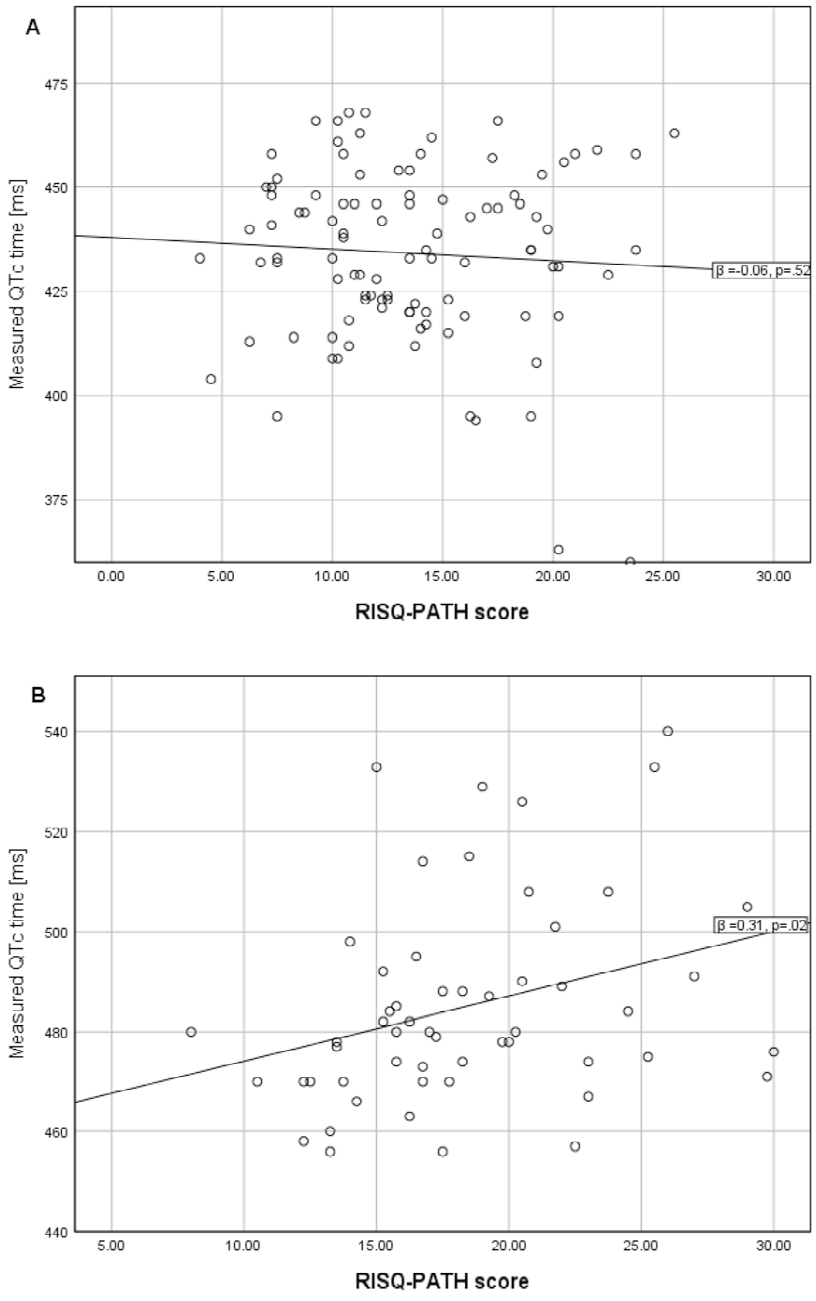

Figure 3 Associations of RISQ-PATH scores and measured QTc interval (A: patients without previously prolonged QTc interval, N = 101; B: patients with previously prolonged QTc interval, N = 55). Standardised regression coefficients (β) and p-values are presented next to the slope.

Discussion

From the internal medicine, rehabilitation, and acute geriatric wards, 81% of admitted patients were exposed to one or more QTDrug. This high utilization rate of QTDrugs highlights the requirement of a clinical risk management to balance risks against therapeutic benefits. We adopted the RISQ-PATH score in our observational, cross-sectional study aiming to investigate its benefits for a broader population of inpatients.

Based on the hierarchical regression analysis we report an association between the RISQ-PATH score and the measured QTc interval. Concerning our specific dataset of 156 patients, we identified the risk factor 'Prolonged QTc' as a moderator for this association. The association between the RISQ-PATH score with the measured QTc interval was significant for the patients with a present prolonged QTc interval. This result implies that the RISQ-PATH score is highly dependent on one specific risk factor. Concluding, if a prolonged QTc interval is present, an association between the RISQ-PATH score and the measured QTc interval exists, whereas with no previously prolonged QTc interval no association between RISQ-PATH score and the QTc interval may be expected.

From the RISQ-PATH score median of 14.6 points a wider spreading of the QTc interval over the definite prolonged QTc time (range 360-540 ms) could be assessed. Furthermore, a small number of patients (N= 11) with a RISQ-PATH score ≤ 15 points had a prolonged QTc interval (mean=471.5 ms ±8.5) which leads to the assumption that a QTc interval prolongation event rarely occurs in this patient population.

There was no association between QTc intervals and number of QTDrugs. This implies that the prediction of the risk for QTc interval prolongation by solely focusing on the medication is not sufficient. This finding is supported by Jardin and colleagues [18], who screened inpatients for risk factors of QTc interval prolongation and reported an association of QTDrug list 1 alone or concomitant with other QTDrugs with QTc interval prolongation, whereas QTDrug from the list 2 and 3 did not show any association with QTc interval prolongation. The study hence questioned the clinical relevance of drug-drug interactions between two QTDrugs of the list 2 or 3. In our population, 68.6% of the patients receiving a QTDrug list 1 did not have a prolonged QTc interval. These results support the conclusion that the prediction of a drug-induced QTc interval prolongation or a TdP remains difficult [10].

Many studies have been claiming female sex as a risk factor, which is consequentially, because women generally have a longer QTc interval than men [19]–[21]. This prevalence did not occur in our study. We detected a higher number of men (N=35) having a QTc interval prolongation compared to 20 women with prolonged QTc interval. Rabkin reported no difference of the QTc interval in women and men at older ages [22]. The older age of our population, which comprised 86.6% (N=175) patients over 65 years old with a mean age of 83 years, would support Rabkin's outcome that the gender is a neglected factor in older patients when estimating the risk for QTc interval prolongation.

Only 16 (ischemic) cardiomyopathy cases were clearly documented in all patients' diagnosis list. The number of cardiomyopathy slightly increased with the ascending RISQ-PATH score. Cardiac failure on the myocardium is linked to a higher risk for QTc prolongation [23]. As the risk factors hypertension and arrhythmia were increased with higher RISQ-PATH scores as well, we may support the findings by other studies, which have reported patients with advanced heart diseases as being at higher risk for QTc interval prolongation [6].

Thyroid disturbance was determined by a positive diagnosis and by finding the substitution with levothyroxine on the medication list. An increasing number of patients with thyroid disturbances was observed with higher RISQ-PATH scores, which supports the effects of thyroid disturbance on ECG measurements [24]. Hypokalaemia and hypocalcaemia affecting the cardiac ion channels and resulting in changes of the QTc interval is widely shown [5], [6], [9], [25], [26]. A n electrolyte disorder should be treated before exposing the patient to further risk factors such as prescribing a QTDrug.

Strengths and limitations

A strength of this study mark the unrestrictive inclusion criteria of inpatient aged older than 18 years with a minimum of one QTDrug, which resulted in a diverse study population at a size of 202 patients. A representative broad population was further enabled by performing this study on three different wards.

Limitations of this study firstly include that missing patient data such as incomplete diagnoses lists or rare documented information of smoking habits led to lower points on the RISQ-PAHT score, since missing values were entered as no risk factor. Hence, the RISQ-PATH score was lower than if all risk factors were available. Secondly, the QTc time was taken from the newest available ECG during a QTDrug treatment and varied

from an ECG on the index day to ECGs being 14 days old. Yet another limitation was the QTDrug categorization, which was adopted from CredibleMeds.org. The categorization of pantoprazole as QTDrug list 3 led to the inclusion of a high number of patients (N=130). The mechanism of pantoprazole to induce a QTc interval prolongation is explained by its changes to the intestinal pH, which may lead to reduced absorptions of magnesium and potassium [27]. But so far, only case reports have linked hypomagnesemia caused by proton pump inhibitors with arrhythmia. On the other hand, amiodarone (QTDrug list 1) rarely provokes TdP and has cardio protective effects, yet is categorized as QTDrug list 1 [28]. These examples show the difficulties associated with predicting the severity of a drug's risk by solely using its classification.

Conclusion

With 81.5 % of inpatients being exposed to at least one QTDrug, this study highlights the requirement of a drug-induced QTc interval prolongation risk management. The RISQ-PATH score was associated with QTc interval prolongation, with the risk factor 'prolonged QTc interval' as the moderator of this association. We hence suggest the development of a different scoring and interpretation of the RISQ-PATH score for patients without a previously present prolonged QTc interval. Having two separate scale interpretations would increase the RISQ-PATH score's capability as a guiding tool for ECG measurements. The RISQ-PATH score summates and weighs risk factors associated with a prolonged QTc interval with the necessary respect to pharmacodynamic drug interactions. Our analyses on this meticulously developed tool however support a simple code of practice: ECG measurements before starting a QTDrug in a patient with a documented prolonged QTc interval.

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GENERAL DISCUSSION AND CONCLUSION

The goals of this thesis were (1) the validation of the Drug-Associated Risk Tool (DART) – a self-administered patient questionnaire as a risk-stratification tool on DRPs – and (2) the external validation of the RISQ-PATH score as a risk-stratification tool on drug-induced QT-prolongation. Concerning the validation of the DART, the study design necessitated the translation and adaption of a measure of DRP relevance. With $CLEO_{de}$ we present a measure of relevance for pharmacists' interventions in the German language, assessed regarding comprehensiveness and linguistic style by clinical pharmacy experts from all German-speaking countries and tested for its interrater and test– retest reliability with 10 Swiss clinical pharmacists. The validation of the DART also necessitated conducting patient interviews in the context of MRs Type 3. The newly developed structured patient interview combined an already established Swiss cognitive service by community pharmacists, the Polymedication Check (PMC), with the Beliefs about Medicines Questionnaire (BMQ), and hence questioned about medication adherence, patient knowledge, handling of medicines, and drug-related concerns about the therapy. The structured patient interview was used for 110 patient engagements and demonstrated its expected additional value by identifying over 41.8% of all DRPs. With

the aid of $CLEO_{de}$ and the structured patient interview, the concurrent criterion validity of the DART was assessed by correlation with data retrieved from MRs Type 3. The statistical analysis demonstrated the ability of the questionnaire to discriminate patients with lower and higher numbers of DRPs: Patients ticking 8 risk factors in the DART showed a median of 3 DRPs, whereas patients ticking 15 risk factors showed 8 DRPs. Discriminant function analysis identified the questions on polypharmacy, adherence, concerns about becoming too dependent on the medicines, heart insufficiency, and diabetes as important discriminators between patients with lower and higher numbers of DRPs. The summated risk score of these five items had an association with the number of DRPs, and therefore allowed validation of the DART at the same time as enabling item reduction. Concerning the external validation of the RISQ-PATH score, we were able to report an association between the score and the measured QTc intervals in a population of hospitalised patients. Our analyses highlighted a significant moderation effect by one of the included risk factors, "Prolonged QTc on a baseline ECG." This moderation effect has implications for practice, as it necessitates the categorisation of patients before interpreting the RISQ-PATH score and drawing conclusions.

I. $CLEO_{de}$

As preparatory steps for the validation study of the DART, we translated the French tool for the assessment of relevance of pharmacists' interventions. We closely followed the "ISPOR Principles of Good Practice for the Translation and Culture Adaption Process for Patient-Reported Outcomes Measurement."[82] The 10 steps included forward and backward translations by 2 independent professional translators, a linguistic evaluation by clinical pharmacists from all 3 German-speaking countries, close contact with the original developers, and a strict documentation of changes, which allowed for a translation being both close to the original and adapted to local modalities. Within a time period of 13 days, we collected 324 interventions performed in routine services by clinical pharmacists in three Swiss hospitals. This sample was used to display acceptability and feasibility of the tool as well as the perceived relevance of the clinical pharmacists' work. The pharmacists who used the tool in their practice reported a time needed of "less than one minute" per intervention, which supports future use of $CLEO_{de}$. As CLEO was designed to be a self-assessment tool for pharmacists, we evaluated the reliability of $CLEO_{de}$ focusing on interrater and test–retest reliability in a sample of 10 clinical pharmacists and 10 cases. The clinical dimension, which focuses on patient-centred impacts (e.g. adherence, quality of life, prolongation of hospital stay, additional treatments), achieved good interrater and excellent test–retest reliability, demonstrating generalisability of the ratings. The obtained interrater reliabilities were in line with the results of the original CLEO: Vo and colleagues reported moderate (cli-

nical), substantial (economic) and fair (organisational) interrater reliability between a sample of pharmacists working at a centralised chemotherapy preparation unit and peer reviewing pharmacists.[86] Hence we were able to present $CLEO_{de}$ as a reliable approach to the estimation of clinical relevance of pharmacists' interventions and, more importantly, to include the tool in the validation study of the DART. The studies on $CLEO_{de}$ also highlighted that the tool's multidimensionality posed issues for clinical pharmacists: The organisational dimension, which focuses on impacts on the work of other care team members, only achieved poor interrater reliability. We argued that in contrast to the clinical dimension, clinical pharmacists might not yet be familiarised with judging their interventions from the perspective of other caregivers: When proposing an intervention, they may not take into account the impact on time expenditure, work load, work place safety, and collaborations of other professions. Interventions do occur, such as warning nurses about the cancerogenous potential of the tablets they are about to crush. With $CLEO_{de}$, the estimation of this intervention's impact on the nurses instead of the patient was possible, but new. We hence stated that the additional point of view presented by $CLEO_{de}$ might foster awareness of currently neglected impacts of interventions. We proposed a more intensive introductory session on $CLEO_{de}$ and regular team assessments to use our tool in clinical practice.

II. Validation of the DART

The DART was able to discriminate between patients with lower and higher numbers of DPRs, identified by MRs Type 3. The MRs Type 3 included the use of the Medication Appropriateness Index,[32] the START/STOPP criteria version 2,[31] current treatment guidelines,[87] and patient interviews. The dataset of 110 patients displayed two clusters: a cluster of patients with a high number of DRPs and a high DART score, and a cluster of patients with a low number of DRPs and a low DART score. By performing a discriminant function analysis, we were able to highlight important items and to improve the correlation of the score with the number of DRPs from weak to moderate at the same time. These results displayed the added benefits of using a cluster analysis and a subsequent discriminant function analysis over scale correlations. The five highlighted items were polypharmacy, diabetes, concerns about becoming too dependent on the medicines, heart insufficiency, and adherence.

– Polypharmacy may be defined as the prescribing of multiple medications to one individual, to treat one complex condition or multiple conditions present simultaneously.[88] The term is inconsistently used with either a neutral or a negative connotation and with various numbers of medications.[89] In the DART, we defined polypharmacy as the presence of five or more medications without regard to their

appropriateness. Self-reported polypharmacy was one of the five discriminatory items for the patient collective with higher numbers of present potential and manifest DRPs within the validation study. This result was in line with research on hospitalisations: Polypharmacy was a determinant for the 332 potentially preventable medication-related hospital admissions of the total of almost 13,000 screened unplanned admissions by Leendertse and colleagues in The Netherlands. Within the multivariate analysis, equal to or greater than 5 chronically used drugs presented with an odds ratio of 2.7 for a preventable ADE including medication errors. The risk of an ADE is estimated to rise from 13% for two concomitantly prescribed medications to 58% for five and 82% for seven or more medications.[90] Polypharmacy remains an independent contributor to the likelihood of truly identified DRPs in hospitalised patients even when MRs are only performed on automated alerts triggered by other risk factors.[91] Polypharmacy is hence often used as risk factor and simple trigger for pharmacists' interventions:[92] Adding a new drug to a persisting drug regimen gets more difficult with each additional treatment.[62]

– As for diabetes mellitus, non-adherence in patients is associated with negative outcomes. The retrospective cohort study of 11,532 patients with diabetes mellitus in a managed care organisation by Ho and colleagues[93] identified 2,456 non-adherent patients with diabetes mellitus. These non-adherent patients showed significantly higher rates of hospitalisation and death, even though they were younger and had fewer comorbidities than the control group. Insulin and oral antidiabetics are drug classes frequently associated with pharmacists' interventions during a hospitalisation,[92] as they are associated with DRPs – as reported by a review over 21 studies.[94]

– The item of the DART on concerns about becoming too dependent on the medicines stems from the BMQ. In 1999, Horne and colleagues introduced the BMQ.[75] With their questionnaire they aimed to develop a method to score cognitive processes involved in medication non-adherence. The final score of the questionnaire is obtained with adherencepromoting feelings of necessity and adherence-repressing thoughts of harm and dependency, rated in 10 questions. In our early research into the risks for developing DRPs, we identified aversion to medication as a risk factor. In our opinion, aversion to medication was best represented with the adherence-repressing items of the validated BMQ. Adherence and concerns about becoming too dependent on the medication are now both validated items of our five items, the reduced DART score.

– Heart insufficiency/heart failure was one of the five discriminatory items for the patient collective of higher numbers of DRPs. A Mann-Whitney U test also revealed a statistically significant correlation between "Yes"-answers on heart failure

and DRPs estimated to be of high clinical relevance. We therefore proposed to use heart failure as trigger for an immediate MR Type 3. Patients with heart failure are required to follow their drug regimen as any other patient collective, but their non-adherence quickly leads to hospitalisation.[95] Missing doses of prescribed diuretics or digoxin will aggravate the symptoms of the disease until inpatient treatment is necessary. Appropriate prescribing is difficult when heart failure is present, as the medicinal treatment of comorbidities may worsen its symptoms.[96] Interventions consisting of MRs and post-discharge follow-up may reduce the hospital admission rate of older people with heart failure.[97]

– In the study of Leendertse and colleagues, non-adherence was one of the risk factors leading to preventable medication-related hospital admissions.[6] Contrary to our validation study, nonadherence was not self-reported but calculated with pharmacy refill data, objectifying and hence solidifying our results. In general, omission of drugs is a frequently identified DRP.[54 98]

Besides performing the cluster analysis with the whole dataset, we re-applied the same methods to a reduced dataset that focused on the DRPs only detectable in patient interviews in order to select items that highlight patients benefiting the most from direct engagement in an MR Type 2a: Within this reduced dataset we identified the use of drugs (non-steroidal antirheumatics, antidiabetics, and digoxin) and restricted kidney function, concerns about dependency, concerns about having to use medicines, use of therapeutic skin patches, preparation of medicines by homecare, and polypharmacy as predictors of patients who benefited the most of interviews. These risk factors for DRPs should be seen in light of the population and the approach we used, which encompassed a patient interview with older, hospitalised patients: In this step of the statistical analysis, all the identified items may lead to counselling of patients, with their underlying problem being patients' insufficient medicines knowledge. Insufficient medicines knowledge by the patient as cause of potential DRPs accounted for 23.2% of all identified issues. Older patients are known to be prone to insufficient medicines knowledge.[99]

Assessing the correlation between DART items and DRPs estimated to be of high clinical relevance revealed four additional risk factors to be considered for future adaption of the questionnaire: Mann-Whitney U-Tests showed a statistically significant correlation between DRPs with the CLEO estimates "major" and "lifesaving" and the DART items on issues such as tabletsplitting, heart failure, and use of oral anticoagulants. Use of steroids was associated with DRPs with "moderate" clinical relevance. Steroids and anticoagulants are drugs frequently associated with rehospitalisation or adverse drug events;[20 100-103] tablet-splitting may lead to problems with handling and subsequently adherence.[104] The items on tablet-splitting and use of oral anticoagulants or steroids

were not of discriminatory value for the two initial clusters of patients. However, they correlated with DRPs estimated to be of high clinical relevance, and hence should be used for risk stratification and as triggers for immediate services. These findings demonstrated the benefits of using different statistical approaches for the identification of correlations.

The combination of the results of different statistical analyses allowed the compiling of a comprehensive table linking items of the DART with suggestions on clinical pharmacy services with different time requirements, allowing resource allocation (Table 2, excerpt from chapter 3 „Assessing the ability of the Drug-Associated Risk Tool (DART) questionnaire to stratify patients according to their risk of Drug-Related Problems"). The items may be used to trigger either an immediate or a later MR Type 3 using medical records, laboratory measurements, and structured patient interviews as source of information, or an MR Type 2 only using medical records and structured patient interviews as source of information.

Table 2 Combination of DART items and possible triggered clinical pharmacy services.

DART item (translated from German)	**Clinical pharmacy service**
I have a heart weakness/heart performance weakness.	Consider immediate MR Type 3
I have trouble taking my medicine because of splitting tablets.	Consider immediate MR Type 3
I use Marcoumar® (phenprocoumon), Xarelto® (rivaroxaban), Sintrom® (acenocoumarol), Eliquis® (apixaban), Lixiana® (edoxaban), or Pradaxa® (dabigatran) at home.	Consider immediate MR Type 3
I use cortisone at home.	Consider immediate MR Type 3
I have diabetes.	Consider MR Type 3
I take more than 5 drugs every day, which are prescribed by my physician.	Consider MR Type 3
Do you sometimes forget to take your medicine?	Consider MR Type 3
I sometimes worry about becoming too dependent on my medicines.	Consider MR Type 3
I use medicines against rheumatism/inflammation at home.	Consider MR Type 2a
I use insulin/medicines against diabetes at home.	Consider MR Type 2a

I use digoxin at home.	Consider MR Type 2a
I sometimes worry about the long-term effects of my medicines.	Consider MR Type 2a
Having to take this medicine worries me.	Consider MR Type 2a
I apply my medication in the form of skin patches.	Consider MR Type 2a
I have a restricted kidney function/kidney dysfunction/kidney disease.	Consider MR Type 2a
The preparation of my medicine is done by a homecare institution.	Consider MR Type 2a

MR Type 3: Medication Review Type 3; Drug therapy evaluations using medical records, laboratory measurements, and the patient's opinions and experiences (i.e. patient interviews). MR Type 2a: Medication Review Type 2a; Drug therapy evaluations using medical records and the patient's opinions and experiences (i.e. patient interviews), without laboratory measurements.[38]

It is possible to compare the performance of the DART to other risk-stratification tools by addressing measures as Area under the Receiver Operating Characteristic curve (AuROC; also known as C-statistic), specificity, and sensitivity.[61] AuROC quantifies the probability that a patient classified for the cluster of patients with higher numbers of DRPs had a higher score of the reduced five items at the same time. The five items achieved an AuROC of 0.865 (SE=0.035, p<.001, 95% CI [.797, .932]), which translates into good performance.[61] At greater than one yes-answer (> 1) for these five items, the ROC curve showed a sensitivity of 74% and a specificity of 82%. These numbers are reassuring, as a lower sensitivity could result in a misclassification of a high-risk patient with resulting patient harm and poor specificity would incorrectly flag low-risk patients for intervention.[61] These numbers also allow for a direct comparison of risk-stratification tools, which was done by Falconer and colleagues in the systematic review on models for predicting adverse drug event risks in inpatients.[61] This review identified 10 studies that described the development of a new risk prediction model but only the BADRI risk score was deemed to be sufficient regarding model development, validation and performance. As already presented earlier, the BADRI risk score consists of the variables hyperlipidaemia, number of drugs (> 8), length of hospital stay (≥ 12 days), use of antidiabetics, and high white cell count on admission.[64] These variables necessitate the deployment of either a care team member or an algorithm in comparison to our patient-administered questionnaire. The BADRI model achieved an AuROC of 0.74 (95% CI 0.68-0.79), a sensitivity of 80% and a specificity 55% at a cutoff at one present risk factor.[61] These numbers were achieved during an external validation, which

elevates the performance above our study results from an internal validation. It is interesting to note, however, that our patient-administered questionnaire performs similarly to a sophisticated model in its primary validation.

Tools like the BADRI risk score take advantage of being deployable as computer-based algorithms that allow for an automated surveillance of the whole hospital.[31 105] This advantage over paper-based solutions like the DART, however, shifts caregivers away from the patients. The WHO expects pharmacists to focus on patient-centred care (i.e. respect the patient's opinions and concerns).[1 6] Patients' opinions and concerns cannot be assessed with automated algorithms processing electronic documentation. We however highlighted the necessity of the assessment of patients' knowledge, opinions, and sorrows for the identification of DRPs. With the DART, we present a paper-based questionnaire that asks the patients about their medicine-use. The questionnaire is intended to be completed by the patient to trigger clinical pharmacy services promoting patient self-care.

III. Identified Drug-Related Problems and Contribution of Patient Interviews

In our validation study of the DART we identified 595 DRPs in 110 patients, with only 2 patients having no DRP. This result conforms with other research, where at least one manifest or potential DRP was reported in 96% of investigated patients.[98] The development of a structured patient interview was a necessity for the validation of the DART as existing tools to detect DRPs in the elderly do not consider the patient's perspective.[98] Our results demonstrated the supplementary value of direct patient engagement in a Swiss geriatric ward and hence support the addition of the patient's perspective to methods of DRP identification: Accessing our patients in direct patient contact accounted for the identification of 41.8% DRPs. And 38.2% of DRPs were only identifiable via interviews but not with any other method of identification (i.e. Medication Appropriateness Index, the START/STOPP criteria version 2). The ability of patient interviews to detect important DRPs has already been shown by others: Viktil and colleagues concluded their study on DRPs in hospitalised Norwegian patients with the statement that almost two fifths of the DRPs were identified during patient–pharmacist contact.[53] The issues detected in the interviews of Vitkil and colleagues were mainly underprescribing, medical chart errors, patient adherence, and the need for patient education. We are able to complement these findings with the main issues we identified during our interviews: We also coded as much as 50.7% of the causes for potential DRPs as lack of medicines knowledge, issues in patient documentation, and missing indication of prescribed drugs. Insufficient knowledge of the patients as cause of the DRP was identified most

prominently in 23.2% of all cases. Maniaci and colleagues reported that 15% of their study participants were unaware of the newly prescribed medication at their discharge and only 64% of all participants knew the purpose of their medication.[99] Poor health literacy is associated with a higher mortality rate.[106]
By using $CLEO_{de}$, we assigned the clinical relevance of minor to the identified DRPs on patient knowledge, adherence, and quality of life because there was no acute danger of hospitalisation or need of an additional treatment or increased surveillance. $CLEO_{de}$ focuses on direct and prompt consequences and hence lowers the estimated clinical relevance of primarily patient-centred DRPs. Patient-centred DRPs like health illiteracy and swallowing difficulties are, however, potential causes of non-adherence, and may cause patient harm in the long run.[106 107] Kwint and colleagues were not bound to predefined levels of an assessment tool and demonstrated that DRPs identified by pharmacists visiting homecare patients were assigned a higher relevance and led to recommendations on drug changes more frequently compared to those identified from objective data (i.e. drug regimen and medical records).[84]

START/STOPP criteria version 2 contributed only 7.9% and 2.4% of identified DRPs, respectively. These proportions are reinforced by findings by Verdoorn and colleagues, who reported a contribution of 19% by the START/STOPP criteria to the overall number of identified DRPs.[108] However, our reported small contributions were influenced by (1) ward personnel being trained in clinical pharmacy activities before study deployment and (2) our decision to exclude the implicit content of the criteria: The STOPP criterion "No indication present" was one of the most identified DRPs in the study by Verdoorn and colleagues[108] and translates into our "missing indication for prescribed medication," covered by our use of the MAI. The MAI was an important contributor for the identification of DRPs: The implicit approach identified 43.9% of DRPs and the patient's score strongly correlated with the patient's number of DRPs. Some criteria of the MAI (i.e. "Is the medication effective for the condition?", "Are the directions practical?") necessitate information only retrievable from the patients themselves, hence the effectiveness of the MAI to identify DRPs should be regarded in the context of our patient interviews. The combination of both, MAI and patient interviews, seems beneficial for the identification of DRPs, but brings together the most timeconsuming approaches. In circumstances like these, the DART could be used to select the patients benefiting the most.

Because we coded the ATC codes for each DRP, we were able to investigate the frequency with which certain drug classes were associated with DRPs. To our knowledge, this is the first such analysis for Swiss geriatric wards. Agents that are reported as frequent triggers for pharmacists' interventions are antibacterial agents, antithrombotic agents, analgesics, and drugs for acid-related disorders.[109] Similarly, we identified analgesics,

antithrombotic agents, and drugs for acid-related disorders and additionally psycholeptics as drug classes most frequently associated with the identified DRPs. Misprescribed analgesics may lead to unsatisfactory pain relief for patients, again only identifiable via direct patient engagement. Under- or overprescribing of antithrombotic agents may lead to serious ADEs, i.e. myocardial infarction or bleeding. Drugs for acid-related disorders are a drug class frequently associated with overprescribing: 25% to 70% of all proton-pump inhibitor (PPIs) prescriptions have no clear indication.[110] As an example, PPIs are appropriately prescribed to prevent upper gastro-intestinal bleeding when non-steroidal anti-inflammatory drugs are used in the elderly to target ossification processes after prosthesis insertions.[87] However, PPIs are often not terminated in regards to the therapy duration.[110] The drug class of psycholeptics, which is additional to other study results, may be explained by our study population: The geriatric and rehabilitation wards were treating chronic pain, such as chronic pain in the lumbar regions associated with intervertebral disk displacement and eradiating nerve pain. Besides treatment with analgesics, this kind of chronic pain is also treated with psycholopetics as co-analgesics.[87] Patients' knowledge of this kind of medication seems especially important as patient leaflets may state unsettling ADRs associated only with higher doses than those used in the treatment of chronic pain. The results on the drug classes most frequently associated with our identified DRPs may be used to adapt the resident physicians' curriculum during training on geriatric wards: The training should encompass guideline compliance concerning the prescription of analgesics, antithrombotic agents, and PPIs, as well as patient counselling.

IV. RISQ-PATH Score and Prolonged QTc Intervals

By performing a hierarchical regression analysis, a moderated hierarchical regression analysis, and a multiple regression analysis, a procedure described by Aiken, West, and Reno,[111] we aimed to investigate the association between the RISQ-PATH score and measured QT_c intervals with a potential moderation effect in mind, such a moderator being a qualitative or quantitative third variable, which partitions an independent variable (i.e. RISQ-PATH score) into subgroups and hence influences the strength of the relation to a dependent variable (i.e. measured QT_c interval). We were able to report an association between the RISQ-PATH score and the measured QT_c interval. Concerning our specific dataset of 156 hospitalised patients, we identified the risk factor "Prolonged QT_c on a baseline ECG" as a moderator for this association: The association between the RISQ-PATH score with the measured QT_c interval was found to be significant only in patients who already had a previously present prolonged QT_c interval, which implied that the RISQ-PATH score is highly dependent on one specific risk factor. We explained that if a prolonged QT_c interval is present, an association between the RISQ-PATH sco-

re and the measured QT_c interval exists, whereas with no previously prolonged QT_c interval no association between RISQ-PATH score and the QT_c interval may be expected. With the performed statistical analysis, we were hence able to suggest the development of a different scoring and interpretation of the RISQ-PATH score for patients without a previously present prolonged QT_c interval. Having two separate scale interpretations would increase the RISQ-PATH score's capability as a guideline for initiation of ECG measurements. Furthermore and more importantly, we were able to suggest a simple code of practice when starting a drug with the potential to prolong the QT_c interval: With due respect to all risk factors and pharmacodynamic drug interactions, just order a ECG measurement for a patient with an already prolonged QT_c interval.

V. Limitations

Limitations of this thesis mainly include the generalisability of the results:

– The validation study of the DART, also including the newly developed structured patient interviews, only included patients admitted to geriatric and rehabilitation wards. The mean age was 76.9 years (SD 10.3), and the mean number of prescribed drugs was 11.0 (SD 4.2). This represents an elderly, highly polymedicated population. This population further deviated from generalisability by excluding patients with eye-sight, handling, cognitive, or language levels prohibiting independent completion of the questionnaire. These criteria led to the exclusion of patients with already arguable health literacy, and importantly, to the exclusion of patients with cognitive impairment (i.e. dementia) – a patient collective that is known to be associated with medication-related hospitalisation.[6] However, we see the DART as a tool to promote patient-empowerment and self-management – constructs that may be already externally restricted in patients dwelling in nursing homes because of their cognitive impairment.

– The external validation of the RISQ-PATH score only included inpatients from geriatric and rehabilitation wards. As such, 137 of the analysed 156 patient datasets (87.2%) were already fulfilling one of the respected risk factors, "age > 65 years." This puts constraints on our results regarding applicability to any other patient population and to the validation of this specific score item.

– Five of the ten clinical pharmacists involved in the validation process of $CLEO_{de}$ had a clinical working experience of less than one year, which may affect their perception of clinical relevance. However, this composition of clinical pharmacists represents the current situation within the Swiss hospitals involved.

Besides restricted generalisability, limitations of this thesis also encompass the absence of outcomes such as re-hospitalisation or mortality. We developed the DART as a screening tool, and as such, the DART is dependent on interventions that change any measurable prospective outcomes (e.g. re-hospitalisation rates). We considered it a necessity to evaluate the performance of our tool before linking it with certain interventions. Falconer and colleagues even called for proven external validity prior to impact studies and implementation in practice.[61] The study design respected this decision by focusing on currently present potential and manifest DRPs instead of prospective outcome measures; however, it may now be argued that higher scores in the DART are associated with higher numbers of DRPs and DRPs are associated with poor health outcomes in general.[95] The correlation of higher DART scores and poor health outcomes may hence be assumed.

VI. Implications for Practice

As a validated tool, the DART may be used as a risk-stratification tool in order to provide medication reviews to inpatients who need it the most. Distributed at the beginning of a hospitalisation, the DART may be completed by the patients themselves without increasing the workload of any caregiver. The statistical analyses allowed for a linkage of items of the questionnaire with certain methods of the study: Based on the answers from the patients clinical pharmacists may decide to perform either an immediate or postponed MR Type 3 or a structured patient interview to identify DRPs (i.e. MR Type 2a). The tool will hence aid clinical pharmacists in allocating their restricted resources and in approaching patients with the appropriate depth of review. When not wishing on a paper-based solution, the few identified risk factors, which do not require direct patient contact, may be incorporated into automated algorithms for patient selection.

We demonstrated the benefits of direct inpatient engagement as opposed to the use of automated algorithms, as we highlighted the number of DRPs only detectable in structured patient interviews on geriatric wards. We were able to pilot a structured patient interview based on the PMC, with only slight modifications by adding items of the BMQ. This modified PMC may be used for future inpatient engagements by hospital clinical pharmacy services to target the patients' medication literacy and documentation and hence help in reducing the number of preventable medication-related hospitalisations.

Structured assessments of medication therapies like those described in this thesis may identify a vast number of DRPs with various implications on treatment safety – from negligible to lifesaving relevance. With $CLEO_{de}$ we adopted an evaluation tool that should help German-speaking clinical pharmacists in self-reflecting on their own interventions.

Used in daily practice and teaching, clinical pharmacists should quickly learn to prioritise their identified DRPs. This prioritisation of DRPs marks a necessity for focused and efficient interdisciplinary communication. When used in research, $CLEO_{de}$ will help in subsetting datasets on the interventions' relevance and in visualising findings.

By identifying a moderation effect for the association between the RISQ-PATH score and the measured QT_c intervals, we were able to support a simple code of practice for one specific DRP: performing an ECG measurement before starting a drug with the potential to prolong the interval for a patient with an already prolonged interval. For this specific subset of patients, the now externally validated tool may be used to predict the QT_c interval. For other patients, we gathered the evidence to suggest the development of a different scale interpretation.

VII. Outlook

As the DART is now validated for a population of hospitalised older patients without cognitive impairment, the questionnaire should be examined for regular pharmacy clients, including adults with an age of below 65 years. This validation would set the foundation for the DART to be used in community pharmacies that aim to promote their patients' self-management. A screening tool like the DART could be used to select patients who actually need an adherence intervention like the PMC. The study on the effectiveness of the PMC concluded with no significant positive effects on adherence and argued that these results were influenced by selection bias as only highly motivated pharmacies and patients agreed to participate.[112] The application of the DART as a screening for patients who would benefit from the PMC seems especially beneficial as the newly developed structured patient interview was based on the PMC. The structured patient interviews detected a proportion of 41.8% of all DRPs that were used to validate the DART. Hence it may be assumed, that the DART identified patients at risk of DRPs who would benefit from a PMC.

Barenholtz-Levy validated her paper-based risk stratification questionnaire on DRPs similarly to our study.[65] Her questionnaire also identified patients presenting with higher numbers of DRPs, but the study population consisted of 40 patients aged over 60 years, recruited at three pharmacies, taking a mean number of 7.3 drugs. It would be of interest to examine our five discriminative items of the DART together with Barenholtz-Levy's questionnaire, both administered at the same time in a community pharmacy. Studying the convergent validity of the DART and of Barenholtz-Levy's measure would further display both questionnaires' ability to be used as a risk-stratification tool on DRPs.

Concerning $CLEO_{de}$, a big dataset of interventions coded for relevance would facilitate the examination of factors that influence the perceived impact. Are there certain interventions that are consistently estimated to be of higher relevance? Are interventions made regularly that are estimated to be of minor clinical relevance but require greater resources? This dataset may be generated by adding $CLEO_{de}$ to an intervention classification (e.g. GSASA classification[113]) for a longer period of time.

Regarding the RISQ-PATH score, the datasets used for the internal and the external validation could be combined. This would generate a large dataset to re-weigh the score's items for patients without an already prolonged QTc interval. By generating this additional scale interpretation, the association between the score and the measured interval could improve even in the absence of the identified moderator "previously present prolonged QTc interval." Enabling this association would reveal the score's true potential as a risk-stratification tool for patients without pre-existing conditions.

VIII. Conclusion

This thesis presents measures of risk and relevance for DRPs: The DART as a measure of risk is now validated regarding its ability to discriminate between low- and high-risk inpatients for DRPs. As a self-administered questionnaire, the DART can be used to stratify hospitalised patients according to their need for clinical pharmacy services. When implemented in practice, the DART will help in hospital pharmacy resource allocation without increasing the workload of any health care professional.

$CLEO_{de}$ is a translated and culturally adapted tool to estimate the relevance of DRPs in three different dimensions. The German version was evaluated in hospital practice and we assessed interrater and test–retest reliability of $CLEO_{de}$, which proved the tool's ability to be used by the intervening pharmacists themselves. When implemented in practice, $CLEO_{de}$ will help in focusing on the most relevant clinical interventions in practice, research, and teaching.

The RISQ-PATH score as measure of risk for a specific DRP is now externally validated. The validation process identified important limitations of this risk-stratification tool and proposed a code of practice for initiating ECG measurements.

This thesis also reports on the performance of a structured patient interview to identify issues on drug-related adherence and patient documentation of hospitalised patients. The combination of the PMC and the BMQ may be used as a template for direct inpatient engagement to improve patients' medication literacy and documentation.

This thesis hence presents a validated self-administered patient questionnaire to stratify for drug-related risk, a validated assessment to estimate the relevance of drug-related problems, a structured patient-interview to identify issues on drug-related adherence and patient documentation, and a valid score to detect patients at risk of drug-induced QT-prolongation. Assessing the risk and relevance of DRPs remains a challenge worth pursuing in order to increase patient and drug safety.

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APPENDICES

I. Project: Translation and Validation of a Tool to Assess the Impact of Clinical Pharmacists' Interventions

CLEO$_{de}$

Evaluation of the impact of a pharmacist's intervention (PI) with the CLEO$_{de}$ tool

Klinische Auswirkung

Grundsatz: Die klinische Auswirkung wird nach einem wahrscheinlichem Szenario und nicht nach schlimmstem/bestem Szenario bewertet.
Die klinische Auswirkung wird aus Sicht des Patienten bewertet.

Erläuterung:
Schaden: Körperlicher Schaden - Beeinträchtigung der physischen und/oder psychischen Fähigkeiten des Patienten.
Lebensqualität: Physische Aspekte (Autonomie, körperliche Fähigkeiten, Fähigkeit tägliche Aufgaben zu erledigen, etc.), psychologische Aspekte (Ängste, Depression, Emotionalität, etc.), soziale Aspekte (bezogen auf das familiäre oder professionelle Umfeld, Freundeskreis, Pflege persönlicher Beziehungen, Teilnahme an Sozial- und Freizeitaktivitäten, etc.) und somatische Aspekte (Symptome der Krankheit).
Überwachung: Nachkontrollen, labormedizinische Kontrollen.
Behandlung: Änderung der Therapie oder zusätzliche medizinische/chirurgische Behandlung.

Score	Auswirkung	Definition
-1C	schädlich/ negativ	Die pharmazeutische Intervention (PI) kann zu negativen Ergebnissen hinsichtlich des klinischen Zustandes, des Wissenstandes, der Zufriedenheit, der Therapietreue (Adhärenz) und/oder der Lebensqualität des Patienten führen.
0C	ohne	Die PI hat keine Auswirkung auf den Patienten hinsichtlich des klinischen Zustandes, des Wissenstandes, der Zufriedenheit, der Therapietreue (Adhärenz) und/oder der Lebensqualität des Patienten.
1C	gering	Die PI kann den Wissensstand, die Zufriedenheit, die Therapietreue (Adhärenz) und/oder die Lebensqualität des Patienten verbessern. ODER Die PI kann einen Schaden beim Patienten verhindern, der keine Überwachung/Behandlung erfordert.
2C	mittel	Die PI kann einen Schaden beim Patienten verhindern, der eine Überwachung oder Behandlung erfordert, aber keine Hospitalisierung herbeiführt oder einen bestehenden Spitalaufenthalt verlängert.
3C	erheblich	Die PI kann einen Schaden verhindern, welcher einen Spitalaufenthalt des Patienten verursacht oder verlängert. ODER Die PI kann einen Schaden beim Patienten verhindern, der eine dauerhafte Invalidität oder Beeinträchtigung verursacht.
4C	lebensnotwendig	Die PI kann einen Schaden beim Patienten verhindern, der eine intensiv-medizinische Behandlung nach sich zieht oder zum Tod des Patienten führt.
NB	nicht beurteilbar	Die verfügbaren Informationen erlauben es nicht, die klinische Auswirkung zu beurteilen.

Wirtschaftliche Auswirkung

Grundsatz: Die Kosten der medikamentösen Behandlung beziehen sich auf die finanziellen Kosten des Krankenhauses.

Erläuterung:
Die Kosten der **medikamentösen Behandlung** beinhalten zwei prinzipielle Aspekte:
- Arzneimittelkosten
- Die Kosten der Überwachung der medikamentösen Behandlung (z.B. Folgeuntersuchungen, Labor, etc)

Score	Auswirkung	Definition
-1E	höhere Kosten	Die PI erhöht die Kosten der medikamentösen Behandlung des Patienten.
0E	keine Veränderung	Die PI verändert die Kosten der medikamentösen Behandlung nicht.
1E	geringere Kosten	Die PI reduziert Kosten bei der medikamentösen Behandlung des Patienten.
NB	nicht beurteilbar	Die verfügbaren Informationen erlauben es nicht, die wirtschaftliche Auswirkung zu beurteilen.

Organisatorische Auswirkung

Grundsatz: Die organisatorische Auswirkung beschreibt den Einfluss auf die Qualität des Behandlungsprozesses aus Sicht des medizinischen Personals.

Erläuterung:
Folgende **Aspekte** sind insbesondere zu berücksichtigen:
- Zeitersparnis
- Verbesserte Kenntnisse
- Vereinfachung der professionellen Tätigkeit
- Vereinfachte Zusammenarbeit
- Erhöhte Sicherheit für das Personal
- Kontinuität der Behandlung

Score	Auswirkung	Definition
-1O	verringert	Die PI reduziert die Qualität des Behandlungsprozesses.
0O	ohne	Die PI hat keinen Einfluss auf die Qualität des Behandlungsprozesses.
1O	erhöht	Die PI erhöht die Qualität des Behandlungsprozesses.
NB	nicht beurteilbar	Die verfügbaren Informationen erlauben es nicht, die organisatorische Auswirkung zu beurteilen.

Factsheet for Expert Translation Validation

Universität Basel

Departement
Pharmazeutische Wissenschaften

DEPARTMENT OF PHARMACEUTICAL SCIENCES

CLEO: Factsheet

Translation of a French Tool to Assess the Impact of Clinical Pharmacists' Interventions

For what stands the abbreviation CLEO?

The abbreviation CLEO represents the three dimensions of the tool: Clinical, Economic, and Organisational

What is CLEO?

CLEO is a multidimensional scale to assess potential impacts of pharmacists' interventions (PI's). The tool displays 3 dimensions, which may be influenced by an intervention. CLEO is based on a systematic review of existing tools and evaluation models of health care interventions.[1]

Who developed CLEO?

The development process was part of the PhD-thesis of Mrs. Thi-Ha VO at the University Grenoble Alpes in France. Seven clinical pharmacists, belonging to the French Society of Clinical Pharmacy, were involved in the development.

Why was CLEO developed?

Clinical pharmacists are increasingly engaged in detecting and resolving drug-related problems within multidisciplinary ward rounds. The majority of existing tools to assess the significance of applied interventions are mainly focused on clinical aspects and fail to detect comprehensive impacts. The goal was to develop a simple, multidimensional, comprehensive, and reliable tool.

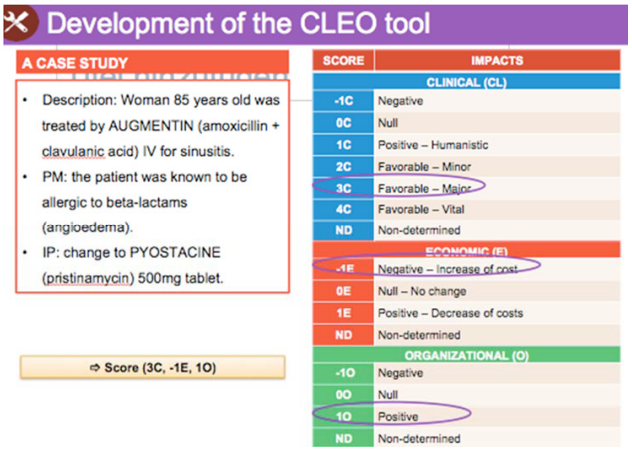
Who will use CLEO?

In Switzerland: After successful translation and re-validation, the tool will be used by Swiss clinical pharmacists and candidates of the „Fähigkeitsausweis Klinische Pharmazie FPH" to assess the significance of their interventions, which are documented with the GSASA-classification system.[2] A direct implementation of CLEO within the GSASA-classification is planned.

Seite 1/2

14.01.2016/Dominik Stämpfli, Pascal Baumgartner

How to use CLEO? (Example)



The pharmacist's intervention may avoid an allergic reaction, which would prolong the ongoing hospitalisation: The clinical impact according to CLEO is $+3^{Cl}$. But the new drug is more expensive: The economic impact is -1^{E}. The patient was changed from i.v. to oral administration: This regimen is simpler and less time-consuming for health care staff: The intervention has a positive organisational impact of $+1^{O}$.

References

1. Vo TH, Charpiat B, Catoire C, Juste M, Roubille R, Rose FX, Chanoine S, Bosson JL, Conort O, Allenet B, Bedouch P. Tools for Assessing Potential Significance of Pharmacist Interventions: A Systematic Review. Drug safety 2015.
2. Maes KA, Tremp RM, Hersberger KE, Lampert ML. Demonstrating the clinical pharmacist's activity: validation of an intervention oriented classification system. International journal of clinical pharmacy 2015; 37: 1162-71.

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Expert Translation Validation Questionnaire

University of Basel
Department of Pharmaceutical Sciences

DEPARTMENT OF PHARMACEUTICAL SCIENCES

University of Basel, Department of Pharmaceutical Sciences, Klingelbergstr. 50, 4056 Basel

Adapted Excerpt FlexiForm Questionnaire: «Kognitives Debriefing der deutschen CLEO-Version»

Hintergrund
CLEO ist ein multidimensionales Evaluierungssystem zur Bewertung der Auwirkung von klinisch-pharmazeutischen Interventionen. Die Entwicklung des französischen Evaluierungssystemes war Teil der Doktorarbeit von Frau Thi-Ha VO an der Universität Grenoble.

Ziel
Ziel ist eine deutsche Übersetzung des Evaluierungssystemes anzufertigen. Für den Abschluss der Übersetzungsarbeiten wird ein kognitives Debriefing durch die Zielpopulation benötigt. Die Zielpopulation besteht bei CLEO aus klinisch tätigen Pharmazeuten. Im Zuge des kognitiven Debriefings sollte das CLEO Evaluierungssystem an Repräsentanten der Zielpopulation in der neuen Anwendersprache nach Verständlichkeit und sprachlichem Stil getestet werden. Daher bitten wir Sie, jedes Level der deutschen Übersetzung des CLEO-Evaluierungssystemes einzeln nach den Kriterien 1. Inhaltliche Verständlichkeit und 2. Sprachlicher Stil zu bewerten. Das Fernziel ist die Integration des CLEO-Evaluierungssystemes in das Schweizer Klassifizierungssystem für klinischpharmazeutische Interventionen.

Auftrag
Bitte füllen Sie den Fragebogen vollständig aus. Nach Beurteilung eines Levels können Sie jeweils Kommentare/ Meinungen zu dem jeweiligen Level anbringen. Am Ende jeder Dimension können Sie jeweils Kommentare/ Meinungen zur jeweiligen Dimension anbringen. Diese sind erwünscht. Die letzte Seite bietet Platz für eine persönliche Einschätzung des CLEO Evaluierungssystemes. Beachten Sie bitte, dass wir als Übersetzer keinen Einfluss auf das zugrundeliegende Konzept haben. Wir wären Ihnen sehr dankbar für eine ausführliche Rückmeldung, da es uns hilft, die Übersetzung vor der geplanten Revalidierung weiter zu verbessern. Zeitaufwand: ca. 30 min.

Fragen
Jeder Inhaltsblock von CLEO wird einzeln auf einer Likert-Skala zu inhaltlicher Verständlichkeit bewertet: schlecht/ schwach/ ungenügend/ genügend/ gut/ sehr gut.
Jeder Inhaltsblock von CLEO wird einzeln auf einer Likert-Skala zu sprachlichem Stil bewertet: schlecht/ schwach/ ungenügend/ genügend/ gut/ sehr gut.

Klinische Auswirkung
- Grundsatz: Die klinische Auswirkung wird nach wahrscheinlichem Szenario bewertet und nicht nach schlimmstem/bestem Szenario. Die klinische Auswirkung wird aus Sicht des Patienten untersucht.
- Erläuterung: Behandlung: Änderung der Therapie oder zusätzliche medizinische/chirurgische Behandlung.
- Schaden: Körperlicher Schaden - Beeinträchtigung der physischen und/oder psychischen Fähigkeiten des Patienten.

University of Basel
Department of Pharmaceutical Sciences
Klingelbergstrasse 50
4056 Basel, Switzerland
pharma.unibas.ch

Dominik Stämpfli, MSc
Clinical Pharmacist FPH CAS, PhD candidate
T +41 61 267 15 29
M +41 76 443 04 09
dominik.staempfli@unibas.ch

University of Basel
Department of Pharmaceutical Sciences

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- Lebensqualität: Physische Aspekte (Autonomie, körperliche Fähigkeiten, Fähigkeit tägliche Aufgaben zu erledigen, ect.), psychologische Aspekte (Ängste, Depression, Emotionalität., etc.), soziale Aspekte (bezogen auf das familiäre, freundschaftliche oder professionelle Umfeld, persönliche Beziehungen pflegen, Teilnahme an Sozial- und Freizeitaktivitäten, etc.) und somatische Aspekte (Symptome der Krankheit).
- Überwachung: Nachkontrollen, labormedizinische Kontrollen.
- -1C = schädlich/ negativ: Die pharmazeutische Intervention (PI) kann zu ungünstigen Ergebnissen hinsichtlich des klinischen Zustandes, des Informationsstandes, der Zufriedenheit, der Medikamententreue und/oder der Lebensqualität des Patienten führen.
- 0C = ohne: Die PI hat keine Auswirkung auf den Patienten hinsichtlich des klinischen Zustandes, des Informationsstandes, der Zufriedenheit, der Medikamententreue und/oder der Lebensqualität des Patienten.
- 1C = gering: Die PI kann den Informationsstand, die Zufriedenheit, die Medikamententreue und/oder die Lebensqualität des Patienten verbessern. ODER Die PI kann einen Schaden verhindern, der keine Überwachung/Behandlung erfordert.
- 2C = mittel: Die PI kann einen Schaden beim Patienten verhindern, der eine Überwachung oder Behandlung erfordert, aber keine Hospitalisierung herbeiführt oder einen bestehenden Spitalaufenthalt verlängert.
- 3C = erheblich: Die PI kann einen Schaden verhindern, welcher einen Spitalaufenthalt des Patienten verursacht oder verlängert ODER Die PI kann einen Schaden verhindern, der eine dauerhafte Invalidität oder Behinderung verursacht.
- 4C = lebensnotwendig: Die PI kann einen Schaden verhindern, der möglicherweise eine intensive Behandlung nach sich zieht oder zum Tod des Patienten führt.
- NE = Nicht ermittelt: Die verfügbaren Informationen erlauben es nicht, die klinischen Auswirkungen zu ermitteln.

Wirtschafltiche Auswirkung

- Grundsatz: Die Kosten der medikamentösen Behandlung beinhalten zwei prinzipielle Aspekte: Die Kosten der medikamentösen Behandlung beziehen sich auf die finanziellen Kosten des Spitals. Medikamentenkosten und die Kosten der Überwachung der medikamentösen Behandlung (z.B. Folgeuntersuchungen, Labor, etc).
- -1E = höhere Kosten: Die PI erhöht die Kosten der medikamentösen Behandlung des Patienten.
- 0E = keine Veränderung: Die PI verändert die Kosten der medikamentösen Behandlung nicht.
- 1E = geringere Kosten: Die PI spart Kosten bei der medikamentösen Behandlung des Patienten.
- NE = Nicht ermittelt: Die verfügbaren Informationen erlauben es nicht, die wirtschaftlichen Auswirkungen zu ermitteln.

Organisatorische Auswirkung

- Grundsatz: Die organisatorische Auswirkung umfasst den gesamten Einfluss auf die Qualität des Behandlungsprozesses aus Sicht des medizinischen Personals. Folgende Aspekte sind zu berücksichtigen: Zeitersparnis, Verbesserte Kenntnisse, Vereinfachung der professionellen Aufgaben.
- Erläuterung: Vereinfachte Zusammenarbeit, Erhöhte Sicherheit für das Personal, Kontinuität der Behandlung.
- -1O = verringert: Die PI verringert die Qualität des Behandlungsprozesses.
- 0O = ohne: Die PI hat keinen Einfluss auf die Qualität des Behandlungsprozesses.
- 1O = erhöht: Die PI erhöht die Qualität des Behandlungsprozesses.
- NE = Nicht ermittelt: Die verfügbaren Informationen erlauben es nicht, die organisatorischen Auswirkungen zu ermitteln.

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Kommentare zu CLEO

- Wie ist Ihr erster Eindruck von CLEO?
- Das CLEO-System könnte ein geeignetes Instrument für die Evaluierung von pharmazeutischen Interventionen in Zukunft sein.
- Haben Sie Anregungen und/oder Verbesserungsvorschläge für das Evaluierungssystem CLEO?

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Evaluation Questionnaire

University of Basel
Department of Pharmaceutical Sciences

DEPARTMENT OF PHARMACEUTICAL SCIENCES

University of Basel, Department of Pharmaceutical Sciences, Klingelbergstr. 50, 4056 Basel

Adapted Excerpt FlexiForm Questionnaire: «Fragebogen zur Benutzung des Tools CLEOde»

Einleitung

Herzlichen Dank, dass Sie CLEOde für uns getestet haben! Ihre evaluierten klinisch-pharmazeutischen Interventionen liefern uns wichtige Daten für die Validierung von CLEOde. Wir bitten Sie nun diesen Fragebogen auszufüllen, um uns ihre Meinung zum Evaluierungssystem CLEOde mitzuteilen.
Ziel des Fragebogens ist es Erkenntnisse über die Appropriateness, Acceptability, Feasabillity und Precision des Evaluierungssystemes zu bekommen.
Der Fragebogen enthält 12 Fragen, das Ausfüllen dauert ca. 5min.
Die Umfrage ist anonym.
Bitte wählen Sie jeweils die Aussage, welche für Sie am Besten zutrifft.
Besten Dank!

Fragen

Jede Frage: Likert-Skala: gar nicht einverstanden, nicht einverstanden, einverstanden, völlig einverstanden, keine Äusserung

- Das Evaluierungssystem $CLEO_{de}$ ist vollständig und beinhaltet alle Dimensionen zur Beurteilung einer klinisch-pharmazeutischen Intervention
- Ich hatte keine Probleme für die klinisch-pharmazeutischen Intervention eine Evaluierung nach $CLEO_{de}$ zu tätigen
- Es sind genügend Evaluierungsstufen vorhanden in der Dimension Klinische Auswirkung
- Es sind genügend Evaluierungsstufen vorhanden in der Dimension Wirtschaftliche Auswirkung
- Es sind genügend Evaluierungsstufen vorhanden in der Dimension Organisatorische Auswirkung
- Die Evaluierungsstufen innerhalb der Dimension Klinische Auswirkung sind klar definiert und voneinander abgegrenzt
- Die Evaluierungsstufen innerhalb der Dimension Wirtschaftliche Auswirkung sind klar definiert und voneinander abgegrenzt
- Die Evaluierungsstufen innerhalb der Dimension Organisatorische Auswirkung sind klar definiert und voneinander abgegrenzt
- CLEOde ist einfach zu gebrauchen
- Das Schulungsvideo mit Fallbeispielen reichen aus um $CLEO_{de}$ anwenden zu können
- Der Zeitaufwand für die Evaluation einer klinisch-pharmazeutischen Intervention mit $CLEO_{de}$ ist angemessen
- Wie lange wurde jeweils für eine Evaluation benötigt? (<10 Sek/ <30 Sek/ <1min/ <2min/ über 2min)
- Ich könnte mir vorstellen das Evaluierungssystem $CLEO_{de}$ auch in Zukunft in meiner praktischen Tätigkeit zu nutzen
- Im Allgemeinen bin ich zufrieden mit dem Evaluierungssystem $CLEO_{de}$
- Das $CLEO_{de}$-System wäre ein geeignetes Instrument für die Evaluierung von klinisch-pharmazeutischen Interventionen
- Haben Sie Anregungen und/oder Verbesserungsvorschläge für das Evaluierungssystem $CLEO_{de}$?

University of Basel
Department of Pharmaceutical Sciences
Klingelbergstrasse 50
4056 Basel, Switzerland
pharma.unibas.ch

Dominik Stämpfli, MSc
Clinical Pharmacist FPH CAS, PhD candidate
T +41 61 267 15 29
M +41 76 443 04 09
dominik.staempfli@unibas.ch

Validation Cases

University of Basel
Department of Pharmaceutical Sciences

DEPARTMENT OF PHARMACEUTICAL SCIENCES

University of Basel, Department of Pharmaceutical Sciences, Klingelbergstr. 50, 4056 Basel

Validation Cases $CLEO_{de}$

PI-Doc Fallbeispiele

F) Frau B., 70 Jahre, 168 cm, 72 kg, wurde wegen einer intraventrikulären Blutung stationär in der Klinik für Neurochirurgie behandelt. Die Blutung wurde operativ versorgt. Die wiederholte mikrobiologische Analyse des Liquors ergab eine Infektion mit einem multiresistenten Koagulase-negativen Staphylococcus aureus. Eine 10-tägige i.v.-Therapie mit Zyvoxid (Linezolid) Beutel à 300 mL 1-0-1 (Fr. 184.50 /Tag) wurde begonnen. Nach der Verlegung auf die periphere Station zeigt sich die Patientin in einem guten Allgemeinzustand. In der Krankenakte sehen Sie, dass die Patientin Vollkost zu sich nimmt. Einer raschen Entlassung steht auch aus medizinischer Sicht nichts entgegen. Sie schlagen vor, die i.v.-Antibiose auf Tabletten (Fr. 94.15 /Tag) umzustellen, da dies zu einer 5 Tage früheren Entlassung der Patientin führen kann.

G) Frau A., 81 Jahre, 167 cm, 59 kg, wird wegen ihres entgleisten Diabetes mellitus Typ 2 behandelt. Aufgrund einer bestehenden depressiven Erkrankung erhält sie laut Kurve Seropram (Citalopram) 20 mg Tabletten 0-0-1 (Fr. 1.10 /Tag). Seit ihrer Einlieferung klagt die Patientin über Schlafstörungen. Sie fragen die Patientin, warum das Präparat abends verordnet wurde. Es fand sich kein plausibler Grund für die abendliche Einnahme. Daher schlagen Sie eine morgendliche Einnahme vor.
H) Frau W., 58 Jahre, 175 cm, 82 kg, wird wegen einer flächigen Entzündung der unteren Extremität in Verbindung einer Fussinfektion bei Diabetes mellitus Typ 2 eingeliefert. Die Patientin hat eine koronare Herzkrankheit (KHK), eine Herzinsuffizienz und erlitt vor einiger Zeit sowohl einen Herzinfarkt als auch einen zerebrovaskulären Insult. Zudem ist sie durch eine Niereninsuffizienz dialysepflichtig. Sie erhält Calcium-Acetat 500 mg Tabletten 1-1-1 (Fr. 0.80 /Tag). Infektiologische Parameter: CRP: +36 mg/L (Referenz: < 5 mg/L), Leukozyten: 13 /nL (Referenz: 3,6 – 10,5 /nL). Die Fussinfektion wird mit Ciproxin (Ciprofloxacin) 500 mg Tabletten ½ - 0 – ½ (Fr. 2.70 /Tag) in Kombination mit Dalacin C 300 mg (Clindamycin) Kapseln 1-1-1 (Fr. 5.50 /Tag) behandelt. Die Infektionsparameter sind darunter leicht fallend und die Patientin hat weder Durchfall noch Erbrechen. Sie erkennen eine Wechselwirkung durch die Kombination Ciprofloxacin und Calcium-Acetat und schlagen vor, die beiden Medikamente im Abstand von mindestens 2 Stunden getrennt einzunehmen.

I) Herr F., 80 Jahre, 172 cm, 54 kg wurde wegen einer traumatischen subduralen Blutung auf der neurochirurgischen Intensivstation behandelt. Zusätzlich hat er eine chronische obstruktive Atemwegserkrankung (COPD), die mit Unifyl Continus (Theophyllin) 200 mg Retardtabletten 1-0-1 (Fr. 0.50 /Tag), Pulmicort Turbuhaler (Budesonid) 0.2 mg 1 Hub 1-0-1 (Fr. 0.55 /Tag) und Oxis Turbohaler (Formoterol) 6 µg 1 Hub 2-0-2 (Fr 1.50 /Tag) prästationär behandelt wurde. Auf der Station verschlechtert sich die pulmonale Situation des Patienten. Nach Rücksprache mit dem Patienten vermuten Sie, dass das Problem in der mangelhaften Handhabung des Turbuhalers und/oder der Inhalationstechnik begründet sein kann. Sie schlagen dem Patienten das Kombinationspräparat Vannair (Budesonid 0.1 mg, Formoterol 6 µg) als Dosieraerosol vor, 2-0-2 (Fr. 3.40 /Tag). Bei dem Patienten sind keine Allergien bekannt.

University of Basel
Department of Pharmaceutical Sciences
Klingelbergstrasse 50
4056 Basel, Switzerland
pharma.unibas.ch

Dominik Stämpfli, MSc
Clinical Pharmacist FPH CAS, PhD candidate
T +41 61 267 15 29
M +41 76 443 04 09
dominik.staempfli@unibas.ch

University of Basel
Department of Pharmaceutical Sciences

DEPARTMENT OF PHARMACEUTICAL SCIENCES

J) Frau K., 77 Jahre, 165 cm, 66 kg, wird wegen einer Unterschenkelfraktur auf der Unfallchirurgie behandelt. Die Patientin hat zudem postoperativ eine Kreatinin-Clearance von 22 mL/Min (nach Cockroft-Gault) und soll laut Verordnungsblatt wie bereits stationär Aldactone (Spironolacton) 50 mg Tabletten 2-0-0 (Fr. 1.10 /Tag) wegen ihres Zustandes nach Myokardinfarkt erhalten. Sie bemerken, dass Sprinolacton in diesem Fall nicht verordnet werden darf und empfehlen dem Arzt, die Therapie mit Spironolacton nicht weiter fortzusetzen.

CLEO FR Fallbeispiele

Beschreibung: Für einen Patient wird aufgrund einer Streptokokkentonsilitis mit Rovamycin (Spiramycin; Makrolid, in der CH ausser Handel) Tabletten 500 mg morgens und abends während 10 Tagen verschrieben. Arzneimittel-bezogenes Problem: Die Dosierung von Spiramycin wird in Mio. U.I. angegeben und beträgt morgens und abends 3 Mio. U.I. Klinisch-pharmazeutische Intervention: Die Dosierungsangabe wird korrigiert auf die korrekte Bezeichnung von 3 Mio. U.I. morgens und abends.

Beschreibung: Patient wird aufgrund einer Dermatophyteninfektion mit Nizoral (Ketoconazol) Crème 2% 2 Mal täglich behandelt (Fr. 3.10 /Tag). Arzneimittel-bezogenes Problem: Für Dermatophyteninfektionen ist eine 1 Mal tägliche Applikation zugelassen, Art und Ausmass der Infektion schreiben keine höhere Dosis vor. Klinisch-pharmazeutische Intervention: Die Applikationsfrequenz wird auf 1 Mal täglich reduziert (Fr. 1.55 /Tag).

Beschreibung: Verschreibung von Colchicin (in der CH ausser Handel) und Klacid (Clarithromycin) Tabletten 2 x 500 mg /Tag. Arzneimittel-bezogenes Problem: Kombination ist absolut kontraindiziert. Die CYP3A und P-gp-Hemmung von Clarithromycin führt zu einer klinisch sehr relevanten Plasmakonzentrationserhöhung von Colchicin mit toxischen Symptomen kommen kann. Speziell Patienten mit Niereninsuffizienz sind stark betroffen, es kam zu Todesfällen. Klinisch-pharmazeutische Intervention: Stopp von Colchicin.

Beschreibung: Kind mit 38 kg wird wegen einer Infektion der Atemwege mit Augmentin (Amoxicillin, Clavulansäure) Sirup gewichtsadaptiert 1 Mal pro Tag während 7 Tagen behandelt. Arzneimittel-bezogenes Problem: Die Verabreichungsfrequenz ist nicht angemessen und birgt das Risiko einer Unterdosierung mit subsequentem Therapiemisserfolg. Klinisch-pharmazeutische Intervention: Frequenzsteigerung auf 3 gewichtsadaptierte Dosiseinheiten pro Tag.

Beschreibung: Patient mit linkventrikulärer Herzinsuffizienz therapiert mit Digoxin Tabletten 0,25 mg 1x /Tag. Arzneimittel-bezogenes Problem: Der aktuelle Kaliumwert beträgt 3,1 mmol/L (Referenz: 3,3 bis 4,5 mmol/L). Eine Hypokaliämie erhöht die Toxizität von Digoxin (Gefahr von Herzrhythmusstörungen). Klinisch-pharmazeutische Intervention: Start Kalium Hausmann (Kaliumcitrat, Kaliumhydrogencarbonat) Effervetten 3 x 1 /Tag und Monitoring des Kaliumspiegels.

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II. Project: Assessing the ability of the Drug-Associated Risk Tool (DART) questionnaire to stratify patients according to their risk of Drug-Related Problems

Drug-Associated Risk Tool (DART)

DART

University of Basel

Patient code: _ _._ _-_ _-_ _ _

Questionnaire for patients

General information

What is your preferred language of communication? _____

What is your current age? _____

My state of health

Yes	No	
☐	☐	I have a restricted kidney function/kidney dysfunction/kidney disease
☐	☐	I have a liver disease/liver dysfunction
☐	☐	I have a heart weakness/heart performance weakness
☐	☐	I have a chronic respiratory disease
☐	☐	I have diabetes
☐	☐	I have trouble remembering things or tend to be forgetful

If you do not take any medication, the questionnaire is finished for you.

My medicine

Yes	No	
☐	☐	I regularly take medicine, which I bought myself without a prescription from my physician (including vitamin supplements).
☐	☐	I take more than 5 drugs every day, which are prescribed by my physician.

I use the following drugs at home (before my hospital stay):

Yes	No	
☐	☐	Sleeping pills
☐	☐	Cortison
☐	☐	Medicine against epilepsy
☐	☐	Phenprocoumon, Rivaroxaban, Acenocoumarol, Apixaban, Edoxaban, or Dabigatran
☐	☐	Trimipramin, Amitriptylin, Imipramin, Doxepin, Dibenzepin, Clomipramin, or Melitracen
☐	☐	Medicine against rheumatism / inflammation
☐	☐	Medicine for drainage (diuretics)
☐	☐	Digoxin
☐	☐	Tolterodin
☐	☐	Insulin / Medicine against diabetes

Please turn the page and fill out the second page of the questionnaire.

Date: _ _._ _ _ . _ _ _ _ **Page 1 of 2** V2.4

Yes	No	
☐	☐	Do you sometimes forget to take your medicine?

Yes	Partially	No	
☐	☐	☐	Having to take this medicine worries me.
☐	☐	☐	I sometimes worry about the long term effects of my medicines.
☐	☐	☐	My medicines are a mystery to me.
☐	☐	☐	My medicines disrupt my life.
☐	☐	☐	I sometimes worry about becoming too dependent on my medicines.

I feel well informed about my medicine.

Strongly disagree	Disagree	Agree	Strongly agree
☐	☐	☐	☐

Application of medicine

The preparation of my medicine:

Yes	No	
☐	☐	is done by myself
☐	☐	is done by a relative / a friend
☐	☐	is done by a pharmacy
☐	☐	is done by a home care institution

I am having trouble with the application of my medicine:

Yes	No	
☐	☐	when splitting
☐	☐	when identifying
☐	☐	when swallowing

I use one of the following application forms:

Yes	No	
☐	☐	Inhalation device
☐	☐	Syringe for self injection
☐	☐	Skin patch

Would you like to tell us more about your health and medicine?

_____

_____

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

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136 **Excerpt study protocol (Appendices separate)**

STUDIENPROTOKOLL
z.Hd. der Ethikkommission Nordwest- und Zentralschweiz

Version V1.4 vom 15. Dezember 2015

DART
Drug Associated Risk Tool
Validierung eines Fragebogens

Unterschriften

Studienleitung, Investigator

Dr. phil. II Markus L. Lampert 15. Dezember 2015 _____

Studienkoordination, Co-Investigator

MSc Pharm Dominik Stämpfli 15. Dezember 2015 _____

Universität Basel
Departement Pharmazeutische Wissenschaften
Klingelbergstrasse 50
4056 Basel, Schweiz
pharma.unibas.ch

Dominik Stämpfli
Eidg. dipl. Apotheker, Doktorand
Pharmaceutical Care Research Group
T +41 61 267 15 29
M +41 76 443 04 09
dominik.staempfli@unibas.ch

Universität Basel

Departement
Pharmazeutische Wissenschaften

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Liste der Mitarbeiter

Studienleitung, Investigator

Dr. phil. II Markus L. Lampert, eidg. dipl. Apotheker

Departement Pharmazeutische Wissenschaften, Pharmaceutical Care Research Group, Universität Basel

Klinische Pharmazie, Spitalapotheke, Kantonsspital Baselland, Standort Bruderholz

Studienkoordination, Co-Investigator

Dominik Stämpfli, MSc Pharm, eidg. dipl. Apotheker

Departement Pharmazeutische Wissenschaften, Pharmaceutical Care Research Group, Universität Basel

Projektpartner

Prof. Dr. sc. nat. Kurt E. Hersberger, Head of Pharmaceutical Care Research Group, eidg. dipl. Apotheker

Departement Pharmazeutische Wissenschaften, Pharmaceutical Care Research Group, Universität Basel

Projektpartner Kantonsspital Baselland, Standort Bruderholz

Victor A. D. Bättig, Stud. Pharm. 3. Studienjahr

Departement Pharmazeutische Wissenschaften, Pharmaceutical Care Research Group, Universität Basel

Universität Basel

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Zielsetzungen und Zweck

Hintergrund, Begründung und Ziel der Studie

Jeder Übertritt eines Patienten aus der ambulanten Situation in ein Akutspital und danach zurück nach Hause oder in ein Pflegeheim stellt eine entscheidende Schnittstelle bei der Arzneimittelversorgung dar. Während des Aufenthalts im Krankenhaus werden Therapien fortgeführt, abgesetzt oder neu begonnen. Dosis- und Formulierungsänderungen, Substitution oder Änderungen des Einnahmeregimes sind typisch für den Spitalaufenthalt. So zeigte eine Befragung von betreuenden Apothekern in Deutschland, dass bei Einlieferung ins Krankenhaus durchschnittlich vier Medikamente abgesetzt wurden. Bei der Entlassung hatten die Patienten im Schnitt sieben Arzneimittel auf ihrer Medikamentenliste, fünf davon wurden im Spital neuverordnet [1]. Eine Studie aus der Schweiz zeigt, dass beim Krankenhausaufenthalt ca. 60% der Medikation verändert wird und 50% der Arzneimittel für den Patienten neu sind [2]. Dies kann zu Arzneimittel-bezogenen Problemen führen und braucht deswegen besondere Aufmerksamkeit und Massnahmen, um die Therapiesicherheit zu garantieren. Bei Spitalaustrittsrezepten stellen wir fest, dass bei 26,0% der Verordnungen klinisch relevante Arzneimittel-bezogene Probleme vorhanden sind [3].

Als effizienter Lösungsansatz steht unter anderem die intensivierte pharmazeutische Betreuung zur Diskussion [4]. Diese kann in den Schweizer Spitälern jedoch aufgrund beschränkter personeller Ressourcen bis heute nur punktuell und nicht systematisch eingeführt werden. Andererseits benötigen nicht alle Patienten im gleichen Ausmass eine pharmazeutische Betreuung. Es gilt somit die beschränkte Ressource an klinisch-pharmazeutischer Kompetenz gezielt für jene Risikopatienten einzusetzen, welche den grössten Nutzen erfahren könnten.

Aufgrund der Bedeutung von Arzneimittel-bezogenen Problemen (DRP) und Arzneimittel-assoziierten Rehospitalisationen, könnte ein gezieltes Screening zur Früherkennung von Risikopatienten einen essentiellen Beitrag zur Verbesserung der Patientenbetreuung leisten. Patienten mit einem erhöhten Risiko für DRP könnten bei Spitaleintritt besser erkannt und während dem Spitalaufenthalt und bei Spitalaustritt individuell und optimal pharmazeutisch betreut werden.

Vor diesem Hintergrund entstand die Idee, ein ausgesprochen praxistaugliches Hilfsmittel zu entwickeln. Als Arbeitstitel wählten wir die Bezeichnung „Drug Associated Risk Tool“ (DART).

Seit Projektbeginn wurden relevante Risikofaktoren für die Entstehung von DRPs in einem Triangulationsprozess aus Literaturrecherche und wissenschaftlich geführter Expertenrunde (Nominal Group Technique) identifiziert [5]. Aus diesen Faktoren wurde ein Patientenfragebogen erstellt, welcher vom Patienten während des Spitalaufenthaltes als Self-Assessment ausgefüllt wird und dadurch mögliche Risikopatienten aufdecken kann. Ziel dieser Studie ist es, den Fragebogen zu validieren (Verständlichkeit und Machbarkeit; Sensitivität und Spezifität der einzelnen Fragen; Korrelation mit identifizierten Arzneimittel-bezogenen Problemen). Aus dem validierten Fragebogen soll anschliessend in Abhängigkeit der ermittelten Sensitivität und Spezifität durch unterschiedliche Gewichtung der diversen Fragen ein Risiko-Score erstellt werden.

Fragestellung/ Studienpopulation

Diese Studie soll als Teilstudie des gesamten DART-Projekts laufen. Das DART ist als zweiseitiger Fragebogen konzipiert, welcher als Self-Assessment vom Patienten selber ausgefüllt werden soll. **Diese**

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Studie soll aufzeigen, ob die im DART abgefragten Risikofaktoren mit der Anzahl an identifizierten Arzneimittel-bezogenen Problemen korrelieren. Die im Fragebogen erfassten Punkte repräsentieren Faktoren, welche mit einem Risiko verbunden sind, ein unerwünschtes Arzneimittelereignis zu erleiden. Die Antworten des Self-Assessment Fragebogens sollen mit Art und Anzahl Arzneimittel-bezogener Probleme verglichen werden, welche mit Hilfe von etablierten Werkzeugen identifiziert werden. Die Fragestellung der vorliegenden Studie lautet: „Werden bei Patienten mit einer höheren Anzahl an zutreffenden Faktoren im DART eine höhere Anzahl an Arzneimittel-bezogenen Problemen identifiziert?".

Die Studienpopulation soll so wenig wie möglich eingeschränkt werden, um ein umfassendes Bild zur Machbarkeit des Self-Assessments zu erhalten. Weitere Definitionen zur Studienpopulation sind dem Einschlusskriterien zu entnehmen.

Hypothese

Mittels eines strukturierten Fragebogens, welcher vom Patienten selber ausgefüllt wird, kann erkannt werden, ob ein Patient die im Vorprojekt als wesentlich definierten Risikofaktoren für das Auftreten von Arzneimittel-bezogenen Problemen aufweist.

Studiendesign

Hauptzielparameter und sekundäre Zielparameter

Hauptzielparameter

1. Korrelation der Patientenantworten aus dem Self-Assessment (DART) mit objektiven Patientendaten aus Krankenakte und Labordaten.

Studiendesign, Studienablauf, Studiendauer pro Proband, Abbruchkriterien

Studiendesign

Die Studie soll im Kanton Baselland durchgeführt werden. Als Studienzentrum dient das Kantonsspital Baselland am Standort Bruderholz.

Studienablauf

Ein Studienapotheker (siehe Liste der Mitarbeitenden) rekrutiert ab einem festgelegten Zeitpunkt alle Patienten, welche die Einschlusskriterien erfüllen, persönlich. Die Patienten werden während ihres Spitalaufenthaltes vom Studienapotheker besucht und über die Studie informiert. Der Patient erhält die Probandeninformation (Appendix I) und hat genug Zeit die Probandeninformation durchzulesen und Fragen dazu zu stellen. Bei Interesse an der Studie und nach Unterschreiben der Einverständniserklärung (Appendix II) erhält der Patient den Self-Assessment Fragebogen (Appendix III) zum Ausfüllen.

Potentielle oder manifeste Arzneimittel-bezogene Probleme werden durch den Studienapotheker in einer systematischen Medikationsanalyse mit den etablierten Werkzeugen „Medication Appropriateness Index" [6], einem Bewertungsschema für die Angemessenheit eines Arzneimittels, und „START/STOPP Version 2" [7], einer Liste mit für geriatrische Patienten möglicherweise unangebrachten Wirkstoffen, erfasst. Zusätzlich sollen in einem Patientengespräch weitere Aspekte der medikamentösen Therapie systematisch erkannt werden. Dieses soll strukturiert auf Basis des für die öffentlichen Apotheken konzipierten Polymedikations-Checks [8] durchgeführt werden. Das

Gespräch zwischen Patient und Apotheker soll Beratungsbedarf und Beratungsbedürfnis, sowie potenzielle Risiken durch die Medikation, inklusive Selbstmedikation, und Anwendungsschwierigkeiten aufzeigen. Das Interview wird anonymisiert mit FlexiForm erfasst [9] (siehe Appendix IV).

Die identifizierten Arzneimittel-bezogenen Probleme werden für alle eingeschlossenen Patienten im GSASA Erfassungstool [10] und in DOCUMENT [11] dokumentiert und klassifiziert.

Die Studiendauer pro Patient beschränkt sich auf die Zeit, welche zum Ausfüllen des Self-Assessment-Fragebogens und das Durchführen des strukturierten Patientengesprächs benötigt wird und beläuft sich schätzungsweise auf maximal 45 Minuten.

Abbruchkriterien

Die Teilnahme an der Studie ist freiwillig. Der Proband kann das Interview mit dem Studienapotheker jederzeit, ohne Angabe von Gründen, beenden.

Massnahmen zur Bias-Minimierung

Verblindung

Die Studienapotheker haben keine Einsicht in die ausgefüllten Fragebogen und behandeln alle eingeschlossenen Patienten gleich.

Randomisierung

Probanden werden nach Spitalabteilung ausgewählt. Es findet keine Randomisierung statt.

Als Bias-Minimierung werden konsekutiv alle Patienten eingeschlossen, welche ihr Einverständnis zur Studienteilnahme gegeben haben und mit den Einschluss- und Ausschlusskriterien vereinbar sind. Die Patienten werden innerhalb eines bestimmten Zeitraumes oder bis zum Erreichen einer bestimmten Anzahl fortlaufend rekrutiert resp. eingeschlossen.

Auswahl von Versuchspersonen

Rekrutierung

Die Rekrutierung der Probanden findet durch den jeweiligen Studienapotheker am Studienstandort Kantonsspital Baselland Standort Bruderholz statt. Ein ärztlicher Mitarbeiter beurteilt die medizinischen Einschluss-/Ausschlusskriterien der zu rekrutierenden Probanden/Patienten und entscheidet zusammen mit dem Studienapotheker über die Eignung zur Studienteilnahme. Der einzelne Patient wird während seines stationären Aufenthaltes vom Studienapotheker mündlich und schriftlich über die Studie informiert und erhält bei Interesse den „Self-Assessment Fragebogen“ zum Ausfüllen.

Einschlusskriterien

1. Alter > 18 Jahre,
2. ausreichende deutsche Sprachkenntnisse in Wort und Schrift, um sich mit dem Studienapotheker zu verständigen und den Fragebogen auszufüllen
3. stationärer Patient

Ausschlusskriterien

1. Gesundheitszustand, welcher eine sinnhafte Unterhaltung nicht zulässt (d.h. Delir, akute Psychose, fortgeschrittene Demenz, Aphasie, getrübter Bewusstseinszustand)

2. Palliativer oder terminaler Patient

Bewertung der Wirksamkeit

Nicht anwendbar.

Bewertung der Sicherheit

Nicht anwendbar.

Statistik

Mittels geeigneter statistischer Methoden (z.B. Pearsonsche Korrelationskoeffizient) soll die Korrelation von Patientenaussagen mit identifizierten Arzneimittel-bezogenen Problemen berechnet werden.

Studienspezifische Pflichten der Versuchsperson

Für die Versuchsperson fallen keine studienspezifischen Pflichten an.

Pflichten des Prüfers

Die Studie wird gemäss Protokoll, GCP, und den geltenden gesetzlichen Bestimmungen durchgeführt. Der Prüfer wird vom Studienkoordinator geschult und verpflichtet sich, sich beim Interviewen des Patienten an die strukturellen und inhaltlichen Vorgaben des Prüfplans zu halten.

Die Studienapotheker verpflichten sich, alle relevanten medizinischen oder pharmazeutischen Probleme, welche sie während des Patienteninterviews neu erkennen, an den behandelnden Arzt weiterzuleiten.

Versicherungsdeckung von Schäden

Für Schäden, die im Rahmen dieser Studie durch die Befragung entstehen sollten, sind die Probanden durch die Versicherungspolice des Studienzentrums versichert (HDI-Gerling Industrie Versicherung AG, Zürich, Police-Nr.: 01055241-14003, Studie 13.034).

Ethische Überlegungen

Nutzen/Risiko

Der Patient wird zu keinem Zeitpunkt der Studie einem Risiko ausgesetzt. Zusätzlich besteht ein möglicher Nutzen für den Patienten insofern, dass durch das Ausfüllen des Fragebogens, das strukturierte Patientengespräch und die systematische Medikationsanalyse medizinisch, pharmazeutische Probleme neu erkannt und an den behandelnden Arzt weitergeleitet werden können.

Einschluss besonders schützenswerter Personen

Demente Patienten können eingeschlossen werden, sofern eine sinnhafte Kommunikation mit ihnen möglich ist.

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Freiwilligkeit der Studienteilnahme

Sowohl die Teilnahme als Proband, als auch die Mitarbeit als Studienapotheker ist freiwillig und kann jederzeit zurückgezogen werden ohne Angaben von Gründen. Zieht ein Studienapotheker die Teilnahme zurück, so können die Studienleitung und der Studienkoordinator einen neuen Studienapotheker in der Studie einsetzen.

Qualitätskontrolle und Qualitätssicherung

Umgang mit Daten

Die Auswertung sämtlicher Daten erfolgt in anonymisierter Form. Um die Rückverfolgbarkeit auf den Probanden sicherzustellen wird jedem Probanden eine eindeutige Laufnummer zugeteilt und auf dem Fragebogen und den zusätzlich ausgefüllten Datenblättern notiert. Die Laufnummer setzt sich aus den Variablen Spital/Abteilung/Studienapotheker/Proband zusammen und wird für sämtliche Dokumentationen als Identifikation des Probanden gegenüber der Studienleitung verwendet. Der Schlüssel wird daher räumlich getrennt von allen weiteren Studienunterlagen aufbewahrt. Eine Decodierung wäre damit im Bedarfsfall zu jeder Zeit möglich.

In sämtlichen aus der Studie resultierenden Publikationen werden die Daten ausschliesslich Rückschlüsse auf die Studienpopulation zulassen und keinesfalls auf Einzelpersonen. Autorisierte Behörden, sowie die Ethikkommission können jederzeit Einsicht in die Dokumente nehmen.

Datenmanagement

Die erhobenen Daten werden anonymisiert aus den Fragebogen und den Patientenakten in Excel und in das Statistikprogramm SPSS für Windows übertragen.

Eine Plausibilitätsprüfung wird vor der Datenanalyse stattfinden. Zudem werden die Daten von zwei voneinander unabhängigen Personen erfasst. Somit können die Dateneingaben miteinander verglichen und bei fehlender Übereinstimmung überprüft werden.

Archivierung und Vernichtung

Der Investigator ist um geeignete Räumlichkeiten und Einrichtung zur Lagerung der Dokumente besorgt (Raum unter Verschluss mit konstanter Temperatur, Ablage über Bodenniveau, von äusseren Einflüssen wie z.B. Licht / Wasser geschützt). Elektronisch gespeicherte Dokumente werden auf einem zentralen Server passwortgeschützt abgelegt. Zugang zu den Dokumenten haben einzig autorisierte Personen (= Studienleitung, Studienkoordinator). Studiendokumente werden bis 10 Jahre nach Studienende vom Studienleiter unter Verschluss gehalten und anschliessend unter seiner Aufsicht vernichtet.

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Literaturverzeichnis

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[9] IT-Services Universität Basel. FlexiForm 2.7.1c

[10] Maes KA, Tremp RM, Hersberger KE, et al. Demonstrating the clinical pharmacist's activity: validation of an intervention oriented classification system. International journal of clinical pharmacy. 2015;37(6):1162-1171.

[11] Pharmaceutical Society of Australia. Standard and guidelines for pharmacists performing clinical interventions, 2011. Zugriff: http://www.psa.org.au/practice-standards/pharmacists-performing-clinical-interventions (25.11.2015)

Patient study information

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Probandinnen-/ Probandeninformation
zur Studie „Drug associated risks: Development of an assessment tool“

Sehr geehrte Probandin, sehr geehrter Proband

1. Auswahl der ProbandInnen

Sie wurden für die Studie angefragt, weil Sie Patientin/Patient des Kantonsspitals Baselland Standort Bruderholz sind.

2. Ziel der Studie

Das Ziel der Studie ist es, mit Hilfe eines Fragebogens mehr über Ihre Gesundheit und Ihre Medikamente zu erfahren. Wir möchten untersuchen, ob dieser Fragebogen geeignet ist, wesentliche Probleme im Zusammenhang mit Ihren Medikamenten zu entdecken. Längerfristig wollen wir damit die medizinischen Leistungen im Spital verbessern.

3. Allgemeine Informationen zur klinischen Studie

Diese Studie wird nach geltenden Schweizer Gesetzen und nach international anerkannten Grundsätzen durchgeführt.

4. Freiwilligkeit der Teilnahme

Ihre Teilnahme an dieser Studie ist freiwillig. Wenn Sie auf die Teilnahme an dieser Studie verzichten, haben Sie keine Nachteile für Ihre weitere medizinische Betreuung zu erwarten. Das gleiche gilt, wenn Sie Ihre dazu gegebene Einwilligung zu einem späteren Zeitpunkt widerrufen. Diese Möglichkeit haben Sie jederzeit. Einen allfälligen Widerruf Ihrer Einwilligung bzw. den Rücktritt von der Studie müssen Sie nicht begründen. Im Falle eines Widerrufes werden die bis zu diesem Zeitpunkt erhobenen Daten weiter verwendet.

5. Studienablauf

Nach Ihrer Einwilligung bekommen Sie von uns einen Fragebogen ausgehändigt. Dieser Fragebogen ist zum selbständigen Ausfüllen gedacht. Wir interessieren uns dabei insbesondere für Ihre Gesundheit und Ihre Medikamente. Zu einem späteren Zeitpunkt werden wir ein Gespräch zu Ihren Medikamenten mit Ihnen führen, welches ca. 20 Minuten dauert.

Im Rahmen dieser Studie finden keine körperlichen Untersuchungen und keine Blutentnahmen statt.

6. Nutzen für die Probandin/den Probanden

Die Teilnahme an dieser Studie steht nicht im Zusammenhang mit Ihrer derzeitigen Behandlung. Falls wir jedoch relevante medizinische Probleme erkennen, werden wir den zuständigen Arzt informieren, damit diese Probleme behoben werden können. Dank Ihrer Studienteilnahme können die Ergebnisse später auch anderen Personen zugutekommen.

7. Vertraulichkeit der Daten

In dieser Studie werden persönliche Daten von Ihnen erfasst. Diese Daten werden anonymisiert. Die anonymisierten Daten sind nur Fachleuten zur wissenschaftlichen Auswertung zugänglich. Ebenso kann die zuständige Ethikkommission Einsicht in die Originaldaten nehmen. Während der ganzen Studie wird die Vertraulichkeit strikt gewahrt. Ihr Name wird in keiner Weise in Rapporten oder Publikationen, die aus der Studie hervorgehen, veröffentlicht.

8. Kosten

Die in dieser Probandeninformation erwähnten Befragungen sind kostenlos. Es entstehen für Sie keine Kosten.

9. Kontaktpersonen

Bei Unklarheiten, welche während der Studie oder nach deren Abschluss auftreten, können Sie sich jederzeit an die untenstehenden Kontaktpersonen wenden.

Dr. phil. II Markus L. Lampert Spitalapotheker FPH Tel. +41 61 436 23 63 E-Mail: markus.lampert@unibas.ch	Dominik Stämpfli Eidg. dipl. Apotheker, Doktorand Tel. +41 61 436 23 54 E-Mail: dominik.staempfli@unibas.ch

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Written patient consent

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Schriftliche Einverständniserklärung des Probanden zur Teilnahme an einer Studie mit Erhebung gesundheitsbezogener Daten

- 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/in: Name und Vorname	
Proband/in: Name und Vorname	
Proband/in: Geburtsdatum	__ __ . __ __ . __ __ __ __

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 Ethikkommission Nordwest- und Zentralschweiz (EKNZ) 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

Probandencode: __ __. __ - __ __ - __ __ __

V2.0, 11.12.2015/Dominik Stämpfli Seite 1 von 1

Ethics approval

17. Dez. 2015

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Universität Basel, Departement Pharmazeutische Wissenschaften, Klingelbergstr. 50, 4056 Basel

Ethikkommission Nordwest- und Zentralschweiz (EKNZ)
Hebelstrasse 53
4056 Basel

Die Ethikkommission Nordwest- und Zentralschweiz hat die vorliegenden Akten

☒ zur Kenntnis genommen
☒ genehmigt

Datum / Unterschrift
17.12.15

Basel, 15.12.2015

Studie 44/13 „Drug Associated Risk Tool (DART): Validierung eines Fragebogens": Amendement

Sehr geehrte Damen und Herren

Im Rahmen der Studie 44/13 würden wir gerne ein Amendement einreichen. Auch möchten wir Sie mit diesem Schreiben über den aktuellen Stand der Forschung informieren.

Seit dem Beginn der Validierungsstudie „Drug Associated Risk Tool (DART): Validierung eines Fragebogens" wurden in mehreren Teilschritten fast 200 Patienten erfolgreich befragt. In Studien in den Jahren 2013 und 2014 (siehe Amendement 2014) wurden Machbarkeit und Verständlichkeit des Patientenfragebogens (DART) überprüft, sowie die Zuverlässigkeit (Sensitivität, Spezifität) der Patientenantworten im Abgleich mit Daten aus Krankenakten bestimmt [1]. Die Resultate haben Frageformulierungen aufgezeigt, welche durch die Patienten unzureichend verstanden wurden. Die betroffenen Fragen wurden überarbeitet, indem sie den Ausdrücken von Packungsbeilagen angenähert wurden. In der Studie im Jahr 2015 (siehe Amendement 2015) wurde untersucht, ob die neu formulierten Fragen besser verstanden werden [2].

In einem nächsten Teilschritt der Validierung soll nun gezeigt werden, dass die im DART abgefragten Risikofaktoren mit der Anzahl identifizierter Arzneimittel-bezogener Probleme korrelieren. Um auch die Patienten-zentrierten Aspekte von arzneimittelbezogenen Problemen abzudecken, möchten wir die objektiven Daten aus Krankenakte und Labor ähnlich Amendement 2014 um ein Patientengespräch ergänzen. Hierzu sind Anpassungen des Studienprotokolls notwendig, welche Sie bitte dem beigelegten Studienprotokoll V1.4 entnehmen. Die Anpassungen, welche hauptsächlich den geänderten Studienablauf und einen Personalwechsel beinhalten, sind im Korrekturmodus dargestellt, was Ihnen die Durchsicht der nötigen Änderungen vereinfachen sollte.

Die ethischen Überlegungen ändern sich nicht: Es werden gesundheitsbezogene Daten erhoben. Der Patient wird zu keinem Zeitpunkt der Studie einem Risiko ausgesetzt. Zusätzlich besteht ein möglicher Nutzen für den Patienten insofern, dass durch das Ausfüllen des Fragebogens und das strukturierte Patientengespräch medizinische und pharmazeutische Probleme neu erkannt und an den behandelnden Arzt weitergeleitet werden können.

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Universität Basel
Departement Pharmazeutische Wissenschaften
Klingelbergstrasse 50
4056 Basel, Switzerland
pharma.unibas.ch

Dominik Stämpfli
dipl. Apotheker, Doktorand
Pharmaceutical Care Research Group
T +41 61 267 15 29
dominik.staempfli@unibas.ch

Universität Basel

Departement
Pharmazeutische Wissenschaften

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Die Probandeninformation wurde um das Patienteninterview ergänzt (beigelegtes Studienprotokoll V1.4, Appendix 1, Änderungen in rot); Die Einverständniserklärung wurde aktualisiert mit Ersatz von „Kantonale Ethikkommission" durch „Ethikkommission Nordwest- und Zentralschweiz (EKNZ)" (Appendix 2, Änderungen in rot).

Wir danken Ihnen herzlich für die Prüfung unserer Eingabe.
Mit freundlichen Grüssen

Dr. Markus Lampert

Dominik Stämpfli, MSc (Pharm)

Beilagen:
- Studienprotokoll (revidierte Version 1.4)
  - Appendix 1: Probandeninformation
  - Appendix 2: Einverständniserklärung
  - Appendix 3: Probanden Self-Assessment Fragebogen
  - Appendix 4: Leitfaden Patientengespräch

Referenzen: [1] Kaufmann C et al. Content validation of a new Tool for the assessment of Drug Associated Risks (DART); Presented at the 43nd European Symposium of Clinical Pharmacy (ESCP) in Copenhagen (Denmark) 22-24 October 2014
[2] Stämpfli D et al. Patients' Understanding of Health-Related Questions in a Self-Assessment Questionnaire; Presented at the 44th European Symposium of Clinical Pharmacy (ESCP) in Lisbon (Portugal) 28-30 October 2015

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III. Project: Patient Interviews as Part of a Comprehensive Approach Contribute to the Identification of Drug-Related Problems on Geriatric Wards

Patient Interview

University of Basel
Department of Pharmaceutical Sciences

DEPARTMENT OF PHARMACEUTICAL SCIENCES

University of Basel, Department of Pharmaceutical Sciences, Klingelbergstr. 50, 4056 Basel

Adapted Excerpt FlexiForm Questionnaire «DART Validierung: Patientengespräch Erfassungsbogen»

Hintergrund, Ziel
- Ich möchte Ihnen nun einige Fragen zum Alltag mit Ihren Medikamenten stellen.
- Dabei möchte ich überprüfen, ob Ihre Medikamente für Sie angepasst sind, wozu ich auch Ihre Meinung brauche.
- Das Gespräch dauert normalerweise ca. 20 Minuten.
- Sie können das Interview natürlich jederzeit unterbrechen oder abbrechen, und Sie können auch einzelne Antworten verweigern.
- Ziel des Gespräches ist es, Schwierigkeiten aufzudecken. Diese werde ich entweder direkt mit Ihnen oder in Absprache mit dem Arzt lösen.
- In diesem Gespräch gibt es keine richtige oder falsche Antwort.

Einverständnis
- Ist das für Sie in Ordnung?

Probandencode

Datum des Interviews

Check Anwendungen
- Beginnen möchte ich mit der Anwendung und dem Umgang mit Ihren Medikamente.
  - Wer übernimmt die Bereitstellung zuhause? (ich selbst/ Apotheke/ Arzt/ Spitex/ Bekannte/Verwandte/ Etwas anderes)
- *Falls andere Person/Institution*: Kommen Sie regelmässig für die Medikamente vorbei? Nehmen Sie das ganze Dosierbox-Abteil (z.B. die morgendliche Einnahme) gleichzeitig ein?
- Wie werden die Medikamente bereitgelegt / Wie bereiten Sie die Medikamente vor? (ohne/ Dosette/ Etwas anderes)
- Sie sind zufrieden mit dieser Art der Bereitstellung?
- Haben Sie Schwierigkeiten wenn Sie die Medikamente teilen müssen?
- Bei welchen (Teilen)?
- Wie gut erkennen Sie die Medikamente?
- Bei welchen (Erkennen)?
- Haben Sie Probleme beim Schlucken von Medikamenten?
- Bei welchen (Schlucken)?
- Was benutzen Sie für spezielle Anwendungsformen? (Inhalationsdevice/ Spritze/Pen/ Pflaster/ Tropfen (oral)/ Tropfen (okulär)/ keine/ Etwas anderes)
- Brauchen Sie noch weitere Informationen von mir zur Anwendung Ihrer Medikamente?

Ist aus Sicht des Apothekers Beratung notwendig?

University of Basel
Department of Pharmaceutical Sciences
Klingelbergstrasse 50
4056 Basel, Switzerland
pharma.unibas.ch

Dominik Stämpfli, MSc
Clinical Pharmacist FPH CAS, PhD candidate
T +41 61 267 15 29
M +41 76 443 04 09
dominik.staempfli@unibas.ch

University of Basel
Department of Pharmaceutical Sciences

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Check ärztlich verordnete Medikamente
Falls Dosette oder nicht selbst gerüstet, nicht zwingend einzeln durchgehen.
- Ich möchte jetzt gerne alle Ihre Medikamente einzeln mit Ihnen durchgehen.
- Wie viele Medikamente wenden Sie derzeit am Morgen an? *Abgleich mit der Liste.*
- *Falls Dosette vorhanden*: Nehmen Sie alle Medikamente gleichzeitig ein? Vor oder nach dem Essen?

Matrix Medikamente (für jedes einzelne Medikament)
- Haben Sie das Medikament bereits vor dem Spitalaufenthalt eingenommen?
- Wie nehmen Sie XY ein? Wann? Wie oft? Vor oder nach dem Essen?
- Was denken Sie, weshalb müssen Sie dieses Medikament anwenden?
- Vergessen Sie manchmal, Ihr Medikament einzunehmen?
- Macht Ihnen die Einnahme von XY Sorgen?
- Vertragen Sie das Medikament gut?
- Denken Sie, dass Sie momentan weitere Beratung zu XY brauchen könnten?

Check Selbstmedikation
- Weiterfahren möchte ich mit Medikamenten, welche Sie selbst kaufen.
- Nehmen Sie Medikamente ein, die Sie ohne ein Rezept des Arztes in der Apotheke oder Drogerie kaufen oder von Freunden und Bekannten erhalten (z.B. Aspirin, Abführmittel, Mittel gegen Magenbrennen)? Dazu gehören auch Vitaminpräparate und pflanzliche Produkte.

Matrix OTC Medikamente (für jedes einzelne Medikament)
- Weshalb nehmen Sie dieses Medikament ein? Welche Beschwerde behandeln Sie damit?
- Hilft das selbst gekaufte Medikament? Brauchen Sie ein weiteres für die Beschwerden?
- Wie oft wenden Sie dieses Medikament an?

Verdacht auf behandelte UAW OTC?
Verdacht auf Interaktion OTC?

Varia
- Sind bei Ihnen Allergien auf Medikamente bekannt?
- Sind die Allergien in den Patientenakten dokumentiert?

Abschluss
- Sind Sie einverstanden, wenn ich einzelne Punkte mit den Ärzten besprechen werde?
- Ich möchte Ihnen nochmals ganz herzlich für Ihre Teilnahme an diesem Gespräch danken.

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CURRICULUM VITAE

PERSONAL INFORMATION

Name	Dominik Stämpfli
Address	General Guisan-Strasse 104 4054 Basel
Birthdate	4th September 1988
Birthplace	Berne, Switzerland
Contact	dominik.staempfli@gmail.com +41 76 443 04 09

PROFESSIONAL ACTIVITY

07/2014 – 05/2018	PhD at the Department of Pharmaceutical Sciences, University of Basel Title of the PhD thesis: "Drug-Related Problems: Assessing Risk and Relevance"
07/2014 – 05/2018	Graduate Teaching and Research Assistant, Departement of Pharmaceutical Sciences, University of Basel
09/2014 – 11/2017	Clinical Pharmacist FPH, Kantonsspital Baselland
12/2013 – 12/2017	Pharmacist, Notfall-Apotheke Basel [Emergency pharmacy]
10/2013 – 04/2014	Internship, Regional Pharmakovigilance Center Basel

EDUCATION

07/2014 – 05/2018	PhD at the Department of Pharmaceutical Sciences, University of Basel
03/2016 – 07/2017	Certificate of Advanced Studies CAS Clinical Pharmacy, University of Basel
12/2014 – 02/2016	Certificate in Data Science at Johns Hopkins University Bloomberg School of Public Health via Coursera
09/2014 – 11/2017	Clinical Pharmacist FPH, Kantonsspital Baselland
09/2013	Federal Diploma as a Pharmacist
09/2011 – 07/2013	Master of Science in Pharmacy, University of Basel Title of the master thesis: "Drug Associated Risks: The Quest for Risk Factors"

RESEARCH PROJECTS

03/2015 – 12/2016	Project coordinator 'progress! Sichere Medikation an Schnittstellen' [safe medication at transitions of care] by the Swiss Foundation for Patient Safety at the Kantonsspital Baselland
07/2014 – 01/2015	Consultant pharmacist accompanying a study on the adaption of the Dutch Pharmaceutical Cost Groups to Swiss conditions carried out by Polynomics AG on behalf of the Swiss Federal Office of Public Health

SCIENTIFIC CONTRIBUTIONS

Stämpfli D, Boeni F, Gerber A, et al. Patient interviews as part of a comprehensive approach contribute to the identification of drug-related problems on geriatric wards. Drugs & Aging [submitted]

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