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Comparison of the OPERAM DRA Adjudication Guide and AT-HARM10 to identify drug-related hospital admissions in older adults.

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1 ABBREVIATIONS

- ADE, adverse drug event
- ADR, adverse drug reaction
- ATC, Anatomical Therapeutic Chemical
- AT-HARM10, Assessment Tool for Hospital Admissions Related to Medications
- CIRS, Cumulative Illness Rating Scale
- CUSL, Cliniques universitaires de Saint-Luc
- DRA, drug-related hospital admission
- DRP, drug-related problem
- eCRF, electronic case report form
- FN, False negative
- FP, False positive
- ICD-10, International Classification of Diseases
- ICED, Index of Coexistent Disease
- IQR, interquartile range
- IRR, inter-rater reliability
- κ, kappa
- MedBridge, Medication Reviews Bridging Healthcare
- N, number
- NNT, Number Needed to Treat
- NNH, Number Needed to Harm
- OPERAM, OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people
- OTC, Over The Counter
- SD, standard deviation
- STOPP/START, Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment
- STRIP, Systematic Tool to Reduce Inappropriate Prescribing
- TN, True negative
- TP, True positive
- UMC, University Medical Center Utrecht
- WHO-UMC, World Health Organization-Uppsala Monitoring Center
- WHO, Word Health Organization

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3 FOREWORD

This dissertation is a retrospective observational multicentric sub-study of the European OPERAM trial. As a master research student at the UCLouvain, I was in charge of developing the design of the sub-study, submitting the analysis plan to the publication committee of the OPERAM trial, ensuring coordination between the two sites involved, collecting data on the Belgian site, analysing data of both sites and writing the draft of the paper.

Indeed, as part of my project, we are collaborating with one of the four OPERAM teams with the aim of publishing a joint article comparing adjudication outcome performed independently by an expert panel using the OPERAM method and students using AT-HARM10 in two European sites. Since patients from Utrecht had been included in the same original OPERAM study, they had same inclusion/ exclusion criteria, and the protocol of this sub-study was respected.

During the two years of my research student training, another collaboration in this project was discussed with teams in Holland, Sweden and Northern Ireland. Unfortunately, protocols were too different to publish a joint draft paper. However, this helped develop a pilot phase and training material for my project.

In addition to the sub-study, this dissertation includes additional analysis :

- a comparison of results between the Belgian and the Dutch site.
- a pilot test on the use of AT-HARM10 at international level.
- an assessment whether the use of the OPERAM method by a student is possible.

In concertation with my promotor, we decided to modify the traditional structure of a dissertation. Instead, the draft paper of the sub-study is in the section “OPERAM sub-study : draft of article” and the additional analyses are presented as extended abstracts.

4 INTRODUCTION

4.1 AGEING POPULATION

“ Around the world, two persons celebrate their sixtieth birthday every second ” It has been found that the global population growth of older people is greater than in any other age cohort [1]. According to WHO [2], the global proportion of people over 65 will double by 2050, from 8% in 2010 to 16% in 2050.

In order to interpret the promotion of older adults’ care as an investment and not as a cost, it is essential to counter any discrimination against this population, known as “**ageism**”, and to dismiss any misconceptions such as the homogeneity, dependence and societal economic burden for this population.

The quality of life is **heterogeneous** and not random because depends on the genetic background, the socio-physical environment and the income of each person allowing access to quality of health care. Therefore, multinational and multidisciplinary studies should be promoted for the analysis of this diversity.

Older people contribute directly or indirectly to the economy, for example in farming or babysitting their grandchildren, allowing parents to work more. On the other hand, they can also represent a cost and time family burden to promote necessary health care. Thus, being healthy in later life would permit to limit the inflation of societal health care costs, although the impact of ageing on health care expenditure is less than cost of news technologies.

Despite the increased life expectancy, the quality of life during these additional years of life has not been clearly demonstrated. On the other hand, a decreased prevalence of severe disabilities has been observed.

The loss of functional and intrinsic capacities and the physiological decline associated with ageing (for example, metabolic changes, increased receptor sensitivity, decreased homeostasis reserves and impaired liver function) should be differentiated from chronological age in completed years : not every older adult should be considered as a geriatric patient. **Frailty** in this population indicates a risk of **geriatric syndromes** (instability, falls, incontinence, discomfort, sensory and intellectual disabilities, immobilization, iatrogenicity, ...) associated with these disabilities. Another risk factor for frailty is multimorbidity [3-6].

4.2 MULTIMORBIDITY

4.2.1 Definition and prevalence

Multimorbidity, defined by WHO [2] as the presence of at least two chronic conditions, characterizes 81.5% of people aged 85 years and over. The most common chronic conditions in primary care in the United States in 2011 were hypertension (33.5%), hyperlipidemia (33.0%) and depression (18.7%) [7].

4.2.2 Measures

Commonly multimorbidity measure is disease counts but is unsuitable if patient data is limited. Weighted indices, such as the Charlson index, the Cumulative Illness Rating Scale (CIRS), the Index of Coexistent Disease (ICED), the Adjusted Clinical Groups (ACG) System and the Duke Severity of Illness, are valid and reliable multimorbidity measures in clinical research [8].

4.2.3 Causes

This global progression of multimorbidity can be explained by, among others, the medical development of diagnostics, the end of large-scale wars and the improvement of living conditions [7].

4.2.4 Consequences

Some combinations of diseases will have a greater impact than others on societal costs (through a synergistic effect of costs) and the need for care [8-10].

4.3 POLYPHARMACY

4.3.1 Definition

Polypharmacy is described as the regular intake of 5 or more drugs, including prescription drugs but also over the counter (OTC) drugs, traditional and complementary medicine [2, 5, 11].

4.3.2 Prevalence

The prevalence of multimorbidity and of polypharmacy, has been increasing for decades and is significantly higher in the elderly cohort. These prevalences may be higher or not among women than among men of similar age from one study to another [7, 9]. So, polymedication is a worldwide problem, with an increasing trend despite a very variable prevalence from one country to another, which can be explained by its operational definition very different from one study to another [2]. For example, according to a 2015 Flemish study [9], the frequency of

polypharmacy is 20% in the overall population studied and is 49.5% and 50.9% within one year in women and men aged 75 years old and over, respectively.

4.3.3 Causes

Patients with chronic diseases consult several specialists in addition to their general practitioner but the lack of communication between the multiple physicians can lead to a growing list of drugs taken by the patient, and thus to polypharmacy [2, 3]. Most of the guidelines that these specialists follow concerns single diseases or similar conditions because most RCT include a homogeneous population and exclude patients with multimorbidity [7, 8, 10]. The transitions of care (admission, transfer, and discharge) without a medication reconciliation can also be considered as risk factor for polypharmacy due to duplication medication for example [2].

4.3.4 Consequences

Inappropriate polypharmacy increases the risk of falls and cognitive impairment, non-adherence to treatment, adverse drug events and drug interactions [2, 3, 11-14]. It can be considered a risk factor for hospital admissions [5, 13, 14] and can "contribute to 4% of the world's total avoidable costs due to suboptimal medicine use" [2]. A discrepancy of more than 60% between the medication history and the actual intake of these drugs demonstrates poor adherence of the entire population due to omission, discontinuation or dosing error [4].

4.4 CLINICAL PHARMACY TO OPTIMIZE PHARMACOTHERAPY

Clinical pharmacists are key partners in the management and prevention of inappropriate polypharmacy, by the means of actions at several levels.

4.4.1 Medication reconciliation

"Up to a quarter of all prescription medications taken by patients prior to admission are not accurately recorded within the medical record." [15] To ensure medication safety during transition of care and to limit medication discrepancies, the hospital nursing and/or medical staff provide a medication reconciliation. It involves a comparison between the admissions orders and a complete and accurate home medication, through the medical record, an admission medication history interview with the patient/ caregiver or the communication with the physician [15-18]. "Pharmacy-led reconciliations provide more accurate medication lists, and identify more discrepancies compared to physician-led or nurse-led medication reconciliation programs." [18]

4.4.2 Medication review

Providing rational prescription of several drugs according available guidelines and taking into account the individual characteristics of the patient improves quality of life and prevents the consequences of diseases. Thus, appropriate polypharmacy will depend mainly on the patient's health condition, lifestyle, income and social security, adherence to the therapy and the therapy itself rather than the number of drugs consumed [2, 11, 19]. Core element of clinical pharmacy, medication review is a structured, comprehensive and critical evaluation of the individual patient's medicines with the aim of optimizing medicines use and improving health outcomes, taking into account the patient's conditions [2, 20]. Considering the number needed to treat (NNT) and number needed to harm (NNH) is important to evaluate the efficacy and benefit/risk ratio of each medication in the decision-making process [2, 6].

A medication review requires multidisciplinary collaboration, education of additional pharmacists and a clear definition of the respective responsibilities. These requirements are a burden, especially in primary care. Indeed, this particular setting lack of continuity between health care providers, of therapeutic monitoring and of an older adults care policy [2, 4, 6, 14, 21-24].

Despite the lack of evidence that medication review has an impact on the number of readmissions and mortality among the older adults (due to the heterogeneity of the nature of the intervention, the duration of the follow-up or the amount of available patient data) [4, 20, 23, 25], a study by Gillespie et al. [4] showed a 47% decrease in emergency room visits, an 80% decrease in drug-related admissions and a cost saving of $230 per patient aged 80 and over through the intervention directed by only a hospital pharmacist. Two systematic reviews have demonstrated that the hospital pharmacist intervention has a positive impact only on the number of unplanned readmissions in patients aged 60 and over with cardiac disease. On account of the poor prognosis of heart failure and its significant impact on hospitalizations, the authors recommend the presence of a pharmacist on the hospital team managing this cardiac pathology [23, 26].

If a non-adherence to treatment, a new symptom appears as a potential adverse event, or if an ineffective/ unnecessary drugs is observed, deprescription can be considered, through for example STOPP/START (Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment) [27] during the intervention [2, 4, 13, 25, 26]. However, "there is a

complex interplay of many factors that lead an individual to accept polypharmacy or resist deprescribing" [12].

Various methods can be used (1) to detect potentially inappropriate prescriptions: Beers criteria [28] and its updated versions as the French tool designed by Laroche et al. [29] and STOPP/START criteria [27] ; Medication Approriateness Index (MAI) [19] or (2) to assess the causality of ADR : Naranjo algorithm [30] and its revised version Liverpool ADR Causality assessment tool (LCAT) [31], WHO-UMC system [32], Kramer algorithm [33]. However, these methods are not universally accepted or suitable because available drugs, clinical practice, guidelines, socio-economic levels and health care systems differ according to countries [28, 29]. Furthermore, they don't allow the identification of all potentially inappropriate medication or ADE. Some limitations were the design of the implicit method based on expert opinions rather than evidence-based methodology [29], the requirement of clinical expertise even with explicit method [29, 30], a questionnaire with too many steps [33], a too time-consuming for polymedicated patients [19, 30, 31, 33] and unsuitable for prescribing in clinical practise [19, 29, 33].

The patient involvement and shared decision making during intervention therefore helps the clinician to understand the patient's preferences, goals and concerns and ensure that the patient is well informed about treatment and alternatives [12, 13, 34].

4.4.3 Education and management

A pillbox, taking drugs during meals, indicating the dosage on the boxes and putting the boxes in strategic places in the home are effective ways to improve adherence to the treatment [3].
Therefore, the main objective of new health care projects would be to optimize functional capacities, i.e., the ability to do and be what one desires, by strengthening and keeping the intrinsic capacities of older adults, i.e., physical and intellectual capacities.

To achieve this goal, the care provided by an adequate health care staff must be harmonized, integrated, age and capacities focused. Hence, safe medication management should be an integral part of the education of physicians, pharmacists and nurses to promote interdisciplinary nature of health care [9, 10, 35, 36].

4.5 DRUG-RELATED HOSPITAL ADMISSION (DRA)

As DRAs are at the heart of this research project, the definition of DRAs and related concepts, such as adverse drug events and drug-related problems, are described here.

4.5.1 Definition and causes of Drug-Related problems (DRP)

A DRP is "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" [37]. DRPs can have negative consequences on health, morbidity and mortality and increase health care costs [24, 38, 39]. Medical errors, adverse drug reactions (ADRs) and adverse drug events (ADEs) are DRPs. Overdose, addiction, treatment failure and non-adherence are also DRPs according to some studies [4, 16, 24, 38, 39] (Figure 1).

4.5.1.1 Medical errors

Medical errors, extrinsic to drug, occur during the prescription, interpretation of the prescription, dispensing, administration and monitoring of the drug [40-42]. The most frequent medical errors in the United States and in Europe are the omission of a dose, the incorrect frequency of use, the use of two drugs with the same therapeutic indication, the intended lower drug doses, but also the confusion about the doctor's instructions and the management of their medication [3]. Perceiving patient's physiological characteristics (renal and hepatic function, allergies), alert messages regarding potential ADEs when prescribing, computerized prescription entry, barcoding and double-checking of medication by a clinical pharmacist within the department would help prevent the adverse and potential morbidity consequences of these errors [38].

4.5.1.2 Adverse Drug Reactions (ADR)

ADRs are unintended, intrinsic problems to the drug at normal doses, not resulting from errors and inevitably cause discomfort or danger to the patient [5, 38, 40].

4.5.1.3 Adverse Drug Events (ADE)

ADEs are any injury due to medication, resulting whether or not from medical errors [37]. If a medical error can cause an injury but the specific circumstances/ chance/ error is intercepted and corrected, the ADE is regarded as potential. An injury resulting from an error will be considered as preventable ADE. In contrast, a side effect or allergy to the drug is considered as a non-preventable ADE, i.e., an ADR. It should be noted that if the allergy is known and the

ADE occurs a second time, this ADR can be considered preventable. Thus, pharmacist's challenge is to reduce the duration or severity of the injury of the preventable ADEs [22, 40, 41].

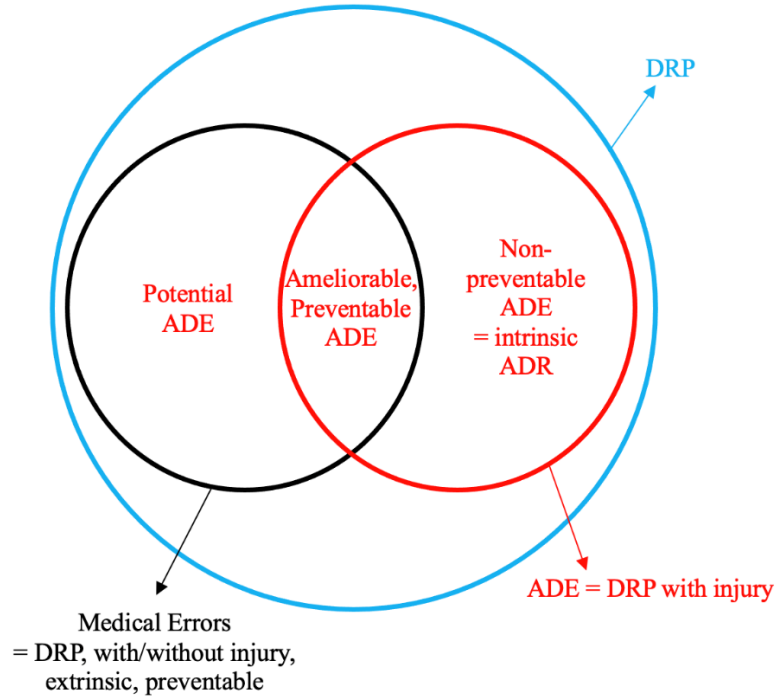

Figure 1. Relationship between the definitions of Drug-Related Problems [2, 38, 40, 41].

4.5.1.4 Drug-related admission (DRA)

Drug-related admissions, (DRA) is a specific subtype of ADE. Throughout this work, DRA is defined as an admission caused by a DRP that is the main or a contributory cause of admission.

Between 6% and 30% of all **admissions among the older adults are due to DRPs** [4-6, 22, 24, 26, 40, 43-45]. This large range of DRA prevalence can be explained by the DRP definitions, DRP prevalences, methods to identify the DRPs, target age ranges, study settings, sample size and study duration which differ greatly from one study to another. As expected, two systematic reviews have shown an increase in the prevalence of DRAs with age [5, 25], with a seven-fold increase in risk among the elderly [46].

As opposed to moderate ADEs, i.e. causing hospitalization or requiring medication adjustment [44], between 3 and 6% of ADEs are considered severe in the U.S., causing life-threatening and permanent damage [43]. Half of DRAs are potentially or definitely preventable [22, 39, 43]. Other consequences of these ADEs are an increase in length of stay and an increased risk

of complications related to hospitalization such as nosocomial infections, cardiovascular disorders and neural disorders [38, 43].

The most common **ADEs causing hospitalization** are gastrointestinal complications (gastrointestinal hemorrhage, peptic ulcer, erosive gastritis, nausea, vomiting, constipation), cardiovascular disorders (hypertension, bradycardia, falls, arrhythmias), kidney disorders, electrolyte disorders (hypo-, hyperkalemia, hyponatremia) and neural disorders (depressed level of consciousness, changes in mental status) and poor glycemic control [22, 43].

Therefore, it is important to identify the most vulnerable patients to these DRAs : older, multimorbid patients with complex polypharmacy and without a good adherent to their treatment. The independent nature of gender and age is contradictory from one study to another. Indeed, increased medication use may be related to gender female while age may be related to increased frailty, altered drug responses due to physiological changes, increased mortality or increased polypharmacy [5, 6, 22, 40, 43-45].

While one of the objectives of the medication review is the prevention of ADEs, the impact of this intervention on the number of DRAs has not yet been sufficiently studied [47]. This is precisely the main outcome of the OPERAM and MedBridge studies.

4.5.2 DRA detection

Detecting ADEs in older patients could be complex owing to the atypical and non-specific symptoms and ADRs in this age range. Consequences of this misunderstanding could be a prescribing cascade, with all repercussions related to polypharmacy [43, 46]. So, determining whether a hospital admission is a DRA is needed. In this sub-study, two methods detecting DRA will be compared.

4.5.2.1 OPERAM

4.5.2.1.1 Context of development

OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people) was a multicenter, cluster randomized, controlled trial undertaken to optimize drug therapy in multimorbid older patients. This European trial was conducted in four university hospital centers: Brussels (Belgium), Bern (Switzerland), Utrecht (Holland) and Cork (Ireland).

Hospital prescribing physician recruitment was carried out as follows : the investigator identified the eligible departments, then the prescribing physicians were enrolled in the study to compose each a cluster of 12 to 38 patients and were randomized in a 1:1 ratio to either the intervention or control group. A total of 2000 patients were recruited, with a similar number of clusters in each site. Written informed consent by patients or the legal representative was required if the patient had a cognitive impairment. Patients in the intervention group underwent the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) intervention, combining STOPP/START criteria [27], and those in the control group received usual care. Telephone interviews at 2, 6 and 12 months after discharge from the index hospital provided follow-up data for the assessment of primary and secondary outcomes. Recruitment of participants took place between December 2016 and the second half of 2019. The period of the collection was therefore two years and one year of follow-up was necessary.

The primary outcome was the first drug-related readmission within one year of index hospitalization. Secondary outcomes were the number of potential hospitalizations, all-cause mortality, number of falls, quality of life, degree of polypharmacy, activities of daily living, drug adherence, number of significant drug interactions, number of drug over- and under-use and number of potentially inappropriate drugs [11].

As DRA was the primary outcome, it was of most importance to have a reliable method to detect DRA. The OPERAM DRA Adjudication Guide (OPERAM method) aimed to evaluate the impact of a drug therapy optimization intervention conducted among 2000 multimorbid older adults and was developed and validated as an early stage of the OPERAM project.

During reliability study, the assessment of sixteen cases generated a moderate IRR between the four European adjudication pairs of research team members with clinical and/or research experience in geriatric medicine (one pair per site) (71% agreement, Fleiss' $\kappa = 0.41$), an almost perfect agreement within each pair (69-94% agreement, Cohen's $\kappa = 0.33$-0.86) and revealed 23 minutes as the mean adjudication time by experts [46].

4.5.2.1.2 Characteristics

The OPERAM study used an explicit and implicit standardized chart review method for older patients based mainly on "triggers" to identify DRAs resulting from an ADR, a drug abuse, an

inappropriate or insufficient drug use. A pair of experts, composed of a physician and a pharmacist, is the target user and their respective skills are complementary.

Figure 2 shows the three steps of this method :
First, patient **data** is analyzed through admission and discharge letters, laboratory data and medication lists.

Next, the potential ADEs which cause the admission is identified by **26 triggers** or by a series of questions for non-triggered ADE (Appendix 1). Triggers, based on the STOPP/ START criteria [27], are specific diagnoses as defined by the ICD-10 (International Classification of Diseases) codes, any irregularities in the patient's condition, laboratory results or a drug prescription that could be considered "hints" requiring further investigation to determine the presence or absence of ADEs or of medical errors. Trigger detection provides convenient and less laborious monitoring of ADEs [41, 48].

The third step is the **adjudication** of admission through a consensus on causality and then on ADE contribution to hospital admission. ADE causality is determined by WHO-UMC (Uppsala monitoring center) criteria [32] and characterizes the relationship between drug and possible ADE as certain, probable, possible, unlikely and unassessable. Degree of certainty is "certain" if the timing is respected, there is no other cause than this ADE and it is definitive. Causality is "probable" if the timing is adequate and another cause is unlikely. Causality is "unlikely" if the timing is inadequate and other more probable causes exist. Causality is "unassessable" if there is insufficient or contradictory information available. The ADE contribution is determined by Hallas criteria which defines the relationship between confirmed ADE and admission [49].

Therefore, a DRA is a hospitalization caused by an ADE that is the main or contributory cause of admission [46].

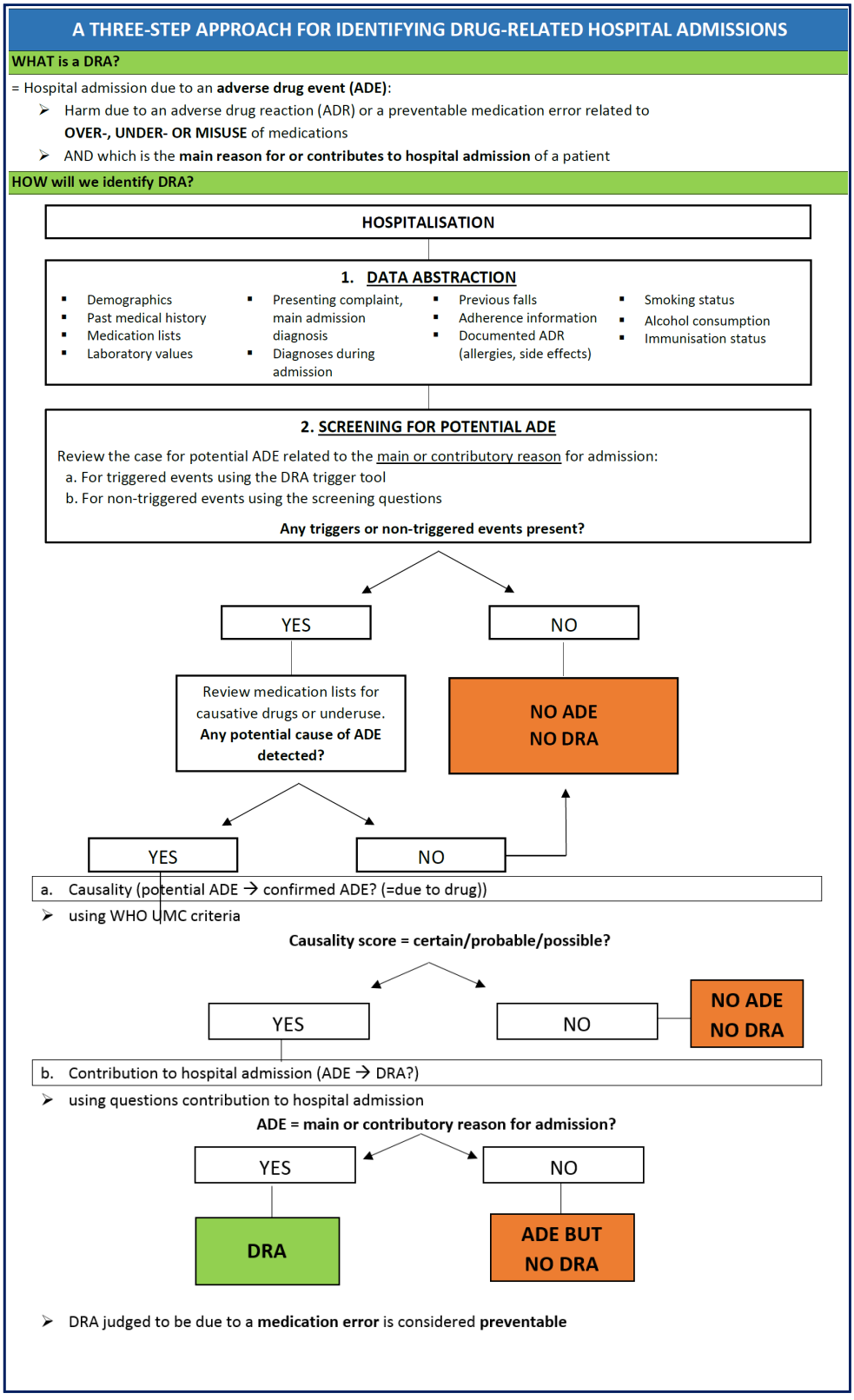

Figure 2. Three-step approach for identifying DRA in the OPERAM method [46].

4.5.2.2 AT-HARM10

4.5.2.2.1 Context of development

AT-HARM10 (Assessment tool for hospital admissions related to medications) was designed during the multicenter, cluster randomized crossover MedBridge study (Medication Reviews Bridging Healthcare) in Uppsala, Enköping, Västeras and Gävle hospitals in 2017. This Sweden study aimed to compare the impact of a comprehensive medication review, with or without an active follow-up, versus a control usual care to the incidence of unplanned hospital visits during a 12-month follow-up period.

During the reliability study, the assessment of one hundred cases generated a moderate agreement among four pairs of under-/postgraduate students (after reviewing supplementary material, receiving a one-hour training by researchers and assess five training cases) with Fleiss' κ = 0.46-0.58. Two pairs analyzed the first fifty admissions (1-50), and the other two pairs analyzed the last fifty admissions (51-100), which explains the range of kappa values. Therefore, the agreement within each pair was moderate to substantial with Cohen's κ = 0.45-0.75 [20].

4.5.2.2.2 Characteristics

As shown figure 3, DRAs identified by this implicit tool (i.e., non-criterion based) composed by ten closed question is a dichotomous variable : admission considered as unlikely or possibly to be drug related. Admission is unlikely to be drug-related if one of the first three questions (**U1-3**) is validated, which are a previously undiagnosed disease, the progression of a known disease or trauma, intoxication or social circumstance. An admission is considered possibly drug-related if the student validates the presence of non-compliance, over-/ underdosage, adverse drug reactions, drug over-/underuse, inappropriate drug selection, drug interactions and failure to receive the drug (**P4-10**). DRA is a hospitalization caused by a DRP as main or contributory cause. This tool is intended to be practical, quick and accessible for final-year undergraduate or postgraduate pharmacy students without a panel of experts. Two students are required to individually analyze hospitalizations before reaching a consensus for the adjudication. During the clinical utility study, the assessment of ten cases by fifteen clinical pharmacists took 6 minutes on average [39].This adjudication time was not estimated when the assessment was done by students.

A precise comparison of the two methods was carried out by Stefanie Thevelin in her thesis, attached in appendix 2 [50].

Table 1 The final version of the assessment tool for identifying hospital admissions related to medications (AT-HARM10)

Question	References	MRP category [2]
U1. Was the admission caused by an infection or a previously undiagnosed disease (e.g. diabetes or heart failure) that is not medication-related?	[44, 45]	n.a.
U2. Was the admission caused by progression of a previously diagnosed disease that is not medication-related?	[19, 21, 41, 46]	n.a.
U3. Was the admission caused by physical trauma, substance intoxication, social circumstances or allergies that are not medication-related?	[19, 21, 41, 46]	n.a.
P4. Is it hinted or stated in the medical record that the admission was medication-related (including non-compliance)?	[21]	Any MRP category
P5. Might (side) effects of the medications the patient was taking (prescribed or not prescribed) prior to hospitalization have caused the admission (including over-treatment)?	[5, 19–21, 25, 41]	5. Overdosage 6. Adverse drug reaction 8. Drug use without indication
P6. Are there abnormal laboratory results or vital signs that could be medication-related and might have caused the admission?	[5, 20, 21, 42]	2. Improper drug selection 5. Overdosage
P7. Was there any drug-drug interaction or drug-disease interaction (i.e. a contraindication) that might have caused the admission?	[11, 25, 43]	2. Improper drug selection 7. Drug interaction
P8. Did the patient have any previously diagnosed untreated or sub-optimally treated (e.g. dose too low) indications that might have caused the admission?	[5, 25, 43]	1. Untreated indication 2. Improper drug selection 3. Subtherapeutic dosage
P9. Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e. failure to receive the medication)?	[5, 11, 25]	4. Failure to receive drug
P10. Is the cause of the admission a response to cessation or withdrawal of medication therapy?	[47]	6. Adverse drug reaction

Three questions are used to identify admissions that are *unlikely* to be medication-related (U1-U3) and seven questions (P4-P10) to identify *possible* medication-related admissions. References to criteria used in existing tools or former studies that were identified in the literature search, and the corresponding eight medication-related problem (MRP) categories by Strand et al. [2], are listed for each question (1–8)

n.a. not applicable, *MRP* medication-related problem

Figure 3. AT-HARM10 [39].

4.5.2.3 Example

In order to understand the practical use of these two methods, a clinical case is taken as an example. A patient comes to the emergency room with complaints of constipation for five days. The medication list, laboratory results and admission and discharge letters are analyzed. In this specific clinical case, the student can interpret constipation as a side effect of the tradonal 50 mg three times a day and the half of durogesic patch 25 mg taken by this patient every 3 days. Question P5 (side effects) of AT-HARM10 is validated : admission is possibly drug-related. The OPERAM experts identified constipation as a trigger event, identified a possible relationship between this constipation (ADE) and the two opioids and then considered that this constipation caused the admission. They also identified as a non-trigger event, the omission of an indicated medication, i.e., under-use of laxatives, as a possible cause of constipation and consider that this constipation caused admission. Therefore, the type of DRA according to the OPERAM method is an adverse drug reaction and under-use of a drug.

To get a good understanding and critical point of view on the OPERAM method and for comparison with AT-HARM10, that I would personally perform during my research project, I met Belgian OPERAM experts during a DRA adjudication session at the CUSL for the OPERAM trial.

4.6 OBJECTIVES

First, this sub-study aims to determine the degree of agreement of DRA detection between the OPERAM method used by an expert panel and AT-HARM10 used by a pharmacy student.

The strategy identifies four secondary outcomes, to be presented within the OPERAM sub-study manuscript :

- (1) Proportions of DRAs detected by AT-HARM10 used by a student and by the OPERAM method used by a panel of experts.
- (2) Categorization of the discrepancies between the student and the OPERAM experts about assessment and about top five of medication classes (Anatomical Therapeutic Chemical level 3).
- (3) Adjudication time and training time needed with AT-HARM10.
- (4) Performance of AT-HARM10 used by a student (versus the OPERAM experts as gold standard) : sensitivity, specificity, accuracy, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio.

Objectives of additional analysis, presented in the dissertation only, include :

- Comparison of results between the Belgian and the Dutch site.
- Pilot study on application of AT-HARM10 by students at international level.
- Assessment whether the use of the OPERAM method by a student is possible.

5 OPERAM SUB-STUDY : DRAFT OF ARTICLE

5.1 TITLE

Comparison of the OPERAM DRA Adjudication Guide and AT-HARM10 to identify drug-related hospital admissions in older adults.

5.2 AUTHORS

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5.3 JOURNAL

This draft paper will be submitted to the British Journal of Clinical Pharmacology (BJCP)

5.4 ARTICLE

5.4.1 Introduction

Worldwide, older population is rapidly expanding [1, 2, 10, 24, 51]. This heterogeneous population is more prone to frailty due to multimorbidity, which leads to polypharmacy [3-6]. Inappropriate polypharmacy increases the risk of falls and cognitive impairment, non-adherence to treatment, adverse drug effects, drug interactions and hospital admissions [2, 3, 5, 11].

Drug-related admissions (DRAs) are hospital admissions for which an unpreventable adverse drug reaction (ADR) or a medication error (including misuse, overuse and underuse of medication) is the main or significantly contributory cause. DRAs contribute to up to 30% of all admissions in older people [4-6, 22, 24, 26, 40, 43-45, 52]. Medication reviews by clinical pharmacists on hospitalized patient aims to reduce the duration or severity of the injury of the preventable adverse drug events (ADE) [22, 40, 41] but its impact on the prevalence of DRAs has not yet been sufficiently studied [47]. This is precisely the purpose of the OPERAM and MedBridge studies.

OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people) was a multicenter, cluster randomized, controlled trial undertaken to optimize drug therapy in 2000 multimorbid older European patients. As first drug-related readmission within one year of index hospitalization was the primary outcome, it was of most importance to have a reliable method to detect DRA. The OPERAM DRA Adjudication Guide (OPERAM method) combined explicit and implicit questions, to be performed by a multidisciplinary panel of experts in 23 minutes on average. This method was validated as an early stage of the trial with a moderate IRR (inter-rater reliability) between adjudication pairs (71% agreement, Fleiss' $\kappa = 0.41$) and an almost perfect IRR within each pair (69-94% agreement, Cohen's $\kappa = 0.33$-0.86) [11, 46].

In 2017, a Sweden team of scientists designed **AT-HARM10** (Assessment tool for hospital admissions related to medications) during the multicenter, cluster randomized crossover MedBridge study (Medication Reviews Bridging Healthcare). This study aimed to compare the impact of a comprehensive medication review, with or without an active follow-up, versus a control usual care to the incidence of unplanned hospital visits during a 12-month follow-up period. AT-HARM10 is intended to be a fast implicit screening tool using 10 closed questions that could be used by pharmacy students in 6 minutes, with associated potential cost savings. The IRR of the tool was moderate among adjudication pairs (Fleiss' $\kappa = 0.46$-0.58) and was moderate to substantial within pairs (Cohen's $\kappa = 0.45$-0.75) [20, 39].

First, this sub-study aimed to determine the degree of agreement of DRA detection between the OPERAM method used by an expert panel and AT-HARM10 used by a pharmacy student.

Secondary objectives included : (1) the comparison of the proportions of DRAs detected by each method, (2) the description of the discrepancies between the student and the OPERAM experts, (3) the measure of adjudication time and training time needed with AT-HARM10 and (4) the assessment of the performance of AT-HARM10 applied by a student (using the OPERAM experts as gold standard).

5.4.2 Materials and Methods

5.4.2.1 Design, setting and participants

This retrospective study included patients from the OPERAM trial who had been recruited at the Cliniques universitaires de Saint-Luc (CUSL; OPERAM Belgian site) and at the University Medical Center Utrecht (UMC; OPERAM Dutch site), had had at least one readmission during follow-up period and for whom an adjudication by the OPERAM's expert panel had been carried out. The OPERAM trial had included patients over 70 years old, multimorbid (i.e., with a minimum of 3 chronic medical conditions according an International Classification of Diseases (ICD-10) codes with an estimated duration of ≥ 6 months or based on a clinical decision), and polymedicated (i.e., taking at least 5 regular medications during at least 30 days) in all the care or emergency units. Exclusion criteria had been to undergo a systematic structured medication review during this hospitalization or within the last two months and the inability to provide or obtain informed consent. Patients scheduled for direct admission to palliative care had also been excluded because drug management in this service varies from others and due to specific condition of these patients [11]. As part of the OPERAM trial, patients had been followed-up for 12 months, during which, in case of non-elective hospitalization, several adjudication expert panels had assessed whether the readmission was drug-related at each site [14].

This retrospective study of the OPERAM trial data was performed by the Belgian student (NCr) and was approved by the Comité d'Ethique Hospitalo-Facultaire Saint-Luc – UCL (2020/13JAN/014) with the Belgian registration number B403/. The Analysis plan was approved by publication committed of the coordination center of the OPERAM study (see Appendix 3).

5.4.2.2 Data source/measurement

The electronic case report form from the OPERAM study included discrete data about the readmissions (date, time, length, type of hospital admission, ward specialty, category of ward, date of arrival at home), patient's health (main complaint, main reason for hospital admission, diagnosis), patient's medication (all medication data collected during the 12 months of the trial i.e. drug name, frequency, interval, strength, unit, route, start date, ongoing, stop date, reason for stopping) and anonymized copies of letters related to the readmission (admission letter, discharge letter, laboratory information). All letters were in the national language of the site.

5.4.2.3 Assessment of DRA

The OPERAM patients from the Belgian and Dutch sites for whom the adjudication of readmission had already been performed by a multidisciplinary expert panel, was reassessed in each site by a final year pharmacy student using AT-HARM10 to determine whether the readmission was drug-related or not. Since hospitalization can be caused by multiple drugs (as main or contributory cause), more than one question of AT-HARM10 could be selected for the same admission. Each included admission was assessed by one student : NCo at the UMC and NCr at the CUSL. The students were completely blinded to the results of the OPERAM's adjudication process by the expert panel and had access to the exact same data. As the primary outcome of OPERAM study was the first drug-related readmission within one year of the index hospitalization, the student could have deduced the OPERAM experts' adjudication if he had known the number of readmissions adjudicated by the experts per patient. For example, if three readmissions for the same patient had been adjudicated by the experts, the student could guess that the first two readmissions were not DRAs. To prevent this bias, the cases were sorted according to a hospitalization identification number which did not allow to guess the chronology per patient. In addition, as the raters (experts and students) became progressively more comfortable with the tools, the order of assessment was randomized for the student to minimize the effect of learning [31, 53], using the internet tool https://de.virtuworld.net/.

5.4.2.3.1 OPERAM DRA Adjudication Guide

The OPERAM method was an explicit and implicit standardized chart review method to be applied by a multidisciplinary panel of experts, composed by a physician and a clinician pharmacist. First, patient data is analyzed through admission and discharge letters, laboratory data and medication lists. Next, the potential ADEs which cause the admission is identified by 26 triggers or by a series of questions. Triggers are specific diagnoses as defined by the ICD-10 codes, any irregularities in the patient's condition, laboratory results or a drug prescription that could be considered "hints" requiring further investigation to determine the presence or absence of ADEs or of medical errors. Trigger detection provides convenient and less laborious monitoring of ADEs [41, 48]. The third step is the adjudication of admission through a consensus on ADE causality (using 5 WHO-UMC (Uppsala monitoring center) criteria [32]) and then on ADE contribution to hospital admission (using Hallas criteria [49]) [46].

5.4.2.3.2 AT-HARM10

AT-HARM10 is intended to be a rapid screening tool that could be used by final-year undergraduate and postgraduate pharmacy students. DRAs identified by this implicit tool composed by ten closed question is a dichotomous variable : admission considered as unlikely or possibly to be drug related according to the two WHO-UMC causality criteria [32]. Admission is unlikely to be drug-related if one of the first three questions (U1-3), i.e., a previously undiagnosed disease, progression of a known disease or trauma, intoxication or social circumstance, is validated. An admission is considered possibly drug-related if the student validates a non-compliance, over-/ underdosage, adverse drug reactions, drug over-/underuse, inappropriate drug selection, drug interactions and failure to receive the drug (P4-10) [39].

5.4.2.4 Agreement definition

AT-HARM10 used only two WHO-UMC causality criteria (possible, unlikely) while the OPERAM method used five (certain, probable, possible, unlikely and unassessable). Both methods agreed in two specific circumstances : (1) AT-HARM10 considered the admission as possibly drug-related (P4-10) and the OPERAM method assessed the certain/ probable/ possible ADE as the main or contributory cause of the admission. (2) Admissions unlikely to be drug-related according to AT-HARM10 (U1-3) and admissions for which the ADE is unlikely/ unassessable and/or ADE isn't the main or contributory reason of the admission according to the OPERAM method.

In order to compare the two methods accurately, if the results (DRA, no DRA) coincided, the student checked whether at least one drug causing admission was in common between both methods.

5.4.2.5 Training of evaluators

5.4.2.5.1 OPERAM experts

During the OPERAM trial, all panel of experts were trained thanks to a webinar. They had access to a video training tutorial [54] and a Standard Operating Procedure [46].

5.4.2.5.2 AT-HARM10

None of the students had experience in using DRA assessment method prior to this project. After considering all instructions of AT-HARM10 and of the protocol, six cases from the reliability study of Thevelin et al. [46] were selected for analysis by both the Belgian (NCr) and

Dutch (NCo) students as training and discussed for increase agreement between them. These six clinical training cases were not included in statistic analysis of the sub-study.

5.4.2.6 Secondary outcomes

5.4.2.6.1 Proportions of DRAs detected by AT-HARM10 used by a student and by the OPERAM method used by a panel of experts

The proportion of DRAs detected by each tool was stated as percentage and McNemar's test [55, 56].

5.4.2.6.2 Categorization of discrepancies between student and the OPERAM experts

Discrepancy of results between the OPERAM experts and AT-HARM10 used by the student was categorized according to a framework developed consensually by the research team in order to exclude any interpretation errors. Depending on the results of the OPERAM method and AT-HARM10, categories were determined in relation to medication, disease and interpretation of letters. Because no discrepancies were observed when the student validated question P7 and P9, no categories were designed in these cases. Since the student could validate several AT-HARM10 questions (P4-10) if hospitalization was caused by several ADEs, several categorizes of discrepancy could be checked.

Highlighting **drug classes** involved (prescribed and omitted) for each DRA identified by both methods was carried out according to the Anatomical Therapeutic Chemical level 3 (ATC3).

5.4.2.6.3 Adjudication time and training time needed with AT-HARM10

The adjudication time included the reading of the admission letter, the discharge letter, the laboratory information, the drug list or any other document in the electronic case report form. Training time was also determined according to the evolution of the required adjudication duration. Knowing the student would become more efficient with training [57, 58], the analysis effectiveness was achieved when the adjudication time from one hospitalization to another was constant and generally didn't decrease.

5.4.2.6.4 Performance of AT-HARM10 used by a student

Gold standard for DRA adjudication is a chart review by a panel of experts. The OPERAM method, includes this chart review, but in structured way, including a trigger tool and implicit questions. For the analysis of sensibility, specificity, accuracy, positive and negative predictive

value, positive and negative likehood ratio analysis, we considered the OPERAM method as a proxy for the gold standard.

5.4.2.7 Sample size

According to Sim et al. [59], the minimum sample size required was 191 patients with a power and alpha as 80% and 0.05 respectively, assuming the value of kappa in the null hypothesis to be 0.40 with a 2-tailed test (considering this value as a moderate agreement), the expected kappa to detect to be 0.60 and the expected proportion of DRA to be around 30% (according to literature). Indeed, the value of kappa in the null hypothesis is higher than zero to be more significant, given better agreement in clinical practice than expected by chance.

5.4.2.8 Statistical analysis

All statistical analyses were performed by the Belgian student (NCr) at the CUSL and the statistical computer programs used were JMP® (SAS Institute Inc., Cary, NC, 1989-2019) and Microsoft Excel®.

Degree of agreement between AT-HARM10 adjudication by a student and OPERAM adjudication by the expert panel was calculated as a percentage agreement (((TP+TN)/N)×100) and Cohen's kappa (κ, agreement corrected for chance between raters). Kappa values of 0 reflect no better agreement than expected by chance, lower than 0.20 poor agreement, between 0.21 and 0.40 fair agreement, between 0.41 and 0.60 moderate agreement, between 0.61 and 0.80 good agreement and between 0.81 and 1.00 very good agreement [60, 61]. The proportion of DRAs detected by each tool was stated as percentage. McNemar's test allows to assess any statistical differences, with a p-value lower than or equal to 0.05 deemed significant [55, 56].

The median time required to adjudicate an admission using AT-HARM10 by students was determined and not the average time, considering the extremes of time values for a few particular hospitalizations not representative of the analysis as a whole. A visual presentation permitted to evaluate evolution of the required adjudication duration. And finally, performance indicators were presented in ratio or percentage.

5.4.3 Results

5.4.3.1 Admission characteristics

Analyzing only readmissions that had already been adjudicated by the OPERAM experts from the Belgian and Dutch site, 193 and 355 readmissions were eligible for this sub-study, respectively. Finally, 376 hospitalizations, balanced by site, were analyzed by pharmacy students using AT-HARM10 (191 by NCr and 185 by NCo). During her analysis, the Belgian student (NCr) excluded 2 hospitalizations deemed unassessable despite experts considered these 2 admissions not drug-related (see Figure 4). In order to ensure an equal number of assessed admissions between the 2 sites, 170 admissions were not assessed by the Dutch student. Table 1 presents patients and hospitalisation characteristics. The mean age of the patients was 78 years old, 38% were female and most patients have at least a high school degree (77%). A very low percentage (5%) lives in a nursing home, the mean units of alcohol per week was 4.30 and the mean number of previous falls and hospitalisations was 1.09 and 1.24, respectively. Most patient were admitted in the surgery (21%) and cardiology (18%) wards, for 9.40 days as mean.

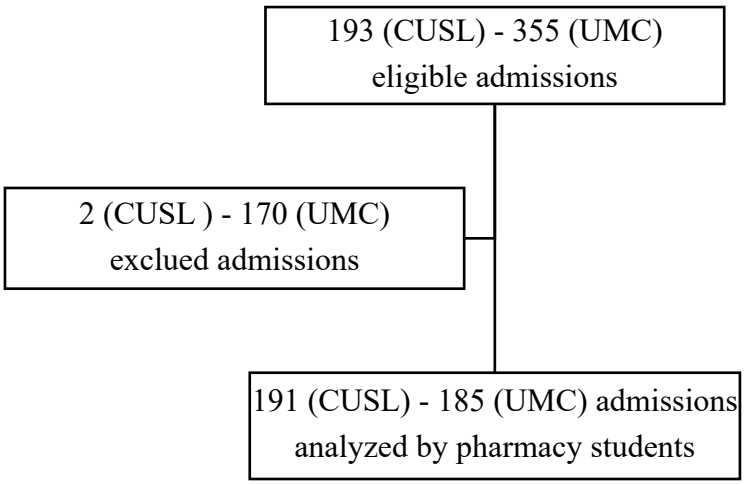

Figure 4. Flowchart of study design

Table 1 Patient characteristics (n=294)

Determinants	Patients (n=294)	Missing data, n
Female sex, n (%)	112 (38)	0
Age, mean years (SD)	78.37 (5.87)	0
Level of education, n (%)		5
Less than high school education	66 (23)	
High school degree	118 (41)	
University degree	105 (36)	
Living in a nursing home, n (%)	12 (5)	34
Alcohol consumption, mean units of alcohol per week (SD)	4.30 (8.37)	2
Mean number of falls of the last year (SD)	1.09 (2.76)	2
Mean number of hospitalisations of the last year (SD)	1.24 (1.64)	1
Length of index hospitalisation, mean days (SD)	9.40 (7.86)	4
Specialty of index hospitalization ward, n (%)		4
Surgery	61 (21)	
Cardiology	53 (18)	
Internal medicine	37 (13)	
Pulmonology	36 (12)	
Emergency	34 (12)	
Urology	32 (11)	
Orthopedics and traumatology	14 (5)	
Intensive care unit	7 (2)	
Neurology	6 (2)	
Endocrinology	5 (2)	
Hepato gastroenterology	5 (2)	

5.4.3.2 Degree of agreement of DRA detection between the OPERAM method and AT-HARM10

As shown in table 2, the degree of agreement of DRA detection between the OPERAM method (used by experts) and AT-HARM10 (used by students) was good with 82% agreement (309/376), Cohen's $\kappa = 0.61$ (95% CI 0.52-0.69) and Cohen's $\kappa_{max} = 0.90$ (the calculation details in appendix 4). It should be stated that Cohen's κ value was in the lower limit of the range 0.61 – 0.80. Regarding hospitalizations considered by the two methods as drug-related, the experts and the student had in common at least one drug responsible for admission in 92% of all DRA (90/98).

Table 2. DRA assessment by the OPERAM method used by experts and AT-HARM10 used by a student.

		OPERAM method used by experts	
		DRA yes	DRA no
AT-HARM10 used by a student	DRA yes	98	25
	DRA no	42	211

5.4.3.3 Proportions of DRAs

With a two-tailed p-value of 0.0378, the McNemar's test shows that there was a statistically significant difference between the two methods in the proportion of DRA detected, which suggests that the OPERAM method was more prone to assess an admission as DRA (37% (140/376)) than AT-HARM10 (33% (123/376)).

5.4.3.4 Discrepancies

Experts and student disagreed on the assessment of 67 hospitalisations out of 376 (18%). As table 3 shows, the main discrepancy between raters was the overestimation of disease impact by student, with 30 hospitalizations concerned, followed by 13 overestimations of underuse of drugs /prevention drugs by student and 9 cases where the experts interpreted more appropriately the letters. As shows table 4, top five of prescribed drug classes most involved in DRAs were similar with both methods : first, cardiovascular drugs (in particular diuretics and agents acting on the renin-angiotensin system), followed by nervous system drugs (especially analgesics), antithrombotics, antineoplastics/ immunosuppressants and glucocorticoids or drugs for acid related disorders. Omitted drug classes most involved in DRAs were cardiovascular drugs and drugs for bone diseases. A more extensive table is available in appendix 5.

Table 3. Discrepancy of results between the OPERAM method and AT-HARM10.

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="3">OPERAM method</td></tr>
<tr><td>No DRA</td><td>ADR, Overuse or Misuse cause DRA</td><td>Underuse cause DRA</td></tr>
<tr><td rowspan="6">AT-HARM10</td><td>U1</td><td rowspan="3">AGREEMENT
N = 98</td><td rowspan="3">Overestimation of disease impact by student
N = 30</td><td rowspan="3">Underestimation of underuse*/prevention** drugs by student
N = 7</td></tr>
<tr><td>U2</td></tr>
<tr><td>U3</td></tr>
<tr><td>P4</td><td>More appropriate interpretation of letters by experts
N = 9</td><td colspan="2" rowspan="4">AGREEMENT
N = 211</td></tr>
<tr><td>P5
P10</td><td>Overestimation of drug impact/ Underestimation of disease impact by student
N = 8</td></tr>
<tr><td>P6</td><td>More appropriate interpretation of laboratory results by experts
N = 1</td></tr>
<tr><td>P8</td><td>Overestimation of underuse*/ prevention** drugs by student
N = 13</td></tr>
</table>

* no treatment, too low dose, too short duration of treatment** examples : vaccines, cardiovascular prevention drug

U1. Was the admission caused by an infection or a previously undiagnosed disease (e.g., diabetes or heart failure) that is not medication-related?

U2. Was the admission caused by progression of a previously diagnosed disease that is not medication-related?

U3. Was the admission caused by physical trauma, substance intoxication, social circumstances or allergies that are not medication-related?

P4. Is it hinted or stated in the medical record that the admission was medication-related (including non-compliance)?

P5. Might (side) effects of the medications the patient was taking (prescribed or not prescribed) prior to hospitalization have caused the admission (including overdosage, adverse drug reaction, drug use without indication)?

P6. Are there abnormal laboratory results or vital signs that could be medication-related and might have caused the admission (including improper drug selection, overdosage)?

P7. Was there any drug-drug interaction or drug-disease interaction (i.e., a contraindication, improper drug selection, drug interaction) that might have caused the admission?

P8. Did the patient have any previously diagnosed untreated or sub-optimally treated indications that might have caused the admission (i.e., subtherapeutic dosage, untreated indication, improper drug selection)?

P9. Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e., failure to receive the medication)?

P10. Is the cause of the admission a response to cessation or withdrawal of medication therapy (adverse drug reaction)?

Table 4. Highlight drug classes most involved in DRAs according to AT-HARM10, the OPERAM method and both methods

Methods	AT-HARM10 no. (%)* (n DRA = 123)		OPERAM method no. (%)* (n DRA = 140)		AT-HARM10 and OPERAM method no. (%)* (n DRA = 98)	
Drugs :	Prescribed	Omitted	Prescribed	Omitted	Prescribed	Omitted
Cardiovascular system	37 (30.1)	28 (22.8)	95 (67.8)	33 (23.6)	30 (30.6)	10 (10.2)
Nervous system	32 (26.0)	2 (1.6)	44 (31.4)	7 (5.0)	21 (21.4)	2 (2.0)
Antithrombotic agents	18 (14.6)	5 (4.0)	31 (22.1)	6 (4.3)	14 (14.3)	2 (2.0)
Antineoplastic agents and Immunosuppressants	17 (13.8)	1 (0.8)	18 (12.8)		13 (13.3)	
Glucocorticoids	12 (9.7)	1 (0.8)	11 (7.8)		7 (7.1)	
Drugs for acid related disorders	4 (3.2)		13 (9.3)		1 (1.0)	
*percentage of DRA caused by this class of drugs						

5.4.3.5 Time

The median adjudication time with AT-HARM10 was 16.5 minutes at the CUSL and the average time was 7.4 minutes at the UMC. Figure 5 shows that the analysis time tend to stabilize after about 50 hospitalisations at the CUSL.

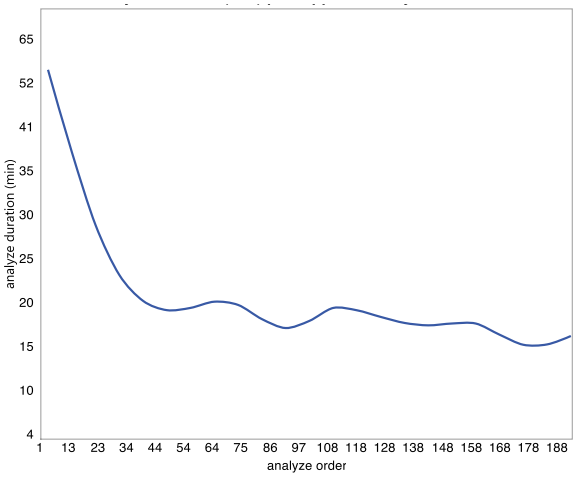

Figure 5. Evolution of the analyze duration required to adjudicate an admission using AT-HARM10 by the Belgian student (NCr).

5.4.3.6 Performance results

The accuracy of AT-HARM10 was 0.82 (309/376) with sensitivity and specificity values as 70% (98/140) and 89% (211/236), respectively. The positive and negative predictive values were 0.80 (98/123) and 0.83 (211/253), respectively. In addition, positive and negative likehood ratio were 6.61 (0.70/(25/236)) and 0.33 ((42/140)/0.89), respectively.

5.4.4 Discussion

Although our results confirm a good rate of agreement between the two methods to detect DRA outcome in clinical research study, the proportion of DRA detected differs and some disagreement persists with an overestimation by students of the disease impact and the underuse of drugs. Even when the analysis is time-efficient, AT-HARM10 didn't have the advantage of a significantly shorter analysis time than with the OPERAM method in the Belgian site (16.5 versus 23 minutes).

The implementation of students in drug therapy management in the dynamic and resource-limited environment of the hospitals saves time for the medical staff, save cost for the hospital (due to the student's increased productivity and autonomy after an initiation initiation period) and provides an opportunity for the student to develop early skills in real-word clinical practice [15-17, 57, 58, 62]. In the literature, doctor of pharmacy students during an advanced pharmacy practice experience were involved in medication reconciliation [15-18, 53, 62, 63] and medication review [15, 16, 53, 62, 63] through a standardized medication history acquisition process [16], an outline for patient interviews [53, 62, 63] or a step-by-step instructions [18] (after didactic protocol orientation and training session). Agreement between students and clinicians for the outcome of medication reconciliation was achieved two of these studies [15, 53]. Students may also be involved in patient enrolment [15-17, 57, 63, 64]. However, these studies have limitations such as a small sample of students or patients, the lack of a standardized process for medication review, and the limited amount of time spent by each student.

Prior to any analysis, it was thought that the incidence of DRA detected by pharmacist students would be higher than the experts (a pair of a physician and a clinical pharmacist) because the underestimation of the proportion of DRAs by the practitioner would offset the overestimation by the pharmacist, expert in pharmacotherapy [25]. It can be explained by the overestimation of disease impact by students according to their focus-pharmacy training. In this sub-study, the proportion of DRAs detected by both methods is higher than the one found in the literature (up to 30% of hospitalizations are drug-related). In fact, the proportion of DRA would be understated according to the design (retrospective, European study) [5, 40, 42, 45]. However, variables in the hospitalization tab of the electronic case report form of this sub-study provide as much information than in prospective studies. The definition of DRA (all DRP considered and not only ADR) and the target population in this study (older, multimorbid patients with complex polypharmacy, i.e., the most vulnerable to DRAs) can explain the results.

The overestimation of disease impact and of underuse of drugs as discrepancies between the student and the experts reflects that detecting a dose problem, the need of an additional drug or

a drug without an indication requires more clinical judgment, is less taught in pharmacy school and less reported in encyclopedia than the detection of a wrong drug, an ineffective drug or an ADR [53].

The OPERAM method consists of a detailed list of suspected causative drugs or causes for underuse of each trigger, in contrast to AT-HARM10 in which no specific drug is mentioned. It was therefore thought that some discrepancies in drug detection between methods would be observed, but the results of this study showed that when both methods considered hospitalization drug-related, the judgment of the AT-HARM10's assessor was able to detect the same drug(s) as OPERAM method in 92% of all DRA. Cardiovascular drugs [4, 5, 22, 25, 40, 43, 44], nervous system drugs [4, 5, 22, 25, 40, 43], antithrombotics [5, 22, 25, 40, 43, 44], antineoplastics/ immunosuppressants [5, 40, 43] and glucocorticoids [22, 40, 43] highlighted as the most prescribed medication related to hospitalization in this study are similar to many meta-analyses and systematic reviews analyzing main medication involved in DRA in older patients. Cardiovascular system drugs are the most common cause of DRA, but cardiovascular diseases are widespread in almost 60% of older people with DRPs [7, 45] and this drug class is usually prescribed to this population [52].

Therefore, the performance of AT-HARM10 assessed in this study confirmed on a larger sample those in the Medbridge study where the gold standard was one consultant physician (geriatrics and primary care specialist) and one senior clinical pharmacist and researcher, neither of whom hadn't been used AT-HARM10 or any other assessment tool [39].

The highlighted advantages of AT-HARM10 would be a usability and time saving during the adjudication. Neither explicit list of trigger nor clinical rules are present in this tool on purpose. It is known that results of an implicit method depend mainly on the assessor's knowledge, but the students' training is not comparable to clinicians' experience. Without requiring the need of experts, potential saving can be observed in research studies where DRA is an outcome. In other hand, degree of subjectivity in the adjudication process with this implicit tool can be higher but criterion-related validity data of this method is available [65]. For timesaving, AT-HARM10 consider two WHO-UMC causality criteria compared to five in the OPERAM method but these two criteria are the most widely used in practice. In the opposite, according to Spinewine et al. [65], implicit indicator to detect inappropriate prescription are more time-consuming than explicit indicator. One way to increase agreement on issues requiring drug and clinical knowledge is the use of standardized reference sources listing well known ADEs with a variety of drugs, the symptoms of a variety of diseases, and the timing of a variety of ADR [66]. That is exactly the design of the OPERAM method, in contrast to AT-HARM10.

Strenghts and limitation

This is the first multicentric research that compares these two recently developed methods while carefully adhering to the design of each one in a large cohort of older patients with polypharmacy and multimorbidity. Experts and students accessed the cases using the exact same rich information about the admission. Available detailed letters was a strength but required extended adjudication time. Two students, from different countries, where pharmacy education might differ (both in their final year but the duration of study differs between countries, i.e., five years in Belgium and six years in the Nederlands), participated in the project. No inter-rater reliability between the two students was calculated before the study but they received similar training, with identical training cases, and had several meetings to insure they worked similarly. Therefore, the generalizability to "any pharmacy student" of the results in terms of agreement with experts, time required, and performance is limited. However, these pharmacy students were completely blinded to the experts assessment and worked alone without any expert support, ensure trustworthiness of findings. It was decided not to have the students assess the cases themselves with the OPERAM method. If the student had analyzed each admission with both methods, even with 2 to 14 days as a time interval [59], he could have remember the elements of the admission analyzed by the first tool, which would have biased the result of the assessment with the second method and would have overestimated Cohen's kappa values.

5.4.5 Perspective

My research experience and the results of this sub-study might suggest the setting of use (research, clinical or training) and the type of user (students or experts) for these tools. DRA detection is a challenge for medical staff and students, requires critical and careful assessment and can be time and money consuming. AT-HARM10 is a valuable screening tool that can be used by students during an emergency room internship for example, as a clinical teaching tool to identify DRA, or during clinical practice if the student's productivity allows it. The OPERAM method is a precise method that can better be applied by experts for clinical research as the average adjudication time does not allow its implementation in clinical practice.

5.4.6 Conclusion

Agreement between the tools was good, showing that both methods can detect DRA outcome as long as assessors respect exactly the way they were designed to. In this sub-study, the OPERAM method was more prone to detect DRA, AT-HARM10 doesn't have the advantage of a significantly shorter analysis time than with the OPERAM method in Belgium and it is known that an implicit process measure depends mainly on the student’s knowledge.

6 ADDITIONAL ANALYSIS

6.1 COMPLEMENTARY STATISTICAL ANALYSIS ABOUT THE ARTICLE : OPERAM SUB-STUDY

This section is structured according to cookbook [67] and Strengthening the Reporting of Observational Studies in Epidemiology [68]. For some methodological aspects and details of calculations of the results of the sub-study, it was more relevant to specify them in the framework of the dissertation rather than in the article.

6.1.1 Sample size calculation

The sample size chosen for the sub-study is higher than what is usually presented for similar studies. We detail here why we made that calculation, which we consider as one of the major strength of our study.

It is found that the minimum sample size required is 165 or 191 patients with a power and alpha as 80% and 0.05 respectively, assuming the value of kappa in the null hypothesis to be 0.40, the expected kappa to detect to be 0.60 and the proportion of positive ratings to be 0.30 or 0.50 [59]. Considering the kappa value of 0.40 as a moderate agreement, the value of kappa in the null hypothesis can be 0.40 with a 2-tailed test. In fact, the value of kappa in the null hypothesis is higher than zero to be more significant, given better agreement in clinical practice than expected by chance [59, 64]. Any value lower than this kappa value in the null hypothesis would be considered as unacceptable in clinical practice [59]. If AT-HARM10 and OPERAM method could be used to identify polymedication and risk (DRA) in multimorbid older patients, and if this categorization determines whether these patients are enrolled or not in a drug management program, the minimum acceptable level of consensus on this categorization can be set at a fairly high level so that decisions regarding patient management can be made with a high degree of coherence. According to literature [4-6, 22, 24, 26, 40, 43-45], between 6% and 30% of all admissions among the older adults are due to DRPs : proportion of positive ratings is estimated as 0.30. But according to my current results, the proportion of positive ratings is almost 0.50. Indeed, the highest value for sample size (191 patients) is chosen.

6.1.2 Cohen’s kappa : Agreement Statistics

6.1.2.1 Cohen’s kappa definition

The degree of agreement between the OPERAM method and AT-HARM10 was evaluated according to a percentage agreement and Cohen's kappa (95% CI). Data reliability analysis is crucial in order to avoid any misinterpretation and biased conclusions. Cohen's kappa (κ) is the

real agreement coefficient between the results of these two methods, eliminating the part due to chance. It is therefore the ratio between the real concordance and the perfect concordance and takes the form :

$$\kappa = (\text{Observed agreement} - \text{Expected agreement})/(1 - \text{Expected agreement})$$

Concordance term refers to the relationship between two independent, mutually exclusive and exhaustive qualitative variables (DRA, no DRA) from two independent series (AT-HARM10 and the OPERAM method used independently).

The observed agreement for the detection of DRA is the ratio between the concordant results (DRA for both methods, no DRA for both methods) and the number of admissions.

The expected agreement, match due to chance, is the ratio between the marginal products of the concordant results sum and the total number of results squared. (Table 5) Observed and expected agreement take the form :

Observed agreement = concordant results/number of admissions = (TP+TN)/n

Experted agreeement= $((TP+FP)\times(TP+FN)+(FN+TN)\times(FP+TN))/n^2$

[42, 59-61, 69, 70]

Table 5 DRA assessment by the OPERAM method and AT-HARM10.

		OPERAM method	
		DRA yes	DRA no
AT-HARM10	DRA yes	TP	FP
	DRA no	FN	TN
FN, False negative ; FP, False positive ; TN, True negative ; TP, True positive			

6.1.2.2 Interpretation of Cohen's kappa

Despite some limitations or paradoxes, Cohen's kappa is the most statistic used to assessed inter-rater reliability. Prevalence index and bias are crucial in the interpretation of the Kappa value. Indeed, the prevalence index indicates an agreement very different between the prevalence of positive classification of an attribute (DRA) and negative classification of the same attribute (no DRA). Rater, bias is the absolute value of the difference in disagreement between the frequency of positive and negative classification of the attribute. Paradoxically, the value of kappa will be lower if the prevalence index is large (explained by a high rate of agreement due to chance) and will be higher if the bias is large [59, 71].

6.1.2.3 Terms of use of Cohen's kappa

The independence of assessment errors (and thus of patients and of assessments) is a use condition of kappa and justifies the design of the sub-study. Each assessor must not be influenced by the results of other assessors and each hospitalization must be submitted by only one paired assessment. So, the student was blinded to the OPERAM experts' results during the adjudication with AT-HARM10. In this sub-study, if the student had analyzed each admission with both methods, even with 2 to 14 days as a time interval [59], he could have remember the elements of the admission analyzed by the first tool, which would have biased the result of the assessment with the second method and would have overestimated Cohen's kappa values. Therefore, the design of the OPERAM method is inappropriate for a student [46]. However, Cohen's kappa does not specify whether the divergence of results between evaluators is due to random (i.e., due to chance) or systematic (i.e., following a consistent pattern) differences [59, 69, 70].

6.1.2.4 Adjusting Cohen's kappa

The maximum Kappa (κ_{max}) had been estimated to reflect the effect on agreement of the divergence in the level of assessor experience, i.e., generating unequal marginal totals (proportion of positive and negative judgments of each assessor). Thus, 1-κ shows the total unachieved agreement (chance excluded), κ_{max}-κ shows same but within the constraints of the marginal totals and 1-κ_{max} demonstrates the unachieved degree of agreement beyond chance as a consequence of imbalance in the marginal totals [59, 69, 70].

6.1.3 Performance statistics

Performance of AT-HARM10 used by the student takes the form :

Sensibility = TP/(TP+FN)

Specificity = TN/(TN+FP)

Accuracy = (TP+TN)/n

Positive predictive value = TP/(TP+FP)

Negative predictive value = TN/(TN+FN)

Positive likehood ratio = Sensibility/(FP/(FP+TN))

Negative likehood ratio = (FN/(FN+TP))/Specificity

6.2 COMPARISON OF SITES

6.2.1 Background and objectives

An analysis by site was suggested to further explore agreement between AT-HARM10 and the OPERAM method and ensure trustworthiness of findings. Indeed, pharmacy education, patient profile and ward specialty might differ according to countries and can influence results. Main objective was to check whether the degree of agreement was similar across sites. Then, secondary outcomes included the comparison across sites about (1) the proportion of DRAs detected by each method, (2) the categorization of the discrepancies between users, (3) the adjudication time and training time needed with AT-HARM10 used by each student and (4) the performance of AT-HARM10 applied by each student (using the OPERAM experts as gold standard).

6.2.2 Methods

Methods were those described within the article but broken down to countries (see pages 26-31).

6.2.3 Results

Table 6 presents patients and hospitalisation characteristics in each site. The difference between sites about the proportion of female sex, the mean age, the pourcentage of patients living in a nursing home was not significant. However, the level of education, the alcohol consumption, the number of previous falls and previous hospitalisations, the length of the index hospitalisation and the specialty of index hospitalization ward were statistically and significantly different.

Table 6 Patient characteristics at the CUSL and at the UMC (n=294)

Determinants	Patients at the CUSL (n=132)	Patients at the UMC (n=162)	Difference test between the two sites : p-values
Female sex, n (%)	51 (39)	61 (38)	0.8631[a]
Age, mean years (SD)	78.64 (6.08)	78.15 (5.69)	0.5036[b]
Level of education, n (%)			<0.0001[a]
Less than high school education (≤9 years of schooling completed)	22 (17)	44 (27)	
High school degree (high school completed)	29 (23)	89 (55)	
University degree	77 (60)	28 (18)	
Living in a nursing home, n (%)	5 (4)	7 (5)	0.7702[a]
Alcohol consumption, mean units of alcohol per week (SD)	5.30 (8.90)	3.50 (7.85)	0.0051[b]
Mean number of falls of the last year (SD)	0.72 (1.45)	1.4 (3.46)	0.0266[c]
Mean number of hospitalisations of the last year (SD)	0.98 (1.29)	1.45 (1.86)	0.0117[c]
Length of index hospitalisation, mean days (SD)	7.31 (6.33)	11.05 (8.55)	<0.0001[b]
Specialty of index hospitalization ward, n (%)			<0.0001[a]
Cardiology	24 (19)	29 (18)	
Emergency	33 (26)	1 (1)	
Endocrinology	5 (4)	0 (0)	
Hepato gastroenterology	4 (3)	1 (1)	
Intensive care unit	5 (3)	2 (1)	
Internal medicine	14 (11)	23 (14)	
Neurology	0 (0)	6 (3)	
Orthopedics and traumatology	14 (11)	0 (0)	
Pulmonology	0 (0)	36 (22)	
Surgery	29 (23) Including 19 (15) for Cardiovascular and thoracic surgery	32 (20)	
Urology	0 (0)	32 (20)	
[a]Pearson test ; [b]Kruskal-Wallis test ; [c]Welch test ; p<0.005 is significant			

We observed site differences in terms of level of agreement between experts and students and prevalence of DRA, as shown in table 7.

Table 7. Summary of the results of AT-HARM10 used by the Belgian and Dutch student.

Sites	**CUSL**	**UMC**
N assessed admissions	191	185
Agreement Experts – Students : %, K, K_{max} Experts – Students	85%, 0.69 (95% CI 0.59-0.80): Good concordance, 0.95	79%, 0.43 (95% CI 0.28-0.56): Moderate concordance, 0.82
DRA proportion detected by student versus by experts	0.45 (86/191) versus 0.48 (91/191)	0.20 (37/185) versus 0.26 (49/185)
Adjudication time, minutes[a]	16.5 (IQR 11-24 ; Min-Max 4-55)	7.4 (SD 1.65 ; Min-Max5.3-11.5)
Sensitivity	81%	49%
Specificity	88%	90%
[a] median time at the CUSL, average time at the UMC		

Indeed, the degree of agreement of DRA detection between experts and student differed according to the country, with a higher Cohen's κ value in Belgium (0.69 vs 0.43) (the calculation details in appendix 4). Experts (using the OPERAM method) and student (using AT-HARM10) had in common at least one drug responsible for the admission for 92% of all DRAs (68/74) in the Belgian site and for the same percentage of all DRAs (22/24) in the Dutch site.

(1) The proportion of admission considered as drug-related according to the two tools is almost double for the Belgian patients than for the Dutch patients. Hence, if the student used AT-HARM10 and experts used the OPERAM method, 45% (86/191) and 48% (91/191) of hospitalizations in Belgium were considered as DRAs, respectively. In contrast, 20% (37/185) and 26% (49/185) of hospitalizations in the Netherlands are considered as DRAs according student and experts, respectively (Table 7).

(2) As table 8 shows, the experts and the student disagreed on the assessment of 15% of hospitalisations (29/191) and of 21% (38/185) in the Belgian site and the Dutch site, respectively. The discrepancies between the student and the experts were explained by the same way at both sites. The Belgian student made more assessment errors regarding the underuse of drugs and the Dutch student about the interpretation of the letters. At the CUSL, both methods identified the prescription of cardiovascular drugs, nervous system drugs, antithrombotics, antineoplastics/ immunosuppressants and glucocorticoids as the most medication related to hospitalizations. At the UMC, cardiovascular and nervous system drugs were the most prescribed drugs involved in DRAs according both methods, but the third class of prescribed

drugs was different between the OPERAM method and AT-HARM10 (antithrombotics and antineoplastics/ immunosuppressants, respectively). As discussed in the draft paper, after the consensus of both raters in each site, the most prescribed drugs related to DRAs were same between the two sites. Results about omitted drugs weren't enough significant at the UMC for the comparison between sites (table 9).

(3) The Belgian student spent significantly more time than the Dutch student in the DRA assessment with AT-HARM10 (16.5 versus 7.4 minutes). At the CUSL, the analysis time tend to stabilize after about 50 hospitalisations. In the Netherlands, however, the training time could not be established because the adjudication time was measured for a number of hospitalizations but not individually (table 7).

(4) And finally, AT-HARM10 had a similar specificity when used by Ncr or NCo (88% versus 90%) but a higher sensibility when used by NCr (81% versus 49%), with the OPERAM experts from each site as gold standard for each student (table 7).

Table 8. Discrepancy of results between the OPERAM method and AT-HARM10.

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="3">OPERAM method</td></tr>
<tr><td>No DRA</td><td>ADR, Overuse or Misuse cause DRA</td><td>Underuse cause DRA</td></tr>
<tr><td rowspan="6">AT-HARM10</td><td>U1</td><td rowspan="3">AGREEMENT
N = 74 (UCL)
= 24 (UMC)</td><td rowspan="3">Overestimation of disease impact by student
N = 12 (UCL)
= 18 (UMC)</td><td rowspan="3">Underestimation of underuse*/prevention** drugs by student
N = 7 (UCL)
= 0 (UMC)</td></tr>
<tr><td>U2</td></tr>
<tr><td>U3</td></tr>
<tr><td>P4</td><td>More appropriate interpretation of letters by experts
N = 3 (UCL)
= 6 (UMC)</td><td colspan="2" rowspan="4">AGREEMENT
N = 88 (UCL)
= 123 (UMC)</td></tr>
<tr><td>P5
P10</td><td>Overestimation of drug impact/ Underestimation of disease impact by student
N = 0 (UCL)
= 8 (UMC)</td></tr>
<tr><td>P6</td><td>More appropriate interpretation of laboratory results by experts
N = 0 (UCL)
= 1 (UMC)</td></tr>
<tr><td>P8</td><td>Overestimation of underuse*/ prevention** drugs by student
N = 9 (UCL)
= 4 (UMC)</td></tr>
<tr><td colspan="5">* no treatment, too low dose, too short duration of treatment** examples : vaccines, cardiovascular prevention drug
U1. Was the admission caused by an infection or a previously undiagnosed disease (e.g., diabetes or heart failure) that is not medication-related?
U2. Was the admission caused by progression of a previously diagnosed disease that is not medication-related?
U3. Was the admission caused by physical trauma, substance intoxication, social circumstances or allergies that are not medication-related?
P4. Is it hinted or stated in the medical record that the admission was medication-related (including non-compliance)?
P5. Might (side) effects of the medications the patient was taking (prescribed or not prescribed) prior to hospitalization have caused the admission (including overdosage, adverse drug reaction, drug use without indication)?
P6. Are there abnormal laboratory results or vital signs that could be medication-related and might have caused the admission (including improper drug selection, overdosage)?
P7. Was there any drug-drug interaction or drug-disease interaction (i.e., a contraindication, improper drug selection, drug interaction) that might have caused the admission?
P8. Did the patient have any previously diagnosed untreated or sub-optimally treated indications that might have caused the admission (i.e., subtherapeutic dosage, untreated indication, improper drug selection)?
P9. Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e., failure to receive the medication)?
P10. Is the cause of the admission a response to cessation or withdrawal of medication therapy (adverse drug reaction)?</td></tr>
</table>

Table 9. Highlight drug classes most involved in DRAs according to AT-HARM10, the OPERAM method and both methods at the CUSL and at the UMC.

Sites	CUSL						UMC					
Methods	AT-HARM10 % (n DRA = 86)		OPERAM method **%** (n DRA = 91)		AT-HARM10 and OPERAM method % (n DRA = 74)		AT-HARM10 % (n DRA = 37)		OPERAM method % (n DRA = 49)		AT-HARM10 and OPERAM method % (n DRA = 24)	
Drugs : n (%)	Pr.	Om.	Pr.	Om.	Pr.	Om.	Pr.	Om.	Pr.	Om.	Pr.	Om.
Cardiovascular system	28 (33)	25 (29)	64 (70)	23 (25)	20 (27)	10 (14)	9 (24)	3 (8)	31 (63)	10 (20)	10 (42)	0 (0)
Nervous system	23 (27)	2 (2)	27 (30)	6 (7)	16 (22)	2 (3)	9 (24)	1 (3)	17 (35)	1 (2)	5 (21)	0 (0)
Antithrombotic agents	16 (19)	4 (5)	18 (20)	2 (2)	11 (15)	2 (3)	2 (5)	1 (3)	13 (27)	4 (8)	3 (12)	0 (0)
Antineoplastic agents + Immunosuppressants	12 (14)	1 (1)	16 (18)	0 (0)	12 (16)	0 (0)	5 (14)	0 (0)	2 (4)	0 (0)	1 (4)	0 (0)
Glucocorticoids	10 (12)	1 (1)	9 (10)	0 (0)	7 (9)	0 (0)	2 (5)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
Drugs for acid related disorders	2 (2)	0 (0)	5 (5)	0 (0)	1 (1)	0 (0)	2 (5)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)
Antibiotics + Antimycotics + Antivirals	3 (3)	0 (0)	7 (8)	0 (0)	2 (3)	0 (0)	4 (11)	1 (3)	2 (4)	0 (0)	0 (0)	0 (0)
AINS	4 (5)	0 (0)	5 (5)	0 (0)	4 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Drugs used in diabetes	3 (3)	1 (1)	2 (2)	0 (0)	1 (1)	0 (0)	1 (3)	1 (3)	2 (4)	0 (0)	2 (8)	0 (0)
Drugs for bone diseases : Ca/vit D, Bisphosphonates	2 (2)	7 (8)	0 (0)	8 (8)	0 (0)	6 (8)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Adrenergics inhalants	1 (1)	0 (0)	3 (3)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Drugs for constipation	1 (1)	1 (1)	2 (2)	4 (4)	1 (1)	2 (3)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Pr., Prescribed ; Om., omitted												

6.2.4 Discussion

With same inclusion criteria, proportion of DRA should be similar between the two sites. With a higher level of education, less previous falls and hospitalisations and shorter index hospitalisations at the CUSL, it was expected the proportion of DRAs was lower in Belgium. The higher likelihood of Belgian patients to be admitted to the emergency department during index hospitalization (26% versus 1%) may be one of the many explanations for this result as the severity of the disease may be greater for patient admitted in this ward and "emergency room visit" could be considered as a trigger for the detection of an ADE [43]. Obviously, a higher number of drugs taken and of chronic diseases in Belgium would have been the most plausible explanation for this result but unfortunately, these data are not available in this sub-study.

In the Belgian site, even when the analysis is time-efficient, AT-HARM10 didn't have the advantage of a significantly shorter analysis time than with the OPERAM method (16.5 versus 23 minutes).The Dutch student analyzed quicker than the Belgian student, but its results were less in agreement with the experts. The divergence of time required to adjudicate can be explained by the difference in pharmacy education (both in their final year but the duration of study differs between countries, i.e., 5 years in Belgium and 6 years in the Nederlands).

6.2.5 Conclusion

Generalizability for the use of AT-HARM10 to "any pharmacy student" of the results in terms of agreement with experts, time required, and performance is limited. Future studies with other education will allow to determine the performance of the student applying AT-HARM10.

6.3 PILOT FOR THE USE OF AT-HARM BY STUDENTS

6.3.1 Background and objectives

While a multidisciplinary panel of experts uses the OPERAM method, AT-HARM10 is intended to be a faster screening tool of ten closed questions that could be used by pharmacy students. The aim of this pilot phase was (1) to compare DRA assessment according to AT-HARM10 used by two pharmacy students from different background : the Belgian (NCr) and a Swedish pharmacy student from the team of the Medbridge project ; (2) to compare with adjudications of an expert panel using the OPERAM method on the same cases and (3) to determine the agreement between these two methods.

6.3.2 Materials and methods

Six cases from the reliability study of Thevelin et al. [46] had been selected. After a first evaluation, an e-meeting was performed between the two student-raters in order to discuss cases and find consensus. AT-HARM10 adjudications by the students were then compared to the OPERAM adjudications for these six cases with a dichotomous outcome variable (yes/ no DRA). First outcome was inter-rater reliability (IRR) on AT-HARM10 answers using Cohen's kappa between the Belgian and the Swedish student before and after the e-meeting. Second outcome was IRR between AT-HARM (consensus after e-meeting) and the OPERAM method using Cohen's kappa.

6.3.3 Results

- Before and after the e-meeting, the IRR on AT-HARM10 answers was 66.67% with κ=0.51 (95% CI -0.04, 1.00) and 100% with κ=1.00 (95% CI 0.43, 1.00) between the Belgian and Swedish students, respectively.
- The IRR between the AT-HARM10 adjudication used by the two students and the Belgian OPERAM experts' assessment was 66.67% with κ=0.25 (95% CI -0.64, 1.00)

6.3.4 Discussion

The tool could be used by pharmacy student with good IRR after a short education. Discussion between the two raters increased agreement between them and allowed a deeper understanding the exact of specific terms of AT-HARM10.On this small sample, the DRA adjudications were comparable between methods. The students highlighted the complexity to determinate the main cause of admission when several causes exist and some subjectivity in some cases. However, AT-HARM10 doesn't differentiate preventable, not preventable and ameliorable ADE but this

tool is intended to be as quick and easy as possible. This pilot study helped to (1) test the feasibility of AT-HARM10 testing across countries by students from different background, (2) to determine how to train all students involved in the international project (e.g., the use of AT-HARM10 by the Dutch student) and locally (for the Belgian student using the OPERAM method).

6.4 USE OF OPERAM METHOD BY A STUDENT

6.4.1 Background and objectives

As part of a discussion across Sweden, the Netherlands and Belgium, the use of the OPERAM method by students was considered. In order to determine whether the use of the OPERAM method by a student is possible, a final year pharmacy student (BB) analyzed some hospitaliations of the OPERAM patients. The degree of agreement of results between the two Belgian students of the Belgian site, one using the OPERAM method and the other using AT-HARM10, is interesting because they will graduate from the same university of the current year.

Main objective was to measure the degree of agreement of DRA detection between an expert panel and a pharmacy student using both the OPERAM method and between the two methods when applied by students (on a subsample).

Secondary outcomes included analyses of student applying the OPERAM method : (1) the determination of the proportion of DRAs, (2) the categorization of the discrepancies with experts, (3) the measure of adjudication time and training time needed and (4) the assessment of the performance of the OPERAM method (using OPERAM experts as gold standard).

6.4.2 Methods

A pharmacy student (BB) collected applied the OPERAM method to a subsample of the admissions from the Belgian site during an internship at the CUSL. This student was trained as follows : after reviewing all articles about the OPERAM study and Supporting Information [11, 46], including a video training tutorial [54] and after a precise explanation of the protocol of the sub-study, 6 clinical training cases were selected and discussed between the two Belgian students (NCr and BB). This student (BB) was blinded to any other results about the assessment of these hospital admissions.

The outcome of the OPERAM method applied by BB was compared to the outcome obtained by the experts using same method and then by another pharmacy student (NCr) who applied AT-HARM10 to the same cases, as a percentage agreement and Cohen's kappa. In order to evaluate discrepancies between experts and BB, three additional categories were needed : Misinterpretation of trigger/ non-trigger, of WHO-UMC criteria and of Hallas criteria by student. All data analysis was performed by NCr.

6.4.3 Results

Analyzing only readmissions that had already been adjudicated by the OPERAM experts from the Belgian site, 193 readmissions were eligible. The number of readmissions analyzed (n=76) was limited because of the restricted duration of his internships. This student excluded one admission deemed unassessable.

Table 10 shows that the degree of agreement of DRA detection between experts and student using both the OPERAM method was fair in the Belgian site, with 65% agreement (49/75), Cohen's $\kappa = 0.29$ (95% CI 0.08-0.51) and Cohen's $\kappa_{max} = 0.89$ (the calculation details in appendix 4). Regarding hospitalizations considered by the OPERAM method as drug-related, users have in common at least one drug responsible for admission for 77% of all DRAs (23/30). Among these 75 hospitalizations, one was excluded by the Belgian student applying AT-HARM10 because deemed unassessable. The degree of agreement of DRA detection between two students, one applying AT-HARM10 and the other applying the OPERAM method, was moderate with 70% agreement (52/74) and Cohen's $\kappa = 0.4190$ (95% CI 0.2251-0.6129) (the calculation details in appendix 4). Regarding hospitalizations considered by both methods as drug-related, the two students have in common at least one drug responsible for admission for 82% of all DRAs (23/28) in the Belgian site.

Table 10. DRA assessment by (1) the OPERAM method used by Belgian experts and student and by (2) OPERAM method used by the Belgian student and AT-HARM10 used by the other Belgian student.

		OPERAM method used by Belgian experts		**AT-HARM10 used by Belgian student**	
		DRA yes	DRA no	DRA yes	DRA no
OPERAM method used by Belgian student	DRA yes	30	15	28	17
	DRA no	11	19	5	24

(1) According to the OPERAM method, the Belgian student considered 60% of hospitalizations as drug-related (45/75) and the experts 55% (41/75). The Belgian student applying AT-HARM detected less DRA (45% ; 33/74).

(2) In the Belgian site, experts and student disagreed for 26 hospitalizations (35%). The results of 9 hospitalizations were different due to an overestimation of underuse drugs by student but the student underestimated it in 3 hospitalizations. The overestimation and underestimation of

disease impact by student explained the discordance of 4 hospitalizations each. The more appropriate interpretation of letters and of laboratory results by experts explained the discordance in 3 and 1 hospitalizations, respectively. The assessment of 4 readmissions was different due to the overestimation of drug impact or underestimation of disease impact by student. The misinterpretation of (non-) trigger, WHO-UMC criteria and Hallas criteria by student caused discordance in 5, 1 and 6 hospitalizations, respectively.

(3) The median adjudication time by the student using the OPERAM method was 19 minutes and the analysis time tend to stabilize after about 20 hospitalizations (Figure 6).

(4) Finally, the sensitivity of the OPERAM method applied by a student was 0.73 (30/41) and the specificity was 0.56 (19/34).

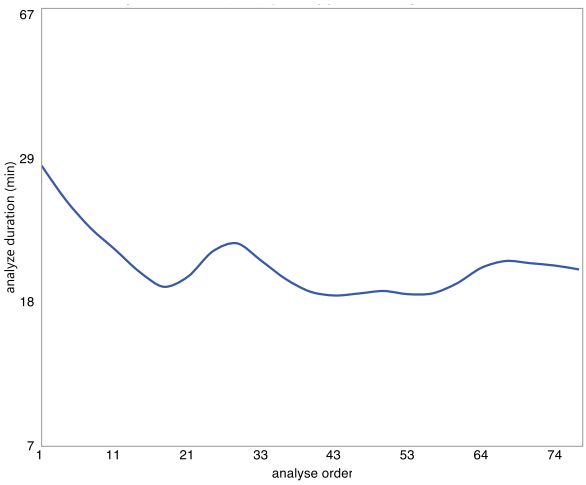

Figure 6 Evolution of the analyze duration required to adjudicate an admission using the OPERAM method by a student.

6.4.4 Discussion

Application of the OPERAM method by a student (BB) led to a fair agreement when comparing with an expert panel. The large difference between κ_{max} and κ (0.89-29=0.60) showed a large total unachieved agreement (chance excluded) within the constraints of the marginal totals. However, agreement between two students from same university, using different method, is moderate. A better concordance between the experts and the Belgian student using AT-HARM10 (NCr) may be explained by a better clinical knowledge of NCr thanks to his registration in Master in Pharmaceutical Sciences, Research Focus (rather than Professional Focus for BB) and a previous hospital internship for NCr (rather than the first one for BB).

The small subsample adjudicated by the Belgian student using the OPERAM method (less than one thousand patients) could explain the overestimation of DRA [5, 45, 52].

The WHO-UMC and Hallas criteria require appropriate clinical judgment, which is supported by the experts' daily clinical experience. Even with a detailed list of trigger, assessor may disagree because the match between the patient's complaint and the list provided requires a clinical judgement [66].

Finally, the student who applied the OPERAM method (BB) provided the following feed-back (translation in English to the exact word) : “The OPERAM method has a precise structure and the triggers help a lot in the admission assessment because all the drugs related to the ADE were mentioned in the same place. As a student, it is difficult to differentiate between possible and probable WHO-UMC criteria because the pharmacy student lacks real clinical experience, especially for the interpretation of diseases. It is even more difficult to identify the main cause of admission. I didn't feel limited by the timer because the quality of the analysis prioritized time efficiency.”

6.4.5 Conclusion

Discrepancies between the student and the experts using both methods highlight the importance of the training of the pharmacist and the added value of a multidisciplinary team of adjudicators for the use of the OPERAM method. Futures larger studies will allow to assess whether the use of the OPERAM method by a research student is possible.

7 GENERAL DISCUSSION

This dissertation compared two recently published methods, one implicit and the other combining implicit and explicit measures and explored the feasibility of DRA detection by pharmacy students, from different backgrounds.

Firstly, the agreement between AT-HARM10 used by the student and the OPERAM method applied by the experts was good at the international level, with 82% agreement. However, the level of agreement with the experts differs between countries (good in Belgium and moderate in the Nederlands) because an implicit tool requires student's judgment, which depends on the individual training and education. The proportion of DRA detected by AT-HARM10 was lower than the OPERAM method and discrepancies between the methods were mostly related to education and less clinical practice experience of the students than the experts. This observation was confirmed by the multicenter analysis of this sub-study, although differences were minimal.

Secondly, as seen in the pilot phase between students and moreover as the performance of AT-HARM10 in this study and in the Medbridge study was similar, the international feasibility of the use of AT-HARM10 by a final-year pharmacy student was evaluated and confirmed : 80% of DRAs identified by the experts were also detected by the student and 89% of hospitalisations considered as non-drug-related by the experts were similarly assessed by the student.

The appendix of AT-HARM10 provides a lot of instruction and examples but there are not so many explanations as in the supporting Information S2 of the OPERAM method. Hence, an e-meeting with one of the Swedish students involved in the design of AT-HARM10 was required. Therefore, AT-HARM10 may have the advantage of a shorter adjudication time than the other method but this is not a widespread result.

However, the 20% of DRAs detected by experts but missed by the students raise some concern in a few contexts where precision is important. The choice of the method assessor (student, experts) can influence the outcome of clinical studies evaluating the impact of a medication intervention on the number of DRAs, such as it was the case in the OPERAM and Medbridge trial. Caution in the choice of tool to detect DRA is essential in research, but also when DRA are used as pay-for-performance indicators. We could imagine to use DRA as an indicator in Belgium to help finance more clinical pharmacy staff.

Thirdly, the experts and the student using both the OPERAM method came to a fair agreement (65% agreement), that confirmed the importance of multidisciplinary users for this method. The physician's judgment is important for the disease-related assessment and for the WHO-UMC and Hallas criteria evaluation and the pharmacist's judgment is important to check triggers. This method requires more adjudication time, even if assessors are different (student or experts) and is an opportunity for the student to develop early skills in clinical pharmacy.

Finally, my research experience and the results of this sub-study might suggest the setting of use (research, clinical or training) and the type of user (students or experts) for these tools. DRA detection is a challenge for medical staff and students, requires critical and careful assessment and can be time and money consuming. AT-HARM10 is a valuable screening tool that can be used by students during an emergency room internship for example, as a clinical teaching tool to identify DRA, or during clinical practice if the student's productivity allows it. The OPERAM method is a precise method that can better be applied by experts for clinical research as the average adjudication time does not allow its implementation in clinical practice.

Agreement between the tools was good, showing that both methods can detect DRA outcome as long as assessors respect exactly the way they were designed to. In this sub-study, the OPERAM method was more prone to detect DRA, AT-HARM10 doesn't have the advantage of a significantly shorter analysis time than with the OPERAM method in Belgium and it is known that an implicit process measure depends mainly on the student's knowledge and education. AT-HARM10 was easy to use, useful but not practical in clinical setting unless the productivity of the Dutch student is widespread.

The comparison of the results of the Belgian student (NCr) with another student (NCo) from an institution in the OPERAM study (Utrecht) will help to determine the most suitable method for future studies at UCLouvain. As external scope, this sub-study will help researchers and clinicians to assess which method suits the best their needs to detect DRAs.

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10 APPENDIXES

10.1 APPENDIX 1 – DRA TRIGGER TOOL OF THE OPERAM DRA ADJUDICATION GUIDE

TRIGGER TOOL TO SCREEN FOR DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PERSONS	
Trigger on admission up to 48h of	**Suspected causative drugs or causes for underuse**
Diagnoses	
Fall and/or fracture	**Use** of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Antipsychotics ☐ Antidepressants ☐ Sedating antihistamines ☐ Opioids ☐ Anticholinergics[a] ☐ Other (*Please specify*):
	Use of any drugs causing orthostatic hypotension? ☐ Calcium channel blockers ☐ Diuretics ☐ α1-receptor blockers ☐ Nitrates ☐ β-blockers ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Direct renin inhibitors (e.g. aliskiren) ☐ Anti-Parkinson drugs ☐ Antidepressants (mainly tricyclic) ☐ Antipsychotics ☐ Gliflozines (SGLT2-inhibitors) ☐ Other (*Please specify*):
	If a fall is caused by hypoglycaemia, look for **use** of drugs contributing to hypoglycaemia (check trigger hypoglycaemia)
	Underuse of any of the following drugs in patients with known osteoporosis and/or history of fragility fracture(s) and/or Bone Mineral Density T-scores of -2.5 or lower in multiple sites? ☐ 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) ☐ Bone anti-resorptive therapy (e.g. bisphosphonates, strontiumranelate,teriparatide, denosumab)
	Underuse of any of the following drugs in patients on corticosteroid therapy ≥ 3 months? ☐ 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) ☐ Bisphosphonates
	Underuse of vitamin D in patients who are housebound and/or experiencing falls or with osteopenia with Bone Mineral Density T-score between -1 and -2.5 in multiple sites?
Confusion/delirium[b]	**Use** of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Antipsychotics ☐ Anti-epileptics ☐ Antihistamines (H1- & H2-receptor blockers) ☐ Antidepressants ☐ Opioids ☐ Dopaminergic agonists ☐ Digoxin ☐ Fluoroquinolones *(dose adjustment in renal impairment required)* ☐ Acetylcholinesterase-inhibitors (new onset confusion in patients with dementia) ☐ Other anticholinergics[a] (*Please specify*):
	Abrupt discontinuation/rapid dose reduction of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Corticosteroids ☐ Dopaminergic agonists ☐ Antidepressants ☐ Opioids ☐ Lithium ☐ Antipsychotics ☐ Other (*Please specify*):
Acute renal impairment**	**Use** of any of the following drugs? ☐ Non-steroidal anti-inflammatory drugs ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Diuretics ☐ Sulphonamides ☐ Cephalosporins ☐ Quinolones (ciprofloxacin) ☐ Aminoglycosides ☐ Vancomycin ☐ Pentamidine ☐ Rifampicin ☐ Acyclovir, valacyclovir, gancyclovir, valgancyclovir, foscarnet, cidofovir ☐ Lithium ☐ Calcineurin Inhibitors (e.g. cyclosporine, tacrolimus) ☐ Cisplatin ☐ Radiology contrast medium ☐ Amphotericin ☐ Bisphosphonates ☐ Other nephrotoxic drugs (*Please specify*):

Dehydration	Use of any of the following drugs? ☐ Diuretics ☐ Gliflozines (SGLT2-inhibitors) ☐ Laxatives ☐ Any drugs causing vomiting ☐ Any drugs causing diarrhoea ☐ Other (*Please specify*):
Bleeding (i.e. major bleeding and clinically relevant non-major bleeding***)	**Use** of any of the following drugs? ☐ Antiplatelets ☐ Vitamin K antagonists ☐ Direct oral anticoagulants ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Selective serotonin reuptake inhibitors ☐ Non-steroidal anti-inflammatory drugs ☐ Other (*Please specify*): ☐ **Underuse** of proton pump inhibitors prophylaxis while - NSAIDs monotherapy (≥ 70 years old) or on concurrent NSAIDs and/or antiplatelets and/or corticosteroids - NSAIDs or antiplatelet or corticosteroids monotherapy with a history of peptic ulcer disease/gastrointestinal bleeding while on these drugs
Stroke	**Underuse** of any of the following drugs in patients with known chronic atrial fibrillation? ☐ Vitamin K antagonists ☐ Direct oral anticoagulants (except valvular atrial fibrillation) **Underuse** of adequate antihypertensive therapy? * *Note*: Adequate antihypertensive therapy is defined according to the recommendations for older patients in the 2013 European ESH/ESC guidelines for the management of arterial hypertension. **Underuse** of any of the following drugs in patients with history of coronary, cerebral or peripheral vascular disease? ☐ Antiplatelets ☐ Statins** (unless end-of-life or > 85 years old) ***Note*: Evidence for statin treatment above the age of 80-85 years is limited and clinical judgement should guide decisions in the very old, taking into account life expectancy, serious adverse events, possible drug interactions. Low to moderate intensity statin regimens are recommended. (**low**: simvastatin 10mg, pravastatin 10-20mg, fluvastatin 20-40mg **moderate**: atorvastatin 10-20mg, Rosuvastatin 5-10mg, Simvastatin 20-40mg, pravastatin 40-80 mg, Fluvastatin 80 mg, Fluvastatin 40 mg BID)
Thromboembolic event (DVT or PE)	**Underuse** of adequate anticoagulation? ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Direct oral anticoagulants ☐ Vitamin K antagonists
(Recurrent) myocardial infarction or ischaemic disease	**Underuse** of cardiovascular secondary prevention? ☐ Antiplatelets (unless already anticoagulated) ☐ Statins** (unless end-of-life or > 85 years old) ☐ β-blocker/ACE-inhibitor or angiotensin receptor blocker /adequate anti-anginal therapy in case of ischaemic disease **Underuse** of adequate antihypertensive therapy? *
Heart failure exacerbation	**Use** of any drugs that could precipitate heart failure exacerbation? ☐ Non-steroidal anti-inflammatory drugs ☐ Corticosteroids ☐ Thiazolidinediones (glitazones) ☐ Non-dihydropyridine calcium channel blockers (verapamil, diltiazem) ☐ Sodium-containing formulations (effervescent, dispersible and soluble medications) ☐ Other (*Please specify*): **Underuse** of any of the following drugs? ☐ β-blockers¥ ☐ ACE-inhibitors¥ ☐ Diuretics *Note*: ¥ β-blocker and ACE-inhibitors in heart failure due to left ventricular dysfunction
COPD exacerbation	**Use** of any drugs that could precipitate COPD exacerbation? ☐ Benzodiazepines with acute or chronic respiratory failure ☐ Opioids ☐ Other (*Please specify*): **Underuse** of any of the following drugs? ☐ Single or dual inhaled bronchodilator therapy (i.e. a β2 agonist and/or anticholinergic bronchodilator) according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) grade
Uncontrolled (non-neuropathic) pain	**Underuse** of adequate pain treatment (according to the WHO analgesic ladder)? ☐ A strong opioid in moderate to severe pain if paracetamol, NSAIDs or weak opioids are not appropriate (e.g. because of insufficient pain relief) ☐ Short-acting opioids for break-through pain during treatment with long acting opioids ☐ Other (*Please specify*):
Gastrointestinal disorders (severe diarrhoea, vomiting)	**Use** of any of the following drugs? ☐ Antibiotics ☐ Laxatives ☐ Selective serotonin reuptake inhibitors ☐ Digoxin ☐ Cholinesterase-inhibitors ☐ Opioids ☐ Non-steroidal anti-inflammatory drugs ☐ Chemotherapy (*Please specify)*: ☐ Other (*Please specify*):

Major constipation or faecal impaction	**Use** of any of the following drugs? ☐ Chronic (stimulant) laxative use ☐ Opioids (look for **underuse of laxatives** with regular opioid use) ☐ Calcium antagonists (Mainly verapamil) ☐ Calcium ☐ Oral iron ☐ Aluminium antacids ☐ Atypical antipsychotics ☐ Tricyclic antidepressants ☐ Bladder antimuscarinics ☐ Other anticholinergic drugs[a] ☐ Other (*Please specify*):
Laboratory values	
INR > 5	Look for evidence of bleeding (see trigger) to determine if an adverse drug event (ADE) has occurred. A raised INR in itself is not an ADE.
Digoxin level > 2ng/ml	Look for signs or symptoms of digoxin toxicity (bradycardia, nausea, diarrhoea, confusion) to determine if a potential ADE has occurred. Not all levels above normal will result in an ADE.
Hypoglycaemia (blood glucose < 4 mmol/L or 72 mg/dl)	Look for symptoms such as lethargy, tremor, confusion, faintness or administration of intravenous or oral glucose. **Use** of any of the following drugs? ☐ Insulin ☐ Oral hypoglycaemic agents(except metformin in monotherapy) ☐ MAO – inhibitors ☐ β-blockers (masking symptoms of hypoglycaemia) **Use** of any drugs that may cause or worsen hyperglycaemia? ☐ Corticosteroids ☐ Atypical antipsychotics (mainly olanzapine & clozapine) ☐ Thiazide diuretics *less frequent* ☐ β-blockers (except carvedilol and nebivolol) *less frequent* ☐ Protease-inhibitors ☐ Calcineurin Inhibitors (cyclosporine, sirolimus, tacrolimus) ☐ Other (*Please specify*): In case hyperglycaemia is part of diabetic ketoacidosis or hyperosmolar hyperglycaemic state in a patient, review for **underuse** of insulin or oral hypoglycaemic agents.
Hyperkalaemia (K^+ > 5.5 mmol/L)	**Use** of any the following drugs? ☐ Intravenous or oral potassium ☐ Potassium-sparing diuretics ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Direct renin inhibitors (e.g. aliskiren) ☐ Non-steroidal anti-inflammatory drugs ☐ Heparins (seldom, mainly when treated > 7days and concomitant other risk factors) ☐ Trimethoprim-sulfamethoxazole ☐ Cyclosporine ☐ Tacrolimus ☐ Other (*Please specify*):
Hypokalaemia (K^+ < 3 mmol/L)	**Use** of any of the following drugs? ☐ Loop diuretics ☐ Thiazide and thiazide-like diuretics ☐ Corticosteroids ☐ Laxatives ☐ Salbutamol (IV or aerosol) ☐ Theophylline ☐ Other (*Please specify*):
Hyponatraemia (Na^+ < 130 mmol/L)	**Use** of any of the following drugs? ☐ Diuretics ☐ Selective serotonin reuptake inhibitors ☐ Tricyclic antidepressants ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Carbamazepine & oxcarbazepine ☐ High dose cyclophosphamide ☐ Other (*Please specify*):
White blood cells < 3000 /mm^3 or < 3 x $10^3/\mu L$	**Use** of any of the following drugs? ☐ Carbamazepine & oxcarbazepine ☐ Antipsychotics (mainly clozapine) ☐ Thyreostatics ☐ Ganciclovir ☐ Immunosuppressants ☐ Chemotherapy (*Please specify):* ☐ Mirtazapine (first 6 weeks of treatment) ☐ Voriconazole ☐ Other (*Please specify*):
Platelet count < 50000 /mm^3 or < 50 x $10^3/\mu L$	**Use** of any of the following drugs? ☐ Carbamazepine & oxcarbazepine ☐ Ganciclovir ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Immunosuppressants ☐ Thienopyridines (mainly ticlopidine) ☐ Quinine sulfate ☐ Sulfamides *Less frequent* ☐ Chemotherapy (*Please specify):* ☐ Other (*Please specify*):
Neutrophils < 1400/mm^3 or < 1.4 x $10^3/\mu L$	**Use** of any of the following drugs? ☐ Ganciclovir ☐ Antipsychotics (mainly clozapine) ☐ Thyreostatics ☐ Thienopyridines (mainly ticlopidine) ☐ Chemotherapy (*Please specify):* ☐ Other (*Please specify*):

Other	
Antidote use or treatments that suggest a potential ADE	**Use** of any of the following drugs on the day of admission? ☐ Flumazenil in a patient on benzodiazepines ☐ Naloxone in a patient on opioids ☐ Phytonadione (vitamin K) in a patient on VKA ☐ Protamine sulphate in a patient on heparins ☐ Oral or intravenous glucose or glucagon in a patient taking hypoglycaemic drugs ☐ Potassium supplements in case of hypokalaemia ☐ Sodium polystyrene (Kayexalate) in case of hyperkalaemia ☐ Adrenaline, antihistamines and corticosteroids (general drug allergy) ☐ Acetylcysteine (paracetamol overdose) ☐ Digoxin antibodies in a patient with supratherapeutic digoxin levels ☐ Oral metronidazole or vancomycin in a patient who has recently been treated with an antibiotic that may cause *Clostridium difficile* associated diarrhoea
Mention of a (potential) ADE in the medical record	Assess causality using the WHO-UMC criteria
Abrupt medication stop within 24h of admission	When medications are stopped or withheld as compared to medications taken at home, look for reasons why this was done. Abruptly stopping medications is a trigger requiring further investigation for cause. A sudden change in patient condition requiring adjustment of medications is often related to an ADE

ADE, adverse drug event; ADR, adverse drug reaction; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; ESH/ESC, European Society of Hypertension/European Society of Cardiology; FEV1, forced expiratory volume in 1 second; INR, international normalised ratio, NSAIDS, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; VKA, Vitamin K antagonists

[a]A list of medications with clinically relevant anticholinergic proprieties is available in the DRA adjudication guide; [b]Detailled definition of trigger available in the DRA adjudication guide

SCREENING QUESTIONS FOR NON-TRIGGERED, SPONTANEOUSLY DETECTED EVENTS

1. Could the main or contributory reason for admission be related to a drug or recent change in medications?

☐ Adverse drug reaction (non-preventable side effect, first allergic reaction)
☐ Overuse of medication(s) (drug without an indication, too long duration of therapy, therapeutic duplication)
☐ Inappropriate discontinuation (removal or dosage decrease) leading to physiological withdrawal signs/symptoms) or return of the underlying disease signs/symptoms
☐ Wrong drug
☐ Wrong dose (supratherapeutic or subtherapeutic)
☐ Clinically significant drug-drug or drug-food interactions
☐ Inappropriate monitoring
☐ Other (e.g. drug not correctly dispensed/prepared/administered)

2. Could the main or contributory reason for admission be related to underuse?

☐ Omission of an indicated drug
☐ Too short duration of medication therapy
☐ Suspected adherence concerns

10.2 APPENDIX 2 – OPERAM METHOD VERSUS AT-HARM10

	DRA adjudication guide	AT-HARM10 tool
Definition of DRA	Hospitalisation resulting from adverse drug reactions and medication errors including overuse, underuse and misuse of medications.	
DRA adjudication strategy	• Trigger-based chart review + screening for non-triggered events • ADE causality assessment + assessment of ADE contribution to admission using the WHO-UMC causality criteria and Hallas criteria.	• Chart review based on 10 yes/no questions to distinguish between unlikely and possible DRA according to the WHO-UMC causality criteria
Data sources	Admission letter, discharge letter, laboratory values, medication lists	
Intended users	Adjudication team (pharmacist and physician)	Final-year undergraduate and postgraduate pharmacy students
Development & validation		
I. Literature review	• Existing tools • Common causes of DRA in older people	• Existing tools
II. Evaluation of content validity	• Overall DRA adjudication procedure: consensus discussion between 3 physicians and 3 clinical pharmacists • Relevance of triggers and screening questions for non-triggered events to screen for DRA: 15-member international multi-disciplinary Delphi survey to score the relevance of each item	• Relevance, comprehensibility and completeness of each question assessed by 7 clinical pharmacists • Relevance of each question: recording of number of times each question was applied for 400 assessments of 100 hospitalisations by 7 pharmacy students
III. Feasibility of use	• Pilot test by a pharmacist and physician on 15 cases and improvement of the guide following feedback • 8 adjudication teams members (physicians and pharmacists) applied the tool to 16 patient cases and measured time spent to complete an adjudication (mean time needed: 23 minutes)	• 15 clinical pharmacists applied the tool to 10 patient cases and assessed user-friendliness and appropriateness • Mean time needed to complete an adjudication: 6 minutes
IV. Inter-rater reliability	• Adjudication of 16 patient cases by 4 international adjudication teams (1 pharmacist + 1 physician per team except for 1 team with 2 physicians): Fleiss' κ =0.41 (IRR between 4 teams) and Cohen' κ = 0.33, 0.42, 0.74, 0.86 (IRR within each team) • Adjudication of 30 patient cases by 4 international adjudication teams (1 pharmacist + 1 physician per team): Fleiss' κ =0.34 (IRR between 4 teams)	• Adjudication of 50 patient cases by 2 pairs of 2 pharmacy students (2 pharmacy students per pair): Fleiss' κ =0.48 (IRR between 2 pairs) and Cohen's κ =0.75, 0.45 (IRR within each pair) • Adjudication of 50 patient cases by pharmacy students (2 pharmacy students per pair): Fleiss' κ =0.46 (IRR between 2 pairs) and Cohen's κ =0.52, 0.57 (IRR within each pair)
V. Criterion-related validity	• Not yet evaluated	• Comparison of adjudications of the 4 pairs of pharmacy students using AT-HARM10 and the adjudications by an expert panel (physician + pharmacist) for 100 patient cases: Sensitivity: 70-86%, Specificity: 70-74%, PPV: 73-74% NPV:71-73%

DRA, drug-related admission; IRR, inter-rater reliability; WHO-UMC, World Health Organisation-Uppsala monitoring centre; PPV, positive predictive value; NPV, negative predictive value

10.3 APPENDIX 3 - OPERAM ANALYSIS PLAN (AP) SUBMISSION FORM

Instructions: please complete the entire form (3-5 pages max.) and send it by email to katharina.jungo@biham.unibe.ch for review by the Publication Committee (PC).
Type of subproject proposal (Check one or two of the answers below)

Abstract	Yes	x	No	
Full manuscript	Yes	x	No	
Sub-Study imbedded in the main trial	Yes	x	No	

Title

Comparison of OPERAM and AT-HARM10 method to adjudicate drug-related hospital admissions (DRA)

Proposed Writing Group (Indicate potential investigators/authors for this project)

First author: Noémie Croix				
Senior author: Wilma Knol, Fatma Karapinar, Nicolas Rodondi, Denis O'Mahony, Olivia Dalleur				
OPERAM sponsor* (if senior author not part of OPERAM): /				
Statistical analysts + site of analysis: Noémie Croix, UCLouvain+ UMC site.				
Provisional list of co-authors: Stefanie Thevelin, Bastiaan Sallevelt, Nicky Cornelissen, Martin Feller				
In case of trial data, sites (single or multicenter): multicenter (UCL site, UMC site)				
Other source of funding in addition to OPERAM (if any): none required				
Ethical committee approval (if needed): CEHF's Reference: 2020/13JAN/014, Belgian registration number : B403/				
Has the AP been circulated to all co-authors for feedback, letting them 10 days to comment?				
Yes	X	No		

* WP leader or other GA members

Background
(Explain briefly why this study is innovative with respect to prior studies done in this field)

Drug-related admissions (DRAs) are hospitalisations resulting from adverse drug events (ADEs) and contribute to up to 30% of all admissions in older people [26, 52]. As part of OPERAM trial, a standardised method to screen for and adjudicate DRAs caused by adverse drug reactions, overuse, underuse and misuse of medications was elaborated and validated [46].
Another method was recently developed in Sweden by Kempen and al: AT-HARM10. While the OPERAM DRA method is comprehensive and designed to be used by a multidisciplinary panel of experts, the AT-HARM10 tool is intended to be a rapid screening tool using 10 questions that could be used by pharmacy students. An admission is considered as unlikely to be medication-related according the question U1 to U3 and as possibly to be medication-related according the question P4 to P10.

- U1. Was the admission caused by an infection or a previously undiagnosed disease (e.g. diabetes or heart failure) that is not medication-related?
- U2. Was the admission caused by progression of a previously diagnosed disease that is not medication-related?
- U3. Was the admission caused by physical trauma, substance intoxication, social circumstances or allergies that are not medication-related?
- P4. Is it hinted or stated in the medical record that the admission was medication-related (including non-compliance)?
- P5. Might (side) effects of the medications the patient was taking (prescribed or not prescribed) prior to hospitalization have caused the admission (including overdosage, adverse drug reaction, drug use without indication)?

- P6. Are there abnormal laboratory results or vital signs that could be medication-related and might have caused the admission (including improper drug selection, overdosage)?
- P7. Was there any drug-drug interaction or drug-disease interaction (i.e. a contraindication, improper drug selection, drug interaction) that might have caused the admission?
- P8. Did the patient have any previously diagnosed untreated or sub-optimally treated indications that might have caused the admission (i.e. subtherapeutic dosage, untreated indication, improper drug selection)?
- P9. Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e. failure to receive the medication)?
- P10. Is the cause of the admission a response to cessation or withdrawal of medication therapy (adverse drug reaction)? [39]

A precise comparison of the two methods was carried out by Stephanie Thevelin in her thesis [72].

	DRA adjudication guide	AT-HARM10 tool
Definition of DRA	Hospitalisation resulting from adverse drug reactions and medication errors including overuse, underuse and misuse of medications.	
DRA adjudication strategy	Trigger-based chart review + screening for non-triggered events ADE causality assessment + assessment of ADE contribution to admission using the WHO-UMC causality criteria and Hallas criteria.	Chart review based on 10 yes/no questions to distinguish between unlikely and possible DRA according to the WHO-UMC causality criteria
Data sources	Admission letter, discharge letter, laboratory values, medication lists	
Intended users	Adjudication team (pharmacist and physician)	Final-year undergraduate and postgraduate pharmacy students
Development & validation		
I. Literature review	Existing tools Common causes of DRA in older people	Existing tools
II. Evaluation of content validity	Overall DRA adjudication procedure: consensus discussion between 3 physicians and 3 clinical pharmacists Relevance of triggers and screening questions for non-triggered events to screen for DRA: 15-member international multi-disciplinary Delphi survey to score the relevance of each item	Relevance, comprehensibility and completeness of each question assessed by 7 clinical pharmacists Relevance of each question: recording of number of times each question was applied for 400 assessments of 100 hospitalisations by 7 pharmacy students
III. Feasibility of use	Pilot test by a pharmacist and physician on 15 cases and improvement of the guide following feedback 8 adjudication teams members (physicians and pharmacists) applied the tool to 16 patient cases and measured time spent to complete an adjudication (mean time needed: 23 minutes)	15 clinical pharmacists applied the tool to 10 patient cases and assessed user-friendliness and appropriateness Mean time needed to complete an adjudication: 6 minutes
IV. Inter-rater reliability	Adjudication of 16 patient cases by 4 international adjudication teams (1 pharmacist + 1 physician per team except for 1 team with 2 physicians): Fleiss' κ =0.41 (IRR between 4 teams) and Cohen' κ = 0.33, 0.42, 0.74, 0.86 (IRR within each team) Adjudication of 30 patient cases by 4 international adjudication teams (1 pharmacist + 1 physician per team): Fleiss' κ =0.34 (IRR between 4 teams)	Adjudication of 50 patient cases by 2 pairs of 2 pharmacy students (2 pharmacy students per pair): Fleiss' κ =0.48 (IRR between 2 pairs) and Cohen's κ =0.75, 0.45 (IRR within each pair) Adjudication of 50 patient cases by pharmacy students (2 pharmacy students per pair): Fleiss' κ =0.46 (IRR between 2 pairs) and Cohen's κ =0.52, 0.57 (IRR within each pair)
V. Criterion-related validity	Not yet evaluated	Comparison of adjudications of the 4 pairs of pharmacy students using AT-HARM10 and the adjudications by an expert panel (physician + pharmacist) for 100 patient cases: Sensitivity: 70-86%, Specificity: 70-74%, PPV: 73-74% NPV:71-73%

DRA, drug-related admission; IRR, inter-rater reliability; WHO-UMC, World Health Organisation-Uppsala monitoring centre; PPV, positive predictive value; NPV, negative predictive value

Study Hypotheses/Specific aims
(List the study hypotheses and specific aims of this subproject)

First, the project aims to compare detection of DRA and determine agreement between a student using the AT-HARM10 method, with the assessment of an expert panel using OPERAM method.

Secondary aims are

- to determine the sensitivity and specificity of AT-HARM10 used by a student (using OPERAM applied by an expert panel as the standard).
- to compare the prevalence of DRA detected by AT-HARM10 used by a student, OPERAM used by a panel of experts and OPERAM used by a student.
- to evaluate the average time required to adjudicate an admission using AT-HARM10 tool and OPERAM tool when used by students.
- to categorize assessment discrepancies between the 2 tools and type of user (panel versus student).

Methods (Describe the methods you plan to use to address the study hypothesis/questions, in particular, if you need specific variables from the OPERAM project to accomplish your goals)

OPERAM patients from the Belgian UCLouvain and Dutch UMC sites, for which the adjudication of readmissions already occurred and was performed by a multidisciplinary expert panel, will be reassessed by pharmacy students using AT-HARM10 and the OPERAM method independently. The students will be blinded to the outcome of the expert panel adjudication process. Subsequently, DRAs detected by AT-HARM10 and OPERAM will be compared and agreement to detect DRAs will be calculated.

Sample size:
We expect the proportion of DRA to be around 30% (according to literature). According to Sim and al., our sample size is calculated to highlight a kappa of 0.60 assuming the value of kappa in the null hypothesis to be 0.40 with a 2-tailed test (considering the kappa value of 0.40 as a moderate agreement). Indeed, the value of kappa in the null hypothesis is higher than zero to be more significant, given better agreement in clinical practice than expected by chance[59]. It is found that the minimum sample size required is 191 patients with a power and alpha as 80% and 0.05 respectively.

Study population with inclusion/exclusion criteria you intend to include

OPERAM patients from the Belgian and Dutch site, who had a readmission during the 12 months follow-up period in the OPERAM trial and who were eligible for DRA adjudication.

Baseline variables needed (If applicable, please be as specific as possible)

No additional data will be needed.
This study will use the documents already uploaded in the eCRF in Hospitalisation and SAE tabs, i.e.:

- Date and time of hospital admission
- Type of admission
- Presenting complaint (main symptom)
- Main reason for hospital admission
- Diagnosis (ICD-10 code based on STRIPA per category)
- Ward speciality
- Length of stay
- Category of ward
- Other wards visited during this hospital stay
- Date of arrival at home
- Completeness: availability of the medication history until day 2 on the discharge summary, downloading of the discharge summary/ all other relevant data source/ all available laboratory values
- Readiness for Adjudication
- Discharge/ Admission letter from the (this) re-hospitalisation

- Laboratory information
- Medication lists (if a separate document available)
- Other source documents (including assessments regarding the hospitalisation)

Medication tab : drug name, drug name (internal), frequency, interval, strength, unit, route, start date, ongoing, stop date, reason for stopping, baseline medication list.

Firstly, the investigators will use a blinded adjudication access to the eCRF. One Belgian student will assess the UCLouvain cases while one Dutch student will assess the UMC cases.
Secondly, they will access the results of the OPERAM adjudication teams to be able to compare the DRAs detected by the OPERAM and AT-HARM10 methods.

Primary and secondary outcome variables needed *(If applicable, please be as specific as possible)*

DRA identification (DRA present yes/no) by AT-HARM10 when applied by students
DRA identification (DRA present yes/no) by OPERAM when applied by students (subsample of cases)

Planned analyses *(Provide a brief description of the statistical analyses)*

Primary analysis: Agreement of DRA detection (Kappa) between the student using AT-HARM10 versus an expert panel using OPERAM tool.
Each included case will be assessed by 1 student. The DRA identification by the student will be compared to the DRA identification already performed during the main trial for the same case by the OPERAM expert panel.
Agreement between AT-HARM10 adjudication by a student and OPERAM adjudication by the expert panel will be calculated as % agreement and Cohen's kappa (95%CI). Kappa values lower than 0.20 reflect poor agreement, between 0.21 and 0.40 fair agreement, between 0.41 and 0.60 moderate agreement, between 0.61 and 0.80 good agreement and between 0.81 and 1.00 very good agreement [69].
Agreement (Kappa) between AT-HARM10 by student and OPERAM expert panel :

		OPERAM by expert panel	
		DRA yes	*DRA no*
AT-HARM10 by student	*DRA yes*	Agreement	Non-agreement
	DRA no	Non-agreement	Agreement

Secondary analysis:
- Prevalence of DRA detected by the 2 tools.
- Training time and adjudication time needed with AT-HARM10 tool by students : median time required to adjudicate an admission using AT-HARM10 tool by students and evolution of the required adjudication duration (we expect analysis duration to decrease progressively over time with training until it stabilizes).
- Categorization of the differences between the student and the OPERAM multidisciplinary expert panel about assessment (including comparison of drugs detected by each type of users at ATC3 level).
- Agreement (Kappa) between the 2 tools when applied by students (on a subsample).
- Accuracy of AT-HARM : Gold standard for DRA adjudication is usually chart review by a panel. The OPERAM method, includes this chart review, but in structured way, including a trigger tool and implicit questions. However, for the following secondary analysis, we will consider the OPERAM method as the gold standard.

Accuracy of AT-HARM10 compared to OPERAM by expert panel:

		OPERAM by expert panel (used as gold standard for these metrics)	
		DRA yes	*DRA no*
AT-HARM10 by students	*DRA yes*	True positive TP	False positive FP
	DRA no	False negative FN	True negative TN

Sensitivity (TP/(TP+FN)), Specificity (TN/(FP+TN)), accuracy ((TP+TN)/total), positive predictive value (TP/(TP+FP)), negative predictive value (TN/(FN+TN)), positive likelihood ratio (sensitivity/(FP/(FP+TN))), negative likelihood ratio ((FN/(TP+FN))/specificity) of AT-HARM10 applied by students (using OPERAM applied by an expert panel as the gold standard).

Recording and calculations will be done by UCL. No recording needs to be performed in the DRA eCRF.

Project Timeline (Indicate the presumed date when the project will be completed, including planned abstract submission)

Data collection: 2020
Data analysis: 2020-21
Communication to scientific meeting: yes
Submission of the manuscript: yes

Expected workload (on a patient basis, including number of patients) for each participating **partner** (in case of a sub-study embedded in trial)

No additional workload. Study will be conducted by a student in pharmacy of UCLouvain and a student at UMC. Other sites are not involved.

10.4 APPENDIX 4 - DETAILED CALCULATIONS OF KAPPA VALUES

OPERAM sub-study : Draft of article

Degree of agreement between the OPERAM method used by the experts and AT-HARM10 used by a student :

$$\kappa = \frac{\frac{98+211}{376} - \frac{(140\times123)+(236\times253)}{376^2}}{1-\frac{(140\times123)+(236\times253)}{376^2}} = 0.61$$

$$\kappa_{max} = \frac{\frac{123+236}{376} - \frac{(140\times123)+(236\times253)}{376^2}}{1-\frac{(140\times123)+(236\times253)}{376^2}} = 0.90$$

Kappa maximum, with a value of 0.90, was determined if it is thought that maximum possible degree of agreement on DRA is limited to 123 admissions and on no DRA is limited to 236 admissions. Indeed, the OPERAM experts judged 140 admissions as DRAs while the student considered 123. Thus, the maximum possible agreement on DRA is limited to 123. The same logic also applies to no DRA numbers.

Comparison of sites

Degree of agreement between the OPERAM method used by the experts and AT-HARM10 used by the student (NCr) at the CUSL :

$$K = \frac{\frac{74+88}{191} - \frac{(91\times86)+(100\times105)}{191^2}}{1-\frac{(91\times86)+(100\times105)}{191^2}} = 0.6949$$

$$K_{max} = \frac{\frac{86+100}{191} - \frac{(91\times86)+(100\times105)}{191^2}}{1-\frac{(91\times86)+(100\times105)}{191^2}} = 0.9474$$

DRA assessment by the OPERAM method used by experts and AT-HARM10 used by the student (NCr) at the CUSL :

		OPERAM method used by Belgian experts	
		DRA yes	DRA no
AT-HARM10 used by Belgian student	DRA yes	74	12
	DRA no	17	88

Degree of agreement between the OPERAM method used by the experts and AT-HARM10 used by the student (NCo) at the UMC :

$$K = \frac{\frac{24+123}{185} - \frac{(49\times37)+(136\times148)}{185^2}}{1-\frac{(49\times37)+(136\times148)}{185^2}} = 0.4277$$

$$K_{max} = \frac{\frac{37+136}{185} - \frac{(49\times37)+(136\times148)}{185^2}}{1-\frac{(49\times37)+(136\times148)}{185^2}} = 0.8193$$

DRA assessment by the OPERAM method used by experts and AT-HARM10 used by the student at the UMC

		OPERAM method used by Dutch experts	
		DRA yes	DRA no
AT-HARM10 used by Dutch student	DRA yes	24	13
	DRA no	25	123

<u>Use of OPERAM method by a student</u>

Degree of agreement between the OPERAM method used by the Belgian experts and a student (BB) :

$$K = \frac{\frac{30+19}{75} - \frac{(41\times45)+(34\times30)}{75^2}}{1-\frac{(41\times45)+(34\times30)}{75^2}} = 0.2935$$

$$K_{max} = \frac{\frac{41+30}{75} - \frac{(41\times45)+(34\times30)}{75^2}}{1-\frac{(41\times45)+(34\times30)}{75^2}} = 0.8913$$

Degree of agreement between the OPERAM method used by the Belgian student (BB) and AT-HARM10 used by the other Belgian student (NCr) :

$$K = \frac{\frac{28+24}{74} - \frac{(33\times45)+(41\times29)}{74^2}}{1-\frac{(33\times45)+(41\times29)}{74^2}} = 0.4190$$

10.5 APPENDIX 5 - DRUG CLASSES MOST INVOLVED IN DRAS ACCORDING TO AT-HARM10, OPERAM METHOD AND BOTH METHODS.

Methods	AT-HARM10 no. (%)* (n DRA = 123)		OPERAM method no. (%)* (n DRA = 140)		AT-HARM10 and OPERAM method no. (%)* (n DRA = 98)	
Drugs:	Prescribed	Omitted	Prescribed	Omitted	Prescribed	Omitted
Cardiovascular system	37 (30.1)	28 (22.8)	95 (67.8)	33 (23.6)	30 (30.6)	10 (10.2)
Glycosids	0	0	1	0	0	0
Antiarrhythmics	2	1	2	0	1	0
Antihypertensives	3	0	1	1	0	0
Diuretics	15	11	41	10	15	4
Beta blocking agents	3	5	13	5	3	2
Calcium channel blockers	0	1	5	2	0	0
Agents acting on the renin-angiotensin system	10	2	28	9	9	1
Hypolipidemiants	4	8	4	6	2	3
Nervous system	32 (26.0)	2 (1.6)	44 (31.4)	7 (5.0)	21 (21.4)	2 (2.0)
Analgesics	12	1	18	6	9	1
Antiepileptics	2	0	4	0	0	0
Dopaminergic agents	4	0	3	0	2	0
Psycholeptics	9	0	12	0	7	0
Antidepressants	5	1	7	1	3	1
Antithrombotic agents	18 (14.6)	5 (4.0)	31 (22.1)	6 (4.3)	14 (14.3)	2 (2.0)
Antiplatelets	8	2	15	1	5	1
Anticoagulants	10	3	16	5	9	1
Antineoplastic agents and Immunosuppressants	17 (13.8)	1 (0.8)	18 (12.8)	0	13 (13.3)	0
Glucocorticoids	12 (9.7)	1 (0.8)	11 (7.8)	0	7 (7.1)	0
Drugs for acid related disorders	4 (3.2)	0	13 (9.3)	0	1 (1.0)	0
Antibiotics + Antimycotics + Antivirals	7 (5.7)	1 (0.8)	9 (6.4)	0	2 (2.0)	0
AINS	4 (3.2)	0	5 (3.6)	0	4 (4.1)	0
Drugs used in diabetes	4 (3.2)	2 (1.6)	4 (2.8)	0	3 (3.1)	0
Drugs for bone diseases: Ca/vit D, Bisphosphonates	2 (1.6)	7 (5.7)	0	9 (6.4)	0	6 (6.1)
Adrenergics inhalants	1 (0.8)	0	3 (2.1)	1 (0.7)	1 (1.0)	0
Drug used in benign prostatic hypertrophy, incontinence	1 (0.8)	0	3 (2.1)	0	1 (1.0)	0
Drugs for constipation	1 (0.8)	2 (1.6)	2 (1.4)	4 (2.8)	1 (1.0)	2 (2.0)
Antigout preparations	0	0	2 (1.4)	0	0	0
Influenza Vaccines	0	1 (0.8)	0	0	0	0
Antianemics	1 (0.8)	1 (0.8)	0	0	0	0
Thyroid hormones	1 (0.8)	0	0	0	0	0
Antiglaucoma	0	1 (0.8)	0	0	0	0
*percentage of DRA caused by this class of drugs						

INTRO

Drug-related admissions (DRAs) are hospital admissions resulting from non-preventable adverse drug events or preventable medication errors and contribute to up to 30% of all admissions in older people. Detecting reasons for hospitalizations in older patients is complex because of their polypharmacy and multimorbidity. Two methods to screen for and adjudicate DRAs caused by adverse reaction, overuse, underuse and misuse of medication were elaborated and validated. While a multidisciplinary panel of experts uses the OPERAM method, AT-HARM10 is intended to be a faster implicit screening tool using 10 questions that could be used by pharmacy students.

METHODS

A comparison of adjudication outcome performed independently by an expert panel using the OPERAM method and students using AT-HARM10 was made on 376 hospitalizations from the OPERAM trial at the Cliniques universitaires de Saint-Luc and the University Medical Center Utrecht. First outcome was the degree of agreement between methods on DRA detection using Cohen's kappa. Secondary aims were (1) to determine proportions of DRAs detected by each method, (2) to categorize discrepancies between the users about assessment and about top five of medication classes (ATC3 level), (3) to evaluate adjudication time and training time needed with AT-HARM10 and (4) to determine performance of AT-HARM10 (OPERAM experts as gold standard).

RESULTS

The DRA detection agreement between methods was good, with 82% agreement and Cohen's $\kappa = 0.61$ (95% CI 0.52-0.69). Methods agreed on at least one common drug responsible for admission in 92% of the DRAs assessed by both methods. The OPERAM method detected 37% of DRA in the cohort while students using AT-HARM10 detected 33% (p-value = 0.0378). The main discrepancies between experts and student were the overestimation by student of disease impact and of underused drugs. Top 5 prescribed drug classes involved in DRAs were similar with both methods : cardiovascular system drugs, nervous system drugs, antithrombotics, antineoplastics/ immunosuppressants and glucocorticoids. Omitted drug classes most involved in DRAs were cardiovascular drugs and drugs for bone diseases. The median adjudication time with AT-HARM10 used by the Belgian student was 16.5 minutes and 7 minutes when used by the Dutch student. The duration of analysis decreased until it stabilized after the first 50 admissions. The sensitivity and specificity of AT-HARM10 were 0.70 and 0.89, respectively.

CONCLUSION

Agreement between the tools was good, showing that both methods can detect DRA outcome in research study as long as assessors respect exactly the way they were designed to. In this sub-study, the OPERAM method was more prone to detect DRA, AT-HARM10 doesn't have the advantage of a significantly shorter analysis time than with the OPERAM method in Belgium and it is known that an implicit process measure depends mainly on the student's knowledge.

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