UCLouvain
Secteur des sciences de la santé

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Stefanie Thevelin graduated as a pharmacist from Ghent University in 2011. She obtained a complementary master's degree in hospital pharmacy (2013) and another in clinical pharmacy (2014). In 2015, she started a PhD project at the Clinical Pharmacy Research Group (UCL), in the context of the European OPtimising thERapy to prevent Avoidable hospital admissions in the Multi-morbid elderly (OPERAM) project.

Inappropriate polypharmacy and related adverse health outcomes represent significant challenges in the ageing multi-morbid population. The European OPERAM randomised controlled trial was undertaken to assess the impact of medication review on drug-related admissions (DRAs) in 2009 older patients with multi-morbidity. In this context, we developed the first standardised chart review method to identify DRAs, a core outcome of medication review that is considered highly important to older people. We highlighted the challenges associated with achieving good inter-rater reliability in DRA adjudication. In a second cross-sectional study, we demonstrated that DRAs resulting from potentially inappropriate prescribing detected by the STOPP/START.v2 criteria, accounted for 40% of admissions in older patients. Thirdly, a multi-centre mixed methods study embedded in the OPERAM trial, provided an in-depth understanding of multi-morbid older people's experience of hospital-initiated medication changes and identified barriers, facilitators and patients' needs in relation to medication review. Finally, a scoping review aims to increase understanding of medication-related preferences of multi-morbid older people in order to inform medication review. Our findings pave the way for a better detection and understanding of DRAs and for medication review services to become more tailored to the preferences and needs of older people with multi-morbidity and polypharmacy.

La polymédication et ses effets indésirables associés constituent un défi important pour la population âgée et multimorbide. Un essai randomisé contrôlé européen, OPERAM, a été mené chez 2009 personnes âgées avec multimorbidité, pour évaluer l'impact d'une revue de médication sur les hospitalisations liées aux médicaments (HLMs). Dans ce contexte, nous avons développé la première méthode standardisée d'analyse de dossier médical pour détecter les HLMs, un outcome important de la revue de médication pour les patients âgés. Nous avons mis en évidence le défi d'obtenir une bonne fiabilité inter-évaluateurs dans la détermination des HLMs. Dans une deuxième étude transversale, nous avons montré que les HLMs résultant de la prescription potentiellement inappropriée selon les critères STOPP/START.v2, représentaient 40% des admissions de patients âgés. Ensuite, une étude de méthode mixte, intégrée dans OPERAM, a permis de comprendre en profondeur l'expérience des personnes âgées par rapport aux changements de médicaments proposés lors d'une hospitalisation et d'identifier les obstacles, facilitateurs et besoins des patients vis-à-vis de la revue de médication. Enfin, une revue de littérature vise à mieux comprendre les préférences des patients concernant leurs médicaments. Nos résultats ouvrent la voie à une meilleure identification et compréhension des HLMs et à des services de revue de médication mieux adaptés aux préférences et besoins des personnes âgées souffrant de multimorbidité et de polymédication.

Stefanie Thevelin 0.0.
Medication review to prevent avoidable hospitalisations in multi-morbid older people

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Medication review to prevent avoidable hospital admissions in older people with multi-morbidity

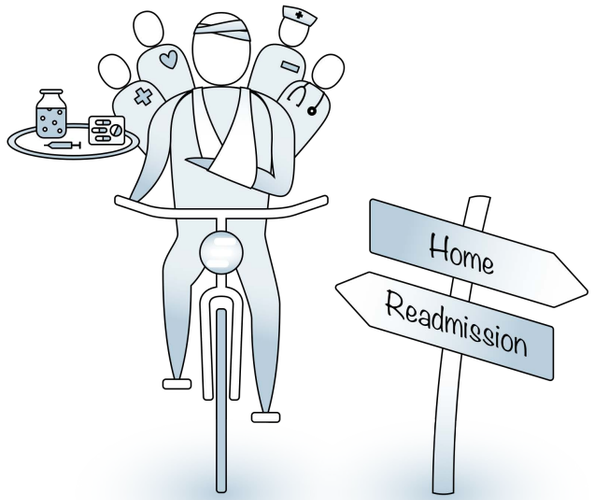
Measuring outcomes that matter to patients

Stefanie Thevelin

January 2020

Thèse présentée en vue de l'obtention du grade de docteur en sciences biomédicales et pharmaceutiques

Secteur des sciences de la santé



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« It is much more important to know what sort of a patient has a disease, than what sort of a disease a patient has. »

Caleb Hillier Parry

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ACKNOWLEDGEMENTS

Four and a half years of research, summarised into 300 pages. This is the result of great teamwork and I would like to thank the amazing group of people that have directly or indirectly contributed to this work.

To Professors Olivia Dalleur, Anne Spinewine and Benoit Boland, thank you for giving me the opportunity to work on this beautiful OPERAM project after our first meeting in 2015. It has been a fantastic experience to share this journey (around Europe) with you and I am grateful for everything that I learned from you. To my promoter Olivia, thank you for all the time and energy you invested in this thesis, for your encouragements, your enthusiasm, your creativity and your trust in me. To my co-promoter Anne, thank you for your advice, your availability, your critical eye and precision helping time and time again to improve the work. To Benoit, special thanks for involving me in various research projects in geriatrics. I enjoyed working together with all of you.

To the members of my steering committee, Professors Isabelle Aujoulat, Bruno Krug, Benoit Boland and Françoise Van Bambeke, thank you for your advice and encouragements since the beginning of this PhD project. To the external jury members, Professors Jesse Jansen and Ulrika Gillespie, many thanks for your critical review of this work and for your valuable comments and suggestions that have improved the thesis manuscript.

Many thanks to the whole OPERAM team. What an astonishing example of international teamwork this was! To the adjudication teams, thank you for your tremendous work and dedication. Special thanks to the Belgian team: Ariane Mouzon, Sophie Marien, François-Xavier Sibille and Fanny Vaillant for the nice collaboration. Thank you Catherine Pétein, Anniek Van Herksen, Kevin Murphy and Beatrice Metry for having explored with me the exciting field of patient experience. Catherine, thank you for the many philosophical discussions during data analysis, it was a pleasure working with you.

I would like to thank all the patients and clinicians who took part in the patient experience study, for sharing their valuable perspectives.

ACKNOWLEDGEMENTS

To Jean-Baptiste Beuscart, thank you for your advice and support during my first year of PhD and for involving me in the development of the core outcome set. Many thanks also to Christina Raae Hansen for involving me in the systematic review on deprescribing.

To team OPERAM St Luc: Charlène Mouafo, Kaoutar Abdellaoui, Anne Fournier, Inès Zougrana, Isabelle Alloo, Halima Cheritel, Samantha Genten, Véronique Legros, Céline Billocq, thank you for being the most kind and motivated colleagues.

I would like to thank the European Union's Horizon 2020 research and innovation programme for making it financially possible to conduct this thesis.

To Kristie Weir, thank you so much for the great collaboration in the scoping review and for always being in a good mood, even though we had to screen several thousands of references!

To my daily 'comité d'accompagnement' during the past four years, the CLIP team: Anne-Laure Sennesael, Sophie Marien, Pauline Anrys, Catherine Pétein, Perrine Evrard, Juliette Lagreula, Angèle Dohou, Ariane Fiogbe, Carine Yehouenou, Delphine Legrand, Anne-Elisabeth Petit… It was a pleasure sharing the (little) office with you. Thank you for the many encouragements during these last months of thesis writing. Special thanks to Séverine Henrard for all the help with statistical analysis.

To my friends and family, thank you for always being there for me and for sharing laughter and doubts. To my parents, thank you so much for your unconditional support in everything that I do. This one is for you too, Tommeke.

And last but not least, thank you Deben. Thanks for your patience and understanding and for being my all-in-one IT problem solver, thesis cover illustrator (even you now know all about patient-centred care!) and for being my biggest support(er) during this PhD adventure and all other adventures.

SUMMARY

Inappropriate polypharmacy and related adverse health outcomes represent significant challenges in the ageing multi-morbid population. Medication reviews are recommended to reduce inappropriate polypharmacy and a patient-centred approach to medication review is considered essential. In this context, the European OPERAM trial was undertaken to evaluate the impact of medication review on drug-related readmissions in 2009 multi-morbid older patients.

This thesis aimed to inform medication review in older people with multi-morbidity and polypharmacy by measuring outcomes that matter to patients. We developed the first standardised method to identify drug-related admissions (DRAs) in older people, a growing patient safety threat and an outcome of medication review that is considered highly important to older people. We highlighted the challenges associated with achieving good inter-rater reliability in DRA adjudication. In a cross-sectional study, we demonstrated that DRAs resulting from inappropriate prescribing detected by the STOPP/START.v_2 criteria accounted for 40% of admissions in older patients. In a multi-centre mixed methods study embedded in OPERAM, we evaluated the patient experience. We showed that patients' attitudes towards hospital-initiated medication changes and medication review were generally positive, but an interplay of factors related to inadequate information and communication, paternalism, patients' beliefs, clinicians' attitudes and doctor-patient relationships may affect effectiveness of medication reviews. Finally, a scoping review will help to increase understanding of medication-related preferences of multi-morbid older people, in order to inform medication review.

Our findings pave the way for a better measurement and understanding of DRAs and for medication review services to become more tailored to the needs and preferences of older people with multi-morbidity and polypharmacy.

ABBREVIATIONS

ACE-inhibitor	Angiotensin-converting enzyme inhibitor
ADE	Adverse drug event
ADR	Adverse drug reaction
AGS	American Geriatrics Society
AT-HARM10	Assessment Tool for Hospital Admissions Related to Medications
BCT	Behaviour change technique
BMQ	Beliefs about medicines questionnaire
CDSS	Clinical decision support system
COPD	Chronic obstructive pulmonary disease
COS	Core outcome set
DRA	Drug-related admission
DREAMER	Drug use Reconsidered in the Elderly using goal Attainment scales during Medication Review
DVT	Deep vein thrombosis
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EU	European Union
FEV_1	Forced expiratory volume in one second
GAS	Goal attainment scaling
GP	General practitioner
HARM study	Hospital Admissions Related to Medication study
HMR	Home medicines review
HCP	Healthcare professional
ICT	Information and communication technology
IHI	Institute for Healthcare Improvement
IMM	Integrated Medicines Management
INR	International normalised ratio
IQR	Interquartile range
IRR	Inter-rater reliability
MAI	Medication appropriateness index
MEDBRIDGE	Medication Reviews Bridging Healthcare
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value
NSAID	Non-steroidal anti-inflammatory drug
OECD	Organisation for Economic Cooperation and Development
OPERAM	OPtimising thERapy to prevent Avoidable hospital admissions in the Multi-morbid elderly

OPT	Outcome prioritisation tool
P4P	Pay-for-performance
PE	Pulmonary embolism
PIM	Potentially inappropriate medicine
PIP	Potentially inappropriate prescribing
PPO	Potential prescribing omission
PPV	Positive predictive value
PREM	Patient-reported experience measure
PROM	Patient-reported outcome measure
RCT	Randomised controlled trial
SDM	Shared decision-making
SDM-Q-DOC	Physician version of the shared decision-making questionnaire
SIMPATHY	Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly
SSRI	Selective serotonin reuptake inhibitor
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older People's Prescriptions
STRIP	Systematic Tool to Reduce Inappropriate Prescribing
STRIP-A	Systematic Tool to Reduce Inappropriate Prescribing-Assistant
TDF	Theoretical domains framework
UBERN	University of Bern
UCC	University College Cork
UCL	Université catholique de Louvain
UMCU	University Medical Centre Utrecht
VKA	Vitamin K antagonist
WHO	World Health Organisation
WHO-UMC	World Health Organisation-Uppsala Monitoring Centre

GENERAL INTRODUCTION

1 INAPPROPRIATE POLYPHARMACY IN OLDER PEOPLE: WHEN TOO MANY MEDICINES LEAD TO ADVERSE OUTCOMES

Polypharmacy, the concurrent use of multiple medicines, is recognised as a major public health challenge.[1,2] The rise in polypharmacy mainly results from the rapid expansion of the ageing population and the associated increase in multi-morbidity (the co-occurrence of two or more chronic diseases).[2-4] More than 50% of older people suffer from three or more chronic diseases.[5] In a Scottish primary care population, respectively 28.6% and 7.4% of patients aged 60-69 years and 51.8% and 18.6% of patients aged ≥80 years, received four to nine and ten or more medications.[6]

Although there is no universally agreed upon definition of polypharmacy, it is often defined as the use of five or more medicines.[2] Rather than a numerical definition of polypharmacy, it is more important to focus on reducing inappropriate polypharmacy (irrational prescribing of too many medicines) and ensuring appropriate polypharmacy (rational prescribing of multiple medicines considering the best available evidence, the individual patient factors and context) (Table 1).

Table 1: Definitions of appropriate and inappropriate polypharmacy

Appropriate polypharmacy	When (a) all medicines are prescribed for the purpose of achieving specific therapeutic objectives that have been agreed with the patient; (b) therapeutic objectives are actually being achieved or there is a reasonable chance that they will be achieved in the future; (c) medication therapy has been optimised to minimise the risk of adverse drug events (ADEs); and (d) the patient is motivated and able to take all medicines as intended.[2]
Inappropriate polypharmacy	When one or more medicines are prescribed that are not or no longer needed, either because: (a) there is no evidence-based indication, the indication has expired or the dose is unnecessarily high; (b) one or more medicines fail to achieve the therapeutic objectives they are intended to achieve; (c) one, or the combination of several medicines cause ADEs, or put the patient at high risk of ADEs or because (d) the patient is not willing or able to take one or more medicines as intended.[2]

The rising prevalence of multi-morbidity and polypharmacy poses challenges on patients, healthcare professionals (HCPs) and health systems. There is robust literature describing the negative clinical, economic and social consequences associated with multi-morbidity and inappropriate polypharmacy.[7] Multi-morbidity is associated with high mortality, poor quality of life, increased health service utilisation including hospitalisation and increased rates of polypharmacy.[4,5,7-9] Polypharmacy is a well-known risk factor for inappropriate prescribing, drug-related problems and adverse drug events (ADEs).[10] ADEs are a leading cause of hospitalisation, increased healthcare costs and are associated with increased mortality.[7,11] According to a Swedish study, fatal ADEs account for 3% of all deaths in the general population, rising to 5% in hospitalised patients.[12-14]

Health systems are still largely organised around the management of single diseases. This systematically disadvantages multi-morbid patients who often receive care from multiple providers, who may not be communicating effectively, resulting in fragmented, poorly coordinated care and medical error.[4,15] Multi-morbid older patients may suffer from a high treatment burden (e.g. healthcare visits, refilling prescriptions, diet, self-managing care) due to complex and potentially harmful treatment regimens and due to the many interactions with care providers across settings.[4,16,17] Furthermore, caregivers suffer from negative outcomes as a result of caring for people with chronic conditions.[18] HCPs face substantial challenges when caring for patients with multi-morbidity, including limited time and resources, difficulties due to poor care coordination, challenges in delivering patient-centred care and shared decision-making and personal reluctance to assume the responsibility of multi-morbidity management.[18,19] Furthermore, the inadequacy of single-disease guidelines and limited evidence-based medicine in multi-morbidity is of concern.[20]

Reorienting the model of care from a paternalistic, disease-oriented and fragmented care system in favour of a patient-centred and integrated health system has been widely advocated as key for modern health and social care and is crucial to improving outcomes in multi-morbid older patients.[4,7,15,21-25] Patient-centred care has been defined by the Institute of Medicine as 'care that is respectful of and responsive to the individual patient's preferences, needs and values and ensures that patient values guide all clinical decisions.'[26] Integrated health services are managed and delivered so that people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease-management, rehabilitation and palliative care services, coordinated across the different levels and sites of care within and beyond the health sector, and according to their needs throughout the life course.[24]

1.1 ADVERSE DRUG EVENTS IN OLDER PEOPLE WITH MULTI-MORBIDITY AND POLYPHARMACY

Definition and classification of drug-related problems

Drug-related problems (DRPs) have been defined in a variable way across studies.[26] We adopted the classification from the World Health Organisation's (WHO) report on medication safety in polypharmacy (Figure 1).[27]

Drug-related problems can be divided into two groups, problems *not* related to an error (adverse drug reactions) and problems related to an error (medication errors). Adverse drug reactions (ADR) always result in patient harm, result from the intrinsic properties of the drug and are not preventable.[26,28] A medication error is defined as 'any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer'. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labelling; packaging; and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.'[27,29]

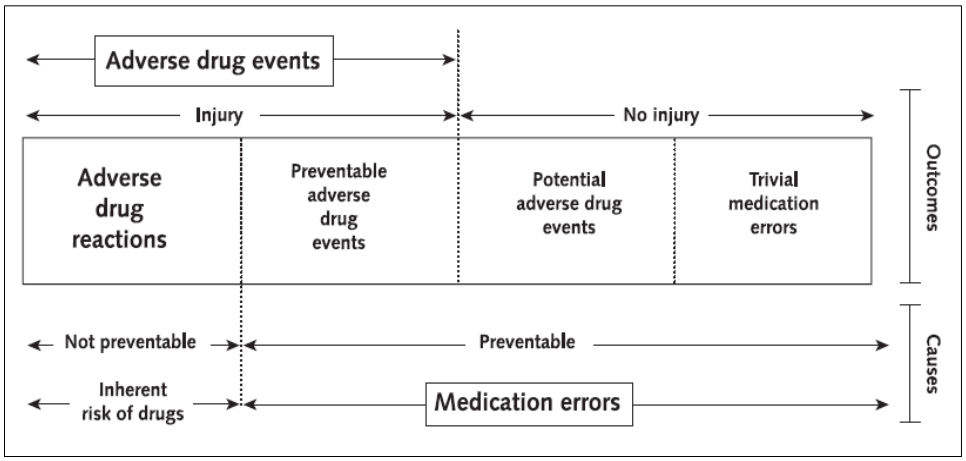

Figure 1: Relationship between adverse drug events, adverse drug reactions and medication errors. Adopted from Otero & Schmitt.[28]

Medication errors may or may not result in patient harm and are preventable.[26,28] Adverse drug events (ADEs) are defined as any harm resulting from the use of a drug and include both non-preventable ADRs, in which no error occurred and preventable medication errors.[2] Definitions and examples of drug-related problems are provided in the glossary of terms (Appendix 1).

In this thesis we focus on a particular type of serious ADEs resulting in hospitalisation: drug-related admissions (DRAs). In this research, we have defined DRAs as hospitalisations resulting from an ADE encompassing non-preventable ADRs and preventable medication errors including overuse, underuse and misuse of prescription and non-prescription medications (all-cause DRA). Furthermore, we can distinguish between drug-related admissions (DRAs) and drug-related *re*admissions. An index admission is defined as the first hospital admission and readmissions are occurring within a specified period after index admission.[30]

Why are older people at high risk of adverse drug events?

Older people have a seven-fold increased risk of experiencing a DRA compared to younger persons.[31,32] Older people frequently suffer from multi-morbidity resulting in polypharmacy, which has been consistently identified as risk factor for ADEs.[33,34] Polypharmacy increases the risk for non-adherence, which may result in therapeutic failure or poor clinical response.[34] Furthermore, living alone, having multiple prescribers and cognitive impairment or poor knowledge of prescribed drugs increases the risk of non-adherence and ADEs.[34] ADEs may be difficult to recognise in older people, as they commonly present as symptoms already prevalent in older people such as falls, cognitive decline, constipation etc. This may be misinterpreted as a new medical problem, leading to the addition of a new drug and increased risk of ADEs – a phenomenon known as 'the prescribing cascade'.[33-35] Furthermore, age-related changes in pharmacokinetics and pharmacodynamics increase the susceptibility for ADEs in older people.[33] In addition, older adults suffer from a greater degree of frailty.[33] Hence prescribing for older people is considered a complex task and finding a balance between treating diseases and preventing ADEs is critical.[9,36,37] Inappropriate prescribing is highly prevalent in older people and is associated with an increased risk of ADEs, healthcare utilisation, morbidity and mortality.[38] Inappropriate prescribing encompasses the prescription of more drugs than are clinically needed (overuse), the incorrect prescription of a drug that is needed (misuse) or the failure to prescribe drugs that are needed (underuse).[36] A systematic review reported a potentially inappropriate prescribing prevalence of 22.6% in community-dwelling older people across Europe.[39] Furthermore, the heterogeneity in older people of the same age, in terms of health and functional status, makes generalisation of prescribing recommendations difficult and a 'one size fits all' approach is inappropriate.[33,36,38] Despite the fact that multi-morbidity is becoming the norm, older multi-morbid patients are largely underrepresented in

randomised controlled trials and most clinical guidelines do not integrate care for multi-morbidity or help clinicians to prioritise recommendations.[4,7,8] Application of single-disease guidelines to multi-morbid patients can act as a driving force for polypharmacy and ADEs.[7-9]

Drug-related admissions: common, costly but preventable

DRAs are a significant patient safety threat in the older population and are associated with adverse clinical and economic outcomes.[30,35,40-43] In the Hospital Admissions Related to Medication (HARM) study, a large multi-centre prospective study on DRAs in The Netherlands, the median length of stay of patients with a preventable DRA was 8 days, 7.2% of patients were admitted to an intensive care unit, 6.3% died and 9.3% experienced a disability after discharge.[41] The average medical cost of a preventable DRA calculated in the HARM study was €5461.[41]

DRAs account for 8.6 million admissions in Europe every year and DRA prevalence rates vary from 6% to 50% of all admissions in older adults.[1,35,44-47] The wide variance in prevalence rates is associated with a considerable heterogeneity in definitions (consideration of ADEs and/or ADRs), methods used to identify DRAs (chart review, administrative database research, spontaneous reporting), the study population (hospital ward, age-groups, polypharmacy etc.) and the setting (all admissions versus acute admissions, continent).[30,48] Few studies include DRAs resulting from poor medication adherence or underuse, although these are major causes of DRAs.[30,48-52] Furthermore, drug-related *re*admissions are highly prevalent.[53] A recent systematic review found a median drug-related *re*admission rate of 21% (interquartile range (IQR) 14-23%) and the majority was preventable (median 69%, IQR 19-84%).[30] The time frame between admissions and readmissions varied from 28 days to 4.1 years, but most studies measured readmissions within 30 days after discharge.[30]

The most frequent types of DRAs in older people are typically gastro-intestinal disorders, cardiovascular, metabolic/endocrine complications, falls and fractures.[31,35,42,54,55] The literature is inconsistent regarding the most commonly involved drugs in DRAs in older people, although nonsteroidal anti-inflammatory drugs (NSAIDs), antithrombotic agents, antidiabetic agents, central nervous system drugs, cardiovascular system drugs and antibiotics are frequently reported.[31,35,42,45,56] Chronic obstructive pulmonary disease (COPD) and heart failure exacerbation, ischaemic heart disease and falls/fractures are frequent causes DRAs related to underuse of medications, mainly resulting from adherence or prescribing problems.[49,50,54,57]

The evidence on the risk factors for DRAs in older people is still poorly understood.[30,35,58] However, data from the HARM study identified clear causative associations between DRAs and a number of risk factors in older people including multi-morbidity, polypharmacy, poor adherence, impaired cognition, impaired renal function and dependent living situation.[42] Furthermore, potentially inappropriate medications are a frequently cited risk factor.[35]

Up to 70% of DRAs in older adults are potentially preventable.[35,47,59] Preventable drug-related (re)admissions result mainly from inappropriate prescribing, monitoring and adherence problems as well as problems with communication of medication-related information at care transitions (between patients and clinicians as well as between clinicians, general practitioners (GPs) and community pharmacists).[2,42,49,51,53-56,59-67] Transfer between care settings is a risk factor for developing ADEs.[68,69] Upon admission to hospital, 27-54% of patients have at least one error in in the medication history, whereas 64-96% of patients experience DRPs after discharge.[70-72] During hospitalisation, frequent changes are made to patients' treatment regimens and inadequate patient education, follow-up and continuity of

care may result in medication discrepancies, inappropriate prescribing, poor adherence and inadequate monitoring of adverse effects.[27,73]

1.2 METHODS TO DETECT ADVERSE DRUG EVENTS

Several approaches to detect ADEs exist including chart review, trigger-based chart review, voluntary reporting, administrative datasets, patient interviews, direct observation.[74-77] All methods have advantages and limitations (Table 2) and the ADE rate depends on the method being used.[2,78] Detection using administrative data systems and incident reporting is less expensive but also less sensitive to ADE detection. In a study comparing detection of DRAs in older people using administrative database coding versus prospective identification based on chart review and patient interviews, in respectively 2.7% and 15% of patients a DRA was detected, suggesting that reliance on administrative coding underestimates the prevalence of DRAs.[78] Retrospective chart review by two or more reviewers has been considered as the gold standard in many patient safety studies.[79] The two stage chart review of the Harvard Medical Practice Study (screening charts for potential adverse events by nurses, which are subsequently reviewed in more detail by physicians to confirm the presence of an ADE) established the standard for ADE detection, however it suffers from several problems: inconsistency in defining ADEs, resource intensiveness, incomplete, poor or confusing documentation in the medical charts, low inter-rater reliability.[74,80] The method has largely been replaced by trigger-based chart review, which has been advocated to be the premier ADE detection method as it has been shown to more efficiently detect adverse events compared to any other method.[74,80,81] The trigger tool methodology is a chart review using triggers to identify possible adverse events.[82,83] Triggers are defined as 'occurrences, prompts or flags' found upon chart review (e.g. hypoglycaemia) that 'trigger' further investigation to determine the presence or absence of an ADE.[74,84] The most well

studied is the Institute for Health Care Improvement's (IHI) Global Trigger Tool, which has demonstrated excellent inter- and intra-rater reliability, very good to excellent sensitivity and excellent specificity when compared to gold standard expert chart review.[74] However, there has been some controversy about the performance of the trigger tool method because of the low positive predictive values of some triggers and poor sensitivity in another study.[85-88] Therefore detection of non-triggered events is recommended.[85] The Global Trigger Tool has been an inspiration for the development of setting-specific trigger tools e.g. in paediatrics, oncology or the nursing home setting.[89-91] Trigger tools have been developed as a manual approach, however there is increasing interest in the development of automated trigger tools using electronic health records, which are less resource intensive.[81]

Regardless of the method being used, ADEs are usually adjudicated in consensus agreement between two reviewers. A pair of a physician and a pharmacist is a recommended approach for evaluation of ADEs given their complementary knowledge and experience.[92,93]

Table 2: Comparison of the four most frequently used methods for detection of medication-related harm. Adopted from Sharek.[74]

Method	Advantages	Limitations
Incident reports	• Well established process in most hospitals • Inexpensive • Easy information to obtain	• Identifies only between 2-8% of harmful events • Focus tends to be on error, not harm • Voluntary nature results in vast underreporting • Can be time-intensive • Often perceived as punitive by staff
Administrative database algorithms	• Standard definitions • Method allows for direct comparison between hospitals • Inexpensive	• Identifies < 10% of all harms[94] • Poor sensitivity and specificity • Focus is on only a few specific harm types, not all-cause harm • Harm easily hidden/missed if not well described in charting • Dependent on accuracy of chart coding
Retrospective/concurrent chart review (e.g. Harvard Medical Practice Study)[80]	• Active surveillance can identify harms not well articulated in charts (if honest communication occurs) • Measures all-cause harm • Provides a rate e.g. harms per 100 admissions or per 1000 patient days	• Substantially underreported harm rates[95,96] • Relies partially on voluntary or verbally solicited identification of harm • Active real time surveillance is resource intensive • Unfocused chart review is also resource intensive • Retrospective review of charts is challenging if poor or incomplete documentation
Trigger-based chart review	• Measures all-cause harm • Measures total harm burden • Provides a rate e.g. harms per 100 admissions or per 1000 patient days • Focusses on harm but includes errors as well • Allows sampling strategy • Relatively efficient: 20 minutes per chart • Can be population specific e.g. paediatrics, geriatrics • Excellent specificity and very good sensitivity • Potential for automation of trigger tools[81]	• Requires training • Resource intensive: IHI recommends 20 charts per month at 20 minutes per chart • Retrospective review of charts challenging if poor or incomplete documentation

Causality assessment

It is often difficult to decide if an adverse clinical event is due to a drug or due to deterioration in the patient's disease state.[35] Therefore, causality assessment is used to evaluate the likelihood that a particular treatment causes a suspected ADE.[97] The most widely used causality assessment criteria are the WHO's Uppsala Monitoring Centre (WHO-UMC) criteria. The WHO-UMC causality criteria take into account clinical-pharmacological aspects of the case history and the quality of documentation, to help distinguish between ADEs with an 'unlikely', 'possible', 'probable', 'certain' or 'unassessable' causal relationship.[98] An inherent problem in identifying ADEs is that most cases concern *suspected* ADEs. ADEs are rarely specific for the drug, diagnostic tests are usually absent and a rechallenge is rarely ethically justified. In practice, few ADEs and DRAs are 'certain' or 'unlikely in older people, most are somewhere in between these extremes i.e. 'possible' or 'probable'.[35,98]

The Hallas criteria can be used to evaluate the contribution of an ADE to hospitalisation.[99] An ADE can be the main reason for admission, when no other symptoms contribute significantly (e.g. hospitalisation for gastro-intestinal bleeding caused by antithrombotic agents). An ADE can also be a contributory reason for admission, where the ADE played a substantial role in the admission, but other factors also contributed significantly (e.g. admission for severe diarrhoea with dehydration, which might have been worsened by the use of diuretics). If the ADE played a minor or uncertain role in the admission and the patient would have been admitted anyway, then the ADE did not lead to admission.[99] Hallas et al. also developed criteria to distinguish between definitely preventable, possible preventable, unavoidable and unclassifiable ADEs.[99] However, determining preventability of readmissions has been shown to be a highly subjective and variable process and there is poor consensus on preventability, not only among physicians but also between patients and clinicians.[100,101]

2 MEDICATION REVIEW TO REDUCE INAPPROPRIATE POLYPHARMACY

A wide range of interventions that directly or indirectly aim to improve inappropriate polypharmacy exist: (i) implementation strategies (interventions designed to bring about changes in healthcare organisations, the use of health services by healthcare recipients or the behaviour of healthcare professionals) e.g. educational programmes aimed at prescribers; (ii) delivery arrangements (changes in how, when and where healthcare is organised and delivered and who delivers healthcare) e.g. pharmacist-led medication review, clinical decision support; (iii) financial arrangements e.g. incentive schemes for changes in prescribing practice; (iv) governance arrangements e.g. changes in government policy or legislation affecting prescribing.[9] In this thesis, we will specifically focus on medication review to reduce inappropriate polypharmacy.

2.1 MEDICATION REVIEW

There is no generally accepted definition of medication review and in this thesis we have adopted the definition of the National Institute for Health and Care Excellence (NICE): medication review is defined as 'a structured, critical examination of a person's medicines with the objective of *reaching an agreement* with the person about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste'.[102] Medication review involves the evaluation of the therapeutic efficacy and harms of each drug in relation to the individual patient and the diseases being treated. It includes considering and addressing issues such as adherence, interactions, biochemical monitoring, patient preferences and understanding of the condition.[103] As a first step, medication review should include medication reconciliation i.e. a formal and collaborative process of obtaining and verifying a complete and accurate list of the patient's current medications – including the name, dosage, frequency and route – to ensure that

precise and comprehensive medication information is transmitted consistently across care transitions.[104] Medication review is an umbrella term encompassing different types of medication review that vary in quality and effectiveness, from prescription reviews (review of prescriptions, usually without the patient) to clinical medication reviews (with the availability of all clinical data and patient present).[105] When we refer to medication review in this thesis, we consider this as a comprehensive medication review conducted in the hospital setting.[105]

Medication reviews are recommended by several guidelines and polypharmacy guidance documents aiming to improve the quality of prescribing and to prevent ADEs.[2,102] In the hospital setting, clinical pharmacists have been introduced into multi-disciplinary teams at ward level to perform medication reviews and in some countries medication reviews are conducted in community pharmacies.[106-108] A recent systematic review and meta-analysis showed that medication review interventions in isolation can improve medication-related outcomes (number of medications, number of medication changes, number of drug-related problems and number of drugs with a dosage decrease), but have a minimal impact on clinical outcomes (no impact on mortality, readmissions and a minimal impact on reducing the number of falls) and no impact on quality of life.[109] A 2016 Cochrane review concluded that medication reviews may reduce emergency department visits, but there was no evidence on the impact on mortality or hospital readmissions. The impact on emergency department visits was more significant in high-risk groups such as older people or patients with polypharmacy.[2,103] However, because of the short-term follow-up and heterogeneity in studies, important treatment effects might have been overlooked. The authors concluded that high-quality cluster randomised trials (to prevent contamination bias) with long-term follow-up (at least 12 months) are needed to provide more definite evidence on the impact of medication review on clinically important outcomes.[103]

Implicit and explicit methods to optimise prescribing

Medication review can be supported by the use of explicit (criterion-based) or implicit (judgement-based) tools, or a combination of both, to evaluate the appropriateness of prescribing.[36] Explicit prescribing criteria to detect potentially inappropriate medications (PIMs, over-and misprescribing) and potential prescribing omissions (PPOs; underprescribing), are based on the patient's drug and disease list and allow to evaluate the pharmacological appropriateness of a patient's drug therapy. The most widely used explicit tool in Europe are the Irish Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria, developed by consensus expert opinion based on review of the evidence.[33,110,111] The first version of the STOPP/START.v_1 criteria were developed in 2008 and have been updated in 2014 to incorporate the most recent evidence.[111,112] The clinical impact of medication review in older people using the STOPP/START criteria has been demonstrated in a number of randomised clinical trials internationally with signification improvement in prescribing appropriateness and reduction in ADEs, polypharmacy, falls and costs.[113,114] A few studies have investigated the association between inappropriate prescribing according to the STOPP/START criteria and hospitalisation, with prevalence rates of PIM/PPO-related hospitalisations varying from 11% to 27% according to STOPP.v_1 and/or START.v_1, up to 40% according to STOPP/START.v_2.[54,55,66,115,116]

However, prescribing appropriateness not only encompasses pharmacological appropriateness. A final judgement about appropriateness using implicit patient-centred approaches remains pivotal and should consider the patient's comorbidities, treatment burden, patient preferences and costs.[36]

The increasing use of electronic medical records and electronic prescribing has led to the development of clinical decision support systems (CDSS) to automatically detect potentially inappropriate prescribing (PIP) based on algorithms of the STOPP/START criteria.[117] CDSS can support HCPs in the prescribing process or during medication review by highlighting PIP instances on which HCPs can take a final decision using implicit approaches.[117]

Deprescribing: Less is more

Deprescribing is a key component of medication review and one of the most common recommendations after medication review.[118] Deprescribing is defined as the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes.[119] Screening tools such as the STOPP criteria or structured deprescribing frameworks can support deprescribing.[111,120-122] Deprescribing is safe and feasible in older adults, given close supervision and monitoring by HCPs.[123-126] Attention should be paid to adverse drug withdrawal effects.[125]

Barriers and facilitators to reducing inappropriate polypharmacy

Three systematic reviews have summarised patient-related and HCP-related barriers and facilitators to reducing inappropriate medications, mostly focussing on the perspectives of older patients and primary care practitioners.[127-131] In an issue of Effectiveness Matters on reducing harm from polypharmacy, the barriers and facilitators identified in these three reviews have been categorised according to the the Theoretical Domains Framework (TDF) (Table 3).[127,132] The TDF is a systematic theory-based approach to behaviour change that can be applied to identify key barriers to changing practice and to design interventions to address these barriers e.g. by linking behaviour change techniques to these barriers.[132-134]

Table 3: Factors related to patients and healthcare professionals that influence deprescribing of inappropriate medications, classified according to the Theoretical Domains Framework.[127-131]

Patient-related factors	Healthcare professional-related factors
• Beliefs about the consequences e.g. perceived effectiveness and adverse effects, hope of future benefit, peace of mind from keeping medications and scepticism about non-pharmacological approaches	• Beliefs about consequences e.g. fears about the possible effects of deprescribing
• Intentions e.g. experimenting with medications to understand the effect of stopping	• Knowledge and skills e.g. being unaware of inappropriate prescribing, need for more education in geriatric pharmacology, lacking confidence, feeling insecure, overwhelmed or inadequately prepared
• Goals e.g. prioritising medicines according to their impact on survival, physical functioning, symptom relief	• Beliefs about the capabilities of others e.g. assuming that older people lack health literacy or don't share information about their medicine intake
• Environmental context and resources e.g. lack of consultation time, GP support or clear procedures, dislike of medications, distrust of the system, perceived lack of generalist knowledge or cooperation between specialists, concerns about pharmaceutical industry influence	• Environmental context and resources e.g. lack of time or remuneration, the impact of multiple disease guidelines, lack of communication or clarity about responsibilities among professional groups
• Social influences e.g. perceived pressure from family or healthcare professionals, the need for a trusting relationship and good communication with the GP	• Social influences e.g patient reluctance, professional attitudes favouring more rather than less medications
• Emotion e.g. fear of worsening illness or withdrawal reactions	

2.2 IMPORTANCE OF A PATIENT-CENTRED APPROACH IN MEDICATION REVIEW

Clarification of key concepts

Castro and colleagues have clarified the three concepts of patient participation, patient-centredness and patient empowerment as well as the relationship between these concepts: 'by focusing on patient participation as a strategy, a patient-centred approach is facilitated, which leads to patient empowerment'.[135] Table 4 presents the definition, antecedents, attributes and consequences of each concept. A plethora of terms are used interchangeably in the literature to refer to the concepts of patient participation (=patient engagement, patient involvement) and patient-centred care (person-centred care, client-centred, family-centred).

Table 4: Clarification of key concepts: patient participation, patient-centredness and patient empowerment. Adopted from Castro et al.[135]

Concept	Definition	Antecedents	Attributes	Consequences
Patient participation	**Individual patient participation** revolves around a patient's rights and opportunities to influence and engage in decision-making about care through a dialogue attuned to his preferences, potential and a combination of his experiential and the professional's expert knowledge. **Collective patient participation** is the contribution of patients or their representing organisations in shaping health and social care services by involvement in a range of activities at the individual, organisational and policy level that combine experiential and professional knowledge.	• Information exchange: meaningful, understandable, individually adapted • Education and support for patients and HCPs to ensure both have the right skills, knowledge and attitudes • Positive attitudes of HCP towards patient participation • Facilitating management and supportive care environment (time and financial resources, guidelines)	• Participation in a mix of activities (shared decision-making, representation in official bodies) • Activation of both patient and HCPs is required • Partnership is key, recognition of patients' experiential knowledge, mutual trust and respect	• Impact on quality of care: ↑accessibility, ↑patient safety, ↑patient satisfaction • HCPs: ↑empathy, better communication skills, which in turn results in better informed and empowered patients
Patient-centredness	Patient-centredness is a **biopsychosocial approach** and attitude aiming to deliver care that is respectful, individualised and empowering. It implies the individual participation of the patient and is built on a relationship of mutual trust, sensitivity, empathy and shared knowledge.	• Patient participation: to determine patients' preferred outcomes • Patient-centred communication • Patient-centred organisational culture: positive impact on HCPs' skills • Coordination and continuity of care: interdisciplinary teamwork	• Biopsychosocial perspective: exploring disease and illness experience, holistic care • Patient as a unique person. Empathy, listening, dignity and respect are essential • Sustainable, genuine relationship	• Impact on quality of care: ↑satisfaction, ↑efficiency, ↓healthcare costs • ↑illness-related knowledge and health behaviour, ↑adherence, ↓healthcare utilisation • Improved health outcomes
Patient empowerment	**Individual patient empowerment** is a process that enables patients to exert more influence over their individual health by increasing their capacities **to gain more control** over issues they consider as important. **Collective patient empowerment** is a process that gives groups the power to express their needs and take action to meet those needs and improve their quality of life.	• Dialogue: effective communication, co-creation rather than transfer of knowledge • Patient-centred approach • Enhancing patients' competencies so that they own the knowledge (health literacy), skills, attitudes to make choices • Patient participation	• Enabling process: facilitated by tools, techniques, support • Personal change: people must be able to effect changes (behaviour, but also their social environment and organisations e.g. hospitals) • Patients are self-determinating agents who have the ability for autonomy (↔ paternalism)	• Integrated self: adjustment to patients' long-term condition, sense of inner strength • Sense of mastery & control: including self-management • Improved quality of life: long-term consequence of patient empowerment

From paternalism to partnership in care

Over the last three decades, paternalistic approaches in healthcare are gradually giving way to patient-centred appoaches.[136] In the paternalistic model, the work of HCPs is centred on the intervention plan and patients do not participate much. In patient-centred approaches, the patient is put at the centre of HCPs' work and care is respectful of and responsive to the individual patient's preferences, needs and values.[137] The patient-as-partner approach is rooted in patient-centred initiatives, but takes a step forward into the realm of true partnership in care, where the patient is considered as the primary decision-maker regarding his health and a member of the healthcare team (Figure 2).[136,138] This approach aims to develop the patients' competency in care instead of merely taking into account patients' preferences and experiences.[136]

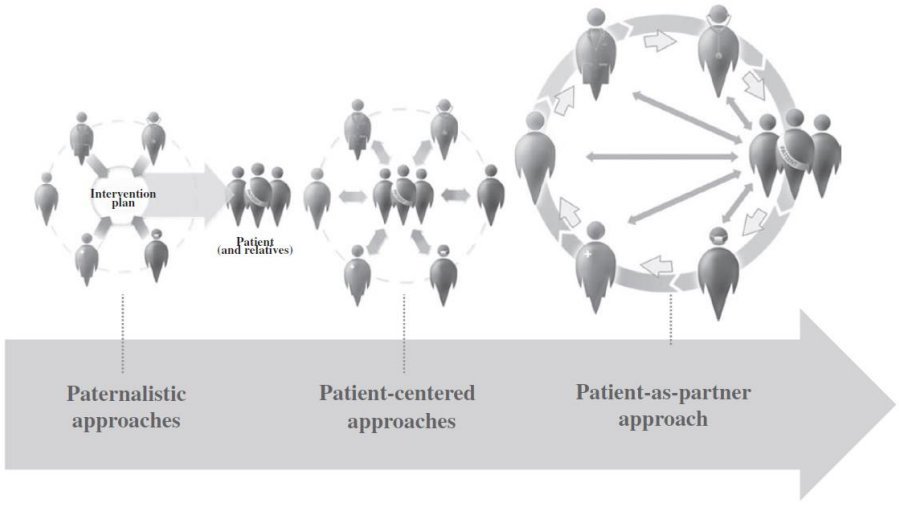

Figure 2: Three patient care models.
©Direction of Collaboration and Patient Parnership, University of Montreal 2013.
Adopted from Karazivan et al.[136]

Patient-centred care is not only ethically appropriate, but has been recognised as a core aspect of high-quality care by the Institute of Medicine.[139] Patient participation or partnership –in clinical decision making (shared-decision making) as well as in the design and implementation of new policies, health systems and services - is argued to be the 'blockbuster drug of the century'.[24,140,141] It is widely believed, although supported by relatively low quality and equivocal evidence, that patient centredness may have beneficial effects on patient experience, health behaviour and health status and may lead to reduced health care costs by avoidance of unnecessary treatment and investigations.[25,139-145] Patient participation in health service design is a powerful lever for quality improvement of health services.[146]

The Montreal model, inspired on the work by Carman et al., is a theoretical framework describing the continuum of patient participation (from information to partnership) at the different levels of the healthcare system (micro-, meso- and macro-level) as well as in education and research (Figure 3).[147,148] The type of patient participation depends on how much information flows between patients and HCPs and how active a role the patient has in decision-making. At the information stage, patients receive information but are not asked for their opinion. At the consultation stage, patients are involved and are being given the opportunity to express their opinion on the situation, but have limited power or decision-making authority. At the partnership stage, patient participation is characterised by shared power and responsibility, with patients being active partners in decision-making and defining agendas.[147] In this thesis, we will focus on shared decision-making (SDM) as a way to engage patients in medication review. SDM is defined as 'an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences'.[137,149]

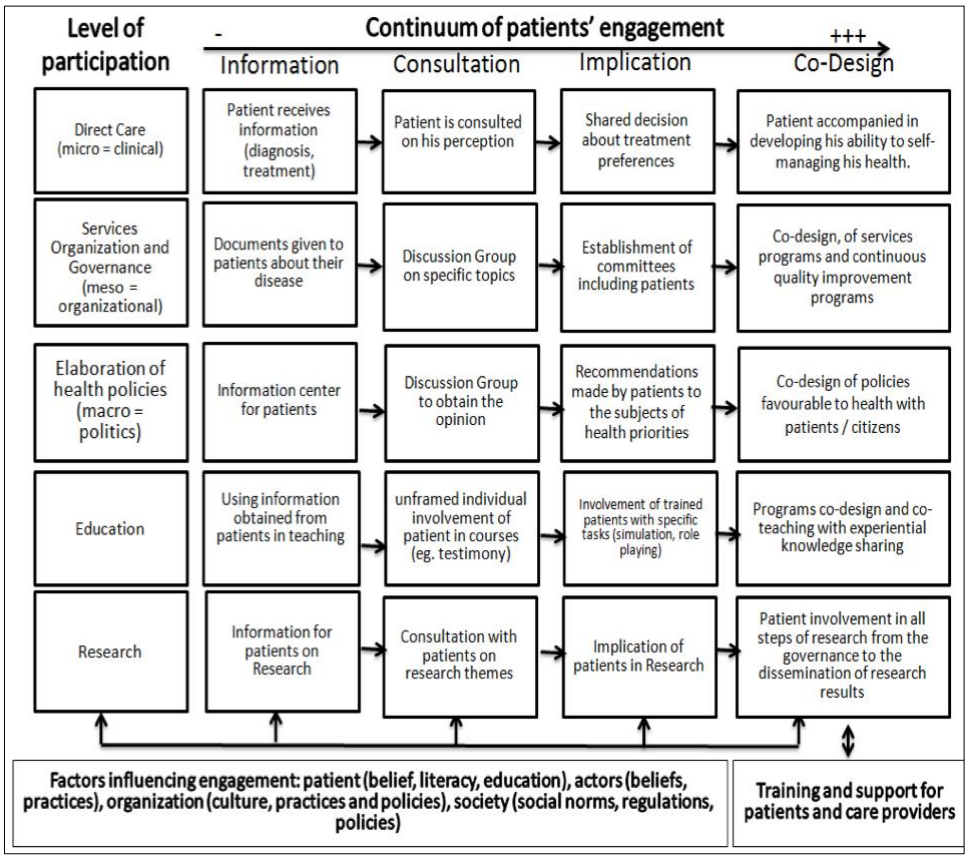

Figure 3: Montreal model describing the continuum of patient participation.
Adopted from Pomey et al.[148]

SDM is most relevant to preference sensitive decisions i.e. when more than one medically reasonable option is available and when there is no best strategy since the option depends on the patient's personal values and preferences.[102] Informing, eliciting and helping patients construct their preferences and priorities is a core aspect of SDM.[150] Preferences refer to healthcare activities (e.g. medications, self-management tasks, healthcare visits, diagnostic testing, procedures) that people are willing and able (or not willing or able) to perform and the care they are willing (or not willing) to receive.[151] Priorities refer to the specific health outcome goals that individuals most desire from their health care given what they are willing and able

to do to achieve these outcome goals (within the context of their healthcare preferences).[151] Decision aids are often used to support patients and HCPs in SDM by making decisions explicit, providing information about options and associated benefits/harms and helping clarify congruence between decisions and personal values and preferences.[152]

Through the use of patient decision aids, which are often considered as proxies for SDM, patients feel more knowledgeable, are better informed and are clearer about their values, have accurate risk perceptions, may have a more active role in decision-making and SDM may improve preference-congruent choices.[152,153] There is increasing evidence that SDM can increase adherence and reduce healthcare costs in some situations, yet further research needs to confirm this.[152,154]

Importance of a patient-centred approach in medication review: Where is the patient we have lost in the diseases?[155]

The need for a patient-centred approach to reduce inappropriate polypharmacy is illustrated in a case report from Carroll and Hassanin, published in JAMA Internal Medicine (Table 5).[156] In this case, inappropriate polypharmacy led to a non-adherence, high treatment burden and a complex treatment regimen resulting in a DRA. Most medications in this case were prescribed in accordance with clinical guidelines and harm was caused by not considering the entire context and individual circumstances of the patient, resulting in inappropriate polypharmacy and multiple hospitalisations. Medicines optimisation in polypharmacy requires more than applying clinical guidelines, but also needs incorporation of patient preferences. Elicitation of patient preferences allows for tailoring the treatment regimen to each patient's individual circumstances, including goals of care and affordability. In this case, the patient's preferences were to minimise pill burden, improve affordability and avoid hospitalisation.[156]

Table 5: Need for a patient-centred approach in polypharmacy: A case of a drug-related readmission. Adopted from Caroll & Hassanin.[156]

An 83-year-old woman with a history of atrial fibrillation and congestive heart failure was admitted to the hospital after presenting with lightheadedness and palpitations, secondary to atrial fibrillation with rapid ventricular response. This was her third admission for atrial fibrillation with uncontrolled heart rate in the past 6 months. Pharmacy records indicated she had not refilled either of her prescribed nodal blocking agents for several months. She was restarted on her reported home dose of metoprolol succinate at 50 mg daily and diltiazem 180 mg daily with prompt normalisation of heart rate. She was discharged the following day. Two days after returning home, the patient presented to the emergency department with a presyncopal episode caused by bradycardia and hypotension after an unintentional metoprolol overdose. She was admitted to the intensive care unit and initiated on a glucagon drip. Her symptoms resolved after 24 hours, and she was transferred to the floor. At discharge, the patient expressed frustration with her home medication regimen, stating that it was confusing, burdensome and expensive. Her pill regimen at home included 11 medications: metoprolol, diltiazem,digoxin, apixaban, atorvastatin, lisinopril, furosemide, ibandronate, loratadine, ranitidine, and a multivitamin. The patient and her family desired to simplify her medication regimen, preferring to continue only those that would help preserve function and keep the patient out of the hospital. At discharge digoxin and atorvastatin were discontinued.

Alignment of treatment recommendations with patient preferences and goals through SDM is particularly important in medication review and to reduce inappropriate polypharmacy in multi-morbid older persons.[5,15,17,122,157,158] Most decisions about stopping, starting, continuing, modifying or selecting medications in medication review in older people with multi-morbidity are preference sensitive. The evidence on the benefit-harm ratio of most medications is limited in this patient population and treatment conflicts (i.e. when the treatment of one condition can result in the worsening of another conditions), treatment burden, time to benefit of medications, prognosis and related patient preferences should be considered in the decision process to minimise harms of overtreatment and burden of care.[5,7,21,122,155,157,159] SDM results in better informed patients who tend to choose more conservative options (e.g. more medication stops, dosage decreases, fewer changes and fewer starts of new medications) facilitating deprescribing and potentially reducing treatment burden.[122,160-162]

Challenges of shared decision-making in older people with multi-morbidity

Despite the advantages of SDM, it remains to become standard clinical practice and several barriers exist to implementation of SDM. Commonly cited barriers from the clinicians' perspective include time constraints, lack of agreement with the applicability of SDM to the patient and to the clinical situation, suggesting that clinicians presume that many patients will not benefit from SDM or to not wish to participate.[163] However it has been shown that clinicians might misjudge patients' desire for participation.[163-165] Patients differ in the extent to which they want to participate in decision-making.[166] There is consensus in the literature that most older people want to participate in decision-making, but they are often not encouraged or enabled to participate in SDM.[167] A systematic review of patient-reported barriers to SDM showed that, in addition to patients' desire for participation, other factors are much more prominent including patient knowledge, power imbalance in the patient-clinician relationship, interpersonal characteristics of clinicians.[163]

Older adults have good experiential knowledge and a strong sense about what matters to them because of a long-standing healthcare experience, however they may face additional age-related barriers to patient participation.[122] Compared to younger people, older people may have more difficulties with understanding information, pay attention to fewer options, tend to focus more on positive information and seek less information.[122] Furthermore, cognitive or communication impairments (hearing loss, speech problems) or poor health literacy or numeracy may further complicate communication, reduce understanding and affect patient participation.[122] Older patients may have strong beliefs that they do not have a role in decision-making, which can be mistaken by clinicians for a lack of interest in patient participation.[164,168]

Communicating uncertainty due to a lack of evidence of the benefits and harms of prescribing/deprescribing medications in older multi-morbid patients is a challenge for clinicians.[122] Most guidelines often only provide generic recommendations on the need for considering patient preferences, but lack specific tools or guidance on how to achieve this.[17,169] The majority of patient education materials and decision aids are not tailored to older people with multi-morbidity, nor are validated in the oldest-old (> 80 years) or in vulnerable people with low health literacy or lower levels of education.[17,153,155,170] Furthermore, deprescribing frequently involves discussions about life expectancy, which may be challenging for clinicians and patients.[122] Prognostic tools or patients' self-rated health might be useful to support estimations of life expectancy to incorporate in SDM.[122]

Elicitation of patient preferences is complex.[150] Preferences may be unstable in complex situations and people construct their preferences as they gain more information.[122,150] Cognitive (how information is presented), emotional and relational factors affect how preferences are constructed.[150] Many clinicians feel uncomfortable commencing conversations about preferences and patients and clinicians vary in their willingness to discuss preferences as part of the clinical encounter.[155,171] Some patients assume that their clinicians already know their preferences.[122] However, studies have demonstrated that clinical guideline or clinicians' recommendations and patient preferences for management of multi-morbidity may be discordant and patient preferences are often misunderstood.[155,172-175] Generic conversation tools to support discussions about patient preferences and goals may support medication-related decision-making in older multi-morbid people and show promise to increase patient participation.[17,176] At the same time, training clinicians in patient-centred communication skills and SDM is paramount.[150]

Practical guidance for SDM to tackle inappropriate polypharmacy

Jansen et al. have outlined four practical steps for SDM about deprescribing in older adults (Table 6).[122] We believe that this guidance would also apply for other types of preference-sensitive decisions in medication review. The four steps include[122]: (i) creating awareness that option exists: the patient and clinician acknowledge that a decision can be made about continuation or discontinuation of medicines and that this requires input from both patient and clinician; (ii) Discussing the options and their potential benefits and harms: this involves ensuring that the patient knows what options exist (including the option to continue medicines) and understands the process of (de)prescribing, the expected benefits and harms of each option and how likely they are to occur; (iii) exploring the patient's preference for the different options: this involves helping the patient identify preferences, priorities and goals regarding (de)prescribing and; (iv) making the decision: deciding whether to (de)prescribe requires incorporation of patient preferences and priorities with information on benefits and harms. Decisions can be made by the patient, collaboratively or deferred to the clinician. Algorithms can support in the process of deciding which medicine to stop first.[120-122]

Table 6: Practical guidance for shared-decision making about deprescribing in older people. Adopted from Jansen et al.[122]

Step	Practical advice
I. Creating awareness that options exist and a decision can be made	• Regularly review medicines; ask about problems, concerns to identify deprescribing opportunities • Explain that there are medication options to consider, including tapering or ceasing • Attitudes to medicines and deprescribing vary widely and need to be actively explored • Establish a trusting relationship before discussing deprescribing • Recognise bias towards the status quo rather than deprescribing; acknowledge this discomfort • When companions are present, check and agree on their role in decision-making • Discuss and agree on the role of the different HCPs in the deprescribing process
II. Discussing the options and their potential benefits and harms	• Improve general understanding: use plain language, avoid medical jargon, use active voice/concrete words, avoid long complex sentences, minimise background noise, face the person when speaking, provide written information, use visual aids, verify comprehension e.g. using the teach-back technique • Improve probabilistic understanding: use absolute risk, simple percentages, or frequencies with a consistent denominator and pictographs • Discuss potential harms of medicines and deprescribing as well as potential benefits • Explain the difference between medicines for prevention *versus* symptom control, health *versus* quality of life as this may be unclear
III. Exploring preferences for (attributes of) different options	• Explore preferences and goals in relation to deprescribing after providing information about potential benefits and harms • Frequently review preferences as they may change over time • Offer to discuss the trade-off between quality and quantity of life but respect those who decline
IV. Making the decision	• Collaborate to find the option that best fits preferences, emphasise that the patients is the expert on his own experience and wellbeing • Support autonomy by eliciting goals and values and offering the opportunity to be involved in or make the final decision • Respect those who want to defer the final decision to others, but encourage them to consider reasons for the decision • Clearly communicate that medicine cessation is provisional, not final, and should be continuously reviewed • Agree on which medicines will be ceased or dose reduced first and the frequency of monitoring and follow-up consultations • Reinstating medicines is one of severable possible outcomes of the discontinuation trial and not a failure

2.3 OPTIMISING THERAPY TO PREVENT AVOIDABLE HOSPITAL ADMISSIONS IN THE MULTI-MORBID ELDERLY: A CLUSTER RANDOMISED CONTROLLED TRIAL OF MEDICATION REVIEW

In line with the call to reduce inappropriate polypharmacy in the ageing multi-morbid population and the need for high-quality trials of medication review, the European OPtimising ThERapy to prevent Avoidable hospital admissions in the Multi-morbid elderly (OPERAM) project was launched in 2015. Part of the research in this thesis was conducted in the context of OPERAM.

The core part of OPERAM is a multi-centre cluster randomised controlled trial (RCT) testing the impact of a complex intervention in the hospital setting (including medication reconciliation, medication review supported by a clinical decision support system integrating the STOPP/START.v_2 criteria, SDM with the patient and communication with the GP) on drug-related *re*admissions as the primary outcome. The OPERAM protocol is described in detail by Adam et al.[177] A study overview and flowchart is presented in Table 7 and Figure 4. Hospitalised patients ≥70 years with ≥3 chronic conditions and concurrent use of ≥5 chronic medications were recruited in four study centres in Bern (Switzerland), Utrecht (The Netherlands), Brussels (Belgium) and Cork (Ireland). The exclusion criteria were reduced to a minimum to allow for maximal generalisability. Only patients planned for direct admission to palliative care, patients having passed a structured medication review within the last two months or patients undergoing a structured medication review other than the trial intervention are excluded.[177]

Patients treated by the same prescribing physician constituted a cluster and clusters were randomised 1:1 to either standard care or the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) intervention with the help of a clinical decision support system (CDSS) called STRIP-Assistant (STRIP-A).[177-179] STRIP is a structured method to conduct a medication review combining implicit and explicit (i.e. the

STOPP/START.v_2 criteria) methods to detect potentially inappropriate prescribing.[111,178] The STRIP-A is a CDSS supporting the pharmaceutical analysis (step 2 of STRIP, see further) by means of (i) taking into account predictable adverse drug reactions, (ii) advising safe and appropriate pharmacotherapy based on the STOPP/START.v_2 criteria, (iii) monitoring clinically relevant interactions, (iv) dosing appropriately in accordance with the patient's renal function.[111,177,179] STRIP-A has been shown to increase the number of correct medical decisions and decrease inappropriate medication decisions.[177,179]

Table 7: OPERAM study population, intervention, control and outcomes.
Adopted from Adam et al.[177]

Population	Older adults (≥70 years) with multi-morbidity (≥3 chronic conditions) and polypharmacy (≥5 regular medications for >30 days).
Intervention	Pharmacotherapy optimisation based on the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) through (i) systematic medication review by a physician and a pharmacist, with support of the STRIP-Assistant (a clinical decision support system taking into account predictable adverse drug reactions, advising safe and appropriate therapy using the STOPP/START criteria, monitoring clinically relevant interactions and dosing appropriately in accordance with renal function); (ii) drug discussion and adaptation with the prescribing physician; (iii) shared decision-making with the patient and (iv) generation of a report with specific recommendations for the patient's general practitioner.
Control	Usual practice and sham intervention using a medication adherence questionnaire by the pharmacist or physician to mimic the intervention and improve blinding of the patient and other team members.
Outcomes	Primary outcome: drug-related readmission within one year after enrolment Secondary outcomes: number of any hospitalisations, mortality, number of falls, quality of life, degree of polypharmacy, activities of daily living, medication adherence, number of significant drug-drug interactions, overuse, underuse and potentially inappropriate medications.

In OPERAM, STRIP was conducted by a duo of a pharmacist and a physician early during the index admission of the study participant of the intervention arm.[177] The nine steps of STRIP are:

1. Structured history taking of medication using a questionnaire based on the medication taken at home: Structured History taking of Medication use questionnaire.[180] (medication reconciliation)
2. Recording of medications and diagnoses in the STRIP-A.
3. Structured medication review including the STRIP-A recommendations by a duo of a pharmacist and physician.
4. Generation of a report with specific recommendations for the prescribing hospital physician (i.e. the patient's treating physician in the hospital).
5. Communication and discussion of the report with the prescribing physician, with possible adaptation of the recommendations. The prescribing physician remained responsible for the final decisions on drug therapy.
6. Shared decision-making (SDM) with the patient to incorporate patient preferences, again with possible adaptation of the recommendations. SDM in OPERAM was inspired on the collaborative deliberation model from Elwyn et al. including: (i) a 'choice talk' (informing the patient that option exists and a decision needs to be made based on what is important to the patient); (ii) an 'option talk' (explaining the options, including the option of *not* changing treatment, the advantages and disadvantages of each option and how likely they are to occur); (iii) a 'preference talk' (discussion of preferences for the different options, supporting the patient in identifying preferences and priorities) and (iv) a 'decision talk' (integrating the patient preferences with evidence on benefits and harms, discussing of the patient's decisional role preference).[122,181,182]

7. Revision based on new data acquired during hospitalisation (e.g. new diagnoses, occurrence of ADRs).
8. Generation of a report with specific recommendations for the patient's GP.
9. Mail delivery of the report to the GP with optional additional direct communication.[177]

The control group received usual care. Patients were partially blinded for allocation to the intervention or control arm. The primary outcome is a drug-related *re*admission, defined as a readmission resulting from an ADE encompassing non-preventable ADR and preventable medication errors including overuse, underuse and misuse of prescription and non-prescription medications. Secondary outcomes include any hospitalisations, all-cause mortality, number of falls, quality of life, degree of polypharmacy, activities of daily living, medication adherence, the number of significant drug-drug interactions, overuse, underuse and potentially inappropriate medications. Patients are followed-up by phone 2, 6 and 12 months after inclusion.[177]

The OPERAM trial started patient recruitment in 2016 and the trial follow-up was completed in 2019.[177] At the time of writing the present thesis manuscript, the final OPERAM trial results were not yet known.

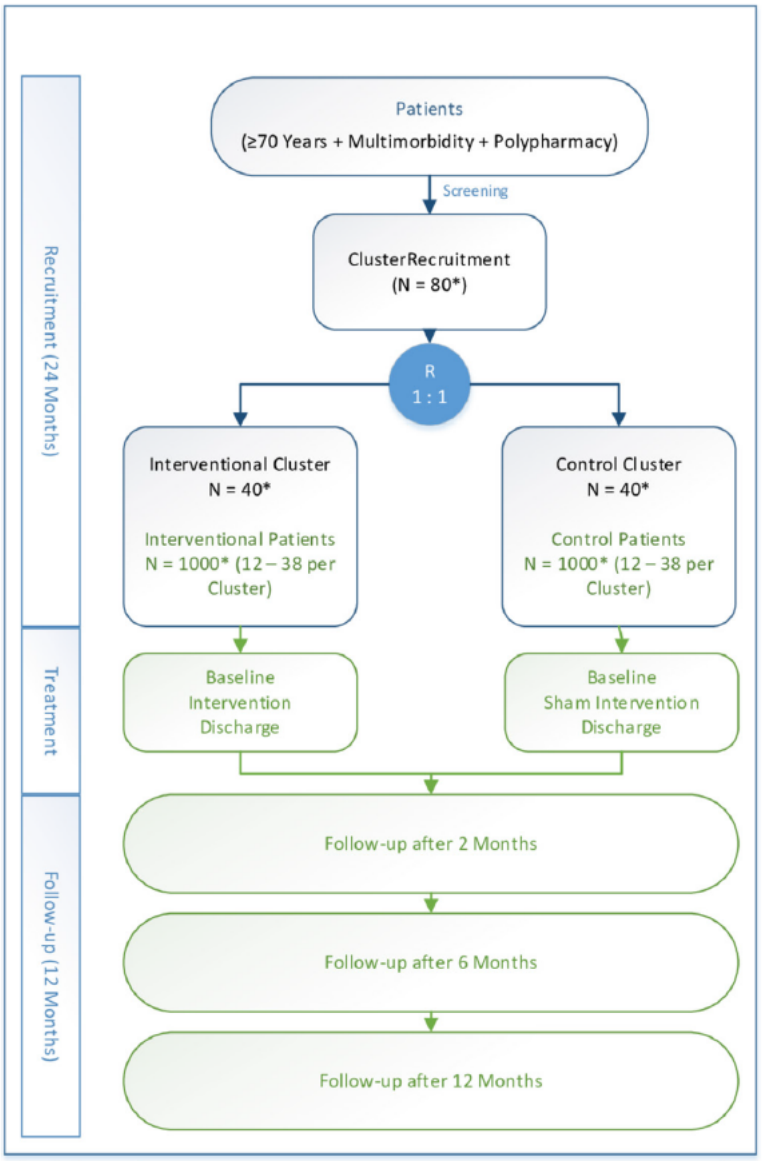

Figure 4: OPERAM study flowchart (*planned numbers).
Adopted from Adam et al.[177]

2.4 STANDARD PRACTICE WITH REGARDS TO MEDICATION REVIEW AND PATIENT PARTICIPATION IN EUROPEAN COUNTRIES

A recent case study of polypharmacy management in nine European countries showed that many polypharmacy management initiatives vary widely across the EU and most countries do not formally address polypharmacy management.[183] A recent survey by Soares et al. showed that medication review services are implemented in 19 out of 34 (55.9%) surveyed European countries, of which six are still in the project phase and so not yet standard practice.[106,184] Medication reviews in the hospital setting are usually conducted as part of clinical pharmacy services, which is the case for the four countries involved in the OPERAM trial.[185,186] However clinical pharmacy services, with a pharmacist working on the ward at least 50% of the time or with pharmacists visiting the ward daily are not very common in European countries, compared to the US for example.[187,188] Only the UK and Ireland have developed these services to a significant extent.[187] In Belgium, the number of hospital pharmacists is limited to 1 hospital pharmacist per 150 beds and structural governmental financing for clinical pharmacy services in hospitals is limited to 0.25 full-time equivalent per 200 beds.[189] In some European countries, various types of medication review services are implemented in community pharmacies such as the 'Polymedication check' for patients with polypharmacy in Switzerland or 'Medicatiebeoordeling' for older patients with polypharmacy with risk factors in the Netherlands.[106-108] In Belgium, research is being conducted on the implementation of medication review in community pharmacies, but this is not yet standard practice.[190,191]

Protecting and promoting patients' rights is crucial to strengthen the patient position in the healthcare system.[192] Patient information and informed consent is a patient right in the four countries involved in OPERAM.[193] The role of patients has been strengthened in many OECD (Organisation for Economic cooperation and Development) healthcare systems, yet patient participation is still limited.[192,194,195] A

positive evolution in OECD countries is the growing role of patient organisations involved in health policy making and increasing collection of patient-reported experience measures (PREMs) to capture patient perspectives as they travel through the health system. However, the use of patient-reported outcome measures to assess patient perceptions of outcomes of care (e.g. quality of life, pain, anxiety) is less developed in OECD health systems.[192]

3 OUTCOMES OF MEDICATION REVIEW THAT MATTER TO OLDER PEOPLE

3.1 CORE OUTCOME SET FOR MEDICATION REVIEW

Outcomes that matter older patients are often lacking in clinical trials.[196,197] The impact of medication review has mostly been evaluated by measuring outcomes such as all-cause hospitalisations, emergency department visits, length of stay and all-cause mortality.[196] However a Delphi study, reflecting the opinions of old and very old persons, healthcare professionals and experts in geriatric pharmacotherapy, showed that these outcomes are not considered essential in medication review in multi-morbid older people.[196] To ensure measurement of outcomes of high relevance to older patients, a core outcome set (COS) has been developed for medication review in older people with multi-morbidity and polypharmacy. Seven core outcomes are recommended to be measured in trials of medication review in older patients with multi-morbidity and polypharmacy: (1) drug-related admissions, (2) overuse, (3) underuse, (4) potentially inappropriate medications, (5) clinically significant drug-drug interactions, (6) health-related quality of life and (7) pain relief.[196] The patient perspective was decisive for the inclusion of certain outcomes in the COS. For instance, where 89% of patients in the Delphi study selected the outcome 'pain relief' for inclusion in the COS, 77% of experts had rejected it.[196]

3.2 DRUG-RELATED ADMISSIONS

Why is it important?

In Chapter I of this thesis, we will focus on the measurement of DRAs. DRAs are the primary outcome in the OPERAM trial and it was the outcome with the highest rate of agreement among older patients, HCPs and experts in the COS for medication review.[196] Furthermore, measuring DRAs is potentially an important issue in the light of the WHO's Global Patient Safety Challenge on medication-related harm, of which one of the objectives is to assess the scope and nature of avoidable harm and to strengthen the monitoring systems to detect and track this harm.[198]

Despite the magnitude of the problem of DRAs and complexity of identifying DRAs in older people, no standardised and validated method to identify DRA in older people existed. In **Chapter 1.1**, we describe the development and validation of the first method to detect DRAs in older people.[199] Short after the publication of our method, another tool called the Assessment Tool for Hospital Admissions Related to Medications, was published in the context of the Medication Reviews Bridging Healthcare (MedBridge) trial.[52] The two tools are discussed and compared in the general discussion of this thesis. In **Chapter 1.2**, we evaluated the inter-rater reliability of DRA adjudication between four adjudication teams in the OPERAM trial. In **Chapter 1.3**, we performed a cross-sectional study to determine the prevalence and types of DRAs related to inappropriate prescribing detected by the STOPP/START criteria.[111,116]

3.3 PATIENT EXPERIENCE

In Chapter 2.1, we performed a multi-centre mixed methods study embedded in the OPERAM trial, to explore the patient experience of medication review and hospital-initiated medication changes in intervention and control groups. Patient experiences are patients' perceptions of the process of care (rather than the outcome), including satisfaction (e.g. satisfaction with information given,) subjective experiences (e.g. pain control), objective experiences (e.g. waiting times) and observations of HCPs' behaviour (e.g. whether or not the patient received discharge information).[138] There is lack of a universally agreed-upon definition of patient experience but core aspects associated with a positive patient experience include: involvement of patients and companions in decision-making, respect for patient preferences, clear information and communication, emotional support, physical comfort, transparency, care coordination, continuity and access to care.[145,200-202] The concept patient experience should be separated from satisfaction, which is only one aspect of patient experience.[138] Patient experience refers to a totality of a patient's care, including the appropriateness of care and the degree to which it meets the patient's needs and goals, rather than only the immediate satisfaction it provides.[25,203]

Why is it important?

Beyond evaluating effectiveness of the OPERAM intervention (drug-related admissions), qualitative research alongside trials can help to better understand implementation of the intervention, contextual factors and mechanisms affecting intervention effectiveness.[204,205] Evaluating the patient experience can provide a 'whole-system perspective' not readily available from effectiveness and safety measures, may reveal aspects that are invisible to researchers and can help identify strengths and weaknesses of services to improve quality.[138,145,203,206] Unlike clinicians, patients have expertise in the realities of their condition, the impact of the disease

and its treatment in daily life and how services should be designed to help them.[140,146,203] Evaluating the patient experience provides a measure of the extent to which care is patient-centred.[202]

Furthermore, patient experience or patient-centredness is considered as one of the core aspects of high-quality care, besides clinical effectiveness and patient safety.[202,206] Patient experience measures are used to drive improvement in quality of care by transforming health systems and services into a more patient-centred model.[138] Whereas a positive patient experience is an important goal in its own right, a rapidly accumulating body of evidence supports the measurement of patient experience.[145,202,207] A systematic review demonstrated the correlation between a positive patient experience and patient safety and clinical effectiveness (e.g. self-rated and objectively measured health outcomes, adherence to medication and medical advice, health behaviour, improved safety practices and reduced resource use) across a wide range of study designs, settings, population groups and outcome measures.[145] A positive patient experience including satisfaction with in-hospital care, being listened to by doctors, follow-up appointment scheduling and readiness for discharge is associated with reduced readmission rates.[145,208,209]

Measuring patient experience

An evidence scan on measuring patient experience by The Health Foundation summarised the different approaches to measure patient or carer experience.[210] The different approaches can be divided according to the depth of information they provide and the extent to which they collect information that may be generalisable to a wider population (Figure 5).[210] There is no single best measurement approach and selecting the method depends on the objective and context of measuring patient experience. In our mixed methods study embedded in OPERAM, we used semi-structured interviews to gain an in-depth understanding of patient experience

and to identify patients' needs, preferences, barriers and facilitators underlying medication review.

The main limitation of measuring patient experience is that experience is influenced by expectations, which in turn depend on preferences, personality and previous experiences with healthcare and treatments. This is especially the case for patient satisfaction measures.[138]

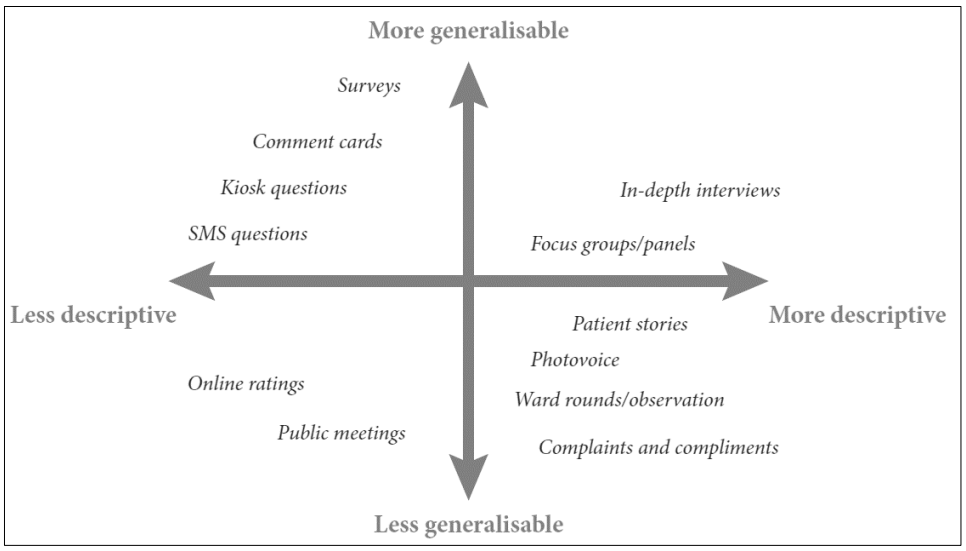

Figure 5: Examples of approaches to measure patient and carer experience of health services. Adopted from de Silva et al.[210]

3.4 MEDICATION-RELATED PREFERENCES

Why is it important?

Along with the shift towards patient-centred care and increasing health policy interest for SDM, research on patient preferences and goals in multi-morbidity is a research priority.[22,154,172,211] It has been argued that there is a disproportional focus on the 'patient information' dimension of patient-centred care, whereas other dimensions such as respecting patient values and preferences have received less attention.[138] Despite the fact that eliciting patient preferences is central to SDM, in a review of SDM only 67% of studies identified 'patient preferences/values' as a component of SDM.[212] Many clinicians feel uncomfortable commencing conversations about preferences and patients and clinicians vary in their willingness to discuss preferences as part of the clinical encounter.[155,171] Moreover, studies have demonstrated that clinical guideline or clinicians' recommendations and patient preferences and priorities for management of multi-morbidity vary and can be an area of disagreement.[172-175] The current void of knowledge on patient preferences in older patients with multi-morbidity and polypharmacy leads to missed opportunities for patient-centred decision making. As a perspective for **Chapter 2.2**, we outline the protocol for a scoping review aiming to synthesize the evidence on multi-morbid older persons' preferences and attributes of preferences for stopping (deprescribing), starting, continuing, modifying or selecting medications in medication review and to identify methods to elicit medication-related preferences in multi-morbidity. Aggregate data on patient preferences are not a substitute for individual patient preferences in clinical encounters. However, collective patient preferences may help to guide clinicians in having preference conversations with their patients in clinical practice and may close the gap between what patients prefer and what clinicians think patients prefer.[172]

Measuring alignment of drug therapy with patient preferences

Patient-reported outcome measures that capture alignment of care with patient preferences and goals has been advocated as a highly relevant in multi-morbidity as well in the context of medicines optimisation.[213-216] Goal attainment scaling (GAS) is a valid and reliable tool for quantification of patient goals and measuring improvement towards these goals and has been shown to be feasible in older people with multi-morbidity.[216] Despite being a core element of medication review, alignment of the drug regimen with the patient preferences has been rarely investigated in trials of medication reviews.[102,197] The recent DREAMeR (Drug use Reconsidered in the Elderly using goal Attainment scales during Medication Review) study, a randomised controlled trial of goal-oriented medication review in older people, was the first to use goal attainment scaling (GAS) as an outcome measure in medication review.[215] Their findings support the use of GAS as an outcome measure in goal-oriented medication review studies. In addition to the patient-reported outcomes 'health-related quality of life' and 'pain' identified in the COS, alignment of drug therapy with patient preferences (e.g. through the use of GAS) should be considered as an additional relevant patient-reported outcome in trials of medication review.

3.5 RESEARCH OBJECTIVES

Quality of care has been defined by the World Health Organisation as the extent to which healthcare services improve *desired* health outcomes.[217] Definitions of healthcare quality differ across institutions but clinical effectiveness, safety and patient-centeredness are defined as core aspects of high quality care and are common to most quality frameworks.[218] These outcomes are intertwined since a positive patient experience is associated with clinical effectiveness and safety including reduced readmission rates.[145,208]

This thesis aims to inform medication review in older people with multi-morbidity by measuring outcomes that matter to patients in relation to clinical effectiveness, safety and patient-centredness. Specific research objectives include (Figure 6):

I. To develop a standardised chart review method to identify drug-related hospital admissions in older people (Chapter 1.1 & 1.2)
II. To compare the prevalence and types of drug-related admissions associated with the STOPP/START criteria v_1 and v_2 (Chapter 1.3)
III. To explore multi-morbid older people's experience of hospital-initiated medication changes and medication review (Chapter 2.1)
IV. To synthesize the evidence on multi-morbid older persons' preferences and attributes of preferences for stopping (deprescribing), starting, continuing, modifying or selecting medications and to identify methods to elicit medication-related preferences in multi-morbidity (Chapter 2.2)

Objectives I and III were undertaken in the context of the OPERAM trial. Details on (personal) contributions to each research part can be found in **Appendix 2**.

This research filled several knowledge gaps in relation to medication review in older people with multi-morbidity. We contributed to better a measurement and understanding of DRAs, a core outcome of medication review important to older patients.[196] Furthermore, we increased the knowledge on multi-morbid older people's experience of and preferences for medicines optimisation. Our findings pave the way for medication review services to become more tailored to multi-morbid older people's needs and preferences.

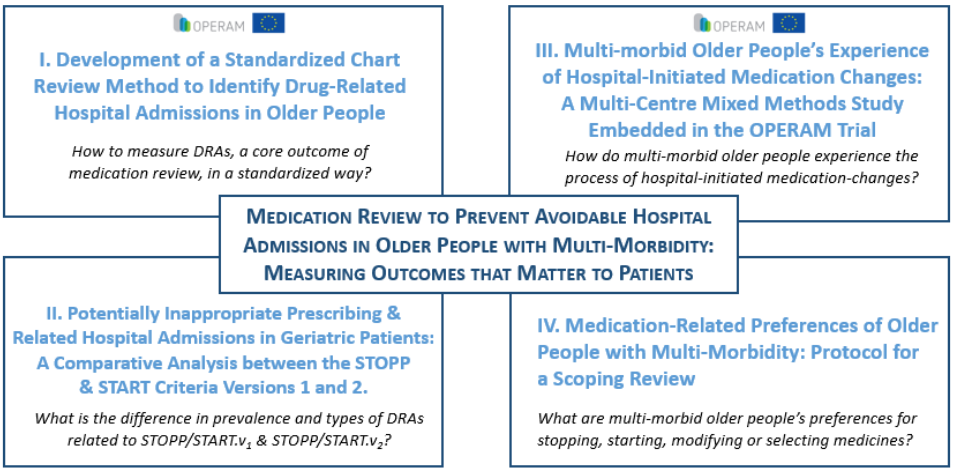

Figure 6: Research objectives

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CHAPTER I
DRUG-RELATED ADMISSIONS

CHAPTER 1.1

DEVELOPMENT OF A STANDARDISED CHART REVIEW METHOD TO IDENTIFY DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PEOPLE

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British Journal of Clinical Pharmacology 2018; 84: 2600-2614

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Drug-related hospital admissions represent a growing patient safety threat in older people.
- Identifying drug-related hospital admissions in older people is complex and there is lack of a standardised approach to identify drug-related hospital admissions.

WHAT THIS STUDY ADDS

- We developed a standardised chart review method to measure drug-related hospital admissions in older persons.
- Content validity, feasibility of use and inter-rater reliability were found to be satisfactory.
- The method can be used as an outcome measure for interventions targeted at improving quality and safety of medication use in older people.

ABSTRACT

Aims: We aimed to develop a standardised chart review method to identify drug-related hospital admissions (DRAs) in older people caused by non-preventable adverse drug reactions and preventable medication errors including overuse, underuse and misuse of medications: the DRA adjudication guide.

Methods: The DRA adjudication guide was developed based on design and test iterations with international and multidisciplinary input in four subsequent steps: literature review; evaluation of content validity using a Delphi consensus technique; a pilot test and a reliability study.

Results: The DRA adjudication guide provides definitions, examples and step-by-step instructions to measure DRAs. A three-step standardised chart review method was elaborated including (i) data abstraction; (ii) explicit screening with a newly developed trigger tool for DRA in older people; and (iii) consensus adjudication for causality by a pharmacist and a physician using the World Health Organisation-Uppsala Monitoring Centre and Hallas criteria. A 15-member international Delphi panel reached consensus agreement on 26 triggers for DRAs in older people. The DRA adjudication guide showed good feasibility of use and achieved moderate inter-rater reliability for the evaluation of 16 cases by four European adjudication pairs (71% agreement, κ=0.41). Disagreements arose mainly for cases with potential underuse.

Conclusion: The DRA adjudication guide is the first standardised chart review method to identify DRAs in older persons. Content validity, feasibility of use and inter-rater reliability were found to be satisfactory. The method can be used as an outcome measure for interventions targeted at improving quality and safety of medication use in older people.

INTRODUCTION

Adverse drug events (ADEs) are a leading cause of iatrogenic harm globally.[1,2] A significant proportion of ADEs results in hospitalisation and these so-called drug-related hospital admissions (DRAs) have serious clinical and economic consequences.[3-6] DRAs can result from non-preventable adverse drug reactions (ADRs) or from preventable medication errors.

Older adults have almost a seven-fold increased risk of experiencing a DRA compared to younger persons due to several risk factors such as multi-morbidity and polypharmacy.[7] Around 70% of DRAs in older people are caused by potentially preventable ADEs mainly resulting from poor medication adherence and inappropriate prescribing.[8-13] The latter includes the prescription or use of more drugs than are clinically needed (overuse), the incorrect prescription or use of drugs that are needed (misuse) and the failure to prescribe or use drugs that are needed (underuse).[14] Identifying DRAs in older people is challenging because ADEs often present as common geriatric problems such as falls, confusion or renal impairment which might be due to the ageing process, underlying diseases or medications.[13,15]

No standardised and validated method to identify DRAs in older people exists in the literature. Yet measuring DRAs is potentially an important issue in the light of the World Health Organisation's (WHO's) Global Patient Safety challenge on medication-related harm.[2] Studies have reported DRA prevalence rates ranging from 6% to 50% of all admissions in older adults.[16-20] The wide variance in prevalence rates is associated with the considerable heterogeneity in definitions and methods used to identify DRAs, the study population and the setting.[20,21] DRA identification often relies on a highly subjective and variable process and few attempts have been made to measure DRA resulting from underuse of medications.[12,19,22,23]

We aimed to develop a standardised chart review method to identify DRAs resulting from ADRs, overuse, misuse and underuse of medications, specific to older people: the DRA adjudication guide. In this paper we present the developmental pathway of the DRA adjudication guide and the evaluation of its content validity, feasibility of use and reliability, which are defined as desirable attributes of a quality measure by the Agency for Healthcare Research and Quality.[24]

The DRA adjudication guide will be used in four European centres to measure the primary outcome DRAs in the OPERAM trial (http://operam-2020.eu) that will assess the impact of a pharmacotherapy optimisation intervention in 2000 multi-morbid older people.

METHODS

Design

The DRA adjudication guide was developed in four steps: (i) the first draft of the guide was developed based on literature review; (ii) this version was subsequently refined based on evaluation of content validity by an expert panel; (iii) user-feedback in a pilot test and (iv) a reliability study (Figure 1).

Literature review

Two literature searches were performed in PubMed by the first author for articles published between 1 January 1990 and 1 August 2015. Screening of titles and abstracts and data extraction was performed by the first author.

A first exploratory search aimed to review existing structured ADE or DRA identification approaches to inform the development of the overall DRA identification strategy. The search included the following medical subject headings (MeSH): 'Patient admission', 'Drug-related side effects and adverse reactions', 'Quality assurance, Health Care', 'Patient outcome assessment'. Studies published in

English, French or Dutch that focused on defining, identifying and/or characterising ADEs or DRAs in the adult in-hospital setting were included.

A second literature search aimed to review common causes for DRAs in older people to inform the development of a trigger tool for DRAs in older people for inclusion in the DRA adjudication guide. To improve efficiency and to standardise identification of ADEs, trigger-based chart review has been advocated as the premier ADE identification approach.[25-27] Triggers are defined as *occurrences, prompts or flags* found upon chart review that *trigger* further investigation to determine the presence or absence of an adverse event.[28] Trigger tools have been designed for a variety of clinical settings but to our knowledge, no trigger tool for identifying DRAs in older people exists. To compile a preliminary trigger tool, the second literature search aimed to identify common causes for DRA in older people and to review previously developed adverse event triggers tools designed for other settings. PubMed was searched using the following search terms and/or combinations: 'Aged'[MeSH], 'Drug-Related Side Effects and Adverse Reactions'[MeSH], 'Hospitalization'[MeSH], 'Trigger'[All fields], 'Adverse drug events trigger tool'[All fields], 'Pharmaceutical preparations'[MeSH], 'Underuse'[All fields], 'Prescribing omission'[All fields]. Studies on hospitalisations in people aged ≥65 years resulting from preventable ADEs and non-preventable ADRs were included. Studies on the development or evaluation of adverse event trigger tools designed for other settings were also included. Studies on DRAs in patients younger than 65 years were excluded. Trigger tool studies focusing on specific patient groups such as surgical patients were also excluded.

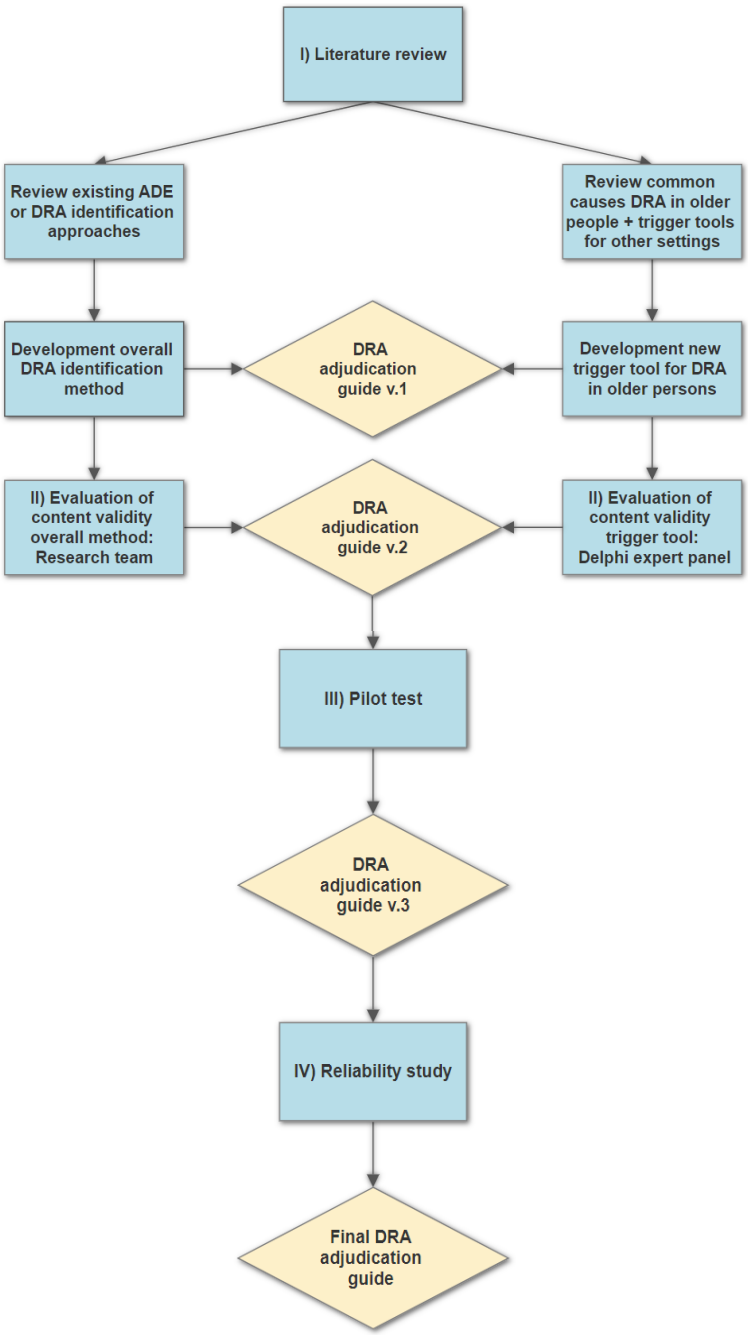

Figure 1: DRA adjudication guide development process
ADE, adverse drug event; DRA, drug-related admission

A data extraction form was developed to document study characteristics including study aims, population, design, setting, methods used to detect ADEs or DRAs, causality algorithms used, professionals involved in ADE or DRA assessment, most frequent causes of DRAs, most frequent medications involved or omitted in DRAs, triggers and their positive predictive value.

Evaluation of content validity

Content validity refers to the relationship between an instrument's content and the construct it is intended to measure.[29] In the absence of a gold standard to measure DRAs, content validity of the DRA adjudication guide was assessed by an expert panel.

First, the overall DRA identification method suggested by the guide was agreed on a consensus basis through face-to-face discussions by three physicians (B.B., J.B.B., J.D.) and two clinical pharmacists (A.S., O.D.) with expertise in geriatric pharmacotherapy and medication safety.

Secondly, a two-round online modified Delphi survey using LimeSurvey® software was conducted to validate the triggers derived from the literature review. The Delphi method is a consensus technique that is widely used for questions addressing medication safety in older adults.[30] A modified online two-round Delphi survey was selected in this study as a way to combine scientific rigor and pragmatism to obtain consensus from a geographically diverse expert panel. Experts were selected based on their recognised academic or clinical expertise on the subject of drug-related morbidity in older patients or were personal contacts. Of the 29 experts invited, respectively 15 and 14 experts from eight different countries took part in the first and second Delphi round (Table 1).

Table 1: Characteristics of Delphi panellists

	Experts invited n (%)	Participation Round 1 n (%)	Participation Round 2 n (%)
Total	29 (100)	15 (52)	14 (48)
Profession, area of expertise			
Physician, geriatric medicine	10 (34)	6 (40)	6 (43)
Physician, internal medicine	8 (28)	2 (13)	2 (14)
Physician, primary care	1 (3)	-	-
Pharmacist, geriatric medicine	5 (17)	4 (27)	3 (21)
Pharmacist, medication safety	5 (17)	3 (20)	3 (21)
Country			
Belgium	5 (17)	5 (33)	4 (29)
Canada	1 (3)	1 (7)	1 (7)
Italy	1 (3)	-	-
Ireland	2 (7)	1 (7)	1 (7)
France	2 (7)	1 (7)	1 (7)
Switzerland	4 (14)	2 (13)	2 (14)
The Netherlands	6 (21)	3 (20)	3 (21)
United Kingdom	2 (7)	1 (7)	1 (7)
United States	6 (21)	1 (7)	1 (7)
Sex			
Female	15 (52)	9 (60)	8 (57)
Male	14 (48)	6 (40)	6 (43)

The Delphi panel was asked to assess the content validity of the preliminary trigger tool, to develop consensus on the most relevant triggers and to identify additional triggers. Furthermore the panel was asked to assess two screening questions for non-triggered, spontaneously detected events. In the first Delphi round, participants were asked to rate for each of the 29 triggers derived from the literature and for the two screening questions, the *relevance to screen for a DRA in older people* on a five-point Likert scale (ranging from *absolutely irrelevant* to *absolutely relevant*; relevance was defined as *the degree to which the item comprehensively includes the full scope of the outcome it intends to measure*). A free-text field was provided for each item, allowing comments to improve the trigger design or to suggest new triggers.

For each item, consensus measurement was based on the median Likert response and the interquartile range. The following cut-off values of consensus were defined before data analysis: consensus that a trigger should be retained if the median score on the five-point Likert scale was ≥4 and the 25th percentile ≥4 (i.e. ≥75% of the experts considered the trigger as *relevant* or *absolutely relevant*); consensus that a trigger should be excluded if the median score was <3 and the 75th percentile <3 (i.e ≥75% of the experts considered the trigger as *irrelevant* or *absolutely irrelevant*); no consensus for triggers that failed to meet either of the latter cut-off values.

Triggers that were accepted or rejected unanimously after the first round were not presented in the second round. In the second Delphi round, participants were asked to rate the triggers for which revisions were suggested in the first round. Furthermore, participants were asked to re-evaluate the equivocal triggers on the five-point Likert scale, taking into account the groups' responses. Participants were provided with a reminder of their own responses from round 1, the median group rating and interquartile range and a summary of the comments made by participants. Equivocal triggers that were rated equivocal again, were not included in the final trigger tool (See BJCP online supporting information S1).

Pilot test

A pilot test was performed aimed at ensuring that the newly developed DRA adjudication guide was a workable instrument and to identify points for improvement. For this purpose, the DRA adjudication guide was piloted independently by a geriatrician and a pharmacist from one centre (J.B.B., S.T.). For the pilot test, 15 cases from a medical record database of frail older patients admitted to a teaching hospital were randomly selected by using a random number generator. The reviewers' suggestions for improvement were discussed within the

OPERAM research team and modifications were subsequently implemented in the DRA adjudication guide.

Reliability study

A reliability study was conducted to assess whether the DRA adjudication guide yields reproducible results when applied by different raters. Raters were OPERAM research team members with clinical and/or research experience in geriatric medicine. Pairs of raters in three centres (Brussels, Cork and Utrecht) consisted of a pharmacist and physician (S.M., F.V., I.W., A.V., S.C., D.O.M.) whereas in one centre (Bern) the pair was composed of physicians only (C.F., C.S.). The raters had no prior experience in using the DRA adjudication guide and were provided with a video training tutorial (https://www.youtube.com/watch?v=fadmO-WcCHM).

For the purpose of the reliability study, each centre provided four cases of multi-morbid older patients including the discharge and/or admission letter, laboratory values and medication lists. Translation of the cases was performed by OPERAM research team members from their mother tongue (Dutch, French, Swiss-German) to English. No formal back-translation process was undertaken.

Raters were asked to first assess the cases individually and subsequently to come to a consensus result on the case within the pair. The time needed to adjudicate a case was recorded. A dichotomous outcome variable (DRA identified yes/no) was defined and inter-rater reliability (IRR) was determined by calculating percentage agreement and agreement corrected for chance *between* pairs of raters from four European centres (Fleiss' κ) as well as *within* each pair (Cohen's κ) for the dichotomous outcome variable. Kappa values were interpreted as slight agreement if <0.20, fair agreement if 0.21–0.40, moderate agreement if 0.41–0.60, substantial agreement if 0.61–0.8 and almost perfect agreement if 0.81–1.00.[31] Next, adjudication results and discrepancies were shared among all raters, who were asked for feedback. The

primary goal was to determine whether discrepancies were due to difficulties in using the adjudication method, missed information or case interpretation.

Ethics approval

The ethics committee from the Cliniques universitaires Saint-Luc (Brussels, Belgium) provided approval for anonymous use of the medical record database (reference number B403201111806).

RESULTS

Literature review and development of the DRA adjudication guide

Development of the overall DRA identification strategy

Twenty-five studies on ADE or DRA identification were reviewed.[3,7,12,26,27,32-51] Chart review by two or more reviewers has been considered as a gold standard in many patient safety studies because of its high ADE yield and high specificity.[32] To evaluate the relationship between drug treatment and the occurrence of an adverse event, several causality assessment methods have been developed. No causality assessment method is universally accepted but expert judgement is the most widely used.[47] Chart review is however often conducted in an implicit and unstructured way, resulting in low IRR.[32] Our method selected to adjudicate DRAs therefore involved a structured chart review with the aid of a trigger tool to improve efficiency and standardisation in ADE detection.[25] Previous research has demonstrated that by restricting ADE detection to trigger tools only, whole classes of ADE can be missed.[32,52,53] Therefore two screening questions for non-triggered, spontaneously detected events were also compiled. The screening questions are general questions designed to help screen for potential DRAs caused by ADRs, overuse, underuse and misuse of medications, not listed in the trigger tool.

A three-step approach for DRA identification based on chart review was elaborated (Figure 2). The three steps include: (i) data abstraction from the medical record into an electronic case report form, the main source documents including the admission and discharge letter, laboratory values and medication lists; (ii) explicit screening for ADE(s) that are potential DRA with the DRA trigger tool and screening questions for non-triggered events; and (iii) adjudication: consensus judgement in terms of ADE causality and ADE contribution to hospital admission with the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) and Hallas criteria respectively.[36,54] Steps 2 and 3 are performed by an adjudication pair composed of a pharmacist and a physician, given their complementary knowledge and experience.[55,56] Definitions, instructions for use and examples are contained in the DRA adjudication guide (See BJCP online supporting information S2).

Development of the trigger tool

Twenty-three studies on common causes of DRAs in older people[3,7-10,12,16,23,38,51,57-69] and 12 trigger tools studies were reviewed.[30,52,53,70-78] Based on the information from the literature and their own clinical expertise, the research team compiled a preliminary list of 29 triggers and two screening questions for non-triggered events related to ADR, overuse, underuse or misuse of medications. Considerations for selecting the triggers were the reported positive predictive value of the triggers, severity (i.e. the trigger should be severe enough to result in hospitalisation) and ease of detection. The triggers were divided in three categories: diagnoses, abnormal laboratory values and *other* triggers (e.g. antidote use). Each trigger was elaborated with potential causative drugs or potential causes for drug underuse based on the STOPP/START criteria version 2 and by consulting pharmacology and pharmacotherapy references.[79] Consequently, each trigger consists of a diagnosis or abnormal laboratory value and a corresponding list of potential causative drugs or causes for drug underuse, allowing explicit chart screening for DRAs.

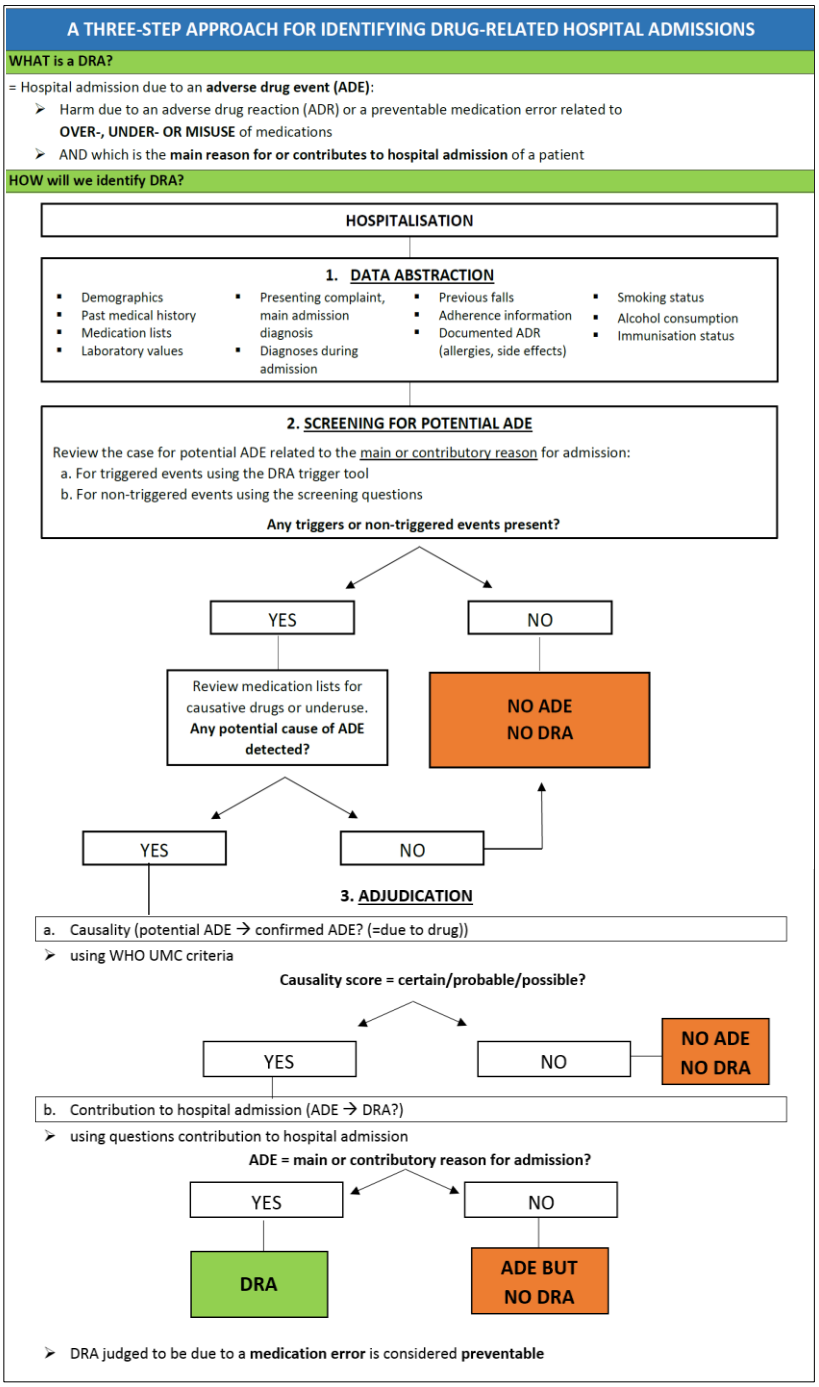

Figure 2: Three-step approach for identifying DRAs

Evaluation of content validity

None of the 29 triggers or screening questions were removed at the end of the first round by the 15-member Delphi panel. Twenty-five triggers and two screening questions for non-triggered events were rated *relevant* or *absolutely relevant* to screen for DRAs in older people. Of the items on which the group agreed, 10 triggers and two screening questions were adopted without alteration in the final tool, whereas 15 triggers were revised according to the participants' suggestions. Revisions included changing cut-off thresholds of laboratory values, adding or removing medications associated with a trigger or adding more detail to the triggers. Four triggers (theophylline level >20 μg/ml, rash, *Clostridium difficile* toxin positive stool, neutrophils <1400/mm³) were rated equivocal.

After the second round, all 15 triggers with revisions were rated *relevant* or *absolutely relevant*. Three out of four equivocal triggers from the first round were rated equivocal again and these were removed from the trigger tool. The trigger neutrophils <1400/mm³ was now rated relevant and was included in the final trigger tool (See BJCP online supporting information S1). Following last refinements, the final 26-item trigger tool was created (Table 2).

Table 2: Trigger tool for drug-related hospital admissions in older persons

TRIGGER TOOL TO SCREEN FOR DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PERSONS		
Trigger on admission up to 48h of admission	**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 ☐ Anticholinergic drugs[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?	

Table 2 (continued): Trigger tool for drug-related hospital admissions in older persons

Confusion/delirium[b]	**Use** of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Antipsychotics ☐ Anti-epileptics ☐ Antihistamines (H1- and 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 anticholinergic drugs[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[b]	**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*)

Table 2 (continued): Trigger tool for drug-related hospital admissions in older persons

Bleeding[b]	**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 20-40 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? *	

Table 2 (continued): Trigger tool for drug-related hospital admissions in older persons

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*):

Table 2 (continued): Trigger tool for drug-related hospital admissions in older persons

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)
Hyperglycaemia (blood glucose > 11 mmol/L or 198 mg/dl)	**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*):

Table 2 (continued): Trigger tool for drug-related hospital admissions in older persons

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/µL	**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/µL	**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/µL	**Use** of any of the following drugs? ☐ Ganciclovir ☐ Antipsychotics (mainly clozapine) ☐ Thyreostatics ☐ Thienopyridines (mainly ticlopidine)	☐ Chemotherapy (*Please specify):* ☐ Other (*Please specify*):

Table 2 (continued): Trigger tool for drug-related hospital admissions in older persons

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; FEV_1, forced expiratory volume in 1 second; ESH/ESC, European Society of Hypertension/European Society of Cardiology; 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 properties is available in the DRA adjudication guide

[b]Detailed definition of trigger available in the DRA adjudication guide (See BJCP online supporting information S2)

Table 2 (continued): Trigger tool for drug-related hospital admissions in older persons

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)	☐ Wrong drug
☐	Overuse of medication(s) (drug without an indication, too long duration of therapy, therapeutic duplication)	☐ Wrong dose (supratherapeutic or subtherapeutic)
☐	Inappropriate discontinuation (removal or dosage decrease) leading to physiological withdrawal signs/symptoms or return of the underlying disease signs/symptoms	☐ 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	☐ Suspected adherence concerns
☐	Too short duration of medication therapy	

Pilot test

The two reviewers involved in the pilot considered the trigger tool as a workable instrument for screening for DRAs. The same sets of triggers were identified by the two reviewers, however adjudication of DRA was the part where most discrepancies arose. Based on feedback from the reviewers, the following modifications were made after the pilot:

- The Naranjo algorithm and Therapeutic Failure Questionnaire[63,80], which were proposed as causality algorithms in the DRA adjudication guide v.1, were replaced by the WHO-UMC causality criteria because they reflect clinical practice better. The WHO-UMC criteria were adapted to allow causality assessment due to medication underuse in line with Klopotowska et al.[32]
- Discharge medications were added to the list of data to abstract to aid in the detection of potential underuse.
- The DRA identification strategy and instructions for use were adapted to the process that both reviewers considered as most practical.

Reliability study

Table 3 provides the level of agreement on the presence of a DRA between all centres and within each pair per centre for 16 cases. The DRA adjudication guide achieved a moderate IRR score *between* adjudication pairs from four European centres (71% agreement, Fleiss' κ=0.41). Agreement *within* each pair varied from fair to almost perfect agreement (69%–94% agreement, Cohens' κ=0.33-0.86). The mean time needed to assess a case individually was 23±6 minutes and the mean time needed for consensus discussion was 13±5 minutes.

No differences in IRR for DRA identification were observed for triggered and non-triggered cases. Detailed analysis of the adjudication results showed that in the majority of cases the same triggers and potential ADEs were identified but discrepancies arose mainly on the level of assessment of contribution to hospital admission. Discrepancies arose for eight cases with more subjective assessments including five triggered cases with potential underuse, two triggered cases with contributory reasons for admission (i.e. an ADE that is not the main reason for admission but plays a substantial role in the admission)[36] and one case with a non-triggered DRA (See BJCP online supporting information S3).

Table 3: Inter-rater reliability for DRA presence between four adjudication pairs and per centre for the evaluation of 16 cases

Raters	% Agreement	Kappa*
Four adjudication pairs	71%	0.41
Centre 1 (two physicians)	94%	0.86
Centre 2 (physician + pharmacist)	75%	0.42
Centre 3 (physician + pharmacist)	69%	0.33
Centre 4 (physician + pharmacist)	88%	0.74

*Respectively Fleiss' and Cohen's κ were calculated to determine the level of agreement between the four adjudication pairs and within each centre

DISCUSSION

To our knowledge the DRA adjudication guide is the first standardised instrument to identify DRAs in older persons caused by ADR, overuse, underuse and misuse of medications. The DRA adjudication guide provides definitions, examples and step-by-step instructions to measure DRAs.

DRA identification is based on chart review with the aid of a trigger tool followed by structured consensus judgement, an approach that has been used successfully in previous ADE studies.[25] The novelty of our method lies in the development of a trigger tool for DRA, specific to older people and allowing explicit DRA screening. The DRA adjudication guide calls for a rigorous evaluation of DRA including triggered and non-triggered events as well as non-preventable ADRs and preventable medication errors, which is the desired broader focus of studying DRAs.[21,32,52,53] Furthermore, an adjudication pair composed of a pharmacist and a physician is a recommended approach for evaluation of ADEs.[55,56]

To improve safety and quality of care, a valid and practical method to measure and understand a problem is a critical approach to any patient safety threat.[1,81,82] It has been acknowledged that patient safety measures are often based on insufficient evidence and finding a balance between scientific soundness and feasibility is a challenge.[81] We addressed these requirements by utilizing a rigorous developmental pathway based on design and test iterations, combining evidence from the published literature with expert opinion and user-feedback from international and multidisciplinary sources. Content validity, feasibility of use and IRR were found to be satisfactory.

Despite the development of a standardised procedure, variability in DRA determination remains. IRR *between* adjudication pairs in four European centres was moderate, which is the most relevant criterion as it is the consensus judgement

between the pharmacist and physician that is of importance. Achieving a good IRR score for ADE identification is a challenge inherent to retrospective chart review studies, with previous adverse event studies reporting κ scores varying from -0.077 to 0.66.[19,32,56,83-85] The trigger tool allowed to detect the same triggers, yet discrepancies arose mainly on the level of assessment of contribution to hospital admission. Expert judgement using causality criteria is not devoid of individual subjective judgements.[47] Exploring the reasons for discrepancies highlighted the need for further training and standardisation of consensus procedures for more subjective adjudications such as underuse. For example, two out of four centres in the present study considered omission of a statin in a 90-year old patient admitted for myocardial infarction as a DRA, whereas there is limited evidence of benefit of statins over the age of 80-85.[86]

Our reliability study is the first one evaluating DRA by international adjudication teams, yet rater pairs only came from four European countries. The IRR score can be considered as a satisfactory result taking into account the following considerations: (i) participants were at the beginning of their learning curve when IRR was evaluated; (ii) composition of adjudication teams varied with regards to profession, clinical experience and experience in ADE identification. It has been shown that IRR among different professions is lower, which explains the almost perfect agreement score in the team that was composed of only physicians.[56]; (iii) cases were collected in four European hospitals and quality of information in source documents such as admission and discharge letters therefore varied. Furthermore, translation of cases into English was needed and was performed by research team members and not by a translation agency, which might have resulted in differences in case quality. Moreover, interpretation of cases and source documents from another country where guidelines and practices might vary, contributes to complexity. However even

if the DRA adjudication procedure is applied correctly by all raters, a certain degree of disagreement is to be expected in adjudication of complex multi-morbidity cases.

The following recommendations to optimise IRR will be implemented in the OPERAM trial: (i) intensification of training and involvement of experienced clinicians in the adjudication teams, (ii) close monitoring of IRR at different time-points to identify discrepancies and (iii) prompt feedback and sharing of questions and experiences among teams.[84,87]

The adjudication guide has several limitations. Firstly, data are collected retrospectively and hence are limited to the information available in medical charts. For assessment of underuse in particular, information on patient preferences, life expectancy or adherence are often undocumented in medical charts.[81] To obtain an accurate picture, prospective identification of DRAs in combination of with patient, caregiver and healthcare professional interviews would be desirable.[33,88,89] Hindsight bias is another limitation of retrospective chart review; knowing the outcome and its severity may influence the adjudication of causation.[90] Furthermore, the response rate of the experts invited to the Delphi survey was limited to 48%, nevertheless the Delphi panel represented various disciplines and countries. Moreover, we did not specify an age cut-off for older people in the Delphi survey, which might have influenced the outcome. However in the literature review on which the preliminary list of triggers was based, we only included studies of patients aged 65 years and older. We therefore believe that our trigger tool is broad enough to trigger DRA in people aged 65 years and older, which corresponds to the World Health Organisation's age cut-off to define older people. Finally, we did not compare the adjudication results from the four teams with a gold standard such as adjudication by an expert panel.

The DRA adjudication guide is time-consuming for use in clinical practice and is designed for research purposes. The method may be used to study incidence of DRAs or drug-related emergency department visits or as outcome measure for the evaluation of interventions to optimise pharmacotherapy in older people.

The performance of the trigger tool for detecting DRAs has not yet been evaluated. A future study will determine the predictive validity, sensitivity and specificity of the trigger tool to detect DRAs in the OPERAM dataset. An electronic trigger tool with improved specificity consisting of drug-disease combinations, could help to identify patients at risk of medication-related harm in electronic patient records.[91]

ACKNOWLEDGEMENTS

This work is part of the project 'OPERAM: OPtimising thERapy to prevent Avoidable hospital admissions in the Multi-morbid elderly' supported by the European Union's Horizon 2020 research and innovation programme under the grant agreement No 6342388, and by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0137. The opinions expressed and arguments employed herein are those of the authors and do not necessarily reflect the official views of the EC and the Swiss government.

We gratefully acknowledge the valuable input of the expert panel in the validation of the trigger tool. Participating experts included: Christine Baumgartner, University of Bern; Manuel Blum, University of Bern; Dominique Bonnet-Zamponi, Assistance Publique Hôpitaux de Paris, Centre of Pharmaco-epidemiology; Pascale Cornette, Université catholique de Louvain; Paul Jansen, University Medical Centre Utrecht; Louise Mallet, Université de Montréal; Zachary Marcum, University of Washington; Ariane Mouzon, Université catholique de Louvain; Denis O'Mahony, University College Cork; Mirko Petrovic, Ghent University; Sarah Slight, Newcastle University;

Annemie Somers, Ghent University; Stephane Steurbaut, Vrije Universiteit Brussel; Patricia van den Bemt, Erasmus University Medical Centre; Tischa van der Cammen, Delft University of Technology.

We thank Stefanie Hossmann and Sven Trelle from the Clinical Trials Unit of the University of Bern, for the work performed to embed the DRA adjudication method in the electronic data collection for the OPERAM trial. We also thank Séverine Henrard from the Université catholique de Louvain for her advice in statistical analysis.

CONFLICT OF INTEREST

There are no competing interests to declare.

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CHAPTER 1.2

INTER-RATER RELIABILITY OF A STANDARDISED CHART REVIEW METHOD TO IDENTIFY DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PEOPLE

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The drug-related hospital admission adjudication guide is a standardised chart review method used to evaluate the primary outcome, drug-related admissions (DRAs), in the European OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly (OPERAM) trial.
- DRA adjudication is performed by adjudication teams in four different study sites. Therefore it is particularly important to monitor inter-rater reliability (IRR) and to ensure standardised adjudication across the four study sites.

WHAT THIS STUDY ADDS

- This retrospective chart review study on 30 patient cases, demonstrated that IRR of DRA adjudication between the four adjudication teams in OPERAM was fair. Several factors, including the quality of information in the medical charts and the inherent need for subjective clinical judgement in the adjudication of complex multi-morbidity cases, may have affected IRR.
- Despite the use of a standardised DRA adjudication procedure, experienced and trained adjudication teams, achieving good IRR for DRA identification remains challenging.

ABSTRACT

Introduction: The drug-related hospital admission adjudication guide is a standardised chart review method used to evaluate the primary outcome drug-related admissions (DRAs) in the European OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly (OPERAM) trial. A DRA is defined as any readmission where the main reason or contributory reason for a patient's admission is caused by an adverse drug reaction or overuse, underuse or misuse of medications. DRA adjudication is performed by an adjudication team at each OPERAM study site in Belgium, Ireland, Switzerland and The Netherlands. This study aimed to evaluate the inter-rater reliability (IRR) of DRA adjudication between the four adjudication teams.

Methods: Thirty consecutive readmissions of multi-morbid older patients enrolled in the trial at the Irish study site were selected for cross-adjudications. A dichotomous outcome variable was defined (DRA identified yes/no) and IRR was determined by calculating weighed percentage agreement and kappa statistics between the four adjudication teams (Fleiss' κ) and between the individual teams per study site (Cohen's κ). A qualitative assessment of the concordances and discordances in DRA adjudication between teams was also performed.

Results: For the evaluation of thirty cases, IRR of DRA identification between the four adjudication teams was fair (68% agreement, κ=0.34). Pairwise agreement between individual teams per study site varied from slight to moderate agreement. Most discrepancies arose for identification of triggers and non-triggered events.

Conclusion: Despite the use of a standardised DRA adjudication guide by experienced adjudication teams, considerable variability in DRA adjudication remains and a degree of subjective clinical judgement is unavoidable in the adjudication of complex cases of older patients with multi-morbidity.

INTRODUCTION

The drug-related hospital admission (DRA) adjudication guide is the first standardised chart review method to identify DRAs in older people resulting from adverse drug reactions, overuse, underuse and misuse of medications.[1] DRA adjudication is based on chart review with the aid of a trigger tool and structured consensus judgement for causality by a pharmacist and a physician.[1] Content validity, feasibility of use and inter-rater reliability of the DRA adjudication guide were tested and found to be satisfactory.[1]

The DRA adjudication guide is used within the European OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly (OPERAM) trial to measure the primary outcome DRAs. OPERAM is a multicentre cluster randomised controlled trial of medication review involving 2009 multi-morbid (≥3 chronic medical conditions) older patients (≥70 years) with polypharmacy (use of ≥5 chronic medications) recruited from four study sites in Bern (Switzerland), Utrecht (The Netherlands), Brussels (Belgium) and Cork (Ireland). The primary outcome of the trial are DRAs, defined as any readmission where the main reason or contributory reason for a patient's admission is caused by an adverse drug reaction or overuse, underuse or misuse of medications.[2] Assessment of the primary outcome DRA is based on the DRA adjudication guide and is performed by an independent and blinded adjudication team at each study site, composed of an experienced pharmacist and physician. Due to legal regulations and language issues (medical charts are in the local languages), centralised adjudication of DRAs in OPERAM could not be performed.[2]

Since DRA adjudication is performed in four different study sites, it is particularly important to monitor inter-rater reliability (IRR) of DRA adjudication and to ensure standardised adjudication across the four sites to avoid site-specific bias.[2] IRR

refers to the reproducibility or consistency of assessments from one rater to another and is an indispensable component of validity of an instrument.[3,4] During the development stage of the DRA adjudication guide, we achieved moderate IRR (71% agreement, κ=0.41) for a pilot evaluation of 16 patient cases by four adjudication teams from four study sites; a satisfactory score. However since the first evaluation of IRR, the composition of most adjudication teams had changed. Therefore the present study aimed to evaluate IRR of DRA adjudication between the four adjudication teams in the OPERAM study sites in Belgium, Ireland, Switzerland and The Netherlands.

METHODS

Study design and setting

As a sub-study of the OPERAM trial, we conducted a retrospective chart review study to determine the IRR of DRA adjudication across the four adjudication teams. Thirty consecutive readmissions of older patients (≥ 70 years) with multi-morbidity (≥ 3 chronic conditions) enrolled in the OPERAM trial in Ireland and who had complete medical charts (medication lists, admission letter, discharge letter and laboratory values available) were selected for cross-adjudications by the four adjudication teams. Patients with incomplete medical charts were excluded. To avoid translation issues, we selected readmitted patients from the Irish OPERAM study site, a university teaching hospital in Cork.

DRA identification strategy in OPERAM

In OPERAM, DRA adjudication is performed using standardised chart review based on a three-step approach: (i) abstraction of a standardised list of data from the medical record into an electronic case report form, the main source documents including the admission and discharge letter, laboratory values and medication lists; (ii) explicit screening for adverse drug events (ADEs) that are potential DRA

with the DRA trigger tool and screening questions for non-triggered events; (iii) adjudication: consensus judgement in terms of ADE causality and ADE contribution to hospital admission with the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) and Hallas criteria respectively.[1,5,6] Adjudication of drug relatedness of each hospitalisation (step ii and iii) is performed by an independent and blinded adjudication team in each study site. The detailed DRA adjudication procedure is described in Chapter 1.1.[1]

IRR study procedure

An iterative process of six rounds of case adjudications and prompt feedback to the adjudication teams was undertaken (Figure 1). Over a period of seven months (January 2019 – July 2019), patient cases were sent to the adjudication teams by email in six rounds with four to six cases per round. After each round, IRR of DRA adjudication was calculated and written feedback on the discrepancies in DRA adjudication across teams was provided, as well as reminders about definitions and adjudication procedures. Furthermore, two telephone conferences were organised after round three and after round five to discuss discrepancies, try to reach consensus on cases and remind adjudication procedures.

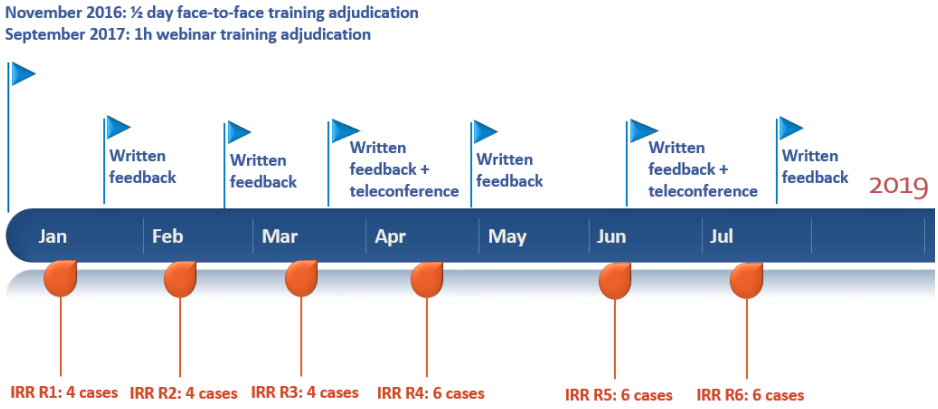

Figure 1: Overview of the iterative process of six rounds of adjudications and feedback
IRR, inter-rater reliability, R, Round

For each patient case, adjudication teams had access to the following anonymised information in the electronic case report form: presenting complaint, main reason for admission, ward specialty, laboratory values, admission and discharge letter including the medication history, discharge medication and medication received during admission. Adjudication teams were asked to document the following aspects of DRA adjudication: (i) type of triggers and/or non-triggered events identified and the corresponding medications involved, (ii) causality assessment according to the WHO-UMC criteria and (iii) assessment of ADE contribution to hospital admission according to the Hallas criteria. Free text fields were provided to note comments.

Training of the adjudication teams in OPERAM

Adjudication teams were composed of experienced clinicians including clinical pharmacists or clinical pharmacologists and specialist physicians in geriatric or internal medicine. The adjudication teams were provided with a standard operating procedure and the DRA adjudication guide, including definitions, instructions for use and examples of practical application of the method. Just before the start of the OPERAM trial, the adjudication teams were trained during a five-hour face-to-face training (November 2016) consisting of theory as well as practicing the DRA adjudication method on test cases. Because of changes in the composition of the adjudication teams, a one hour webinar training (https://www.youtube.com/watch?v=ctBkVqhHAww) on DRA adjudication was also organised just before the start of adjudications in the OPERAM trial (September 2017). Furthermore throughout the OPERAM trial, adjudication teams could consult the research team members responsible for DRA adjudication to discuss problems, to ask questions or to assist adjudication teams during their meetings. To ensure the learning curve had passed, evaluation of IRR took place after all adjudication teams had performed at least 20 adjudications at their own study site.

Data analysis

The unit of analysis for IRR was the identification of a DRA (DRA identified yes/no). IRR for DRA identification was determined by calculating weighed percentage agreement and agreement corrected for chance (kappa statistics) between the four adjudication teams (Fleiss' κ) as well as between the individual teams per study site (pairwise Cohen's κ) for the dichotomous outcome variable (DRA identified yes/no). Kappa values were interpreted as slight agreement if <0.20, fair agreement if 0.21–0.40, moderate agreement if 0.41–0.60, substantial agreement if 0.61–0.8 and almost perfect agreement if 0.81–1.00.[7] A qualitative assessment of the concordances and discordances in DRA adjudication between the teams was also performed at the level of the trigger identification, identification of non-triggered events, ADE causality assessment and assessment of ADE contribution to hospital admission.

Ethics approval

Approval for the overall OPERAM study was granted by the ethics committee at each study site.

RESULTS

Study population

The patient characteristics are presented in Table 1. The median age of the 30 selected readmitted patients was 83 years. The majority of patients were admitted to medical wards for infectious diseases, gastro-intestinal problems or cardiovascular problems.

Table 1: Patient characteristics (*n* = 30)

Variable	Value
Age (years; median [P_{25}-P_{75}])	83 [76–87]
>70-≤80 years (*n*, [%])	13 [43]
>80-≤90 years (*n*, [%])	14 [47]
>90 years (*n*, [%])	3 [10]
Sex (*n,* [%])	
Female	16 [53]
Male	14 [47]
Length of stay (days; median [P_{25}-P_{75}])	9 [6-16]
Ward type (*n*, [%]))	
Medical ward	27 [90]
Surgical ward	3 [10]
Main cause of hospitalization (*n*, [%]))	
Infectious diseases	10 [33]
Diseases of the digestive system	5 [17]
Cardiovascular problems	4 [13]
Syncope & collapse	3 [10]
Diseases of the nervous system	2 [7]
Diseases of the blood	2 [7]
Fall-related problems	1 [3]
Mental and behavioural disorders	1 [3]
Miscellaneous	1 [3]
Diseases of the musculoskeletal system and connective tissue	1 [3]

Agreement on DRA identification between adjudication teams

Table 2 displays the level of agreement on the presence of a DRA between all four adjudication teams and between individual teams per study site. For the thirty patient cases, the four adjudication teams agreed upon 14 cases and disagreed upon 16 cases for DRA presence, representing fair agreement (68% agreement, Fleiss' κ=0.34, p <0.001) (Table 2). The Fleiss κ score would be regarded as low, indicating a considerable degree of variation in DRA adjudication between the four sites. Pairwise agreement between individual sites showed moderate agreement between Ireland and The Netherlands (77% agreement, κ=0.53) and fair agreement between Belgium and Ireland (70% agreement, κ=0.40), between Belgium and Switzerland (70% agreement, κ=0.33), between Belgium and The Netherlands (67% agreement, κ=0.34) and between Switzerland and The Netherlands (60% agreement, κ=0.29). There was slight agreement between Ireland and Switzerland (60% agreement, κ=0.20). The pairwise agreement between sites shows that much of the variation lies with Switzerland, with Switzerland and the other sites having the lowest three kappa values. Agreement for the set of cases per round varied from slight to moderate agreement with 71% agreement (κ=0.32) in round I, 58% agreement (κ=-0.11) in round II, 71% agreement (κ=0.04) in round III, 78% agreement (κ=0.50) in round IV, 58% agreement (κ=-0.01) in round V and 69% agreement in round VI (κ =0.07).

Table 2: IRR for DRA identification between the four adjudication teams and between individual teams per study site for evaluation of 30 patient cases

Adjudication teams	% agreement	Kappa[a]
Four adjudication teams	68	0.34
Ireland – The Netherlands	77	0.53
Belgium – Ireland	70	0.40
Belgium – Switzerland	70	0.33 [NS]
Belgium – The Netherlands	67	0.34 [NS]
Switzerland – The Netherlands	60	0.29
Ireland – Switzerland	60	0.20 [NS]

DRA, Drug-related hospital admission; IRR, Inter-rater reliability

[a]Respectively Fleiss' and Cohen's κ were calculated to determine IRR between the four adjudication teams and between the individual teams per study site.
Kappa values are interpreted as slight agreement if <0.20, fair agreement if 0.21–0.40, moderate agreement if 0.41–0.60, substantial agreement if 0.61–0.8 and almost perfect agreement if 0.81–1.00.[7] Statistically significant value $p<0.05$ unless [NS].

For the 14 cases on which the four adjudication teams agreed, there were 4 cases with no DRA and 10 cases with a DRA identified. The qualitative assessment of the concordances and discordances in DRA adjudication between teams showed that two DRAs involved non-triggered events (two patients admitted with an infection and use of immunosuppressive drugs) and eight DRAs were identified by triggers (acute renal impairment in a patient on a diuretic and ACE-inhibitor; heparin-induced thrombocytopenia; bleeding and use of an anticoagulant; hyponatraemia in a patient taking an antidepressant, an anti-epileptic drug and a proton pump inhibitor; hypotension secondary to isosorbide mononitrate, mentioned as an ADE in the medical record; hematemesis and gastro-intestinal disorders in a patient taking an anticoagulant, antidepressant and ferrous fumarate; fall associated with diziness in a patient taking tolterodine and lercanidipine, ischaemic heart disease and underuse of adequate secondary prevention).

For the 16 cases on which the adjudication teams disagreed, there were discrepancies in DRA adjudication because (i) either trigged events were not identified by all teams (6 cases), a combination of triggered and non-triggered

events were not identified by all teams (7 cases) or a non-triggered event was not identified by all sites (1 case). (ii) Discrepancies also arose at the level of causality assessment, where all teams agreed upon the triggers but disagreed on ADE causality assessment (2 cases). Feedback from the adjudication teams highlighted they experienced difficulties with navigating through medical notes from another hospital and that the quality of information in the medical records was at times poor or highly variable between cases, resulting in uncertainty about diagnoses and medications the patients were taking.

DISCUSSION

This study demonstrated that IRR of DRA adjudication between four adjudication teams in the OPERAM study sites in Belgium, Ireland, Switzerland and The Netherlands is fair. Despite several efforts to increase IRR including the use of a standardised DRA adjudication guide, trained adjudication teams involving experienced clinicians and continuous monitoring of IRR with prompt feedback, considerable variability in DRA adjudication remains. We did not observe a trend towards higher levels of agreement with more cases completed, suggesting that a learning curve did not influence levels of agreement.

Although trigger-based chart review is advocated as the premier ADE identification approach, achieving good IRR for ADE identification is a challenge inherent to chart review studies with kappa values varying from -0.77 to 0.66, whether there is a standardised procedure or not.[1,8-15] Compared to the pilot evaluation of IRR, the adjudication teams were more trained and more experienced in the present study, yet IRR was lower (71% agreement, κ=0.41 *versus* 68% agreement, κ=0.34). This indicates a high degree of subjectivity in DRA adjudication rather than differences in experience level of the adjudication teams.

The IRR score should be interpreted in the light of several considerations: (i) Firstly, feedback from the adjudication teams highlighted that the quality of information about diagnoses and medications in the medical charts was at times poor and highly variable depending on the ward specialty, which has been previously reported.[16,17] In several instances, uncertainty about a diagnosis or medication history resulted in discrepancies between teams in trigger identification. Future studies evaluating IRR might consider using clinical vignettes or standardising the clinical information provided to ensure comprehensive clinical and medication details are available for every case. However the use of real patient cases and

original data sources in our study better reflects the clinical reality. Combining chart review with prospective methods such as patient or clinician interviews about the origin of the hospitalisation might also increase IRR, yet this would be time consuming both for research and clinical practice.[11,18,19] (ii) For pragmatic reasons, patient cases were selected from the Irish study site. Therefore three out of four adjudication teams had to interpret medical notes from another country, where practices and medications may vary. For instance, for a certain case one team did not identify the trigger constipation secondary to Galfer (ferrous fumarate), although this was mentioned as an ADE in the medical notes. For assessment of the primary outcome DRA in the OPERAM trial, each adjudication team will assess cases of their own study site. (iii) The DRA adjudication guide is a standardised yet not fully explicit method. Notwithstanding the use of an explicit trigger list, established definitions and causality criteria, assessment of ADE causality and ADE contribution to hospitalisation remains prone to subjective clinical judgment.[15] Although the trigger tool was applied perfectly, disagreements about ADE causality assessment between teams were the principal cause of disagreement in two cases. Even after discussing these cases during telephone conferences it was not always possible to reach consensus between the four adjudication teams. This not surprising since the OPERAM trial involves multi-morbid older patients, where a gold treatment standard is often lacking and a certain degree of disagreement in DRA identification is unavoidable.[10] (iv) Few studies have evaluated IRR across four international multidisciplinary teams and heterogeneity in raters and conditions studied negatively affects IRR.[1,10] Previous studies identifying DRA by raters in single centres in single countries achieved moderate to substantial agreement for DRA identification.[20-22] All adjudication teams involved experienced clinicians, yet some teams adjudicated more exhaustively compared to others, especially in searching for non-triggered events. Rather than written feedback, more meetings

between the teams to discuss cases might have further standardised adjudication styles between teams. However, it has been previously demonstrated that discussion of cases and sharing knowledge among experts increases intra-rater agreement, but not IRR.[8]

Poor IRR in DRA identification between adjudication teams may imply an over- or underestimation of the true occurrence of DRA in the OPERAM trial. However, adjudication teams are blinded to study arm allocation of patients and potential site-specific bias in DRA adjudication will not affect the difference in DRA prevalence rate between intervention and control groups.

Limitations

This study has several limitations. We did not evaluate intra-rater reliability, IRR between pairs of raters in each site or IRR between physicians only and pharmacists only. We did not consider this assessment as essential, since in OPERAM, it is the consensus judgement between the pharmacist and the physician that is of importance, both having complementary knowledge and experience.[9,23] Furthermore intra-rater agreement, agreement within pairs of raters or between the same professions is expected to be higher compared to IRR between four international, multidisciplinary adjudication teams.[8-10,24] Although kappa statistics are frequently used to measure IRR, Cohen's kappa is influenced by the prevalence of DRA and the symmetry of the ratings.[25-27] For instance, for both set of cases in rounds I and III we achieved 71% percentage agreement, whereas the kappa values varied from κ=0.32 (fair agreement) in round I to κ=0.04 (slight agreement) in round III .[27] These kappa values should therefore be interpreted with caution and percentage agreement should be used to aid in the interpretation of IRR.[27] Hindsight bias is a general weakness of retrospective studies; knowing the outcome and severity that may influence adjudication of causation.[28] Finally, we only defined DRA identification as an outcome variable and we did not calculate IRR for

trigger identification or causality assessment. However we performed a qualitative assessment of discrepancies to better understand the causes of discrepancies.

CONCLUSION

Despite the use of a standardised DRA adjudication procedure by experienced adjudication teams, IRR was fair. The DRA adjudication is a standardised yet not fully explicit method and subjective clinical judgement is unavoidable in the adjudication of complex cases of older patients with multi-morbidity.

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CHAPTER 1.3

POTENTIALLY INAPPROPRIATE PRESCRIBING AND RELATED HOSPITAL ADMISSIONS IN GERIATRIC PATIENTS: A COMPARATIVE ANALYSIS BETWEEN THE STOPP AND START CRITERIA VERSIONS 1 AND 2

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Drugs & Aging 2019; 36: 453-459

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- A study conducted by our research group in 2008, demonstrated an association between preventable hospitalisations in geriatric patients and inappropriate prescribing detected by the Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria version 1 (v_1).
- In 2014 the STOPP/START criteria v_1 were updated, comprising a 31% increase in prescribing criteria.
- No studies have evaluated the potential clinical impact of the STOPP/START.v_2 criteria compared with the STOPP/START.v_1 criteria in terms of their association with drug-related admissions (DRAs).

WHAT THIS STUDY ADDS

- More DRAs in geriatric patients were associated with potentially inappropriate medicines (PIMs) and/or potential prescribing omissions (PPOs) identified by STOPP/START.v_2 compared with STOPP/START.v_1 (40% versus 23% of all admissions), a significant difference.
- Admissions for falls and fractures associated with PIMs of fall-risk-increasing drugs and/or PPOs of musculoskeletal system drugs were the most common type of DRA.
- STOPP/START.v_2 PIMs and PPOs warrant specific attention during medication review in older persons as they are frequently associated with preventable DRAs.

ABSTRACT

Background: Older persons are at significant risk of drug-related admissions (DRAs). We previously demonstrated that 27% of hospitalisations in geriatric patients were associated with potentially inappropriate medicines (PIMs) and/or potential prescribing omissions (PPOs) identified by the Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria version 1 (v_1). The updated STOPP/START criteria version 2 (v_2) comprised a 31% increase in prescribing criteria.

Objective: As a secondary analysis of our study conducted in 2008, we aimed to compare the prevalence and types of DRAs identified by STOPP/START.v_1 and STOPP/START.v_2.

Methods: We applied the STOPP/START.v_2 criteria to a subset of 100 consecutively admitted geriatric patients selected from our original cross-sectional study of 302 patients. A geriatrician and a pharmacist adjudicated whether the identified PIMs and PPOs were related to acute hospitalisation. Admissions were defined as DRAs if the identified PIM(s) and/or PPO(s) were related to the main cause of admission or played a significant contributory role in the admission.

Results: The median patient age was 83 years and the median number of medications at home was eight. Compared with STOPP/START.v_1, STOPP/START.v_2 not only yielded more instances of inappropriate prescribing but also targeted significantly more PIMs and PPOs associated with preventable DRAs (23% *versus* 40% of all admissions, $p<0.001$). PIMs of fall-risk-increasing drugs and PPOs of musculoskeletal and cardiovascular system drugs were most frequently associated with DRAs.

Conclusion: The latter instances of inappropriate prescribing with major clinical relevance warrant particular attention during medication review in older persons.

INTRODUCTION

Hospitalisations resulting from adverse drug events, so-called drug related hospital admissions (DRAs), represent a growing patient safety threat in the older population and are associated with adverse clinical and economic outcomes.[1-6] Up to 75% of DRAs are potentially preventable.[1,7,8] Several studies, including a study conducted by our research group and published in *Drugs & Aging*, demonstrated an association between preventable hospitalisations and inappropriate prescribing.[9-12] Inappropriate prescribing encompasses the prescription of more drugs than are clinically needed (overprescribing), the incorrect prescription of drugs that are needed (misprescribing) and the failure to prescribe drugs that are needed (underprescribing).[13]

In 2008, the first version of the STOPP (Screening Tool of Older People's Prescriptions) and START (Screening Tool to Alert to Right Treatment) criteria were developed as an explicit tool to detect potentially inappropriate medicines (PIMs; over- and misprescribing) and potential prescribing omissions (PPOs; underprescribing).[14] To incorporate the most recent evidence, the STOPP/START criteria version 1 (v_1) were updated in 2014.[15] The updated STOPP criteria version 2 (v_2) include the addition of general implicit criteria targeting prescriptions with an inappropriate indication or inappropriate duration of therapy, a list of drugs to monitor in renal insufficiency, and vaccines. The main changes in prescribing recommendations occurred for antiplatelet agents, anticoagulants, cardiovascular system, central nervous system and musculoskeletal system drugs, among others. Several criteria from STOPP/START.v_1 have been removed in STOPP/START.v_2 because of weak or equivocal supporting evidence, including the START.v_1 criteria regarding antiplatelet and statin therapy for primary prevention in diabetes mellitus. Changes in recommendations between STOPP/START.v_1 and

STOPP/START.v_2 are provided in **Appendix 3**. The STOPP/START.v_2 criteria resulted in 80 STOPP and 34 START criteria compared with 65 STOPP and 22 START criteria in version 1, a 31% increase in prescribing criteria.[15]

Not surprisingly, research comparing the two versions of the STOPP/START criteria found increased prevalence rates of inappropriate prescribing events with the updated criteria.[16,17] However, no studies have evaluated the potential clinical impact of the STOPP/START.v_2 criteria compared with the STOPP/START.v_1 criteria in terms of their association with DRAs. As a secondary analysis of our study conducted in 2008, we aimed to compare the prevalence and types of DRAs identified by STOPP/START.v_2 and STOPP/START.v_1 in a sub-sample of patients selected from our original study.

METHODS

For this comparative analysis, the last one hundred consecutively admitted geriatric patients were selected from the original dataset of 302 patients.[9] For pragmatic reasons, only a sub-sample of 100 patients was selected and no a priori sample size calculation was performed. In the original study by Dalleur et al., the following inclusion criteria to receive a comprehensive geriatric assessment by the inpatient geriatric consultation team were used: age 75 years or older, at risk of functional decline (as defined by an Identification of Seniors at Risk (ISAR) score of ≥2/6 [18]), acute admission (as opposed to an elective admission) to non-geriatric units of a teaching hospital in Brussels, Belgium. In the original study, the patients were included by the inpatient geriatric consultation team, a multi-disciplinary team that aims to improve care for older patients admitted to non-geriatric units according to the principles of comprehensive geriatric assessment.[19] The patients' datasets were compiled based on chart review and patient and/or carer interviews and included demographic, clinical and medication data, prospectively collected by

the inpatient geriatric consultation team in 2008. Medication data included prescription and over-the-counter medicines taken daily or 'as needed' just before hospitalisation.

A geriatrician with expertise in geriatric pharmacotherapy and a last-year medical student (B.B. & L.E.M.) reviewed the 100 patient datasets to identify PIMs and PPOs using STOPP/START.v_2. Next, a geriatrician and a pharmacist (B.B. & S.T.) with experience in geriatric pharmacotherapy and DRA adjudication independently assessed whether these PIMs and PPOs were related to hospitalisation and thus a potential DRA. In case of disagreement, a clinical pharmacist with expertise in geriatric pharmacotherapy and DRA adjudication (O.D.), was involved to establish consensus. For assessing the link between inappropriate prescribing and hospitalisation, the adjudicators reviewed the datasets including demographic data, the patient's comorbidities, the patient's home medications, the main admission diagnoses as documented in the discharge letter and the identified PIMs and PPOs present upon admission. In line with the method used in the original study based on STOPP/START.v_1 and the Hallas definition (Table 1), admissions were defined as preventable DRAs if the identified PIM(s) and/or PPO(s) were related to the main cause of admission (e.g. hospitalisation for gastro-intestinal bleeding and PIMs of antithrombotic agents and/or PPOs of proton pump inhibitors) or played a significant contributory role in the admission (e.g. hospitalisation for severe diarrhoea with dehydration and PIMs of diuretics; the diuretics might have worsened dehydration).[9,20]

Inappropriate prescribing events and DRAs related to STOPP/START.v_1 for the 100 patients were extracted from our original study for comparison. Descriptive statistics were used to present the data. The McNemar test was performed in the R software package to compare prevalence rates of DRAs between STOPP/START.v_2 and v_1. The ratio v_2/v_1 for DRAs detected by STOPP/START.v_2 and v_1 was calculated.

For patients who presented with one or more PIMs and/or PPOs, the positive predictive value of the STOPP/START.v_2 and v_1 criteria for having a related DRA was calculated. Inter-rater reliability for DRA identification between the geriatrician and the pharmacist was determined for the 100 cases by calculating percentage agreement and agreement corrected for chance (Cohen's κ).

Ethics approval

The ethics committee from the Cliniques universitaires Saint-Luc (Brussels, Belgium) provided approval for anonymous use of the medical record database (reference number B403201111806).

Table 1: Adjudication of drug-related admissions based on the Hallas definition[20]

DRA – Main reason for admission	The inappropriate prescribing event was related to the primary cause of admission and no other diseases or symptoms contributed significantly to the admission.
DRA – Contributory reason for admission	The inappropriate prescribing event played a substantial role in admission but other factors also contributed significantly.
No DRA	The inappropriate prescribing event played a minor or uncertain role and the patient would have been admitted without occurrence of the inappropriate prescribing event. Other symptoms or circumstances were the reason for admission.

DRA, drug-related admission

RESULTS

The patient characteristics are presented in Table 2. The median age was 83 years and 62% of patients were female. The 100 patients were prescribed a total of 789 daily medications at home with a median number of eight medications.

Table 2: Patient characteristics (*n*=100)

Variable	Value
Age (years; median [P_{25}-P_{75}])	83 [79–86]
Female (*n*)	62
Living alone (*n*)	56
No. of medications per patient (median [P_{25}-P_{75}])	8 [6–9]
ISAR score (median [P_{25}-P_{75}])	3 [3–4]
Geriatric syndromes (*n*)	
Previous falls	52
Dependency in ADL (Katz score ≥ 9/24)	31
Malnutrition	22
Cognitive disorder	16
Most frequent morbidities (*n*)	
Hypertension	74
Atherosclerosis	55
Renal failure (GFR <50 ml/min)	43
Atrial fibrillation	35
Diabetes type 2	26
Osteoporosis	20
Depression	22
Main cause of hospitalization (*n*)	
Cardiovascular problems	57
Fall-related problems	27
Gastro-intestinal problems	9
Miscellaneous	7

ADL, Activities of Daily Living; GFR, Glomerular Filtration Rate

As shown in Table 3, applying STOPP/START.v_2 compared with v_1 resulted in a more than threefold increase in PIMs and a nearly twofold increase in PPOs. STOPP.v_2 mainly targeted PIMs of medications prescribed without an indication and compared with STOPP.v_1, pointed at more PIMs of benzodiazepines and Z-drugs. START.v_2 targeted more PPOs of calcium, vitamin D, bisphosphonates, angiotensin-converting enzyme (ACE)-inhibitors and β-blockers, whereas START.v_1 targeted more PPOs of antiplatelet agents and statins including for primary cardiovascular prevention in diabetic patients (17%) (Table 3).

Table 3: Most frequent PIMs and PPOs detected using the STOPP/START criteria version 1 (v_1) and version (v_2) (*n*=100)

	STOPP v_1	STOPP v_2	START v_1	START v_2
Total *n* of PIMs or PPOs	57	206	101	193
Median [P_{25}-P_{75}]) *n* of PIMs/PPOs per patient	0 [0-1]	2 [1–3]	1 [0–2]	2 [1-3]
N of patients with one or more PIMs or PPOs	39	87	57	79
Prevalence most frequent PIMs & PPOs (*n*)				
Drugs without an indication	-	94	-	-
Drugs beyond the recommended duration	-	10	-	-
Duplicate drug class prescriptions	6	6	-	-
Central nervous system				
Benzodiazepines	19	41	-	-
Z-drugs	-	10	-	-
Musculoskeletal system				
Calcium and/or vitamin D	-	-	14	62
Bisphosphonates	-	-	10	23
Cardiovascular system				
ACE-inhibitors	-	-	9	14
β-blockers	10	2	1	18
Antiplatelet agents	8	3	20	6
Statins	-	-	26	17

PIM, Potentially Inappropriate Medicine; PPO, Potential Prescribing Omission; START, Screening Tool to Alert to Right Treatment; STOPP, Screening Tool of Older People's Prescriptions

Overall, inappropriate prescribing events (PIMs and/or PPOs) detected by STOPP/START.v_2 compared with STOPP/START.v_1 were related to hospitalisation in 40% and 23% of patients, respectively. In other words, preventable DRAs were listed 1.7-fold more often in STOPP/START.v_2 compared with STOPP/START.v_1, a significant difference (p<0.001). For patients who presented with one or more PIMs and/or PPOs, the positive predictive value of STOPP/START.v_2 for a having a related DRA was 0.41, compared with 0.31 for STOPP/START.v_1 (Table 4). Ninety-one percent of DRAs related to STOPP/START.v_1 PIMs or PPOs, were adjudicated as being the main cause of admission, compared with 85% of DRAs related to STOPP/START.v_2. Likewise, 9% and 15% of DRAs related to STOPP/START.v_1 and STOPP/START.v_2, respectively, were adjudicated as playing a significant contributory role in the admission.

There was substantial agreement between the geriatrician and the pharmacist for DRA identification; 90% agreement, κ=0.79 (95% confidence interval 0.66-0.91, p<0.001).[21]

Table 4 summarises the principal reasons for admission and the related PIMs and PPOs. Both STOPP/START.v_1 and v_2 targeted mostly hospitalisations for PIMs of fall-risk-increasing drugs, PPOs of musculoskeletal system drugs and PPOs of cardiovascular system drugs. However the total number of DRAs targeted by the updated criteria has nearly doubled. PIM- and/or PPO-related hospitalisations for falls and fractures were the most common DRAs, accounting for 45% of DRA according to STOPP/START.v_2. PPO-related hospitalisations for cardiovascular problems (ischaemic heart disease, heart failure, atrial fibrillation) accounted for 33% of DRAs according to STOPP/START.v_2. Unlike STOPP/START.v_1, STOPP/START.v_2 also targeted PIM-related admissions for medications prescribed without an evidence-based indication documented in the medical chart, accounting for 7.5% of DRAs. For instance one patient was admitted for acute

kidney failure and drug rash with eosinophilia and systemic symptoms (DRESS syndrome) and was prescribed allopurinol without evidence of an indication of clinical gout. Other examples of PIM-related admissions for medications prescribed without an indication included admissions for bleeding events with inappropriate prescriptions of nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs) and antiplatelet agents.

Table 4: Prevalence of DRAs related to STOPP/START criteria v_1 and v_2 (*n*=100)

		STOPP/ START.v_1	STOPP/ START.v_2	Ratio v_2/v_1
Patients with one or more PIMs and/or PPOs (*n*)		75	97	1.29
Total DRAs (PIM- and/or PPO-related) (*n*)		23[a]	40[a,b]	1.74[a]
Positive predictive value[c] (95% confidence interval)		0.31 (0.21-0.42)	0.41 (0.31-0.52)	
Patients with one or more PIMs (*n*)		39	87	2.23
PIM-related DRAs (*n*)		11	23[b]	2.09[b]
Reason for admission	***PIMs identified***			
Fall and/or fracture	Benzodiazepines, Z-drugs, neuroleptics, anticholinergics including tricyclic antidepressants	7	14	
Acute kidney failure	Diuretics, xanthine oxidase inhibitors	0	2	
Bleeding	NSAIDs, SSRIs, antithrombotic agents	1	3	
Heart failure exacerbation	NSAIDs	1	1	
Ischaemic heart disease, peak hypertension	NSAIDs	0	1	
Complete heart block	β-blockers (and hypoglycaemia)	1	0	
Syncope associated with Lewy body dementia	Neuroleptics	1	1	
Syncope associated with swallowing disorder	Z-drugs, neuroleptics	0	1	
Patients with one or more PPOs (*n*)		57	79	1.39
PPO-related DRAs (*n*)		12	22[b]	1.83[b]
Reason for admission	***PPOs identified***			
Fall with fracture	Vitamin D, calcium, bisphosphonates	4	8	
Ischaemic heart disease	ACE-Inhibitors, β-blockers, antithrombotic agents, statins	5	7	
Heart failure	ACE-inhibitors	3	5	
Atrial fibrillation	β-blocker	0	1	
COPD exacerbation	Bronchodilators	0	1	

DRA, Drug-Related Admission; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; PIM, Potentially Inappropriate Medicine; PPO, Potential Prescribing Omission; SSRI, Selective Serotonin Reuptake Inhibitor; START, Screening Tool to Alert to Right Treatment; STOPP, Screening Tool of Older People's Prescriptions

[a]Significant difference (McNemar test, $p<0.001$)

[b]As patients could have several inappropriate prescribing events (PIMs/PPOs) related to the admission, the numbers may not add up to the stated totals. For 5/40 DRA related to STOPP/START.v_2 there were both PIMs and PPOs involved. Therefore the reported v_2/v_1 ratio's for PIM-related admissions (2.09) and PPO-related admissions (1.83) are higher than the overall v_2/v_1 ratio (1.74) for DRAs related to PIMs and/or PPOs. The latter ratio represents the main study outcome.

[c] Positive Predictive Value: the number of patients with a DRA related to a PIM and/or PPO divided by the number of patients who had one or more PIMs and/or PPOs according to STOPP/START.v_1 or v_2 in our sample.

DISCUSSION

We demonstrated that compared with STOPP/START.v_1, STOPP/START.v_2 not only yields more instances of inappropriate prescribing but also targets significantly more PIMs and PPOs associated with preventable DRAs (23% *versus* 40% of admissions; p<0.001). These instances of inappropriate prescribing with major clinical relevance warrant particular attention during medication review in older persons. In particular PIMs of fall-risk-increasing drugs and PPOs of musculoskeletal system drugs (vitamin D, calcium, bisphosphonates) were most frequently associated with DRAs.

- To our knowledge, this is the first study to compare the association between acute hospitalisations and PIMs and PPOs identified by the STOPP/START criteria v_1 and v_2 in geriatric patients. Previous research investigating the association between hospitalisations and inappropriate prescribing according to STOPP.v_1 and/or START.v_1 has reported DRA prevalence rates varying from 11% to 27% of admissions, which is in line with our DRA prevalence rate of 23% based on STOPP/START.v_1.[9-12] Using the STOPP/START.v_2 criteria in the same 100 patients, we found a high DRA prevalence rate of 40%, suggesting that the updated STOPP/START.v_2 criteria have a significantly better potential for targeting PIMs and PPOs associated with preventable medication-related harm.

For the sake of comparison, we applied the STOPP/START.v_2 criteria developed in 2014 to prescribing data from 2008. Therefore one might argue that our PIM prevalence of 87% might be an overestimation, yet it is still in line with the PIM prevalence range of 42-89% reported by previous studies that have applied the STOPP.v_2 criteria in the inpatient setting.[22] Few studies have reported PPO prevalence rates using the START.v_2 criteria. Our PPO prevalence of 79% is higher

than the 69% and 67% prevalence rates reported by Counter et al. and Wauters et al., conducted in the inpatient setting and community setting, respectively.[22,23] However, these studies did not include the complete set of START criteria in their analysis.

This study had a number of limitations. First, the mono-centric study design limits the broader international relevance of our findings. Moreover, our sample size was small and cases were not selected at random - only the last 100 consecutive patients were included. However, the aim of this secondary analysis was to compare the prevalence and types of DRAs identified by STOPP/START.v_1 and STOPP/START.v_2. The cross-sectional study design is well-suited to estimate prevalence rates and can give an indication of the association between inappropriate prescribing and DRAs; however, it does not allow for definite conclusions regarding the causal relationship. Whether medication review using the STOPP/START.v_2 criteria is effective in reducing DRAs in multi-morbid older persons is currently being investigated in a large-scale multi-centre randomised controlled trial called OPERAM (http://operam-2020.eu).

We did not consider patient preferences, life expectancy, exposure length and time until benefit of medications, which are also essential elements for assessment of appropriateness of prescribing, yet these are often undocumented in medical charts.[13,24,25] Hindsight bias is another limitation of retrospective chart review; knowing the outcome and its severity may influence the adjudication of causation.[26] Finally, DRA adjudication was based on clinical judgment. We did not use a standardised DRA adjudication approach with causality assessment to be in line with the method used in our original study for the sake of comparison.[27] Nevertheless, adjudication was performed by a geriatrician and a pharmacist duo, which is a recommended approach for evaluation of adverse drug events, and

there was substantial agreement for DRA identification between both reviewers.[28,29]

CONCLUSION

Compared with STOPP/START.v_1, STOPP/START.v_2 not only yields more instances of inappropriate prescribing but also targets significantly more PIMs and PPOs associated with preventable DRAs. These instances of inappropriate prescribing with major clinical relevance warrant particular attention during medication review in older persons. The results of this small cross-sectional study do not allow for definite conclusions regarding the causal relationship between hospital admissions and inappropriate prescribing events, in particular for potential prescribing omissions, and will need to be investigated further in prospective studies.

ACKNOWLEDGEMENTS

The authors would like to thank Adeline Gaillet and Alexandra Le Brun for their assistance in data collection.

CONFLICT OF INTEREST

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

The authors (Stefanie Thevelin, Leïla El Mounaouar, Sophie Marien, Benoit Boland, Séverine Henrard, Olivia Dalleur) have no conflicts of interest that are directly relevant to the content of this study.

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CHAPTER II
OLDER PEOPLE'S EXPERIENCE OF AND PREFERENCES FOR MEDICATION REVIEW

CHAPTER 2.1

MULTI-MORBID OLDER PEOPLE'S EXPERIENCE OF HOSPITAL-INITIATED MEDICATION CHANGES: A MULTI-CENTRE MIXED METHODS STUDY EMBEDDED IN THE OPERAM TRIAL

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In preparation

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- A patient-centred approach is considered essential to medicines optimisation in older people with multi-morbidity.
- The OPERAM trial is a multi-centre cluster randomised controlled trial involving 2009 multi-morbid older people, assessing the impact of medication review on drug-related readmissions.
- Beyond evaluating the clinical effectiveness of the OPERAM intervention, exploring the patient experience facilitates a more comprehensive understanding of contextual factors and mechanisms affecting medication review effectiveness.

WHAT THIS STUDY ADDS

- Embedded in the OPERAM trial, this mixed methods study provides an in-depth understanding of the patient experience of medication review and hospital-initiated changes.
- Patients' attitudes towards medication review and hospital-initiated medication changes were generally positive. However, an interplay of factors related to inadequate information and communication, paternalism, patients' beliefs, clinicians' attitudes and doctor-patient relationships, may affect medication review effectiveness.

ABSTRACT

Background: Inappropriate polypharmacy is a significant problem in the ageing multi-morbid population. A patient-centred approach to medicines optimisation is considered essential. The OPERAM trial is a multi-centre cluster randomised controlled trial involving 2009 multi-morbid older persons evaluating the impact of medication review on drug-related readmissions.

Objective: We conducted a multi-centre mixed methods study embedded in the OPERAM trial to explore multi-morbid older patients' experience of hospital-initiated medication changes. Exploring the patient experience facilitates a more comprehensive understanding of contextual factors and mechanisms affecting medication review effectiveness.

Methods: Semi-structured interviews and the Beliefs about Medicines Questionnaire were conducted with a purposive sample of 48 patients (70-94 years) from four European countries enrolled in the OPERAM trial. Interviews were analysed using the Framework approach. Quantitative data on the level of patient participation from clinicians' perspectives were also collected.

Results: Themes emerging from the interviews included: (i) lack of information and communication about medication changes, (ii) paternalistic decision-making predominates with variable satisfaction, (iii) barriers and facilitators to information and patient participation, (iv) positive attitudes towards medication review and acceptance of medication changes, (v) barriers and facilitators to acceptance of medication changes, (vi) importance of coordination between secondary and primary care. Patients' attitudes towards medication review and hospital-initiated medication changes were generally positive, however an interplay of factors related to inadequate information and communication, patients' beliefs, clinicians' attitudes and doctor-patient relationships may affect intervention effectiveness.

Paradoxical to patients' experiential accounts, prescribing clinicians reported high levels of patient participation in decision-making.

Conclusion: To meet patients' needs, future medicines optimisation interventions should enhance information exchange, better prepare patients and clinicians for partnership in care and foster collaborative medication reviews across care settings.

INTRODUCTION

Inappropriate polypharmacy and related adverse health outcomes represent significant challenges in the ageing multi-morbid population.[1,2] Decisions about stopping, starting or modifying medicines in multi-morbid older patients are often 'preference sensitive'; the limited evidence about the benefit of most medications, treatment conflicts, treatment burden, patient preferences and prognosis should be considered in the decision-making process.[2-8] A patient-centred approach incorporating patient preferences in treatment decisions through shared decision-making (SDM), has been advocated as pivotal to improving quality of care and reducing harms of overtreatment in multi-morbid patients.[2,6,9-12]

Medication reviews are recommended to reduce inappropriate polypharmacy in older patients, yet the impact on clinical outcomes remains uncertain.[13-15] The European OPERAM trial is a multi-centre cluster randomised controlled trial involving 2009 multi-morbid older patients evaluating the impact of a complex intervention including medication review and SDM on drug-related readmissions. The OPERAM intervention is described in detail elsewhere.[16] Beyond evaluating effectiveness of an intervention, qualitative research alongside trials can help to better understand implementation of the intervention, contextual factors and mechanisms affecting intervention effectiveness.[17,18] Evaluating the patient experience can provide a whole system perspective, may reveal aspects that are invisible to researchers and can help identify strengths and weaknesses of services to improve quality.[19-21] There is lack of a universally agreed-upon definition of patient experience but core aspects associated with a positive patient experience include: involvement of patients and companions in decision-making, respect for patient preferences, clear information and communication, emotional support, physical comfort, transparency, care coordination, continuity and access to

care.[19,22-24] A positive patient experience is correlated with clinical effectiveness and safety including reduced readmissions.[19,25] Few qualitative studies have explored multi-morbid older patients' experience of hospital-initiated medication changes and further research into multi-morbid patients' perspectives on medicines optimisation is warranted.[26-30] This study, embedded in the OPERAM trial, aimed to explore multi-morbid older patients' experiences of hospital-initiated medication changes in four European countries.

METHODS

Study design and setting

We conducted a multi-centre mixed methods study combining both qualitative and quantitative data. Semi-structured interviews were performed within one month after discharge, to gain an in-depth understanding of patient experience of hospital-initiated medication changes. The NHS Patient Experience Framework was used to underpin the interviews.[22] The findings from the interviews were triangulated with quantitative data from the Beliefs about Medicines Questionnaire completed by patients and with the clinicians' perspective of patient participation in decision-making.[31,32] Participants were recruited from teaching hospitals in urban settings in Belgium, Ireland, Switzerland and the Netherlands.

Participant selection

Patients enrolled in the OPERAM intervention or control arms, who met the mixed methods study inclusion criteria (Table 1) were eligible to participate. We selected a purposive sample by screening the medical records of potentially eligible patients to ensure heterogeneity in terms of age, gender, study arm (intervention/control), hospital ward, educational background and living situation (at home/nursing home). We decided *a priori* to aim for 10 to 15 participants per country to have a broad range of patient perspectives from different backgrounds. Patients were

approached face-to-face during their hospitalisation by OPERAM researchers. Patients were recruited after the OPERAM trial had been running for twelve months; hence researchers had become experienced in delivering the intervention. All research team members delivering the intervention were trained prior to the start of the OPERAM trial and standard operating procedures on intervention delivery were provided. Researchers also received a 45 minute webinar training on the principles of SDM, based on the collaborative deliberation model.[6,33,34]

Table 1: Inclusion and exclusion criteria of the OPERAM trial and the embedded mixed methods study

OPERAM trial	Mixed methods study embedded in OPERAM
Inclusion criteria • 70 years or older • Multi-morbidity (≥ 3 chronic conditions ≥6 months) • Polypharmacy (≥ 5 chronic medications) Exclusion criteria • Direct admission to palliative care • Having passed a structured medication review within the last two months	Inclusion criteria • ≥ 1 change in chronic medication proposed during hospitalisation e.g. the addition, discontinuation or modification of a medicine such as the dose or dose form. The medication change could be a result of the OPERAM intervention or usual care. • Informative patients willing to share their experience Exclusion criteria • Inability to provide informed consent • Patients with confusion, dementia or severe cognitive impairment • Unacceptable living distance from the clinical sites (for pragmatic reasons)

Qualitative data collection and analysis

Semi-structured interviews were conducted by research team members (S.T., C.P., B.M., A.V.H., K.M.) in each site in the local language. All interviewers had a background in healthcare as researchers and/or as healthcare professionals (pharmacy, public health/nursing, psychology and geriatric medicine), were trained in qualitative interviewing and had no direct clinical relationship with patients. The interview was preferably scheduled within one month (mean: 28 days) after discharge to avoid recall bias and took place at the patient's home or at the hospital before or after an outpatient consultation. The patient was invited to have a companion present if this reflected the usual situation. Interviews were conducted between January 2018 and February 2019 and lasted an average of 36 minutes (range: 19 – 80 mins).

A semi-structured topic guide **(Appendix 4)** was developed in English based on the NHS patient experience framework **(Appendix 5)** and the OPERAM intervention components.[22] The topic guide consisted of eight open-ended questions with follow-up prompts covering the following aspects: information about medication changes; participation in decision-making; involvement of companions; perspectives on medication review in general; patient experience of and acceptance of hospital-initiated medication changes; transition to primary care and related barriers, facilitators and patients' needs. The topic guide was translated into the local languages and piloted with at least three patients in each study site. A webinar training session and standard operating procedures were provided to train the interviewers (available upon request). Interviewers took field notes during the interview to document contextual aspects, interviewees' behaviour and reflections about the interview.

Interviews were recorded and transcribed verbatim in the native language. Data collection and analysis occurred simultaneously to allow incorporation of interesting findings in the topic guide for the next interviews. Thematic analysis was performed using the Framework approach by three researchers (S.T., C.P., B.M.) combining pharmacy, nursing/public health and psychology perspectives. The Framework approach is a systematic approach for categorising and organising the data and involves familiarisation with the interviews, developing a thematic framework, coding, charting the data into the framework and interpreting the data.[35,36] QSR International's NVivo 11 software was used to facilitate data analysis. Firstly, two researchers (S.T. and C.P) familiarised themselves with a sub-set of interviews by reading and re-reading the transcripts and field notes to identify themes. Themes were compared and discussed between the two researchers to develop an initial coding framework. Codes were partly pre-defined by the study objectives/interview schedule but mainly arose inductively from the data to dictate themes and categories. Subsequently, the coding framework was applied to the next set of transcripts. To minimise subjectivity, the first 15 interviews from Belgium were coded concurrently by S.T. and C.P. Codes applied for the first 15 interviews were compared and discussed until consensus to refine the coding framework. The coding framework contained definitions for application of each code. After analysis of a first set of interviews, the initial coding framework and illustrative quotes were discussed within the research team, which helped to identify overlap between themes, themes that should be separated and to refine organisation of themes and categories into the coding framework. Next, the Swiss interviews were coded independently by S.T. and B.M. (who conducted the Swiss interviews). Agreement on coding across all themes for a set of 3 transcripts was satisfactory, with Cohen's κ scores of 0.83 and 0.84 between S.T. and C.P. and between S.T. and B.M. respectively. S.T. continued with coding independently the

interviews from the Netherlands and Ireland, with regular cross-checks with the interviewers if needed. The coding framework was constantly refined during further analysis until no new codes emerged. Data saturation, defined as the point where themes and categories become repetitive between participants, was reached after analysis of the first 15 Belgian interviews.[37] The coding framework did not change considerably following analysis of subsequent interviews from the other sites. Throughout the coding, the researchers created analytical memo's to write down impressions, ideas and early interpretation of the data. When all data were coded and summarised, the coding framework was reviewed to make connections within and between participants and themes. Barriers and facilitators were identified and linked to the major themes. Interpretation of the findings was supported by the use of the analytical memos, looking for deviant cases, going back to the literature, discussion within the research team and feedback from the interviewers from all sites on the preliminary results. Qualitative results were triangulated with the quantitative data collected during the interpretation stage.

A summary of the qualitative findings was sent to the interviewers from each site and as well as to nine Belgian OPERAM patients for validation. Participants were asked to what extent the findings corresponded to their experience and to report any disagreement. None disagreed with the themes reported and some patients stressed themes that they considered as most important.

We used the consolidated criteria for reporting qualitative research for designing and reporting this study.[38] Rigour was addressed throughout the various stages of the research process as described in Table 2.[38-40]

Table 2: Rigour addressed throughout the research process.[38-40]

Reflexivity	• The researchers who drafted the study protocol (S.T., O.D., A.S.) have a background in pharmacy and had pre-conceptions about the topic by prior literature review and because of their involvement in the OPERAM trial. Feedback on the study protocol was provided by a sociologist and multidisciplinary research team members from the four countries involved. • Data collection was performed by researchers and/or healthcare professionals from four different countries (S.T., K.M., C.P., A.V.H., B.M.) who have backgrounds in pharmacy, nursing/public health, geriatric medicine and psychology respectively. All interviewers were trained in qualitative research methods and had no direct clinical relationship with the patient to limit the risk of response bias. All researchers performed 3 pilot interviews. Not all interviewers were blinded to the intervention or control arm allocation of the patients because of their role in the OPERAM trial, which might have influenced the data collection.
Credibility	• Several researchers from different countries and backgrounds were involved in data collection and analysis, helping to prevent bias from a single researcher excessively influencing data analysis. • Respondent validation: The results were validated by sending nine OPERAM patients a summary of the findings. Patients were asked to what extent the findings corresponded to their experience and to report any disagreement. None disagreed with the themes reported. • Data analysis was documented in detail. The coding framework contained definitions and rules for application of each code to allow explicit and transparent data analysis. • Transcriptions were performed by local researchers in each site in the native language, to avoid losing nuances in the data by translation. To account for the chance of linguistic misinterpretation during data analysis, a native speaker was involved in analysis of the Belgian (CP), Dutch (ST) and Swiss (BM) interviews. Analysis of the Irish interviews was performed by a researcher with a good command of the English language (ST) with cross-checks with the native speaker who conducted the Irish interviews (KM) in case of uncertainty about meaning. A selection of quotes from the Belgian, Swiss and Dutch study participants were translated from French, Swiss German and Dutch into English by a translation agency.
Transferability	• Thick description of setting and participants was performed. Transferability is enhanced by including participants from four different countries and healthcare settings as well as by including a purposive sample to ensure variation in several patient characteristics.

Quantitative data collection and analysis

Beliefs about Medicines Questionnaire (BMQ)

To complement the findings from the interviews, patients' beliefs about medicines were assessed quantitatively using the BMQ at the end of the interview.[31] Understanding patients' beliefs about medicines is important because they may influence the acceptance of medication changes and adherence.[41-43] The BMQ consists of the BMQ-General and BMQ-Specific, evaluating beliefs about medicines in general and beliefs about medicines prescribed for personal use respectively.[31] The BMQ-General assesses beliefs that medicines are overused by physicians (General-Overuse) and beliefs that medicines are harmful (General-Harm). The BMQ-Specific assesses beliefs about the personal need for medicines to maintain health (Specific-Necessity) and concerns about the potential adverse effects of medicines (Specific-Concerns). Items on the BMQ subscales are scored on a 5-point Likert scale varying from 1="strongly disagree" to 5="strongly agree". Higher scores indicate stronger beliefs in the concepts of the sub-scale. Median scores for the four sub-scales were calculated. For the BMQ-Specific, the necessity-concerns differential was calculated by subtracting the concerns score from the necessity score resulting in four attitudinal groups: accepting (necessity ≥15, concerns <15), ambivalent (necessity ≥15, concerns ≥15), sceptical (necessity <15, concerns ≥15) and indifferent (necessity <15; concerns <15).

Clinicians' perspective on patient participation in decision-making about medication changes

For the patients enrolled to the intervention arm, we collected the following implementation data on patient participation in decision-making on medication changes, a component of the OPERAM intervention, as perceived by the research clinician who delivered the intervention:

- Whether medication changes were discussed with the patient (yes/no)
- Whether formal SDM was performed (yes/no) (according to the standard operating procedure on SDM used in the OPERAM trial, based on the collaborative deliberation model from Elwyn et al.[6,33,34])

Furthermore, the patients' prescribing clinicians (i.e. the physician or pharmacist who proposed the medication changes to the patient as part of the OPERAM intervention or usual care) were asked to complete the physician version of the shared decision-making questionnaire (SDM-Q-DOC). The SDM-Q-DOC is a validated 9-item questionnaire assessing the level of SDM as perceived by the physician during a consultation.[32] The SDM-Q-DOC includes nine statements that should be scored on a 6-point Likert scale ranging from "0=completely disagree" to 5=completely agree". Scores range between 0 and 100 with 0 representing the lowest possible level of SDM and 100 the highest possible level.[32] The SDM-Q-DOC was administered as soon as possible after discharge of the patient via email or by completing a hard copy of the questionnaire. For pragmatic reasons, only clinicians from the OPERAM sites in Belgium and Switzerland were invited to complete the SDM-Q-DOC. The quantitative data obtained were summarised using descriptive statistics.

The implementation data on SDM and results from the SDM-Q-DOC were subsequently triangulated with the extent of patient participation reported by the patients in the semi-structured interviews. The following question from the topic guide explored patient participation in decision-making: 'When deciding to change a medication, there are three possible ways to proceed. It is either the doctor that decides alone, or it is the patient that takes the decision alone or it is a shared decision. How was the decision of changing your medication taken during your hospitalisation?' Corresponding verbatim was coded as 'paternalistic decision-making' if the patient reported that the decision was taken by the clinician and the patient was informed afterwards. Verbatim was coded as 'patient participation in decision-making' if the patient reported some extent of patient participation, varying from patients reporting having been asked for their approval on medication changes (patient consultation), decision shared or having decided autonomously after being informed.

Ethics approval

Approval for the study was granted by the ethics committee at each study site (Belgium: Cliniques universitaires Saint-Luc, Brussels, reference B403201629175; Ireland: Clinical Research Ethics Committee of the Cork Teaching Hospitals, reference ECM 3 (nn) 05/12/2017; Switzerland: Kantonale Ethikkomission Bern (KEK), Basec-Nr.: 2016-01200; The Netherlands: University Medical Centre Utrecht, reference NL58279.041.16) and written informed consent was obtained from all patients before interviewing.

RESULTS

Description of participants

Of the 73 patients approached, 57 patients agreed to participate (acceptance rate=78%). Sixteen patients declined to participate for reasons including not interested, not comfortable talking about doctors to researchers, feeling 'too old'. Nine patients agreed to participate but dropped-out of the study (died, too ill, no longer interested, could not be contacted after discharge, not within time limit) resulting in a sample of 48 patients. The patient characteristics are presented in Table 3.

Table 3: Patient characteristics (*n*=48)

Variable	Value
Age (years; median [P_{25}-P_{75}])	76 [72–81]
≥70-≤80 years (*n*, [%])	34 [71]
>80-≤90 years (*n*, [%])	13 [27]
>90 years (*n*, [%])	1 [2]
Sex (*n*, [%])	
Female	23 [48]
Male	25 [52]
No. of medications on admission (median [P_{25}-P_{75}])	10 [7-14]
Total no. of medication changes proposed during admission (median [P_{25}-P_{75}]; [range])	4 [2-6; 1-13]
n [%] of patients with ≥1-≤4 changes	29 [60]
n [%] of patients with ≥5-<10 changes	17 [35]
n [%] of patients with ≥10-≤13 changes	2 [4]
Proposed medication stops (median [P_{25}-P_{75}]; [range])	1 [0-2; 0-10]
Proposed medication starts (median [P_{25}-P_{75}]; [range])	1 [1-2; 0-10]
Proposed medication modifications (median [P_{25}-P_{75}]; [range])	0 [0-1; 0-3]
Country (*n*, [%])	
Belgium	15 [31]
Ireland	7 [15]
Switzerland	11 [23]
The Netherlands	15 [31]
OPERAM study status (*n*, [%])	
Control group	21 [44]
Intervention group	27 [56]
Ward specialty (*n*, [%])	
Medical ward	36 [75]
Surgical ward	12 [25]
Length of stay (days; median [P_{25}-P_{75}])	9 [7-11]
Educational level (*n*, [%])	
Less than high school completed	7 [15]
High school degree	23 [48]
Post-secondary degree	18 [37]
Place of residence (*n*, [%])	
Home	45 [94]
Nursing home	3 [6]
Interview with (*n*, [%])	
Patient	31 [65]
Patient and companion	17 [35]

Table 4: Themes, categories and illustrative quotes related to multi-morbid older people's experience of hospital-initiated medication changes

Theme	Category	Illustrative quotes
I. LACK OF INFORMATION AND COMMUNICATION ABOUT MEDICATION CHANGES	Satisfaction with information received	*Patient, Ireland: 'Well if they mentioned a medication, I wouldn't know what it was for and they would tell me then…or what effect it was going to have. And he'd say "do you understand what I've been saying?" and I'd say "no" and he'd explain it then. And that was fine. It was clear. I felt that they granted me the… that I'd understand them…that I knew what they'd be talking about.'* *Patient, The Netherlands: 'If you don't ask about it [for information about medication changes], they don't tell you anything; but if you do ask, then they're quite willing to tell you stuff, but I don't think that's really right. You should do that when you're planning to make those [medication] changes'* *Patient, Belgium: 'No-one explained anything to me! When I was discharged they just told me, so you've got this and that, and this instead of that. And that's all… As for the whys and wherefores, I've no idea.'*
	Lack of recall	*Patient, Belgium: 'Because when the doctor explains things, you understand at the time… but then I start having doubts and feel I have to do some research… I'm not totally lost, but I find myself thinking, ooh, what's that and what about that? Have I understood it right?'*
	Limited opportunities for questions	*Patient, Switzerland: 'But they were all stressed all the time, anyway. And they would just come along in a hurry. They come and they go and that's it, it's done… I could only ask the nurses; the doctor only came around very rarely. And when he came, he asked, how are you, and stuff and stories. It's a case of such and such. And then, goodbye, thanks, and they were gone again already.'*
	Use of jargon and language issues	*Patient, Belgium: 'And when you start asking why – sometimes, I think they find it hard to explain things. // Yes, they have all their drug lingo. And that's what's difficult to grasp at times – well, for me anyway.'*
II. PATERNALISTIC DECISION-MAKING PREDOMINATES , VARIABLE SATISFACTION	Paternalistic decision making	*Patient, Belgium: 'It's sort of due to the system, you know. They're the ones who decide on the treatment and then they pass that on to a head nurse to administer or something like that. And well, you don't get a say in the matter, do you? When it comes down to it, all you have to do is swallow what they put in your mouth.'* *Patient, Ireland: 'They disregarded the people. And now these weren't people that, you know, had problems taking on board what they were saying. But they just said "we'll do this, this and this" and they'd be gone!'* *Patient, The Netherlands: 'That wasn't discussed with me [stop amlodipine and lisinopril]. I suddenly realised, hey, I'm not being given those [medications] anymore.'*

Table 4: Themes, categories and illustrative quotes related to multi-morbid older people's experience of hospital-initiated medication changes

II. PATERNALISTIC DECISION-MAKING PREDOMINATES , VARIABLE SATISFACTION	Patient-centred decision making	*Patient, Belgium: 'I don't have anything to say, as I made the decision [decision to not commence a statin proposed as part of the OPERAM intervention] freely. It can't be any other way. I can't imagine another situation where the nurse, pharmacist, doctor or whatever takes on the role of an instructor, telling the patient "you have to do this, you need to do that", etc.'* *Patient, Switzerland: 'So it's up to me to take them. That means I decide myself. I could refuse to take them, after all. I would have the right to do that. So they just proposed them to me and then it would be up to me...// Yes, actually up to me. Because, as I said, he did say that to me: I could also refuse to take them. But the consequences then would be X and Y.'*
	Discussion of patient preferences	*Patient, Belgium: 'And I told them that my policy was to live for as long as possible because the fact that I'm alive, even if I'm not leading a very active life, also keeps my wife alive and relatively fit. And that's what has always been our guide.'*
	Satisfaction with participation in decision-making	*Patient, The Netherlands: 'Well, I didn't have any say in that and I have to say, honestly, that I don't think that's right... No, they don't have to consult me, but I do want to be informed about it.'* *Patient, Ireland: 'I hadn't [the desire to ask] because they completely ignored me...As if I wasn't there at all. // I thought they should have discussed it [decision to commence opioids] with me because I was the person taking them. They were prescribing it to me.'...//* *'I thought it was very bad. The doctor that charged me £400 [Irish currency pre-Euro]. And never even spoke to me.'*
III. BARRIERS AND FACILITATORS TO INFORMATION AND PATIENT PARTICIPATION	Beliefs about patient role [barrier or facilitator]	*Patient, Ireland: 'Well, when you're in hospital and you're getting medication, you just take it. You don't ask questions like.'* *Patient, The Netherlands: 'I assume the doctor knows more about it than I do, so I have to accept it.'* *Patient, Belgium: 'I just want to understand what's wrong with me and whether there's any chance of improvement.... I need to know and I need to understand.'*
	Health literacy and personal resources [facilitator]	*Patient, Belgium: 'Yes and especially as I'm really keen on that. I have to know the package leaflets by heart, all the contra-indications. I'm a bit obsessed now. I love knowing exactly what I'm in for. When I take any medication, especially a new medication. Or when the dose is changed too.'* *Patient, Switzerland: 'But I was on top of the medication situation. And now too. I know what I'm taking and why.'*
	Involvement of companions [facilitator]	*Patient, Belgium: 'So if my grandson hadn't intervened, maybe they wouldn't have given me Lyrica and wouldn't have discussed things with me more.'*

Table 4: Themes, categories and illustrative quotes related to multi-morbid older people's experience of hospital-initiated medication changes

III. BARRIERS AND FACILITATORS TO INFORMATION AND PATIENT PARTICIPATION	Interpersonal characteristics of the clinician [barrier or facilitator]	*Patient, Ireland: 'I was on [loperamide], that transformed my life 30 years ago. This [medication] came along and it transformed me but they seemed to dismiss that like you know….Oh they just, they just more or less dismissed…I don't think they were listening at all. And I'll be quite honest with you.'* *Patient, Belgium: 'There's a lot of time spent on the patient's experience, their feelings, in a desire – a sincere one, I believe – to help them and not just bombard them with prescriptions that may or may not be helpful. I think that's really nice because all too often in hospitals you feel a bit like a number.'*
	Trust and clinician-patient relationship [barrier or facilitator]	*Interviewer: 'My question is, what prevented you from being involved in the decision yourself?' Patient, Switzerland: 'I trusted them blindly.'* *Patient, Belgium: 'So I might say my breathing isn't great, can I increase my diuretics a little bit? And before you know it, it's done. The initiative usually comes from me, though. Whether or not I complain about my health. And since I was admitted for a month and a half, I had time to talk. I know them [hospital staff] all, you know.'*
	Bad timing of medication discussions [barrier]	*Patient, Belgium : 'For three or four days after the operation you're in a foggy sort of state [laughs], and, as far as I was concerned, the medication problem wasn't important to me at all, not at all… It was just a detail for me.'*
	Overwhelmed by multiple clinicians involved in care [barrier]	*Patient, Switzerland: 'If the same doctor came each time, then you could build up a relationship. And then you might have other questions and things might work differently. Yes, that mightn't be a bad idea.'*
IV. POSITIVE ATTITUDES TOWARDS MEDICATION REVIEW AND ACCEPTANCE OF MEDICATION CHANGES	Medication review is 'a good thing' but the GP should be involved	*Patient Switzerland: 'Yes, I do think it's a good idea to review things. What had built up, too, over a lifetime and over the whole period. And situations and illnesses change too.'* *Patient, Belgium: 'So at that point there should be another person there, the GP. It's a good idea for them to be involved in the discussion.'*
	Acceptance of hospital-initiated medication changes	*Patient, Switzerland: 'I just take what the doctors prescribe, and I do so consistently. It mightn't taste great, but I take them. [laughs]'* *Patient, The Netherlands: I take it because it's prescribed, and that's that.* *Patient, Ireland: 'I'm only taking one [instead of the prescribed oxycodone 10mg BD] going to bed at night. Because if I took one during the day when I come down here, I'd be sleepy all day.'*

Table 4: Themes, categories and illustrative quotes related to multi-morbid older people's experience of hospital-initiated medication changes

V. BARRIERS AND FACILITATORS TO ACCEPTANCE OF MEDICATION CHANGES	Beliefs about medicines [barrier or facilitator]	*Patient, Belgium: 'Well, generally speaking, all these medicines are pretty essential for me, you know, so it's very important. Especially the latest ones – I now take Zyrtec and Imodium to help me make it through the day. I have to take them, you see. Otherwise, I just wouldn't be able to cope.'* *Patient, Switzerland: 'And then I changed that again and took my old painkillers. And now I have them again. I just find they help me. When I take one of those three times a day, then I can feel pretty good.'* *Patient, Belgium: 'I mean, they're using a sledgehammer to crack a nut. With a whole host of side-effects, it's just not necessary.'*
	Medication changes perceived as minor [facilitator]	*Patient, The Netherlands: 'They are minor changes – that's not hard to decide. Look, they're nothing drastic, so no, it wasn't difficult.'* *Patient, Belgium: 'It's no big deal for me. Because I feel like my oesophagitis isn't very serious after what I've been through. As soon as they tell you you've got cancer, and not a minor cancer, mind you – it's the pancreas after all, which is a serious matter – anything to do with my oesophagitis is not a priority for me, it's just not in the same league…'*
	Experiencing benefit or harm from a medication change [barrier or facilitator]	*Patient, Ireland: 'I do feel in the short, the short time that I'm on them. I feel possibly that my chest is a little freer.'* *Patient, Belgium: 'With an anxiety attack you feel like you're going to explode! When you have an attack like that. It's really… it like something's got you by the throat. You can't escape from it [voice breaks, pause]… No, without Seroxat, things aren't good at all. [silence]'*
	Trust and balancing advice between different healthcare providers [barrier or facilitator]	*Patient, Switzerland: 'But when someone says to me, "Your liver results are too high, so we have to change a medication," then I trust them.'* *Patient, Belgium: 'Because anyway with all the changes they suggested, I went to see my GP – I have a lot of confidence in her, she's obviously known me for years, keeps an eye on me… And as for the statins [prescribed as part of the OPERAM intervention], I said that I wouldn't take them. Since she [the GP] was not at all in favour of using statins, I didn't pursue the matter.'* *Patient, Switzerland: 'From three sides, more or less, the GP, the hospital, and you (OPERAM Study), you were all agreed. Everybody came to the same conclusion, except for one medication. And that reassured me.'*

Table 4: Themes, categories and illustrative quotes related to multi-morbid older people's experience of hospital-initiated medication changes

V. IMPORTANCE OF COORDINATION BETWEEN SECONDARY AND PRIMARY CARE	Better preparation for discharge	*Patient, Belgium: 'But I think that someone who's getting sent home needs more in the way of interaction. I knew I was going home and my daughters were waiting for me and all that. So my case is a bit special, but I suppose when you're old and alone, the situation has to be reviewed at a time like that. Because once you're home, are you in a position to take your medication properly?'*
	Follow-up support	*Patient, Switzerland: 'Afterwards, I asked her [the GP], "Why don't I have to take those brown ones [tablets] anymore?" And she said it was because of my blood pressure. That had changed. So she explained why. And then I was reassured.'* *Patient, Belgium: 'That's the problem: when they change something, they do it at the hospital and there's no follow-up outside.'*
	Poor communication between primary and secondary care	*Patient, The Netherlands: 'But I've noticed that sometimes there's a time lag. One day, the specialist tells you that this and that have to be doubled because…and so on. And a week later you go along and ask for the medication at the pharmacy and they still aren't in the picture. So they give you the old box again. So there's always some problem at the pharmacy. And I find that annoying – surely it doesn't have to be like that in this digital day and age.'*

Semi-structured interviews

The thematic analysis resulted in six themes and 24 categories, organised according to the process of medication review and SDM (Table 4). Our aim was to describe patient experience across a diverse sample, rather than reporting country-specific or study-arm specific findings. However it should be noted that major themes did not differ between the four countries or between intervention and control arms. These findings suggest that cultural differences did not substantially affect patient experiences, nor did the OPERAM intervention.

Theme I: Lack of information and communication about medication changes

Patients' satisfaction with information received about medication changes was mixed. More than half of the patients reported a lack of information, in particular on the indication of medicines, the reason for changing or side effects. At the extreme, eight patients said they received no information at all and others said they had to ask for information themselves. Inadequate information or communication resulted for some patients in lacking understanding of medication changes, confusion or anxiety. Other patients were satisfied because they were well-informed, and some were satisfied although reporting having received very limited information.

Some patients expressed having problems recalling the medication changes or the information received. Others stated that information was provided hurriedly with limited opportunities for questions. Some patients had difficulties with the jargon used by clinicians or the fact that the information was not provided in their native language.

Many patients emphasised the need for more information, medication counselling, providing a written medication list, providing information in lay language at a moment when the patient feels well, taking more time for providing information,

taking time to reassure the patient, giving patients access to the medical record. Several patients highlighted that they would like to be informed about their medicines during hospitalisation and not only at discharge.

Theme II: Paternalistic decision-making predominates, variable satisfaction

Patients predominantly experienced a paternalistic decision making process (37/48 patients), in which decisions to change medicines were taken by the clinician and patients were informed afterwards. A minority of patients (11/48 patients) reported active participation in decision-making. Active patient participation varied between patients being asked for their approval, decision shared or patients deciding autonomously after being informed. Some patients participated by proposing medication changes themselves.

One participant had open discussion about preferences in the context of medication-related decisions. Several patients commented that 'You go to the doctor to be healed, not to discuss preferences'. Others assumed that clinicians know their preferences, whereas a minority of patients would like to have preference discussions.

Patients' satisfaction with participation in decision-making was mixed. The majority of patients were satisfied with the paternalistic decision making approach and said they preferred to be informed rather than actively involved. Eleven patients were dissatisfied with paternalistic decision-making and preferred to be more involved. All patients with patient-centred decision-making were satisfied with information received and with participation in decision-making.

Perceptual differences between patients and their prescribing clinicians in relation to patient participation in decision-making

Paradoxical to patients' experiential accounts reported in the interviews, quantitative data on SDM from the prescribing clinicians' perspective revealed high levels of patient participation in decision-making (Table 5). According to implementation data, for 23/27 (85%) of the interviewed intervention patients, medication changes were discussed and for 19/27 (70%) intervention patients, formal SDM was performed in addition to discussion of medication changes. Eleven Belgian and six Swiss clinicians completed the SDM-Q-DOC (response rate=65%) and reported a high median score of 76. Patients however displayed mixed perceptions about participation in decision-making with 37/48 (77%) of all patients in the study reporting paternalistic decision-making compared with 11/48 (23%) patients reporting having participated in decision-making.

Table 5: Perceptual differences between prescribing clinicians and their patients in relation to patient participation in decision-making about medication-changes

Clinicians' perspective on patient participation in decision-making	
Implementation data on the SDM component of the OPERAM intervention for intervention patients (*n*=27)[a]	
n[%] of intervention patients for whom medication changes were discussed	23 [85]
n[%] of intervention patients for whom formal SDM was performed	19 [70]
SDM-Q-DOC score (median [P_{25}-P_{75}])[b]	
Total participating prescribing clinicians (*n*=17)	76 [69-82]
Prescribing clinicians' intervention group (*n*=10)	77 [74-81]
Prescribing clinicians' control group (*n*=7)	69 [53-81]
Patients' perspective on participation in decision-making	
n [%] of patients reporting participation in decision-making[c]	
All patients (*n*=48)	11 [23]
Intervention patients (*n*=27)	8 [30]
Control patients (*n*=21)	3 [14]

SDM, shared decision-making; SDM-Q-DOC, physician version of the 9-item SDM questionnaire
[a]Implementation of SDM as perceived by the research clinician who performed the OPERAM intervention. Formal SDM was defined according to the standard operating procedure on SDM used in the OPERAM trial, based on the collaborative deliberation model.
[b]SDM-Q-DOC scores were available for 17/48 interviewed patients' clinicians (from both intervention and control groups). The SDM-Q-DOC was completed by the research clinician (intervention group) or the patients' prescribing clinician (control group) who proposed the medication changes to the patient. Scores on the SDM-Q-DOC range between 0 and 100 with 0 representing the lowest possible level of SDM and 100 the highest possible level.
[c]As reported by patients in the semi-structured interviews. Decision-making was classified as 'patient participation in decision-making' if the patient reported some extent of patient participation, varying from patients reporting having been asked for their approval on medication changes (patient consultation), decision shared or having decided autonomously after being informed. Decision-making was classified as 'paternalistic decision-making' if the patient reported that the decision was taken by the clinician and the patient was informed afterwards.

Theme III: Barriers and facilitators to information and patient participation

Predominant paternalistic decision-making, often associated with inadequate information and communication, as explained in themes I and II, was the main barrier for patients to be well-informed and to participate in decision-making. In addition, patients reported several barriers and facilitators related to their beliefs, resources, clinicians and the patient-clinician relationship.

Beliefs about patient role

Overwhelmingly patients said they believed 'doctors know best' and considered themselves lacking competence to be involved in medication-related decision-making. This belief was closely linked with trust in doctors and was accompanied by a passive attitude and not asking for information, a barrier to be well-informed and to patient participation. Some patients specifically referred to this passive role while in hospital: 'In hospital you just take medications, you don't ask questions.'

Others described a more active role in decision-making varying from sharing experiences with medications, to questioning what the doctors propose, or some strongly believe 'the patient has the last word' about treatment. These patients said they take responsibility and proactively ask for information to ensure they understand. The belief that patients have a role in decision-making, showed to promote patient participation and can counter the lack of information received.

Health literacy and personal resources

Knowledge and understanding of medications acted as facilitators to patient participation. Patients with unmet information needs regarding the medication changes, described various ways in which they independently gained access to additional information e.g. by searching on the internet or by consulting a companion, the community pharmacist, general practitioner (GP) or specialist physician.

Involvement of companions

Whereas for most patients companions were not involved in their care, some patients perceived involvement of companions as a facilitator for being well-informed about medication changes e.g. by helping to remember the information received, by obtaining extra information from the clinician or for language support. For one patient, involvement of a companion enabled patient participation in decision-making.

Interpersonal characteristics of the clinician

Many patients said they valued being treated as individuals and appreciated clinicians listening to them, reassuring them, being understanding, being cordial, which acted as facilitators for patient participation. In contrast, some patients reported negative experiences with dismissive clinicians neglecting their needs and focussing solely on treating a disease, which acted as barriers to patient participation.

Trust and the patient-clinician relationship

Trust in doctors was for some patients a barrier to patient participation because it reinforces a passive attitude ('doctors know best'). On the other hand, one patient reported that a long hospitalisation allowed him to build a relationship with clinicians, which was a facilitator for patient participation.

Bad timing of medication discussions

Several patients reported that hospitalisation was not the right time to discuss medication changes because they were too ill or too fatigued, acting as a barrier to patient participation.

Overwhelmed by multiple clinicians involved in care

The fact that multiple clinicians were involved in care, was for some patients a barrier to asking questions and being involved.

Theme IV: Positive attitudes towards medication review and acceptance of medication changes

Patient perspectives on medication review were generally very positive. Patients acknowledged the importance of checking the appropriateness of their medication and stopping unnecessary medicines. Many patients expressed a desire to take less medicines. Several patients considered medication review desirable in hospital because specialists were around or they felt closely monitored, whereas others emphasised the need for more involvement of their GP. Several patients considered the GP or the community pharmacist to be the more appropriate person for medication review because of trust, a good and long-standing relationship and the medical overview that they have. One patient enrolled to the intervention arm had a very strong opinion about this and considered the proposed medication changes in hospital as critical of the GP and did not accept any of the proposed medication changes.

The majority of patients reported having accepted and implemented the hospital-initiated medication changes, compared to a minority of patients that did not implement the changes, following the GP's advice or on their own initiative. Others said they would give the medication change 'a try' and would reconsider definite implementation later. Some patients implemented on their own initiative additional strategies to cope with medication changes including dose reduction because of side effects, self-medication, 'grandmothers' remedies' or self-monitoring blood pressure.

Theme V: Barriers and facilitators to acceptance of medication changes

Beliefs about medicines

Necessity and concern beliefs were identified as key barriers or facilitators to acceptance of medication changes. The majority of patients accepted the medication changes and acknowledged the necessity for a change (e.g. physical need for a change, usual treatment perceived as burdensome or ineffective) or believed in a long-term effect (facilitators). On the other hand, low necessity beliefs about medicines (e.g. usual treatment perceived as necessary or important) or concerns about medicines (e.g. fear of side effects), acted as barriers or facilitators to acceptance of medication changes. For example, one patient with severe stenosis of one carotid artery, who was enrolled to the intervention arm and who reported being very satisfied with the SDM intervention he experienced, did not accept a statin because his necessity beliefs did not outweigh his fear of side effects. In addition, his GP did not agree with commencing a statin.

Beliefs about medicines reported in the interviews were in line with the results from the BMQ (Table 6). For 90% of patients, the necessity-concerns differential was positive, indicating that they believed that benefits outweighed concerns. When participants were categorised by attitudinal group, 71% of patients were accepting, 21% were ambivalent, 6% were indifferent and 2% were sceptical.

Medication changes perceived as minor

Patients who perceived their medication changes as minor ('it is only a small change'), reported they easily accepted the change. Several patients considered a medication change as a minor issue in relation to their illness perception e.g. a decision to start a proton pump inhibitor for symptomatic oesophagitis was considered as minor compared to the cancer the patient suffered from.

Table 6: Patients' beliefs about medicines (*n*=48)

BMQ subscale	Median score [P_{25}-P_{75}]	*n* [%] of patients above the scale midpoint
General-Overuse[a]	13 [10-15]	25 [52]
General-Harm[a]	11 [8-12]	10 [21]
Specific-Necessity[b]	21 [17-24]	40 [83]
Specific- Concerns[b]	12 [10-14]	11 [23]
Necessity-concern differential[c]	8 [4-12]	43 [90]

BMQ, Beliefs about Medicines Questionnaire
[a]Scale ranges from 4 to 20 where high scores indicate negative beliefs about medicines.
[b]Scale ranges from 5 to 25, higher scores indicate stronger necessity or concern beliefs.
[c]Scale ranges from -20 to 20, positive scores indicate that the patient perceives necessity outweighs concerns.

Experiencing a benefit or harm from a medication change

Patients described the impact of a medication change on symptom control and side effects as attributes affecting the definite implementation of medication changes. Practical effects (e.g. taking less medicines, smaller pills, easier medicines packaging) were cited as facilitators to accept medication changes. However even if patients were dissatisfied with medication changes, this does not necessarily imply non-acceptance of changes e.g. if necessity beliefs were stronger.

Trust and balancing advice between different healthcare providers

Trust in doctors acted a facilitator to accept the medication changes. Several patients reported receiving conflicting advice from different healthcare providers, which may act as a barrier to accepting the medication changes. Patients explained how they choose to either follow the GP's or the specialist physician's recommendations, depending on whom they trusted more. In contrast, when the GP confirmed the medication change or the medication change had been previously proposed by a specialist physician, patients reported it facilitated acceptance and it reassured them. The majority of patients reported that their GPs

approved the medication changes and some patients explained that their GPs did not question decisions from the specialist physician.

Theme VI: Importance of coordination between secondary and primary care

Many patients reported having received good follow-up support from their GP and appreciated the fact that the GP was updated about the medication changes. However, some patients experienced a lack of follow-up support. One patient experienced severe psychological distress because of the withdrawal of his antidepressant. He felt abandoned by the hospital physician and by the GP, neither of whom provided adequate psychological support. A few days later, the patient was readmitted with a panic attack. Some patients had problems with a lack of prescription refills after discharge and others were confused because of the generics received in hospital and branded medication received at home. Several patients highlighted the need for better preparation for discharge, good follow-up support and better communication between primary and secondary care.

DISCUSSION

This study provides an in-depth understanding of multi-morbid older patients' experience of hospital-initiated medication changes and identified barriers, facilitators and patients' needs in relation to medicines optimisation. Patients generally displayed positive attitudes towards medication review and hospital-initiated medication changes. However, an interplay of factors related to inadequate information and communication, patients' beliefs, clinicians' attitudes and doctor-patient relationships may affect effectiveness of medication review.

Patients frequently reported problems of inadequate information and communication about medication changes, which concurs with previous research on patient experiences of hospital-initiated medication changes or medication

review.[26-28,44-48] Inadequate information is a significant barrier to SDM.[49] Paternalistic decision-making was predominantly reported by patients from intervention and control groups, suggesting that SDM was not perceived to have been largely used in the OPERAM trial. Interestingly, we found discordance between patients' accounts of paternalistic decision-making and clinicians reporting high levels of SDM according to quantitative measures. Despite observations demonstrating the contrary, "we are already doing SDM" is a frequently reported attitude of clinicians, which might be due to a lack of understanding of what real SDM is about.[50,51] The webinar training provided to clinicians delivering the intervention was likely not sufficient to equip them with the full range of skills to perform highly effective SDM.

Moreover, patients were not specifically prepared for SDM in the OPERAM trial. Although eliciting patients' preferences is a cornerstone of SDM and is important to medicines optimisation in multi-morbidity, most patients reported not to expect preference discussions to be part of the clinical encounter. Paternalistic views and expectations on decision-making are especially engrained in older people, which can be mistaken by clinicians for a disinterest in patient participation.[49,51,52] Although several patients recognised their experiential role in medication-related decision-making, most patients have strongly rooted beliefs that 'doctors know best' and are satisfied with participation in terms of being informed or asked for their opinion, rather than taking the final decision. Heterogeneity in patients' preferences for receiving treatment information and participation in health decisions has been consistently demonstrated, although studies also showed that most older persons want their perspectives to be heard and participate more if their physician encourages participation.[27,53-59] Patient preferences for participation should be explicitly elicited and respected, rather than based on assumptions about the preferred patient role and recognising that patient information and

informed consent for medical interventions is a patient right in most European countries. SDM in older patients with multi-morbidity is a complex process and there is no single best way of doing SDM, rather it should be adapted for factors important to each individual patient.[60] Even if a patient prefers to defer decision-making to the clinician, the GP or a companion, but is involved in information exchange and preference discussions, this should still be considered SDM.[61]

Several patients emphasised the importance of a long-term trusting relationship such as with the GP for discussions about their medicines as well as the need for good coordination between primary and secondary care. In OPERAM, GPs were not directly involved in the medication review process and only received a letter with the proposed medication changes after the patient's discharge. To overcome some of the patient-reported barriers to medication review in hospital (e.g. absence of trusting long-term relationships, conflicting advice between different healthcare providers), involving GPs earlier in the medication review process seems essential. Compared to unidirectional communication, consensus and close collaboration between hospital specialists and follow-up care professionals in medication reviews may lead to higher acceptance rates of medication plans post-discharge.[62,63] Collaborative medication reviews by geriatricians and GPs have been suggested as an effective medication optimisation strategy for older patients with polypharmacy.[63]

Beyond the beliefs about patient role, trust and patient-doctor relationships, patients reported additional barriers and facilitators to SDM and several of these have been reported previously in the literature.[49,64-68] Hospitalisation has been considered as one of the most disempowering situations for patients.[45] Patients' accounts of lack of information, feeling too ill or too fatigued, poor understanding of jargon terms used by clinicians, dismissive clinicians, limited opportunities for questions and multiple clinicians involved in care, highlight the powerlessness

some patients may experience during hospitalisation, all a barrier to SDM.[52] Conversely, health literacy, involvement of companions, being treated respectfully as an individual and being listened to, were mentioned as facilitators to SDM. Moreover, decision characteristics may affect SDM.[49] Patients might not expect or want to have a voice in decisions about medicines as opposed more significant decisions such as cancer treatment or end-of-life discussions. Successful implementation of SDM in routine practice requires a combination of interventions at the macro-, meso- and micro-level. This includes training healthcare professionals in SDM, supporting and preparing patients and companions to engage in SDM, SDM tools, a patient-centred culture and incentives to foster cultural and attitudinal changes to SDM.[50,51,55,59,67,69] Bedside nursing shift handovers and ward rounds have been recommended as ideal opportunities to exchange information and engage patients in decision-making.[45,66]

Despite limited patient participation, patients' attitudes towards medication review and hospital-initiated medication changes were generally positive, with the majority of patients reporting having accepted the medication changes. Acceptance of medication changes is likely to drive adherence and persistence.[43] An interplay of beliefs about medicines, illness perception, experience with medication changes, trust and balancing advice between different providers affect acceptance of medication changes, which echoes findings from previous studies.[43,70-74] Given limited patient participation in decision-making, patient beliefs about medicines and preferences were unlikely to have been sufficiently addressed.

We observed little cross-country variation in themes, suggesting that cultural factors did not substantially affect patient experience. This might be explained by the fact that patients were all involved in the OPERAM trial and all were

hospitalised. Moreover, no major differences in standard practice regarding medication review exist across the four countries.

Strengths and limitations

Due to the qualitative nature of our study, generalisability of our findings to the whole OPERAM population or general population of older people is limited. There is a large heterogeneity within the older population in terms of health status and functional capacity in older people.[75,76] However, most patients in our study were in their seventies, had a high level of education, lived independently at home and did not suffer from cognitive impairment. The views expressed in the study therefore represent the perspectives of cognitive fit, educated older people with multi-morbidity rather than the oldest old or patients with low educational levels, impaired cognition or functional status. Furthermore, all interviewees took part in the OPERAM trial and it therefore might have been the more willing participants with potentially more positive experiences, although interviewees were not reluctant to share negative experiences. However, transferability of our findings was enhanced by interviewing a relatively large purposive sample of patients from multiple European countries with variation in patient characteristics.

We did not perform a formal process evaluation of the OPERAM trial, rather we focussed on the patient experience and triangulated our qualitative results with quantitative measures on the extent of patient participation in decision-making for a sub-sample of patients and clinicians.[17] The extent of participation in decision-making from the patient perspective was only evaluated qualitatively using an open-ended question in the semi-structured interviews. Concordance between patients and clinicians on patient participation would likely have been higher if we would have used a patient-reported SDM questionnaire.[77] Self-report SDM measures broadly indicate satisfaction with decision-making rather than the quality

of the interaction and are susceptible to social desirability and response biases, which may also explain the high SDM ratings by clinicians.[7879] Furthermore, we only conducted the SDM-Q-DOC for a proportion of clinicians and cannot rule out that some of the SDM-Q-DOC questionnaires were completed with some delay, which may lead to recall errors and imprecise rating of the SDM process. It might have been useful to integrate observations or interviews with the involved clinicians to provide a deeper understanding of the patient-clinician dyad.[78]

Not all interviewers were blinded to the intervention or control arm allocation of the patients because of their role in the OPERAM trial, which might have influenced the data collection. Credibility of our findings was enhanced by respondent validation and by integrating perspectives from different backgrounds in protocol development, data collection and analysis. However our findings are influenced by interpretation mainly from a healthcare providers' perspective.

CONCLUSION

Multi-morbid older patients generally displayed positive attitudes towards medication review and hospital-initiated medication changes. However, an interplay of factors related to inadequate information and communication, patients' beliefs, clinicians' attitudes, trust and doctor-patient relationships highlight the complexity of medication review with SDM in multi-morbid older patients and may affect its effectiveness. On the one hand many (but not all) patients retain very paternalistic views on medication-related decision-making, whilst simultaneously placing a high value on information exchange, involvement of their GPs and companions, empathetic and trusting patient-clinician relationships and a collaborative approach across care settings, all of which promote a patient-centred integrated care system. To meet patients' needs, future medicines optimisation interventions should enhance information exchange, better

prepare patients and clinicians for partnership in care and foster collaborative medication reviews across care settings.

ACKNOWLEDGEMENTS

This work is part of the project 'OPERAM: OPtimising thERapy to prevent Avoidable hospital admissions in the Multi-morbid elderly' supported by the European Union's Horizon 2020 research and innovation programme under the grant agreement No 6342388, and by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0137. The opinions expressed and arguments employed herein are those of the authors and do not necessarily reflect the official views of the EC and the Swiss government.

We thank all patients, their companions and clinicians who participated in this study for their time and contributions. We thank Reto Auer from the University of Bern for his help in designing the study and Olivier Schmitz from the Université catholique de Louvain, Belgium for his feedback on the study protocol.

CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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FOREWORD CHAPTER 2.2

Although eliciting patient preferences is a cornerstone of shared decision-making and most decisions about medications in older people with multi-morbidity are preference sensitive, only one patient in our mixed methods study (Chapter 2.1) had an open discussion about preferences. Several patients commented 'you go to the doctor to be healed, not to discuss preferences', illustrating that patients don't expect preference discussions as part of the medical encounter. Others assumed that clinicians already know their preferences. However, discordances between what patients prefer and what doctors *think* patients prefer are commonplace.[1,2] Although not a substitute for individual patient preferences in clinical encounters, aggregate data on patient preferences have been suggested to be a valuable source of information for clinicians to reduce the mismatch between clinicians' recommendations and patient preferences.[1] In addition to information on benefits and harms of different treatment options, decisions aids might also incorporate aggregate data on patient-reported outcomes or patient preferences e.g. by reporting facts such as '95% of older patients with polypharmacy would be willing to have a statin deprescribed if their doctor said it was possible'.[3] However, large databases on patient preferences would therefore be needed. As a first step to gain a better understanding of medication-related preferences of older people with multi-morbidity, in this chapter 2.2 we outline the methodology for a future scoping review on medication-related preferences of older people with multi-morbidity. For this review we collaborate with Kristie Weir from the Sydney Health Literacy Lab, a behavioural science and communication research group from the University of Sydney. The results of this review will be published in a future study.

PERSPECTIVE FOR CHAPTER 2.2

MEDICATION-RELATED PREFERENCES OF OLDER PEOPLE WITH MULTIMORBIDITY: PROTOCOL FOR A SCOPING REVIEW

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In preparation

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Incorporating patient preferences into treatment decisions is key to medicines optimisation in older people with multi-morbidity, although it is not yet standard clinical practice.
- Patient preferences are often misunderstood and there may be discordances between what patients prefer and what clinicians think patients prefer.
- A better understanding of patient preferences in multi-morbidity and polypharmacy is a research priority.

WHAT THIS STUDY ADDS

- In this chapter we outline the protocol for a scoping review aiming to synthesize the evidence on multi-morbid older persons' preferences and attributes of preferences for stopping (deprescribing), starting, continuing, modifying or selecting medications and to identify methods to elicit medication-related preferences in multi-morbidity.
- This scoping review may inform patient-centred decision-making in medication review for multi-morbid older people and may close the gap between what patients prefer and what clinicians think patients prefer.

ABSTRACT

Introduction: Elicitation of patient preferences for informing treatment decisions is crucial to medicines optimisation in older people with multi-morbidity. However there is a scarcity of knowledge on patients' preferences, which may lead to missed opportunities for patient-centred decision-making. This scoping review aims to synthesize the evidence on multi-morbid older persons' preferences and attributes of preferences for stopping (deprescribing), starting, continuing, modifying or selecting medications and to identify methods to elicit medication-related preferences in multi-morbidity.

Methods: We will conduct a scoping review according to the methodology of the Joanna Briggs Institute. The following databases will be searched from their inception to April 2019: Medline, Embase, PsycINFO, CINAHL and the Cochrane library. Grey literature will be retrieved from screening reference lists of the included studies and from Google Scholar. Qualitative, quantitative and mixed methods primary research and trials reporting on preferences for stopping (deprescribing), starting, continuing, modifying or selecting medications or methods to elicit medication-related preferences in multi-morbid patients aged ≥ 65 years will be included. Two reviewers will independently perform title/abstract and full text screening. Data will be extracted by one reviewer and checked for accuracy by a second reviewer. Critical appraisal of the included studies will be performed. The results will be presented as a descriptive numerical summary of the characteristics of the included studies and a narrative synthesis of the results answering each of the research objectives.

Discussion: This study will increase understanding of multi-morbid older persons' medication-related preferences. Despite the fact that aggregate data on patient preferences are not a substitute for individual patient preferences in clinical

encounters, we anticipate that this review may inform patient-centred decision-making in medication review in multi-morbid older people and may help to guide clinicians in having preference conversations with their patients. Furthermore this review could inform patient-centred outcomes research, patient-tailored guideline development or help to identify decisions that are particularly preference sensitive.

INTRODUCTION

Inappropriate polypharmacy is a significant problem in the older population and is associated with adverse health outcomes.[4,5] A paradigm shift from a disease-centred approach in favour of a patient-centred approach has been advocated as key to improving outcomes in multi-morbid older patients.[5-10] The question 'what matters to you?' embraces the ambition of patient-centred care that promotes patient-centred communication and shared decision-making (SDM) as a way to operationalize this paradigm shift.[11-14] Informing, eliciting and helping patients construct their preferences and priorities is a core aspect of SDM.[13] Preferences refer to healthcare activities (e.g. medications, self-management tasks, healthcare visits, diagnostic testing, procedures) that people are willing and able (or not willing or able) to perform and the care they are willing (or not willing) to receive.[15] Priorities refer to the specific health outcome goals that individuals most desire from their health care given what they are willing and able to do to achieve these outcome goals (within the context of their healthcare preferences).[15]

Alignment of treatment recommendations with patient preferences and goals through SDM is particularly important to medicines optimisation in multi-morbid older persons.[9,16-19] Most decisions about stopping, starting, continuing, modifying or selecting medications in medication review in multi-morbid older people are preference sensitive. The evidence on the benefit-harm ratio of most medications is limited in this patient population and treatment conflicts, treatment burden, prognosis should be considered in the decision process to minimise harms of overtreatment and burden of care.[5,10,16-18,20] Incorporating patient preferences into treatment decisions can improve health outcomes, patient satisfaction and adherence to treatment plans.[20]

However, most clinical guidelines and decision-support tools are not tailored to multi-morbid older patients and allowing patient preferences to guide treatment decisions is not standard clinical practice.[9,12,14,20-23] Many clinicians feel uncomfortable commencing conversations about preferences and patients and clinicians vary in their willingness to discuss preferences as part of the clinical encounter.[20,23] Furthermore, studies have demonstrated that clinical guideline or clinicians' recommendations and patient preferences for management of multi-morbidity may be discordant and patient preferences are often misunderstood.[1,20,24-26] A better understanding of patient preferences in multi-morbidity is a research priority and is central to managing polypharmacy in older persons.[1,7,19,27-30] Moreover, it has been argued that there is a disproportional focus on the 'patient information' dimension of patient-centred care, whereas other dimensions such as respecting patient values and preferences have received less attention.[30]

This scoping review aims to increase understanding of medication-related preferences of older people with multi-morbidity by answering the following question: 'What is the extent, range and nature of the literature on multi-morbid older persons' preferences for stopping (deprescribing), starting, continuing, modifying or selecting medications?' More specifically, we aim to synthesize the evidence on multi-morbid older persons' preferences and attributes of preferences for stopping (deprescribing), starting, continuing, modifying or selecting medications and to identify methods to elicit medication-related preferences in multi-morbidity.

METHODS

We will conduct a scoping review according to the framework of the Joanna Briggs Institute and the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews (PRISMA-ScR).[31,32] There is no generally

accepted method to synthesise evidence from preferences research.[33-35] Evidence synthesis of patient preference studies is complicated by a heterogeneity of conceptualisations of patient preferences across disciplines, resulting in different definitions and measurement methods.[33-36] A scoping review allows to present an overview of the extent, range and nature of the evidence and is particularly suited to summarize a body of knowledge that is complex and heterogeneous in methods or discipline.[32] Unlike systematic reviews addressing questions of effectiveness, scoping reviews are useful for answering broader research questions, notwithstanding that the same sound and rigorous literature review method is used (Table 1).[37]

Table 1 : Comparison between systematic and scoping reviews.
Adopted from Armstrong et al.[38]

Systematic review	Scoping review
• Focused research question with narrow parameters • Inclusion/exclusion criteria usually defined at outset • Quality filters often applied • Detailed data extraction • Quantitative synthesis often performed • Formally assesses the quality of studies and generates a conclusion relating to the focused research question	• Research question(s) often broad • Inclusion/exclusion can be developed *post hoc* • Quality not an initial priority • May or may not involve data extraction • Synthesis more qualitative and typically not quantitative • Used to identify parameters and gaps in a body of literature

Inclusion and exclusion criteria

We will include qualitative, quantitative or mixed methods primary research and trials reporting on patient preferences for stopping (deprescribing), starting, continuing, modifying or selecting prescription or non-prescription medications or reporting methods to elicit medication-related preferences in patients aged ≥65 years (≥ 80% of the sample ≥ 65 years) with multi-morbidity (two or more chronic conditions) and polypharmacy (use of multiple medicines, no numerical definition). In medicine and for the purpose of this review, preferences are broadly defined as

'the desirability of a health-related outcome, process or treatment option'.[39] In case papers involve carers in the preference elicitation process, we will also include carers' preferences. We will only include studies published in the English language without restrictions on publication date. Literature reviews, consensus reports, expert opinions and commentaries will be excluded. Preference studies in patients < 65 years, preference studies for other interventions than medications and studies reporting on preferences for specific medications for single diseases or treatment domains will be excluded. Preference studies in the palliative care or the end-of-life setting will be excluded, because the focus of medicines optimisation in this setting is different.[40]

Search strategy

The search strategy combines controlled vocabulary and free text terms related to the concepts (i) 'older people, multi-morbidity, polypharmacy'; (ii) 'patient preferences' and (iii) 'medication'. In the medical literature the concept patient preference is not clearly defined and includes related concepts such as: 'priorities', 'values', 'goals', 'patient perspectives', 'views', 'beliefs', 'attitudes', 'utility', 'perception', 'expectations', 'concerns', 'desires', 'needs', 'acceptability' etc.[33,34] A variety of preference measurement methods have been used including qualitative research, standard gamble, discrete choice experiments, time trade-off, revealed preferences studies, contingent valuation studies and other kinds of surveys using ranking and rating techniques.[35] The search strategy was informed by previous literature reviews on patient preferences and was reviewed by an academic librarian.[41-44] An iterative process of building the search, running an initial search and refining the search strategy based on relevant articles retrieved was performed. The Medline search strategy was developed first (Appendix 6) and subsequently translated to the other databases. We will search the following databases from their inception to April 2019: Medline (Ovid), Embase (Ovid), PsycINFO (Ovid), CINAHL

(Ebsco) and The Cochrane library. Grey literature will be retrieved from screening reference lists of the included studies and from Google Scholar using the advanced search facility. The first 300 URLs from the Google Scholar search will be screened, which is the recommended amount for screening for retrieving grey literature.[45] The web browser cache will be cleared before the search to minimise Google Search optimisation and the results will be sorted by relevance.

Study selection

The search results from the database search will be imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) for automatic deduplication. Two reviewers (S.T. and K.W.) will independently screen titles and abstracts for eligibility against the inclusion and exclusion criteria and subsequently the full text of potentially eligible publications. The first 300 URLs of the Google scholar search will be exported into an Excel file using the SEOQuake add-on for Mozilla Firefox. The two reviewers will independently screen the 300 URLs against the inclusion criteria. Disagreements on study selection between the two reviewers will be resolved by consensus or the help of a third reviewer if required (S.M.).

Data extraction process

A standardised data extraction form was developed consistent with the review objectives and based on a form used in a previous systematic review on patient preferences.[46] The data extraction form will be pilot-tested on a sub-set of studies by all authors involved in the scoping review and the form will be refined accordingly. One reviewer will subsequently perform data extraction on all study data and the second reviewer will check the extraction of every study for accuracy. Data extraction on the main study outcomes i.e. preferences, attributes of preferences or preference elicitation methods will be performed independently by both reviewers. Disagreements will be discussed to reach consensus and the data extraction form

will be continuously updated in an iterative process. The following data will be extracted if available (depending on studies included): study citation, study characteristics (study design, setting, aim), number and characteristics of study participants, to which review objective the study relates (stated preferences, attributes of preferences, preferences elicitation methods), type of preference elicited (treatment option, health outcome, process), type of decision (options available) or type of preference attribute, patient information of the options (patient education materials or decision aids used, patient knowledge collected), actual or hypothetical decision, name and type of preference elicitation method, validity testing of preference elicitation method if reported, study findings (stated preferences or attributes of preferences reported as qualitative syntheses, quantitative results, recommendations/key findings), concordance preferences-treatment, if reported. Authors will be contacted to provide further information if required.

Critical appraisal of included studies

Critical appraisal is optional in a scoping review.[32] Data quality and validity of the preference studies will be appraised using the Joanna Briggs Institute critical appraisal tools.[47] Critical appraisal will be performed independently by two reviewers (S.T., K.W.) and disagreements will be resolved by discussion. However, the quality of the studies does not serve as an inclusion criterion, all studies will be included in data synthesis irrespective of their risk of bias.

Synthesis of the results

Synthesis of the results will depend on the literature found and will be an iterative process. A descriptive numerical summary of the characteristics of the included studies will be provided. Given the expected heterogeneity across the included studies in terms of methods and findings (quantitative or qualitative), we will perform a narrative synthesis of the results answering each of the research

objectives.[48] The principal summary measure will be the preferences stated, attributes of preferences and the preference elicitation methods. Furthermore, the broader implications of the findings for practice and for future research will be discussed.

Consultation and knowledge translation

Consultation is an optional stage but recommended in a scoping review.[31,37] As part of a previously conducted multi-centre mixed methods study, forty-eight European multi-morbid older patients' medication-related preferences have been explored using semi-structured interviews and the Outcomes Prioritization tool.[49] The results of this study will be used for validation of the findings from the scoping review.

DISCUSSION

This protocol outlines the methodology for a scoping review of the peer reviewed and grey literature on multi-morbid older persons' medication-related preferences. This review will increase understanding of medication-related preferences of older people with multi-morbidity and the available preference elicitation methods. This review may inform patient-centred decision-making in medication review in the context of multi-morbidity and polypharmacy, where limited other evidence is available.[50] Aggregate data on patient preferences are not a substitute for individual patient preferences in clinical encounters. However, collective patient preferences may help to guide clinicians in having preference conversations with their patients in clinical practice and may close the gap between what patients prefer and what clinicians think patients prefer.[1] Furthermore this review may inform patient-centred outcomes research, patient-tailored guideline development or help to identify decisions that are particularly preference sensitive or gaps in the literature to guide a future research agenda.[33,36]

Strengths and limitations

To our knowledge, this is the first scoping review on multi-morbid older persons' medication-related preferences, a highly relevant topic for medicines optimisation in multi-morbid older people. We will use a sound and rigorous scoping review methodology reported according to the PRISMA extension for scoping reviews.[31,32] Our review has potential limitations. For feasibility reasons, we will restrict our grey literature search to Google Scholar only. Although Google scholar is recommended for grey literature searching, we may overlook relevant reports from additional grey literature repositories.[45] To mitigate this, we will also screen reference lists of studies included in the review. The heterogeneity of key words related to the concept of patient preferences prohibits a highly sensitive and specific search. Although we will apply a comprehensive search strategy, we cannot rule out that we might miss relevant publications. We will exclude patient preferences for specific medications for single diseases or treatment domains, yet some of these preferences studies might be relevant in the context of multi-morbidity. However this is a deliberate choice as our aim is to focus on preferences in relation to the various choices and benefit-harm trade-offs that multi-morbid older patients face during treatment decisions.[9]

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GENERAL DISCUSSION

1 WHAT WE DID AND WHAT WE FOUND: A BRIEF OVERVIEW

Medication reviews are recommended to reduce inappropriate polypharmacy and related adverse health outcomes, a significant problem in the growing population of older people with multi-morbidity.[1-4] A patient-centred approach, incorporating patient preferences into treatment decisions through shared decision-making (SDM) is considered essential to medicines optimisation in multi-morbid older people.[3,5-9] Due to a lack of high-quality evidence, the impact of medication review on hard clinical outcomes such as hospitalisations and mortality remains uncertain.[1] In this context, the European OPtimising ThERapy to prevent Avoidable hospital admissions in the Multi-morbid elderly (OPERAM) randomised clinical trial was undertaken to test the impact of medication review on drug-related readmissions in 2009 multi-morbid older patients from Belgium, Ireland, Switzerland and the Netherlands.[10] Beyond evaluating clinical effectiveness and safety of interventions, the use of patient-reported outcome measures and patient-reported experience measures is increasingly advocated to make health services more patient-centred and to drive quality improvement.[11]

This research aimed to inform medication review in older people with multi-morbidity by measuring outcomes that matter to patients. The objectives of this thesis were: 1) to develop a method to measure drug-related admissions (DRAs), a core outcome of medication review for older people with multi-morbidity; 2) to measure and compare the prevalence and types of DRAs related to the STOPP/START criteria v_1 and v_2; 3) to explore multi-morbid older people's experience of hospital-initiated medication changes and medication review; 4) to review medication-related preferences of older people with multi-morbidity.

In Chapter 1.1, we describe the development of a standardised chart review method to identify DRAs in older people resulting from adverse drug reactions, overuse, underuse and misuse of medications: the DRA adjudication guide. DRA adjudication is based on chart review with the aid of a trigger tool and structured consensus judgement for causality by a pharmacist and a physician. Content validity, feasibility of use and inter-rater reliability of the DRA adjudication guide were tested and we consider the DRA adjudication guide to be a valid tool to identify DRAs in older people with multi-morbidity.

The DRA adjudication guide is used within the OPERAM trial by adjudication teams from the four study sites to measure the primary outcome DRAs. In Chapter 1.2, we conducted a retrospective chart review study to evaluate the inter-rater reliability (IRR) of DRA adjudication between the four adjudication teams at each OPERAM study site. For the evaluation of thirty admissions of multi-morbid older patients, inter-rater reliability of DRA adjudication between the four teams was fair (68% agreement, κ=0.34). Despite the use of a standardised DRA adjudication guide by experienced and trained adjudication teams, achieving good IRR for DRA identification remains challenging in complex cases of multi-morbid older patients. However, IRR was evaluated across four international teams in conditions that well reflect clinical practice.

Since inappropriate prescribing is a major cause of DRAs, DRAs resulting from inappropriate prescribing are of particular interest. In Chapter 1.3, we conducted a cross-sectional study to compare the prevalence and types of DRAs identified by the STOPP/START criteria v_1 and v_2 in a sample of 100 consecutively admitted older people. Compared with STOPP/START.v_1, STOPP/START.v_2 not only yielded more instances of inappropriate prescribing but also targeted significantly more potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) associated with preventable DRAs (23% vs 40% of all admissions, p<0.001).

PIMs of fall-risk increasing drugs and PPOs of musculoskeletal system and cardiovascular system drugs were most frequently associated with DRAs. The latter instances of inappropriate prescribing with major clinical relevance warrant particular attention during medication review.

In Chapter 2.1, we conducted a mixed methods study embedded in the OPERAM trial to explore multi-morbid older people's experience of hospital-initiated medication changes and medication review. Semi-structured interviews and the Beliefs about Medicines Questionnaire were conducted with a purposive sample of 48 patients from four European countries enrolled in the OPERAM trial. A lack of information about medication changes and paternalistic decision-making was frequently reported. Patients' attitudes towards medication review and hospital-initiated medication changes were generally positive, however an interplay of factors related to inadequate information and communication, patients' beliefs, clinicians' attitudes and doctor-patient relationships may affect medication review effectiveness. To meet patients' needs, future medicines optimisation interventions should enhance information exchange, better prepare patients and clinicians for partnering in care and foster collaborative medication reviews across care settings.

In Chapter 2.2, we outline the outline the protocol for a scoping review aiming to synthesize the evidence on multi-morbid older persons' preferences and attributes of preferences for stopping (deprescribing), starting, continuing, modifying or selecting medications and to identify methods to elicit medication-related preferences in multi-morbidity. We anticipate that this review may inform patient-centred decision-making in medication review in multi-morbid older people and may help to guide clinicians in having preference conversations with their patients.

2 CRITICAL APPRAISAL

In this chapter, we discuss the added value, strengths and limitations of the research conducted in this thesis.

2.1 ADDED VALUE OF THIS RESEARCH

Throughout this thesis we adopted a patient-centred perspective by focusing on outcomes that matter to older patients, a highly relevant topic in the light of the global call for health services to become more patient-centred.[5] In Chapter I, we contributed to better a measurement and understanding of DRAs, a growing patient safety threat and an outcome of medication review that is highly important to older people with multi-morbidity and polypharmacy.[12] Identifying DRAs in older people is challenging and was, upon till now, often conducted in an implicit and unstructured way.[13] The DRA adjudication guide is the first method allowing standardised measurement of DRAs in older people, an important step forward in DRA detection. The DRA adjudication guide can be used as an outcome measure for medicines optimisation interventions or to study the incidence of DRAs or drug-related emergency department visits. In our cross-sectional study, we increased the knowledge on potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) that are frequently associated with preventable DRAs and demonstrated that, compared with STOPP/START.v_1, the STOPP/START.v_2 criteria have a significant better potential to target inappropriate prescribing events associated with preventable DRAs. In Chapter II, our mixed methods study on the patient experience of hospital-initiated medication changes, provides an in-depth understanding of factors underlying the effectiveness of medication review and the OPERAM intervention. Furthermore, this study helped to identify salient elements to ensure a positive patient experience, a key factor for preventing readmissions.[14]

Finally, the scoping review will increase understanding of patients' medication-related preferences in order to inform medication review. Our findings pave the way for a better measurement and understanding of DRAs and for medication review services to become more tailored to multi-morbid older people's preferences and needs.

Thanks to the OPERAM project, we had the opportunity to involve multidisciplinary researchers from different European countries in the development of the DRA adjudication guide and in the mixed methods study, enhancing the international relevance of our findings.

2.2 STRENGTHS AND LIMITATIONS

Wide range of research methods

To answer our research questions, we explored a wide range of research methods. We performed the development and validation of an outcome measure, including a Delphi survey and a reliability study. Furthermore, we conducted a cross-sectional study, a mixed methods study combining qualitative and quantitative methods, and a scoping review.

Balance between comprehensiveness and feasibility in DRA adjudication

A strength of the DRA adjudication guide is that it considers the full scope of adverse drug events that may contribute to hospitalisation including adverse drug reactions, overuse, underuse and misuse of medications. Few studies and tools consider DRAs resulting from medication underuse and adherence problems, yet this may lead to an underestimation of the prevalence of DRAs since these problems are major causes of DRAs.[15-20]

The DRA adjudication guide calls for a standardised and comprehensive evaluation of DRAs including triggered and non-triggered events, which is recommended in

order not to miss any classes of ADEs.[13,21,22] The originality of the DRA adjudication guide lies in the newly developed trigger tool for DRAs in older people, which was validated for content by an international, multidisciplinary Delphi panel. The DRA trigger tool allows standardised and explicit screening for potential DRAs, followed by structured causality assessment based on established causality criteria. The flipside of a comprehensive adjudication is that it is resource intensive to use; the mean time needed for one DRA adjudication is 23 minutes and adjudication should be performed by an expert panel of a pharmacist and a physician.

Validity of the DRA adjudication guide

A valid and practical method to measure and understand a problem is a critical approach to any patient safety threat.[23-25] We used a rigorous developmental pathway based on design and test iterations, combining evidence from the published literature with expert opinion and user-feedback from international and multidisciplinary sources. Content validity, feasibility of use and inter-rater reliability, defined as desirable attributes of a quality measure, were evaluated.[26]

Despite development of a standardised procedure, inter-rater reliability (IRR) of DRA adjudication was found to be only fair to moderate in two distinct IRR studies (Fleiss' κ=0.34 and 0.41). Another recently developed tool to identify DRAs, the Assessment Tool for Hospital Admission Related to Medications (AT-HARM10 tool) achieved better IRR scores with Fleiss' κ scores of 0.46 and 0.58 in two IRR evaluations, although relying on more implicit clinical judgement. However, where the IRR of the AT-HARM10 tool was assessed in a single centre between two pairs of raters with backgrounds in pharmacy, IRR of the DRA adjudication guide was assessed between four international pairs of raters involving both pharmacists and physicians. Achieving good IRR is a challenge inherent to chart review studies and heterogeneity in professional backgrounds as well as in study conditions (e.g. assessment of cases

from another hospital) might negatively affect IRR.[27,28] To our knowledge, we performed the first cross-country evaluations of IRR of DRA adjudication.

The performance of the DRA trigger tool in terms of predictive validity, sensitivity and specificity to detect DRAs has not yet been evaluated, which is a limitation. However the main purpose of the trigger tool as used in the OPERAM trial was to standardise screening for DRAs.

Limitations of retrospective chart review

DRA adjudications in our studies rely on chart review by an expert panel, which is considered as the gold standard approach for identifying adverse drug events (ADEs).[28] However, ADE identification using retrospective chart review is subject to the quality of documentation and aspects needed for assessment of underuse such as patient preferences, life expectancy and adherence, are often undocumented in medical charts. Combining chart review with prospective methods such as clinician or patient interviews are an additional valuable information source for DRA identification and may increase IRR.[16,28-34] Eliciting the patient's perspective on admission may help to better understand the circumstances around admissions, ascertain the medication history or assess treatment adherence.[16] In a recent systematic review on drug-related readmissions, the highest prevalence rate of DRAs originated from a study that interviewed patients.[16] Furthermore, patients and clinicians have divergent opinions on the preventability of readmissions, which bolsters the argument for including the patient perspective.[16,29-31] However, this approach would be resource intensive.

DRA identified by the STOPP/START criteria might underestimate the true prevalence of DRA

Our cross-sectional study (Chapter 1.3) increased understanding of the prevalence and types of preventable DRAs resulting from inappropriate prescribing events identified by the STOPP/START criteria. Previous research already confirmed that the updated STOPP/START.v_2 criteria target more instances of inappropriate prescribing compared with the first version, but our cross-sectional study is the first to demonstrate that STOPP/START.v_2 criteria target significantly more preventable DRAs.[35,36] To allow for comparison with the DRAs related to STOPP/START.v_1 identified in the original study, we only considered DRAs resulting from inappropriate prescribing (over-, under- and misuse) rather than all-cause DRA (including adherence, adverse drug reactions). Therefore the prevalence of DRAs resulting from inappropriate prescribing in this study may be an underestimation of the true prevalence of DRAs. Previous research with STOPP/START.v_1 demonstrated that the majority of drug-related problems identified during medication review are not associated with the STOPP/START criteria.[37] This is the reason why in our DRA adjudication guide, we consider all-cause DRA and include triggered and non-triggered events.

Generalisability of the findings of the cross-sectional study with STOPP/START

The main limitations of the cross-sectional study are the small sample size and the monocentric study design, limiting generalisability of the findings. Our primary aim was to determine the prevalence and types of DRAs related to STOPP/START.v_1 and STOPP/START.v_2, for which a cross-sectional design is well-suited, yet it does not allow for establishing causal relations between inappropriate prescribing and DRAs.[38,39] However several large prospective longitudinal studies, providing a more robust approach to assess the impact of inappropriate prescribing, have confirmed

the association between inappropriate prescribing according to the STOPP criteria and/or START criteria version 2 and hospitalisations.[38,40,41]

It should also be noted that the STOPP/START.v_2 criteria were already five years old at the time of the study and explicit criteria remain susceptible to changes and updates to incorporate the most recent evidence.[42]

In-depth understanding of factors affecting medication review effectiveness

Our mixed methods study provides an in-depth understanding of factors affecting medication review effectiveness from the patient's perspective. However, we did not conduct a formal process evaluation of the OPERAM trial. Beyond outcome evaluations, process evaluations of complex interventions are recommended to support interpretation of the results and inform policy makers for future implementation of interventions.[43] Given the time consuming character of qualitative research, we chose to focus on experiences of patients, being the most relevant stakeholders to evaluate and to help improving the quality of health services.[44,45] We triangulated our qualitative results with quantitative measures on the extent of patient participation from the clinicians' perspective for only a sub-sample of patients and clinicians, which gave us some idea about the implementation of the SDM component of the OPERAM intervention. However, the extent of participation in decision-making from the patient perspective was only evaluated qualitatively using an open-ended question in the semi-structured interviews. Concordance between patients and clinicians on patient participation would likely have been higher if we would also have used a quantitative patient-reported SDM questionnaire.[46] Self-report SDM measures broadly indicate satisfaction with decision-making rather than the quality of the interaction and are susceptible to social desirability and response biases, which may also explain the high SDM ratings by clinicians.[47,48] Integrating observations or interviews with the

involved clinicians and researchers might have further underpinned our understanding of the patient-clinician dyad.[47]

Transferability of the findings of the mixed methods study

Due to the qualitative nature of our study, generalisability of our findings to the whole OPERAM population or general population of older people is limited. There is a large heterogeneity within the older population in terms of health status and functional capacity.[49,50] The patients included in the mixed methods study took all part in the OPERAM trial, most were in their seventies, most lived independently at home and none suffered from cognitive impairment. Therefore the views expressed in the study represent the perspectives of cognitive fit, educated older people with multi-morbidity rather than the oldest old or patients with an impaired cognition or functional status. However, we enhanced transferability of our findings by including a relatively large purposive sample of patients from four European countries with variation in patient characteristics. However, by no means the patient experience study can be used to challenge the intervention implemented as part of the OPERAM trial, neither does it enable a quantitative comparison of patient experiences between the full sample of control versus intervention patients.

Credibility of the findings of the mixed methods study

Credibility of the findings was enhanced by respondent validation and by integrating perspectives from different countries and backgrounds in protocol development, data collection and analysis. However, our findings are influenced by interpretation mainly from healthcare providers' perspectives involved in the OPERAM project.

Scoping review

Strengths of the scoping review include the originality of its aim, the rigorous scoping review methodology and the extensive search strategy of the peer reviewed and

grey literature. However, we cannot rule out that we overlooked publications in the grey literature or due to language issues.

Strengths and limitations of the OPERAM intervention

The OPERAM trial has several important strengths: it is a large-scale multicentre cluster randomised trial undertaken in older people with multi-morbidity, an understudied population.[10] The broad inclusion criteria and few exclusion criteria provide good external validity.[10] The STRIP intervention combines implicit prescribing tools with the explicit STOPP/START criteria and SDM with the patient as critical steps to reduce inappropriate prescribing and DRAs.[51] However according our mixed methods study on patient experiences, an interplay of factors related to inadequate information and communication, paternalistic decision-making, patients' beliefs, clinicians' attitudes, trust and doctor-patient relationships may affect effectiveness of medication reviews. The potential weaknesses of the OPERAM trial might have been the lack of adequate preparation of clinicians and patients for SDM, the lack of direct involvement of the OPERAM team in the discharge process to provide patient education on medication changes, the lack of extended post-discharge follow-up to reinforce medication-related information and the lack of direct involvement of primary care providers in medication review. Future medicines optimisation interventions should therefore better prepare patients and clinicians for SDM, enhance information exchange at discharge (e.g. teach-back technique) and post-discharge (e.g. follow-up phone calls or home visits, in collaboration with the community pharmacist) as well as enhance collaboration between hospital clinicians and primary care providers in medication review. In chapter 3.2, we provide practical recommendations on how to address these aspects.

3 MEDICATION REVIEW TO PREVENT AVOIDABLE HOSPITAL ADMISSIONS IN MULTI-MORBID OLDER PEOPLE: IMPLICATIONS FOR RESEARCH AND PRACTICE

In this chapter, we reflect on two main topics:

- Measuring DRAs as an outcome measure for medication review interventions
- Strategies to reduce DRAs, with a particular focus on improving the patient experience of medication review

3.1 MEASURING DRUG-RELATED ADMISSIONS

In Chapter I, we focused on measuring DRAs. DRAs were the outcome with the highest rate of agreement among all stakeholders (old and very old persons, HCPs and experts) in the Delphi study on the core outcome set for medication review in older people with multi-morbidity and polypharmacy.[12] Hence, DRAs should be part of the outcomes measured in medication review interventions.

However, DRAs are not a patient-centred outcome measure and one might argue the relevance of measuring DRAs for evaluating the effect of a trial of medication review with SDM. Indeed, there might be a paradox between a SDM intervention and the outcome DRA when a DRA occurs even though the patient experienced a valid SDM process. For instance, during a SDM process a patient might decide not to take a certain medication which may result in disease deterioration and a DRA, but at least the decision was taken in concordance with the patient's preferences. On the other hand, SDM has been shown to result in better informed patients, choosing more conservative options (e.g. more medication stops, dosage decreases, fewer changes and fewer starts of new medications), and it thereby may facilitate deprescribing and reduce ADEs and DRAs.[9,52] Beyond health-related quality of life and pain, which were identified as patient-reported outcomes in the core outcome set for medication review, alignment of drug therapy with patient preferences (e.g.

through goal attainment scaling), medication regimen complexity and treatment burden should be considered as other relevant patient-reported outcomes for medication review with SDM.[12,53-56]

Based on the lessons learned in our studies and the international literature, we provide recommendations for measuring DRAs for research and practice in **Box 1** and in the next paragraphs.

Box 1: Recommendations for measuring drug-related admissions (DRAs)

- DRAs should be part of the outcomes of all medication review interventions.
- The full scope of DRAs should be measured i.e. those resulting from adverse drug reactions and medication errors including overuse, underuse and misuse.
- An expert panel consisting of a pharmacist and physician is essential for DRA adjudication, given their complementary knowledge and experience.
- High-quality information is required for DRA adjudication. The admission and discharge letter, laboratory values and medication lists should be the minimum set of data sources.
- Depending on the resources available, balance the importance of comprehensiveness and feasibility of DRA adjudication to select an appropriate validated tool for measuring DRAs: the DRA adjudication guide or the AT-HARM10 tool.
- Where possible, involve patients' perspectives in the assessment of readmissions.

Drug-related admissions, what to measure?

In line with internationally accepted definitions of ADEs, we advocate for the measurement of the full scope of ADEs resulting in hospitalisation i.e. non-preventable adverse drug reactions and preventable medication errors including overuse, underuse and misuse of medications.[16,57,58]

In our definition of DRA, we included ADEs with a possible, probable or certain causal link according to the WHO-UMC causality criteria.[59] However in practice, many ADEs only have a '*possible*' causal link, meaning that the event could be due to the drug or there may be an equally likely explanation for the event (e.g. a concurrent disease) and there is no information on what happened after drug withdrawal.[59] This 'light' definition of ADEs may result in a high DRA yield. However, we believe that disregarding ADEs with a possible causal link is not appropriate, especially in older patients with polypharmacy who are particularly sensitive to ADEs and for whom a 'cocktail' of different possible ADEs may eventually result in severe harm. For instance, in our inter-rater reliability study, admissions for infections in patients using chronic corticosteroids were frequently adjudicated as possible ADEs contributing to admission and thus these possible ADEs can cause severe patient harm.

Measuring drug-related admissions, which tools to choose?

The DRA adjudication guide (Chapter 1.1) and the Assessment Tool for Hospital Admission Related to Medications (AT-HARM10 tool) have been developed and validated for measuring DRAs in older people and are based on chart review.[19,60] Differences and similarities between the two tools are presented in Table 1. Both tools were developed in the context of clinical trials of medication review and consider all-cause DRAs resulting from adverse drug reactions, overuse, underuse and misuse of medications. The tools have been designed and validated using an

iterative process including literature review (v_1), evaluation of content validity (v_2), feasibility of use (v_3), inter-rater reliability (v_4) and criterion-related validity (AT-HARM10 only). The DRA adjudication guide was designed to be comprehensive and standardised and uses an explicit trigger-based approach to DRA identification by an expert panel. Conversely, the AT-HARM10 tool was designed to be practical, not resource intensive and uses a more implicit approach to DRA identification. AT-HARM10 is based on ten yes/no questions and is validated for use by pharmacy students. The AT-HARM10 tool may therefore be more practical and less costly to use, yet potentially at the expense of a more comprehensive and sound adjudication. We believe that a combination of a physician's and a pharmacist's perspective is essential for DRA adjudication, since both have complementary knowledge and experience.[61] Therefore, the AT-HARM10 tool might be further validated for use by a panel of medicine and pharmacy students. The value of the DRA adjudication guide and AT-HARM10 should be determined in future studies. Depending on the resources available for DRA adjudication, we recommend to consider the importance of feasibility and comprehensiveness in DRA adjudication to select the most appropriate tool. Another option would be to use the AT-HARM10 tool to quickly rule out hospitalisations that are unlikely to be medication-related and to use the DRA adjudication guide to perform an in-depth adjudication.[19]

Table 1: Comparison of two validated tools to measure DRAs in older people: The DRA adjudication guide and the AT-HARM10 tool

	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 DRAs in older people	• Existing tools
v1 **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 DRAs: 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
v2 **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
v3 **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

Optimising inter-rater reliability of DRA adjudication

Notwithstanding the use of a standardised tool and trained and experienced adjudicators, we demonstrated in Chapter 1.2 that it is difficult to achieve good inter-rater reliability of DRA adjudication. Recommendations to optimise IRR of DRA adjudication are displayed in **Box 2**.[27,34] DRA adjudication of more complex multi-morbidity cases can be challenging. Therefore, all adjudicators should be adequately trained in DRA adjudication and should have sufficient clinical experience in geriatrics.[27] Our training materials developed for DRA adjudication can be used for this purpose. In our study, IRR was evaluated in study conditions that well reflect clinical reality, rather than using clinical vignettes. In this 'real life setting', retrieving and interpretation of information in the medical notes is often complicated because of poor documentation or because of a highly variable quality of information. Standardisation of clinical information and data quality checks might increase IRR.[62] However, even if the DRA adjudication procedure would be applied perfectly, a degree of disagreement seems unavoidable in the adjudication of complex multi-morbidity cases, where a gold standard treatment is often lacking.[27] To minimise bias due to subjectivity, DRA adjudication by only one adjudication team should be preferred over multiple teams. In case multiple adjudication teams are needed (e.g. in the OPERAM trial), monitoring of IRR with prompt feedback and regular meetings between the teams to discuss cases and share knowledge are recommended. For instance, in collaboration with the adjudication teams, we developed a set of adjudication rules to handle certain types of ADEs that are prone to subjectivity e.g. it was decided that omission of a statin for patients aged >85 years or at the end-of-life and who are admitted for ischaemic heart disease or stroke, should not be considered as underuse because of the limited evidence of benefit of statins over the age of 80-85 years.[63] It might be worthwhile to expand this set of adjudication rules.

Readmissions in the era of patient engagement

High-quality information is required for a good DRA adjudication. However chart review is limited to the documentation of information. In particular for the adjudication of DRAs resulting from medication underuse or adherence issues, an important cause of DRAs, combining chart review with patient interviews is recommended to assess adherence, the medication history, patient preferences or recent medication changes, which are often undocumented or unclear in the medical charts.[16,28-34] Combining chart review with prospective methods such as clinician or patient interviews may also increase IRR.[34]

Box 2: Recommendations for optimising inter-rater reliability of DRA adjudication

- Adjudicators should be adequately trained in DRA adjudication and should have sufficient clinical experience.
- High-quality information is required for DRA adjudication and the clinical information should be standardised.
- In case of multi-centre studies, one adjudication team is recommended over multiple teams to minimise bias due to subjectivity in DRA adjudication.
- In case multiple adjudicators are needed, IRR should be monitored and regular meetings between the adjudication teams should be organised to discuss cases and share knowledge.
- Where possible, involve patients' perspectives in the assessment of readmissions.

3.2 REDUCING DRUG-RELATED ADMISSIONS: FINDING THE SWEET SPOT

A variety of interventions have been tested to reduce medication-related harm, with variable success and no clear path for finding the sweet spot of meaningfully improving clinical outcomes in a clinically scalable and cost-effective way.[64] Preventable drug-related (re)admissions result mainly from drug-related problems (inappropriate prescribing, monitoring and adherence problems) and problems with communication of medication-related information at care transitions (between patients and clinicians or between clinicians, GPs and community pharmacists).[18,65-73] Hence medication review interventions in isolation without co-interventions have no impact on clinical outcomes.[74] Multi-faceted pharmacist-led interventions combining medication reconciliation, medication review, patient-centred education and extended post-discharge monitoring and follow-up (e.g. phone calls, home visits) are needed and show promise to reducing readmissions and drug-related readmissions in older people.[75-78] Most pharmacist-led interventions to individualise and optimise treatment in older inpatients follow the Integrated Medicines Management (IMM) model.[79,80] The IMM model is a multi-faceted interdisciplinary method where the pharmacist, as part of a multidisciplinary team, provides medication reconciliation, medication review, patient counselling and dissemination of correct information at care transitions.[79,81] An example of a successful intervention to reduce DRAs is the Pharm2Pharm care transition and care coordination programme in the US, leading to an impressive 36% reduction in DRAs in older adults and a 2.6:1 return on investment.[77] The intervention focussed on patients at high risk of medication-related harm and included medication reconciliation, medication review, patient education and coordinated hand-off to the community pharmacist, who provided follow-up support, all reinforced by health information technology.[77] It remains to be seen whether the OPERAM intervention will be effective in reducing DRAs and sufficiently addressed the risk factors causing

preventable readmissions. In the next paragraphs, we reflect on several strategies to reduce DRAs in practice **(Box 3)**. In particular, we focus on how and why the OPERAM intervention might have worked from the patient's perspective and how to tailor medication review services to patients' needs **(Box 4-7).**

Box 3: Recommendations for detection and prevention of DRAs in clinical practice

Need for multi-faceted pharmacist-led interventions

- Multi-faceted pharmacist-led interventions combining medication reconciliation, medication review, patient-centred education and follow-support and monitoring, show promise in reducing DRAs.

Improve detection and reporting of DRAs

- Organisations should support a 'fair blame' culture that encourages reporting and learning from medication-related harm.
- Healthcare providers should be adequately trained in the detection and documentation of medication-related harm as part of geriatric pharmacotherapy courses and continuing education.
- Greater involvement of clinical pharmacists can support detection of DRAs and prompt corrective actions. To support detection of DRAs in practice, the AT-HARM10 tool is most feasible for use but a second opinion of a physician is recommended.
- Readmission rates as a quality indicator for in-hospital quality of care should be used with caution and seems not appropriate as a tool for a pay-for-performance scheme. DRAs do not meet the requirements for a quality indicator.

Identification of patients at risk of DRAs

- Identification of patients at high-risk of DRAs might be useful to target preventive interventions. However, the available risk prediction tools are currently not feasible for use in practice and warrant further improvement.
- According to the WHO, patients at risk due to polypharmacy who might benefit from medication review include: nursing home residents, multi-morbid patients (>2 chronic conditions), frailty, patients taking ≥10 medications, patients with dementia, palliative care situations.

Improve detection and reporting of medication-related harm

One of the objectives of the WHO's Global Patient Safety Challenge is to assess the scope and nature of avoidable harm and to strengthen the monitoring systems to detect and track this harm.[82] All healthcare professionals have the responsibility to document and report ADEs to the patient safety incident reporting or pharmacovigilance systems.[72,83] Reporting harm to learn from medication incidents is crucial for the implementation of preventive interventions, to reduce harm from

re-occurrence and to monitor improvement.[72,84] However, there is likely an under-detection and underreporting of medication-related harm in administrative databases, when compared to research quantifying ADEs.[72,85]

Organisations should support a 'fair blame' culture, ensuring that robust and transparent processes are in place to identify and report, investigate and learn from medication-related incidents. Healthcare providers should explain to patients and their companions how to identify and where to report medication-related incidents.[86]

However not all healthcare professionals are able to detect ADEs or DRAs. Detection of ADEs in older people is complicated by an often atypical and non-specific presentation.[83] Whereas a patient taking insulin who is admitted for hypoglycaemia is easily recognised as a DRA, less obvious DRAs such as an admission for heart failure exacerbation in a patient who recently started taking an NSAID, can be difficult to detect.[64] Adequate training in geriatric pharmacology and in detection and recognition of ADEs/DRAs in older people, may improve recognition of medication-related harm. In older persons admitted to hospital, the differential diagnosis should always include the possibility of an ADE and the medical complexity should always be considered before prescribing a new drug. Furthermore, it is particularly important to communicate ADEs to the patient and to the primary care providers in order to prevent re-occurrence.[83] Greater involvement of clinical pharmacists in patient care within multidisciplinary geriatric teams may help to detect ADEs and prompt corrective actions.[83] As we showed in Chapter 1.3, STOPP/START.v_2 PIMS and PPOs are frequently associated with preventable DRAs.

To support DRA identification in practice, the AT-HARM10 tool may be feasible to use, but we would recommend involvement of a second opinion from a physician. In the future, automation of the DRA trigger tool to flag potential DRAs might be

useful to support detection, although subsequent clinical judgement remains necessary. However, the predictive validity of the individual triggers first needs to be determined to obtain a tool with increased sensitivity and specificity.

Should we measure readmissions as a quality indicator?

Unplanned readmissions within 30 days of discharge are considered major adverse events.[31] In several countries, readmissions are used as an indicator of the quality of care within hospitals and some governments use readmissions in the context of pay-for-performance systems, penalising hospitals with higher readmission rates.[87,88] As part of the Health System Performance Assessment in Belgium, avoidable hospital admissions for asthma and diabetes complications are measured to evaluate the quality of first-line care and continuity and coordination of care.[89] In addition, seven-day unplanned readmissions are measured as part of the Flemish indicator project (VIPP²) project.[89,90] These indicators are not part of the Belgian Pay for Performance (P4P) programme for general hospitals, which seems to be a good choice.[91] Indeed, the validity of all-cause unplanned readmissions as a quality indicator is debated because of problems with administrative data incompleteness and the fact that it does not differentiate between non-preventable and preventable readmissions (i.e. preventable readmissions are what we actually want to measure and those that can be improved).[31,87,92,93] However, determining the preventability of readmissions is a highly subjective and variable process. There is poor consensus on preventability, not only among clinicians, but also between patients and clinicians.[31,94] Furthermore, causes of readmissions might lay outside the influence of the hospital.[68] Hence tying financial penalties the complex phenomenon of readmissions seems problematic.[95]

One might argue the relevance of specifically measuring DRAs or drug-related *re*admissions as a quality indicator, respectively for the effectiveness of primary care or as a measure of in-hospital quality of care. Important attributes of quality

indicators include (i) the importance of what is being measured (including impact on health, policy importance); (ii) scientific soundness (i.e. validity, reliability, evidence-base for the measure) and (iii) feasibility (i.e. cost of measurement, data needs).[96,97] In addition to the challenges already present for measuring all-cause readmissions, monitoring DRAs would even be more complex. Rather than using administrative data that are standard available for all readmissions, detailed clinical information would be needed to adjudicate the presence of a DRA and information outside the scope of the medical record might be required (e.g. quality of discharge instructions). Given the challenges of feasibility and reliability in measuring DRAs, DRAs would not make a good quality indicator.

Prediction tools to identify patients at high risk of drug-related admissions

Patients who may benefit from medication review might need to be prioritised given the limited resources in most healthcare systems. The WHO recommends the following criteria to select patients at high risk where medication review may be useful: nursing home residents, patients on high-risk medications, patients taking ≥10 medicines, multi-morbidity (≥2 chronic conditions), frailty, dementia and palliative care situations.[72]

One strategy for preventing DRAs is to identify patients at high risk of DRAs and to target preventive interventions (e.g. medication review or care coordination services) and resources to these patients.[83,98] Prediction models can accurately predict readmissions and, as opposed to clinical judgement, produce objective and consistent judgements regarding readmission risk.[31,99] Electronic health records provide potential to integrate prediction tools in clinical decision support systems to alert HCPs about a high (D)RA risk.[98]

Several readmission risk prediction tools have been developed, however few attempts have been made to develop tools to predict the risk of DRAs.[99-102] A fundamental problem is that evidence on the risk factors for DRAs is inconsistent, caused by the heterogeneity in population studied as well as the definitions of DRAs and detection methods.[16,71,103] To our knowledge, three prediction models have been developed that take into account medication use as a potential predictor of readmissions.

The Prediction of hospitalisation due to Adverse Drug Reactions in Elderly Community dwelling patients (PADR-EC) score is a tool to identify community-dwelling patients at increased risk of DRA.[98] The PADRE-EC score includes 5 clinical variables (drug changes in the preceding 3 months, renal failure, dementia, number of antihypertensives, anticholinergics) and was externally validated in a cohort of 240 Tasmanian patients ≥65 years admitted to hospital. Because of the low specificity and discriminative power of the tool, further refinements are needed before implementation in practice.[98]

The 80+ score was developed to predict rehospitalisation and mortality in older hospitalised patients and was internally validated using a sample of 368 older Swedish patients admitted to hospital. The score, consisting of seven variables (impaired renal function, pulmonary disease, malignant disease, opioid prescription, a drug for peptic ulcer disease or for gastro-intestinal reflux disease, or an antidepressant) showed good discriminative power to predict rehospitalisation and mortality in older inpatients.[104] However the score has not been externally validated.

Another strategy to select patients at risk of DRAs is the use of automated algorithms in the medical record based on drug-disease combinations. In the US, Olson and colleagues developed an automated algorithm to predict older persons' risk of DRAs. The algorithm calculates patients' high risk medication regimen scores, composed

of polypharmacy (≥9 medications), potentially inappropriate medications (based on the AGS 2003 Beers criteria) and medication regimen complexity (based on the Medication Regimen Complexity Index).[105] However, the algorithm should be updated to incorporate the most recent version of the Beers criteria.[106] Furthermore, information regarding diseases and medications should be available in standardised coded format.[105]

Hence, none of these tools are feasible for use in practice at the moment. Moreover, the predictive capacity of these tools is limited because they do not take into account underuse, adherence issues or problems related to care coordination as risk factors.

Focus on patient experience as a strategy to reduce drug-related admissions

Research has demonstrated that a positive patient experience including satisfaction with in-hospital care, being listened to by doctors, follow-up appointment scheduling and readiness for discharge is associated with reduced readmission rates.[14,29,107] Evaluating the patient experience of hospital-initiated medication changes in the OPERAM intervention and control groups (Chapter 2.1), allowed a better understanding of what happened 'underneath the surface' of the OPERAM trial and highlighted several barriers and facilitators underlying the effectiveness of medication review. Furthermore, it highlighted salient elements of a positive patient experience and factors that need to be addressed to make medication review more patient-centred. On the one hand many patients retain very paternalistic views on medication-related decision-making, whilst simultaneously placing a high value on information exchange, involvement of their GPs and companions, empathetic and trusting patient-clinician relationships and a collaborative approach across care settings, all of which promote a patient-centred integrated system.

Patients' attitudes towards medication review were generally very positive. However, we did not observe major differences in themes reported between

intervention and control patients, suggesting that the OPERAM intervention did not substantially affect patient experiences. An interplay of factors related to inadequate information and communication, paternalism, patients' beliefs (about the patient role and about medications), clinicians' attitudes and doctor-patient relationships may affect the effectiveness of the OPERAM intervention. Examples of these different underlying factors are presented in Box 4 *(*links to the themes identified in the interviews are shown in brackets). To improve the patient experience of medication review or hospital-initiated medication changes, we concluded that enhancing information exchange, better preparing patients and clinicians for partnering in medication review and fostering collaborative medication reviews across settings, is essential. Based on the findings from our mixed methods study and the international literature, in the next paragraphs we provide recommendations on how to address these factors and tailor medication review services to the needs and preferences of older people with multi-morbidity.

Box 4: Patient stories on hospital-initiated medication changes

Jack, OPERAM control group patient

Jack was admitted to hospital for heart failure exacerbation. In hospital, the cardiologist decided to withdraw his paroxetine because of QT prolongation. According to Jack it was abruptly stopped. The nurse told Jack it was necessary to stop paroxetine because of his cardiac problems, which he understands (*necessity beliefs*). However, Jack tells the nurse that he is very worried about the abrupt stop and the fact that there is no replacement therapy. The nurse tells him that the cardiologist will take care of it, but Jack didn't get further follow-up since. At discharge, Jack receives very limited information about the changed medications 'take this and this instead of this' (*paternalism, lack of information*). Jack also got a new prescription for alprazolam for anxiety, however Jack refuses to take it because he dislikes that type of drugs (*concern beliefs*). In the days after discharge, Jack suffers from severe psychological distress and anxiety (*experiencing harm from a medication change*). Jack's daughter decides to call the cardiologist to ask what to do, however she receives a dismissive response (*companion involvement, dismissive clinician)*. When Jack consults his GP, he tells him that he can't overrule the prescription from the cardiologist and it is up to the cardiologist to find a solution (*lack of follow-up support*). Jack feels abandoned both by the hospital physician and by the GP. A few days later, Jack is readmitted to hospital with a panic attack and asthenia. The adjudication team adjudicated the case as a drug-related admission due to the stop of paroxetine.

Adam, OPERAM intervention group patient

Adam was admitted to hospital for femoroplasty in a context of lower extremity arteriopathy. Adam strongly beliefs he should be involved in decision-making (*recognising experiential patient role*) and he was very satisfied with the OPERAM shared decision-making intervention. He valued the patient-centred approach and had a good contact with the friendly and empathetic OPERAM research clinician *(patient-centred approach, good interpersonal skills).* As part of the OPERAM intervention, Adam was proposed to start a statin because he suffered from severe stenosis of one carotid artery. However, Adam is worried about the side effects of statins and in general he distrusts the pharmaceutical industry, which he beliefs uses approaches like Monsanto-type multinationals relying on techniques of scrambling the truth (*high concern beliefs)*. Furthermore, Adams' GP isn't happy to start a statin and Adam decides to follow the GP's advice, with whom he has a long-standing, trusting relationship (*trust in GP, conflicting advice from GP*). Instead, Adam and his GP decide to start a red yeast rice supplement to treat his high cholesterol.

Louise, OPERAM intervention group patient

Louise was admitted to the orthopaedics ward for a knee replacement. As part of the OPERAM intervention, she was proposed to start alendronate for her osteoporosis. However, Louise did not completely understand the information received (*lack of understanding of medication changes)* and was not at all convinced of the added value of alendronate *(low necessity beliefs*). Furthermore, she considered the proposed changes as critical of her GP, in which she has high trust, and she decided not to accept the proposed medication changes (*trust in GP*).

Mary, OPERAM control group patient

Mary was admitted to the internal medicine ward with pneumonia. She had a good contact with her treating clinician in hospital, who was empathetic and took the time to listen to the Mary's other problems (*patient-centred approach, good interpersonal skills)*. This allowed Mary to tell the clinician that she doesn't sleep well at night because she has to get up frequently to take cold showers because of the pain in her legs, as she suffers from polyneuropathy. Mary's grand-son, also a doctor, told her that she might benefit from taking pregabaline (*companion involvement)*. Mary and her grand-son subsequently discussed the option of starting pregabaline with the clinician and together they decided to give it a try. Since Louise started to take pregabaline, she feels much better (*experiencing a benefit from the medication change*).

'When I was discharged they just told me, so you've got this and that and this instead of that. And that's all.' [Patient, Belgium] – Enhancing information provision on medication changes

Several patients had unmet information needs regarding their medication changes or had problems recalling the information received. Barriers for patients to be well-informed included paternalistic decision-making, the use of jargon by clinicians and having limited opportunities for questions. Many patients stressed the importance of good preparation for discharge, medication counselling and the need for timely (preferably before discharge), clear, written information. Patients also highlighted the importance of using lay language and taking time for information provision, at a moment the patient feels well. For others, involvement of companions helped them to remember the information received or to obtain additional information.

In the OPERAM intervention group, medication changes were discussed with the patient during their hospitalisation. However, patients did not receive written information and there was no involvement of the OPERAM research clinicians in discharge counselling. Discharge counselling was performed according to usual practice by the local clinicians, which might explain the lack of information reported both in intervention and control groups.

Medication counselling should be imperative for medication changes implemented in hospital in order to improve medication safety at care transitions.[108,109] Involvement of companions should be encouraged as it may help patients to be better informed. Reinforcing information using the teach-back technique (asking patients to repeat the information and instructions provided), providing written information or post-discharge follow-up (e.g. drug information units in hospitals, follow-up calls, home visits or follow-up by primary care providers) are effective in improving patient knowledge and understanding.[108,110,111] Furthermore, patient participation in decision-making is crucial for preference sensitive decisions and can

improve patient knowledge. Strategies to enhance patient participation and communication skills are discussed in the next paragraph.

Box 5*:* Recommendations to enhance information exchange on hospital-initiated medication changes

- Provision of timely, clear, written information and medication counselling in lay language is crucial to increase patient knowledge and understanding of hospital-initiated medication changes.
- Involvement of companions may help patients to be better informed.
- Reinforcing the information received using the teach-back technique and post-discharge follow-up, can improve patient knowledge and understanding of hospital-initiated medication changes.

'When you're in hospital and you're getting medication, you just take it. You don't ask questions.' [Patient, Ireland] – Preparing patients and clinicians for partnering in medication review

SDM was a component of the OPERAM intervention and is key to medicines optimisation in multi-morbid older persons.[8,9,112-115] However both in intervention and control groups, patients frequently reported paternalistic decision-making and a lack of information regarding their medication changes. Patients' beliefs about medicines were identified as a major barrier or facilitator for accepting the proposed medication changes. Given the limited patient information and participation, these beliefs were likely not sufficiently addressed.

A lack of information is an evident barrier to SDM, but only providing information is not sufficient; patients need both knowledge and power to participate in decision-making.[116-119] Patients' accounts of having limited opportunities for questions, poor understanding of the jargon used by clinicians, feeling too ill or too fatigued, being overwhelmed by multiple clinicians involved in care, dismissive clinicians etc. highlight the powerlessness some patients experienced during hospitalisation. Furthermore, most patients retain very paternalistic views on medication-related decision-making ('doctors know best'), do not expect discussions about preferences and undervalue their role in decision-making. Conversely, patients recognising their

experiential role, health literacy, involvement of companions, being listened to and trusting patient-clinician relationships, were identified as facilitators to patient participation. Nor patients, nor clinicians in the OPERAM intervention arm were adequately prepared for or skilled in patient participation.

The most commonly cited barriers to SDM from the clinicians' perspective include time constraints, lack of agreement with the applicability of SDM to the patient and to the clinical situation.[119] However, it has been shown that clinicians might misjudge patients' desire for participation.[118-120] A systematic review of patient-related barriers to SDM showed that, in addition to patient preferences for participation, other factors affect participation including knowledge, power imbalance in the patient-clinician relationship, interpersonal characteristics of clinicians etc.[119] Not only structural and process barriers should be tackled such as time and tools to perform SDM, but also attitudinal changes of patients and clinicians are required.[117,118] A Cochrane review concluded that it is uncertain whether any interventions for increasing the use of SDM by HCPs are effective because of low-quality evidence.[121,122] The authors concluded that interventions targeting both patients and clinicians show most promise.[121] In the next paragraphs, we provide recommendations based on the international literature to enhance the uptake of SDM at the micro- (direct care), meso- (organisational design and governance) and macro-level (health policy) by preparing patients for SDM, improving clinicians' skills in SDM and create an enabling environment for SDM **(Box 6)**.

Box 6: Interventions at the micro-, meso- and macro-level to prepare patients, clinicians and organisations for partnership in care

Micro-level (direct care)

- Patient preferences for patient participation vary and should be explicitly elicited and respected, rather than based on clinicians' presumptions about the preferred patient role, which may be incorrect.
- Question prompts, patient decision aids and conversation tools can increase patient knowledge and can facilitate patient participation.
- Special attention should be paid to the health literacy of older patients and communication should be tailored accordingly.
- Involvement of companions in medication review should be encouraged as it may facilitate patient participation and can help patients to be better informed and understand medication-related information.
- Patient preferences should be documented in the medical record to ensure patient preferences are communicated across settings. Patient preferences should be regularly reassessed as they may change over time.

Meso-level (organisational design and governance)

- Patients should be empowered to participate in care from within the organisation. To tackle deep rooted paternalistic views on decision-making, educational approaches to raise awareness about SDM among patients are needed.
- Visible organisational buy-in and senior-level support from within the healthcare organisation is essential to promote patient participation.
- Clinical pathways might need to be adapted to support effective SDM and should be supported by all members of the healthcare team.
- Measuring patient participation to demonstrate the impact on practice, may help to engage clinicians and to ensure that high-quality SDM is occurring.

Macro-level (policy making)

- Training in the principles of patient-centred care, SDM and communication skills should be integrated in academic curricula and continuing education of all health professionals.
- Clinical guidelines and clinical decision-support systems should be adapted to incorporate guidance and tools to elicit patient preferences.
- Health information technology should be adapted allow for documentation of patient preferences in the medical record.
- Patient participation may be spurred by incentives.

1) *Raising awareness about SDM*

Paternalistic views and expectations on decision-making are especially engrained in older people or people with lower educational levels and can be mistaken by clinicians for a lack of interest in patient participation.[117,118] In general, there is consensus in the literature that most older people want to participate in decision-making, but they are often not encouraged or enabled to participate in SDM.[116] Efforts to prepare patients for SDM are needed and patients should be informed about what SDM entails, what to expect and why it is important.[117] Informing patients about SDM through posters or videos in waiting rooms, on websites or in the media or flyers sent ahead of consultations, can promote positive attitudes towards SDM.[118,123] In several countries, campaigns exist to raise awareness about SDM by encouraging patients to ask questions (what are my treatment options, what are their benefits and harms and how likely are they to happen to me?) e.g. Ask Share Know (http://askshareknow.com.au), Ask 3 questions (https://bnssgccg.nhs.uk/health-advice-and-support/ask-3-questions/, https://3goedevragen.nl/), Choosing Wisely.[72,119,124]

However, not all patients want participation. Patients in our mixed methods study varied in their preferences for receiving information and participation in decision-making, which has been consistently demonstrated in previous studies.[125,126] It is therefore essential that patient preferences for participation are elicited and respected, rather than based on clinicians' presumptions about the preferred patient role, which may be incorrect.[118,120]

2) *Train clinicians in SDM and patient-centred communication*

It has been argued that SDM has arrived too early and too late - too late for the need and too early for the level of preparation among clinicians.[127] Paradoxical to patients' accounts in our mixed methods study, prescribing clinicians in OPERAM reported a high level of patient participation. "We are already doing SDM" is a frequently reported attitude of clinicians and is a barrier to SDM.[118,128] Clinicians delivering the OPERAM intervention attended a 45 minute webinar training on SDM, which was likely not sufficient to equip them with the skills to perform highly effective SDM.

Increasing understanding among HCPs of what SDM entails and how it differs from current practice is essential to implement SDM and training has a positive impact on SDM skills and patient participation.[116,118] Training in the principles of patient-centred care and SDM (e.g. through interactive skills training workshops) should be integrated in the mandatory academic curricula, assessments and continuing education of all HCPs and interprofessional SDM training programs should be encouraged.[118,129-131] A German train-the-trainer program has been implemented in practice and has shown to be feasible for bridging interprofessionalism and SDM.[128,132] However, a wide variety of SDM training programs exist and few are rigorously evaluated, making it difficult to assess which programs are most effective.[129]

As mentioned by one of our interviewed patients 'I hadn't [the desire to ask] because they completely ignored me, as if I wasn't there at all', clinicians attitudes may act as barriers to patient participation.[116] Conversely, patients valued being treated as individuals and appreciated clinicians listening to them, being understanding and hearty, which acted as facilitators to SDM. Communication and interpersonal skills are essential for SDM.[116] It has been argued that medicine has overemphasised general intelligence whereas emotional intelligence has received less attention.[131] Listening, building trust, empathy and communication skills are needed to facilitate

SDM, patient education, promoting adherence or behaviour change (e.g. motivational interviewing).[131] Patient-centred communication skills should be part of the curriculum and assessments of all HCPs.[131]

The main barriers for patients to accept proposed medication changes, were patients' beliefs about medicines, which were likely not sufficiently addressed. Training healthcare providers in motivational interviewing (a patient-centred approach aimed at ensuring adequate patient behaviour e.g. medication adherence, typically by exploring personal perspectives and perceived barriers) might be particularly useful.[133-135] Ravn-Nielsen and colleagues demonstrated that a multi-faceted in-hospital intervention combining medication review with motivational interviewing and post-discharge follow-up, reduced short- and long-term readmission rates.[76] Using motivational interviewing techniques is appropriate when the aim is to support change away from risky behaviour (e.g. medication non-adherence) and when there is clear evidence for a preferred course of action. In contrast, SDM aims to help patients become well-informed and develop preferences for different reasonable options, in case of preference sensitive decisions.[135] However both motivational interviewing and SDM are patient-centred techniques that respect autonomy and build relationships based on respect for and curiosity about the patient as a person. Providing patient-centred care in practice requires clinicians to be able to recognise clinical situations that require different approaches. Where needed, both approaches can be integrated when both behaviour change and choosing between different treatment options are relevant.[135]

3) *Patient decision aids and conversation tools for medication review*

Interventions designed to help patients address their information needs within consultations such as decision-coaching and question prompt lists, show promise in increasing patient participation in trial settings (significantly increase of question asking, patient satisfaction, recall of information and decrease in anxiety).[117,136,137]

Patient decision aids are considered as the gold standard among patient education methods and have been shown to have a positive impact on patient knowledge, decisional conflict, informed choice, patient participation and decision-self-efficacy.[138] According to a Cochrane review, decision aids can facilitate the adoption of SDM by clinicians, reduce the proportion of patients with passive behaviour and can reduce overuse of treatments not associated with benefits.[128,138,139]

However most patient education materials and decision aids are disease-specific and most are not tailored to the needs of older people with multi-morbidity, nor are not validated in the oldest-old (> 80 years) or in vulnerable people with low health literacy or lower levels of education.[8,115,138,140] An environmental scan showed that only 37% of patient education materials for deprescribing, presented balanced information about potential benefits and harms of deprescribing, most focussed on deprescribing of medications for symptom control (rather than preventive medications) and were not tailored to patients with low health literacy.[138]

The NICE guideline on multi-morbidity recommends using its supporting database on treatment effects of drug classes to inform discussions between patients and clinicians in medication reviews.[141,142] Also the Scottish guideline on polypharmacy provides information on the number needed to treat and number needed to harm of commonly prescribed medications.[143,144]

It is unlikely that a single decision aid could incorporate the evidence for multiple chronic conditions, decisions, potential interactions and combinations.[8] Generic conversation tools to support discussions about patient preferences and goals provide a more flexible approach to medication-related decision-making in multi-morbid older people and show promise to increase patient participation.[8,145] Examples of conversation tools intended for use in the context of medication review are discussed below.[55,145-147]

The Outcome Prioritization Tool (OPT) consists of four visual analogue scales, each representing a universal health outcome: life extension, preserving independence, reducing pain or reducing other symptoms. Each outcome can be rated from 0-100 using the trade-off principle by ranking outcomes in order of importance.[146] The OPT captures wat is important to patients when facing trade-offs and demonstrated content validity, yet test-retest reliability was only fair to poor.[146] The feasibility for using the OPT in routine practice should be further evaluated, since GPs considered the tool as time consuming (mean duration 31 minutes).[147,148] A pilot study demonstrated that using the OPT during medication review in general practice resulted mainly in medication stops and dosage decreases, suggesting that it facilitates deprescribing.[52]

Furthermore, Goal Attainment Scaling (GAS) is a valid and reliable tool for goal setting, measuring improvement towards these goals and facilitating patient participation.[149] GAS has been evaluated for goal-oriented medication review in the DREAMER study.[55] GAS is based on a 6-point scale (-3 to +2), goals have to be formulated SMART (specific, measurable, acceptable, realistic and timebound) and were formulated jointly by the patient and pharmacist after a patient interview on medication use and health-related complaints.[150] Goals could be diverse, ranging from improving activities of daily living, to reducing health-related complaints or number of medications.[150]

The Medicines Conversation Guide has been developed in Australia for use by accredited pharmacists in the context of Home Medicines Review (HMR), a medication review service in the patient's home. The guide aims to increase patient participation by supporting discussions about medication-related preferences and goals and was found to be an acceptable addition to the HMR. The GP's perspective on the guide and the impact on GPs' decisions should be further evaluated.[145]

In Belgium, patient associations have developed a visual self-completion instrument to help patients with chronic conditions formulate their goals in order to promote preference conversations and SDM with health providers.[151] To avoid increasing consultation times, the idea is that patients fill out the instrument by themselves or with the help of a companion before a consultation. Interventions to achieve goals can be subsequently discussed with clinicians during consultations. However, comprehensibility, feasibility of use and impact of using the tool still need to be evaluated. Our scoping review will further explore the available tools to elicit preferences of multi-morbid older people in the context of medication review.

4) *Considering health literacy of patients*

Adequate health literacy is essential for patient understanding of medical information and for patients to feel empowered to participate in health decisions.[152] However, 47% of the European population is considered to have inadequate health literacy to access, understand and act on health information and the proportions might be even higher in older people.[138,153] In particular in older people, a decrease in cognitive function and reading fluency negatively affects health literacy (i.e. recall and processing of health information).[153] However, in many OECD countries, increasing health literacy is seldom a public health objective.[154]

It has been argued that SDM may increase health inequalities as SDM may primarily benefit those patients who are educated, have higher health literacy and are able to express their needs.[155] However, systematic reviews have demonstrated a positive impact of decision aids across sociodemographic patient groups. The gains were largely consistent in more vulnerable patients such as older people or those with lower levels of education or income.[140,155,156]

Notwithstanding, efforts to increase health literacy are needed to facilitate patient participation. While no one model exists for improving health literacy, encouraging

informed-patient choice, promoting patient education and investing in decision aids (tailored to patients with low health literacy) are essential elements.[154] A Belgian initiative to increase health literacy is the development of a platform where patients can access reliable, evidence-based information in lay language.[157] Raising awareness among HCPs to the difficulties experienced by patients with low literacy and the need for tailored communication, might also be beneficial.[128,158] Checking understanding using the teach-back technique, use of visual information or animations and involvement of companions, may increase understanding for patients with low health literacy.[158]

5) *Encourage involvement of companions*

Involvement of companions of older people should be encouraged, although there are few studies considering family-centred approaches in SDM.[116,159] Most of our interviewed patients would like to have a companion involved in decision-making, although this rarely happened in practice. For some patients, involvement of companions acted as a facilitator for them to ask questions, obtain information, remember the information received or to participate in decision-making, which has been previously demonstrated.[152]

6) *Clinical guidelines, clinical decision support systems and medical records should be adapted to facilitate a patient-centred approach*

Most guidelines only provide generic recommendations on the need for considering patient preferences.[8,160] To support clinicians in practice to identify and document patient preferences, guidelines and clinical decision support systems should incorporate specific guidance and tools to elicit patient preferences and facilitate a SDM approach with their patients.[114] To effectively use information about patient preferences in care, systems should be adapted allow documentation of patient preferences in the medical record and medication review reports, ensuring that patient preferences are transferred to the next setting.[115,161] However, this would

require standardised forms and tools and there is not yet a standard representation of preference-related concepts and terminology available in a computerised system.[115,162] Preferences and treatment goals have to be re-assessed regularly, as they may change over time in the light of new problems.[161,163]

Mulley and colleagues have argued that databases of aggregate patient preferences would be useful for HCPs to make a 'provisional preference diagnosis', although such databases are currently sparse to non-existent.[161] Routinely documenting patient preferences in the medical record may address the need for large heterogeneous populations to examine outcomes that really matter patients.[164] Our scoping review will also shed light on aggregate preferences in the context of medication review in older people with multi-morbidity.

7) *Foster a culture of patient participation*

Relying on clinicians and patients alone to implement SDM without system-based support is unlikely to be successful and sustainable.[116] Achieving SDM will require a cultural shift, which might be challenging when clinicians already feel pressured by workload and the burdens of clinical documentation.[165] Creating a patient participation culture and visible organisational buy-in and senior-level support from within the healthcare organisation is essential to promote patient participation.[116,117] If SDM is presented as an organisational priority to drive improvement, it may lead to greater implementation by clinicians because they see SDM as something the organisation does, rather than another initiative being imposed on them and competing with other demands.[117]

Time constraints are among the most frequently reported barriers to SDM, although there is no evidence that SDM increases consultation times if good decision aids are used.[128,139] Clinical pathways might need to be adapted to support effective SDM and to ensure that it is not a burden to clinicians.[127] For instance, the University Hospitals

of Geneva have simplified clinical and administrative processes using tools from lean management and design thinking, to optimise the time spent with patients and companions, increase patient participation, communication and multidisciplinary collaboration.[166] SDM is not the sole responsibility of doctors and should be supported by all members of the clinical team including nurses and pharmacists.[117]

Likewise, for patients it is important to promote SDM from within the organisation e.g. by framing messages as 'your local hospital/doctor/nurse/pharmacist want(s) to know what matters to you'.[117] This indicates to patients that the local health organisation and clinicians want patients to participate.[117,167] Examples of policies and practices that positively influence patient participation during hospitalisation include bedside nursing shift handovers (nurses who are coming and going off duty give their change of shift report at the patient's bedside), bedside rounding (conducting physician and interdisciplinary rounds at the patient's bedside) or tell-us cards (communication tools to facilitate communication between patients and nurses).[167,168] Furthermore, including patients or representatives as advisers in quality improvement initiatives through the use of patient-reported experience measures (PREMs) further promotes a patient-centred culture.[167]

8) *Measuring SDM*

The perception that SDM will lead to improved patient outcomes and health processes are among the most frequently reported facilitators for implementation of SDM.[169] In the belief that 'what gets measured gets done', measuring patient participation to demonstrate the impact on practice may help to engage clinicians as well as to ensure that high quality SDM is occurring rather than clinicians checking a box in the patient record.[127,170] Brief patient-reported measures of SDM are the most scalable means to measure SDM in clinical encounters.[48] However, patient-report measures of SDM are hampered by social desirability bias as well as hindsight and outcome biases that unconsciously make patients judge the quality of decision-

making based on the outcome or expectations of outcome rather than the actual process.[47,118,127] Moreover, patients may not fully identify SDM if they have not experienced it previously.[47,118] To date there is no consensus about how to best measure SDM, although CollaboRATE shows promise in overcoming these problems.[118,127,171] Measuring SDM using self-report or observer measures is limited since these measures are based on theoretical models of SDM and require that all SDM steps are covered within one encounter.[47] However in practice, (multiple) healthcare decisions may be made in a distributed manner across different consultations and/or with different healthcare professionals and companions.[47] Furthermore, clinicians may adapt their SDM approach based on contextual factors such as the patient's emotional response or previous knowledge of treatment options. Hence a consultation which does not cover all aspects of SDM according to SDM tools, may only be a snapshot of an entire SDM process and is not necessarily reflective of a poor SDM encounter.[47]

Linking quality improvement initiatives with implementation of SDM may help to embed SDM.[118] Several hospital accreditation bodies have stressed the need for patient and/or companion involvement at the micro- and meso-level.[172] In Belgium, PREMs are a quality indicator in the pay-for-performance program, although the PREMS measured do not specifically address patient participation.[91]

9) *Incentivising SDM*

The health system must signal that it values patient participation. Patients and organisations operate within a broader social and political environment influenced by social norms and policies.[167] Patient participation may be spurred by incentivising SDM, although appropriate summative measurement methods are first needed.[47,127,170,173] Whereas patient information and informed consent is in the legislation on patients' rights in most European countries, SDM is not. In the US for example, Washington State passed legislation incentivising SDM an alternative to

traditional informed consent procedures for certain preferences-sensitive decisions e.g. for stroke prophylaxis in atrial fibrillation or for osteoarthritis.[127,173] Clinicians are required to use certified decision aids and patients need to sign an attestation that they used the decision aid with the clinicians, deliberated options and decided on a course of action.[127] Although SDM should not be mandatory for every decision, reimbursement incentives and increased protection from litigation, may help to ensure clinicians feel rewarded for their time.[127]

'There should be another person there, the GP.' [Patient, Belgium]. Importance of involvement of a trusted 'ally' and continuity of care for patient-centred medication review

SDM depends on building a good relationship in the clinical encounter.[116] Trust has been shown to influence patient preferences for participation and may at times act as a facilitator or a barrier to patient participation.[116,119,174,175] We showed in our mixed methods study how some patients had high trust in the expertise of clinicians in hospital, whereas for other patients, the absence of a long-standing, trusting patient-clinician relationship or having multiple clinicians involved in care, was a barrier to SDM and/or acceptance of the medication changes. Continuity of care or seamless care are global priorities for patient-centred health services and is paramount for reducing DRAs.[111,176] Seamless care with regards to medications at care transitions requires a combination of interventions targeted at the level of health policy, patients and providers, including national guidelines and campaigns, incentives, electronic healthcare infrastructure, medication reconciliation, patient participation and patient education at and after discharge, shared responsibility for continuity etc.[72,111,177-179] It is beyond the scope of this thesis to go into detail about strategies to improve seamless care, but we would like to highlight the aspects of continuity of care important to patients in medication review.

Several patients stressed the need for more involvement of the GP or community pharmacist for discussions about medicines because of trusting, long-standing relationships (relational continuity of care). Continuity of patient-professional relationships are key to engage older patients in SDM and older patients consider a trusted 'ally' to support them throughout the vulnerable ageing process as highly important.[174] SDM in older patients may come in different shapes and sizes. Even if a patient prefers to defer decision-making to someone trusted e.g. the clinician, the GP, the community pharmacist, a nurse or a companion, but is involved in information exchange and preference discussions, this should still be considered

SDM.[175] Especially for older patients with multi-morbidity, SDM and medicines optimisation should not be restricted to one patient and one clinician in one consultation, rather integrated and interprofessional approaches to SDM are needed.[118,128]

We showed in our mixed methods how conflicting advice from different healthcare providers (e.g. OPERAM intervention versus GP recommendations) at times resulted in non-acceptance of the proposed medication changes (even with SDM) because patients follow the advice of whom they trust most. Conversely, good continuity of care (e.g. the GP agreeing with the medication changes proposed as part of the OPERAM intervention), reassured patients and was a facilitator for implementing the medication changes. In OPERAM, GPs received a letter with the proposed medication changes after the patient's discharge, but were not directly involved in medicines optimisation. It has been demonstrated that a lack of direct contact and a lack of explicit feedback makes it difficult for GPs to take up the challenging role of coordinating care between hospital and home.[177] To overcome some of the patient-reported barriers to medication review in hospital (e.g. absence of trusting long-term relationships, conflicting advice between different healthcare providers), involving GPs earlier in the medication review process seems essential. In addition to step 5 of the OPERAM STRIP intervention (discussion of the recommendations with the prescribing physician in hospital – see General Introduction p. 39), STRIP might benefit from an additional step of discussing the proposed recommendations with the patient's GP to reach consensus.[10] Compared to uni-directional communication, consensus and close collaboration between hospital specialists and follow-up HCPs in medication review may lead to higher acceptance rates of medication changes post-discharge.[180,181]

Furthermore, patients described the importance of follow-up support from the GP or community pharmacist for obtaining additional information regarding the medication changes. Since 2017, the reimbursed pharmaceutical care service 'reference pharmacy' was introduced in Belgian community pharmacies for patients with chronic conditions.[182,183] Patients can appoint a community pharmacy as their reference pharmacy, providing individualised medication-related support and advice as well as an updated medication scheme to the patient and to other HCPs, fostering continuity of care, interdisciplinary collaboration and a trusting relationship between the patient and community pharmacist.[182,183] Hence, the reference pharmacy should play a key role in follow-up on hospital-initiated medication changes after discharge. However, to date no specific service exists for discharged patients and information exchange with the (reference) pharmacy is not standard practice.[184]

Box 7*:* Importance of continuity of care for patient-centred medication review

- Recognise that SDM is not restricted to one consultation or one clinician but should be distributed across healthcare professionals. Trust and continuity of patient-provider relationships are highly important to engage older patients in SDM and involving a trusted 'ally' in decision-making should be encouraged.
- Enhanced collaboration with primary care providers and patient-follow up beyond the walls of the hospital, is essential for patient-centred medication review, either for reinforcing information regarding hospital-initiated medication changes or to discuss the proposed medication changes in a SDM process with a primary care provider, according to the patients' preferences.

3.3 POLYPHARMACY MANAGEMENT REQUIRES A SYSTEM WIDE APPROACH

Medication review interventions in isolation are unlikely to address the problem of polypharmacy, but a system wide approach is required.[72,74] In the light of the WHO's Global Patient Safety Challenge, countries are urged to take action to implement polypharmacy management programs.[72] In Belgium, there is currently no polypharmacy guideline or no polypharmacy management programme implemented. However, initiatives such as the reference pharmacy targeting patients with chronic conditions and polypharmacy are important steps in that direction.

The European SIMPATHY project (Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly) developed change management tools to maximise the odds of successful implementation of polypharmacy management programs.[84] In addition to change management tools, key factors for polypharmacy management include multidisciplinary collaboration and involvement of pharmacists in multidisciplinary teams, incorporation of medication review in clinical pathways for patients with multi-morbidity and transfer of information across care settings. Furthermore, the organisational culture (culture of the healthcare system as a whole and cultural norms within given professions), should be considered to overcome barriers.[72] The SIMPATHY consortium formulated six key recommendations for the implementation of polypharmacy programmes: 1) Use a systems approach with multidisciplinary clinical and policy leadership. A systems approach for polypharmacy management is defined as an operating mechanism where stakeholders (provider organisations across different healthcare settings, regulators, policy-makers and patients) work jointly towards achieving optimal and sustainable use of medicines in multi-morbid patients, supporting them to live healthy and active lives[84]; 2) Nurture a culture that encourages and prioritises the

quality and safety of prescribing (to enable HCPs to discuss polypharmacy issues, to make patients feel safe to ask questions, to make patients expect medication review and integrated care); 3) Ensure patients are integral to the decisions made about their medications and are empowered to do so; 4) Use data to drive change (development of polypharmacy measures and indicators); 5) Adopt an evidence-based approach with a bias towards action where evidence is limited; 6) Utilise, develop and share tools to support implementation (use of a change management strategy, standard principles for medication review and patient engagement supported by tools).

4 RESEARCH AGENDA

The studies conducted as part of this thesis address several knowledge gaps, yet also generate new research questions. In Table 2, a research agenda is proposed.

Table 2: Research agenda

Drug-related admissions
• Development of an automated DRA trigger tool to facilitate the detection of DRAs in electronic medical records. Determination of the predictive validity, sensitivity and specificity of the DRA trigger tool and would first be needed to improve its performance. • Characterisation (type, preventability) of DRAs detected in the OPERAM dataset to better understand the problem of DRA in European multi-morbid older people. • Development of a DRA risk prediction tool DRA based on the OPERAM dataset to identify patients at high risk of DRAs. • To evaluate the performance of the DRA adjudication guide and the AT-HARM10 tool in a comparative analysis.
Patient-centred medication review
• Identify potential intervention functions and policy categories that are most likely to achieve implementation of medication review with SDM in practice: perform a theoretical analysis of the barriers and facilitators identified in our mixed methods study, complemented with clinician-reported and organisational barriers. • Research is needed on the development and evaluation of conversation tools or decision aids that can support decision-making regarding medications in multi-morbid older patients. The feasibility of the available conversation tools for incorporating patient preferences in treatment decisions should be further evaluated, including the relevance for older patients and clinicians, how preferences are translated into treatment decisions and the effect on health outcomes and patient-centred outcomes.

Better detection and monitoring of medication-related harm is critical to improve quality and safety of care. The development of tools the can aid in the detection of adverse drug events is a research priority in polypharmacy.[3] The DRA adjudication guide and AT-HARM10 tool address the lack of tools for detection of DRAs, but are intended for research purposes. To address the problem of under-detection and underreporting of medication-related harm in clinical practice, automated detection of DRAs in the electronic medical record may offer a real-time adverse event detection, allowing for timely corrective actions.[185] The issues of inter-rater reliability and resource-intensiveness of the DRA adjudication guide could be

overcome by computerising the DRA trigger tool to identify patients with a high likelihood of DRA in the electronic patient record. However, the performance of the DRA trigger tool in terms of predictive validity, sensitivity and specificity to detect DRAs should first be evaluated. Like other screening tests, trigger tools tend to have a high sensitivity and relatively low specificity.[186] It would be necessary to determine the positive predictive value (PPV) of each trigger (number of times a DRA is identified by the trigger/number of triggers detected in the charts) as well as the sensitivity (number of trigger-positive charts that the expert panel judged to have a DRA) and specificity (number of trigger-negative charts that the expert panel judged to have no DRA) of the overall trigger tool. The current version of the trigger tool is a comprehensive list and its performance could be optimised by refining the trigger list based on the PPVs of the individual triggers.

Furthermore, characterising the type of DRAs (medications involved, preventability) detected in the OPERAM control group, may help to better understand the scope of the problem of DRAs in a relatively large dataset of multi-morbid older European patients. Identifying subgroups of patients that will most likely benefit from medicines optimisation interventions is a research priority in polypharmacy.[3] One strategy would be to focus on patients at high risk of DRAs. However, the evidence on the risk factors of DRAs is conflicting because of the heterogeneity in defining and measuring DRAs.[16] Given that in OPERAM we considered all-cause DRAs (including underuse) and used a comprehensive DRA adjudication method, the OPERAM database provides potential for the development of a prediction tool for multi-morbid older patients at high-risk of post-discharge DRAs.

Given the fact that the DRA adjudication guide is a comprehensive DRA identification method, but also resource intensive to use compared to AT-HARM10, it would be interesting to perform a comparative analysis of the prevalence and types of DRAs identified by the DRA adjudication guide and the AT-HARM10 tool. Adjudications

with the both tools could be compared with a gold standard expert panel to evaluate the performance of both tools.

Beyond studying the effectiveness of medication review as in the OPERAM trial, it is necessary to study the implementation of medication review interventions in practice. Implementing medication review with SDM will require significant behaviour change of both clinicians and patients.[114] A theoretical underpinning to identify barriers to behaviour change and to design targeted interventions to address these barriers, has been shown to be more successful in changing behaviour compared to non-theory driven interventions.[187,188] The theoretical domains framework (TDF) is a systematic and theory-based approach that can be used to map identified barriers to theoretical domains e.g. knowledge, skills, beliefs about consequences.[189,190] The theoretical domains can in turn be linked to specific behaviour change techniques (BCTs) e.g. shaping knowledge, use of a credible source, incentives, which are the active components of interventions related to each domain.[189-192] It would be interesting to use the TDF and BCTs to perform a theoretical analysis of the barriers and facilitators identified in our mixed methods study, complemented with clinician-reported and organisational barriers, in order to identify potential intervention functions and policy categories that are most likely to achieve implementation of medication review with SDM in practice.

More research is needed on the development and evaluation of tools that can support decision-making regarding medications in multi-morbid older patients. The feasibility of the available conversation tools for incorporating patient preferences in treatment decisions should be further evaluated, including the opinions of patients and providers, how to best implement these tools, how preferences are translated in specific treatment decisions as well as the impact of using these tools on health outcomes and patient-reported outcomes.

5 CONCLUSION

Drug-related admissions (DRAs) matter to patients. However, twenty years after the publication of the Institute of Medicine's report '*To Err Is Human'*, putting patient safety on the international agenda, rates of medication-related harm are still stunningly high.[84,193] The good news is that most harm is preventable. Multi-faceted interventions such as the OPERAM intervention, combining medication reconciliation, medication review, shared decision-making and post-discharge follow-up by primary care providers, have potential for reducing DRAs.

Better detection and monitoring medication-related harm is critical.[82] We contributed to better a measurement and understanding DRAs, an outcome of medication review that is considered highly important to older people with multi-morbidity and polypharmacy.[12] However, we also highlighted the challenges of achieving good inter-rater reliability in the adjudication of complex cases of older multi-morbid patients. To improve detection and prevention of DRAs in practice, automated DRA detection in electronic records could be a valuable future direction.

Our mixed methods study of patient experience showed that patients, despite mostly paternalistic views, place a high value on information exchange, involvement of companions, empathetic and trusting patient-clinician relationships and a collaborative approach across care settings, all of which promote a patient-centred integrated system. After eons of deeply engrained paternalistic practices and behaviour, several patient-related, HCP-related and organisational barriers need to be addressed to foster patient-centred medication review in practice. Asking what matters, listening to what matters and doing what matters to patients is the undeniable and challenging way forward.[194]

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APPENDIX

APPENDIX 1: GLOSSARY OF KEY TERMS

Adverse drug event	Any injury resulting from medical interventions related to a drug. This includes both adverse drug reactions in which no error occurred and complications resulting from medication errors.[1]
Adverse drug reaction	A response to a drug which is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological function. Adverse drug reactions are non-preventable, e.g. an anaphylactic reaction induced by penicillin in a patient who received the antibiotic for the first time is an adverse drug reaction. Adverse drug reactions are often classified as Type A and Type B. *Type A adverse drug reaction* An augmented pharmacologically predictable reaction which is dose dependent. It is generally associated with high morbidity and low mortality. *Type B adverse drug reaction* A bizarre reaction which is unpredictable pharmacologically and is independent of dose. It is generally associated with low morbidity and high mortality.[1]
Behaviour change technique	An observable, replicable and irreducible component of an intervention designed to alter or redirect causal processes that regulate behaviour.[2]
Care coordination	A proactive approach in bringing care professionals and providers together around the needs of service users to ensure that people receive integrated and person-focused care across various settings.[3]
Care transitions	The various points where a patient moves to, or returns from, a particular physical location or makes contact with a health care professional for the purposes of receiving health care.[1]
Content validity	The relationship between an instrument's content and the construct it is intended to measure.[4]
Continuity of care	The degree to which a series of discrete health care events is experienced by people as coherent and interconnected over time, and consistent with their health needs and preferences.[3]
Criterion-related validity	A measure of the validity of a tool by correlating the results with those from some other measure, ideally a gold standard, which has been used and accepted in the field.[5]
Deprescribing	The process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes.[6]

Drug-related admission	A hospitalisation resulting from an adverse drug event encompassing non-preventable adverse drug reactions and preventable medication errors including overuse, underuse and misuse of prescription and non-prescription medications.
Frailty	Medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death.[7]
Health education	Any combination of learning experiences designed to help individuals and communities improve their health, by increasing their knowledge or influencing their attitudes.[8]
Health outcome goals	Health outcome goals are the health and life outcomes that people desire from their health care. To inform decision-making, goals should be specific, measurable, actionable, realistic, and timely (SMART) and aligned with what matters most to the individual (individual values).[9]
Index admission	First hospital admission
Integrated care	Integrated health services are managed and delivered so that people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease-management, rehabilitation and palliative care services, coordinated across the different levels and sites of care within and beyond the health sector, and according to their needs throughout the life course.[3]
Inter-rater reliability	The reproducibility or consistency of assessments from one rater to another.[4,10]
Intra-rater reliability	The reproducibility or consistency of repeated assessments performed by a single rater.
Medication adherence	The degree to which use of medication by the patient corresponds with the prescribed regimen.[1]
Medication discrepancy	Any difference between the medication use history and the admission medication orders. Discrepancies may be intentional, undocumented intentional or unintentional discrepancies.[1]
Medication reconciliation	A formal and collaborative process of obtaining and verifying a complete and accurate list of the patient's current medications – including the name, dosage, frequency and route – to ensure that precise and comprehensive medication information is transmitted consistently across care transitions.[11]
Medication error	Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution;

	administration; education; monitoring; and use.[27,29] Medication errors are preventable, e.g. a patient with a documented ACE-inhibitor allergy admitted with angio-oedema is a preventable medication error due to misprescribing.
Medication-related harm	Patient harm related to medication. It includes preventable adverse drug events (e.g. due to a medication error or accidental or intentional misuse) and non-preventable adverse drug events (e.g. an adverse drug reaction).[1]
Medication review	A structured, critical examination of a person's medicines with the objective of *reaching an agreement* with the person about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste.[13]
Medication safety	Freedom from accidental injury during the course of medication use; activities to avoid, prevent, or correct adverse drug events which may result from the use of medications.[1]
Medicines optimisation	Ensuring that the right patients get the right choice of medicine, at the right time. By focusing on patients and their experiences, the goal is to help patients to (a) improve their outcomes; (b) take their medicines correctly; (c) avoid taking unnecessary medicines; (d) reduce wastage of medicines; and (e) improve medicines safety.[1]
Multi-morbidity	The presence of two or more long-term health conditions, which can include (a) defined physical and mental health conditions such as diabetes or schizophrenia; (b) ongoing conditions such as learning disability; (c) symptom complexes such as frailty or chronic pain; (d) sensory impairment such as sight or hearing loss; and (e) alcohol and substance misuse.[1]
Number needed to treat	The average number of patients who require to be treated for one to benefit compared with a control in a clinical trial. It is defined as the inverse of the absolute risk reduction. So if treatment with a medicine for one year reduces the death rate over five years from 5% to 1%, the absolute risk reduction is 4% and the NNT is 100/4 =25.[14]
Negative predictive value	The percentage of admissions identified by the tool as *no* drug-related admissions that are truly not related to medication according to the gold standard.[5]
Number needed to harm	The average number of people exposed to a medication for one person to suffer an adverse event.[14]
Patient-centred care	Care that is respectful of and responsive to the individual patient's preferences, needs and values and ensures that patient values guide all clinical decisions.[12]
Patient-centred communication	Patient-centred communication is based on a moral philosophy that calls for healthcare professionals to expand upon the biomedical approach to care by (i) helping patients feel understood through inquiry into patients' needs, perspectives,

	and expectations; (ii) attending to the psychosocial context; and (iii) expanding patients' involvement in understanding their illnesses and in decisions that affect their health.[15]
Patient empowerment	Individual patient empowerment is a process that enables patients to exert more influence over their individual health by increasing their capacities to gain more control over issues they consider as important.[2]
Patient participation	Individual patient participation revolves around a patient's rights and opportunities to influence and engage in decision-making about care through a dialogue attuned to his preferences, potential and a combination of his experiential and the professional's expert knowledge.[16]
Patient preferences	Healthcare preferences refer to healthcare activities (e.g. medications, self-management tasks, healthcare visits, diagnostic testing, procedures) that people are willing and able (or not willing or able) to perform and the care they are willing (or not willing) to receive.[9]
Patient priorities	Patient's health priorities refer to the specific health outcome goals that individuals most desire from their health care given what they are willing and able to do to achieve these outcome goals (within the context of their healthcare preferences).[9]
Patient-reported experience measures	Patient reported experience measures (PREMs) measure patients' perceptions of their experience of the process -rather than outcome- of care. Patient-reported experiences (PREs) encompass satisfaction (e.g. with information given by nurses and doctors), subjective experiences (e.g. control of pain), objective experiences (e.g. waiting time before first appointment) and observations of healthcare providers' behaviour (e.g. whether or not a patient was given discharge information).[17]
Patient-reported outcome measures	A patient-reported outcome (PRO) is any report of the status of a patient's health condition (e.g. quality of life, symptoms, treatment effects, functioning) elicited directly from the patient, without interpretation of the patient's response by a clinician or anyone else. Tools used to capture information about PROs, mostly questionnaires and survey's, are called patient reported outcome measures (PROMs). A distinction can be made between generic and condition-specific PROMS.[17]
Pharmaceutical care	The pharmacist's contribution to the care of individuals in order to optimise medicines use and improve health outcomes.[18]
Pharmacovigilance	Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem
Polypharmacy	Polypharmacy is the concurrent use of multiple medications. Although there is no standard definition, polypharmacy is often

	defined as the routine use of five or more medications. This includes over-the-counter, prescription and/or traditional and complementary medicines used by a patient.[1]
Positive predictive validity	The percentage of admissions identified by the tool as drug-related admissions that are truly related to medication according to the gold standard.[5]
Potentially inappropriate prescribing	The prescription of more drugs than are clinically needed (overuse), the incorrect prescription of a drug that is needed (misuse) or the failure to prescribe drugs that are needed (underuse).[19] Potentially inappropriate medicines (PIMs) refer to over- and misuse, whereas potential prescribing omissions (PPOs) refer to underuse.
Preference sensitive decisions	When more than one medically reasonable option is available and when there is no best strategy since the option depends on the patient's personal values and preferences.[13]
Seamless care	The desirable continuity of care delivered to a patient in the health system across the spectrum of caregivers and environments.[20,21]
Self-management	The individual's ability to manage symptoms, treatment, physical and psychosocial consequences and life style changes inherent to living with a chronic condition and to affect the cognitive, behavioural and emotional responses necessary to maintain a satisfactory quality of life.[16]
Sensitivity	The probability that the tool will detect drug-related admissions among the admissions that are truly related to medication according to the gold standard.[5]
Specificity	The probability that the tool will detect *no* drug-related admissions among admissions that are truly not related to medication according to the gold standard.[5]
Shared decision-making	An approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences.[22,23]
Side effect	A known effect, other than that primarily intended, related to the pharmacological properties of a medication.[1]
Teach-back technique	Asking patients to repeat the information and instructions provided as a strategy to increase understanding.
Time to benefit	The time between the preventive intervention (when complications and harms are most likely) to the time when improved health outcomes are seen.[24]
Values	Fundamental beliefs about one's self and life, what matters most to a person.[25]

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APPENDIX 2: CONTRIBUTIONS TO THE RESEARCH CONDUCTED

GENERAL

The promoter Olivia Dalleur and co-promoter Anne Spinewine have contributed significantly to the overall concept of the PhD thesis as well as to the concept and design of the individual studies included in this thesis.

CONTRIBUTIONS TO OPERAM-RELATED RESEARCH INCLUDED IN THIS THESIS

Chapters 1.1, 1.2 and 2.1 of this PhD thesis were conducted in the context of the OPtimising thERapy to prevent Avoidable hospital admissions in the Multi-morbid elderly (OPERAM) project. OPERAM is funded by the European Union's Horizon 2020 research and innovation programme and by the Swiss State secretariat for Education, Research and Innovation. The OPERAM consortium consists of a nine partners located over seven European countries (Figure 1). The consortium was built to address the call topic *"Comparing the effectiveness of existing healthcare interventions in the elderly"* and combines complementary and trans-disciplinary expertise in different fields, including clinical research in older people, clinical trials, systematic reviews, pharmaco-economics, medical software development etc. Each consortium partner was allocated one or more work packages. The Université catholique de Louvain (UCL) was the leader for three work packages, of which two are included in this thesis: 1) To develop a standardised chart review method to adjudicate DRAs (Chapters 1.1 and 1.2); 2) To develop a core outcome set for medication review among older people with multi-morbidity; 3) To explore patient perspectives of the STRIP intervention (Chapter 2.1). As part of my PhD thesis, I took the lead on work packages 1 and 3 and Jean-Baptiste Beuscart, a postdoctoral researcher, took the lead on work package 2. All work packages of UCL involved close collaboration with the partners from the University of Bern (UBERN), University College Cork (UCC), and University Medical Centre Utrecht (UMCU).

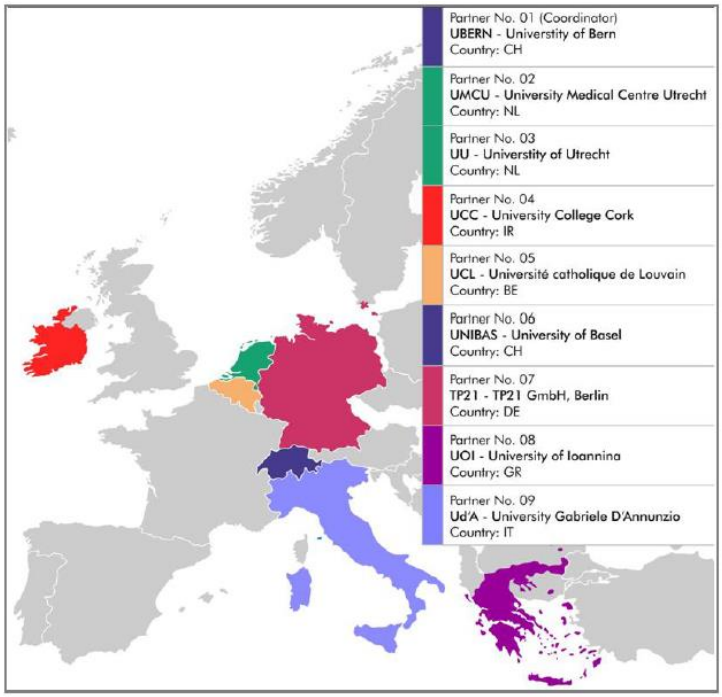

Figure 1: The OPERAM consortium

CHAPTER 1.1: DEVELOPMENT OF A STANDARDISED CHART REVIEW METHOD TO IDENTIFY DRUG-RELATED ADMISSIONS IN OLDER PEOPLE (UCL OPERAM WORK PACKAGE 1)

Stefanie Thevelin conceptualised and designed the study, performed the literature review and pilot test, performed analysis and interpretation of data resulting from the validation, pilot and reliability studies and drafted the DRA adjudication guide. Olivia Dalleur and Anne Spinewine conceptualised and designed the study, participated in the development and validation of the DRA adjudication guide and performed analysis and interpretation of data resulting from the validation, pilot and reliability studies. Jean-Baptiste Beuscart participated in the development and validation of the DRA adjudication guide and performed the pilot test. Benoit Boland, Jacques Donzé and Nicolas Rodondi participated in the development and validation of the DRA adjudication guide. Sophie Marien, Fanny Vaillant, Ingeborg

Wilting, Ariel Vondeling, Carmen Floriani, Claudio Schneider, Shane Cullinan and Denis O'Mahony participated in the reliability study. Stefanie Thevelin drafted the initial manuscript and all authors critically revised and approved the final manuscript.

CHAPTER 1.2: INTER-RATER RELIABILITY OF A STANDARDISED CHART REVIEW METHOD TO IDENTIFY DRUG-RELATED ADMISSIONS IN OLDER PEOPLE (UCL OPERAM WORK PACKAGE 1)

Stefanie Thevelin conceptualised and designed the study, performed data collection and analysis and provided feedback to the adjudication teams on the concordances and discordances in DRA adjudication (in written + telephone conferences). Ariane Mouzon, François-Xavier Sibille, Sophie Marien, Fanny Vaillant, Lisa Bretagne, Fanny Lindemann, Irene Scholz, Martin Feller, Carole Elodie Aubert, Marih O'Leary, Denis Curtin, Ingeborg Wilting and Clara Drenth performed the DRA adjudications. Olivia Dalleur, Anne Spinewine, Nicolas Rodondi, Wilma Knol and Denis O'Mahony conceptualised and designed the study. Séverine Henrard and Stefanie Thevelin performed the statistical analysis.

CHAPTER 2.1: MULTI-MORBID OLDER PEOPLE'S EXPERIENCE OF HOSPITAL-INITIATED MEDICATION CHANGES: A MULTI-CENTRE MIXED METHODS STUDY EMBEDDED IN THE OPERAM TRIAL (UCL OPERAM WORK PACKAGE 3)

Stefanie Thevelin conceptualised and designed the study, performed data collection and data analysis. Catherine Pétein and Beatrice Metry performed data collection and data analysis. Luise Adam, Kevin Murphy and Anniek Van Herksen performed data collection and were involved in data interpretation. Olivia Dalleur and Anne Spinewine conceptualised and designed the study and were involved in data analysis and interpretation. Nicolas Rodondi, Wilma Knol and Denis O' Mahony conceptualised and designed the study. Stefanie Thevelin drafted the initial manuscript and all authors critically revised and approved the final manuscript.

PERSONAL CONTRIBUTIONS TO OPERAM-RELATED RESEARCH NOT INCLUDED IN THIS THESIS

TO DEVELOP A CORE OUTCOME SET FOR MEDICATION REVIEW IN OLDER PATIENTS WITH MULTI-MORBIDITY AND POLYPHARMACY (UCL OPERAM WORK PACKAGE 2)

- Systematic review of outcomes reported in trials of medication review in older people, the need for a core outcome set (Beuscart et. al., 2017)[196]: data extraction on outcomes and outcome measurement instruments for RCT protocols included in the review, in collaboration with Jean-Baptiste Beuscart.
- Review and approval of the manuscripts on the core outcome set.[196 195,218]

IDENTIFICATION OF BEHAVIOUR CHANGE TECHNIQUES IN DEPRESCRIBING INTERVENTIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS (HANSEN ET AL., 2018)[219]

- Behaviour change analysis: identification of behaviour change techniques in deprescribing interventions using the Behaviour Change Techniques taxonomy version 1, in collaboration with Christina Raae-Hansen.[220]
- Review and approval of the final manuscript.

GENERAL PERSONAL CONTRIBUTIONS DURING THE COURSE OF THE OPERAM STUDY

- Training of the adjudication teams from the four OPERAM study centres: face-to-face + webinar trainings on DRA adjudication + continuous support for all questions related to DRA adjudication throughout the trial.
- Development of the electronic case report form for data collection on DRA adjudication in the OPERAM trial, in collaboration with the Clinical Trials Unit from UBERN.
- Language validation, pilot testing and evaluation of usability of the STRIP Assistant version 2.0 in collaboration with UCL, UBERN, UCC and UMCU.
- Development of standard operating procedures used in the OPERAM trial (questionnaires, shared decision-making, DRA adjudication) in collaboration with UCL, UBERN, UCC and UMCU.

- Involvement in telephone follow-up of the Belgian OPERAM patients.
- Notification of the OPERAM trial to the Belgian regulatory authority in collaboration with UCL, UBERN, UCC and UMCU.

NON-OPERAM RELATED RESEARCH INCLUDED IN THIS THESIS

CHAPTER 1.3: POTENTIALLY INAPPROPRIATE PRESCRIBING AND RELATED HOSPITAL ADMISSIONS IN GERIATRIC PATIENTS: A COMPARATIVE ANALYSIS BETWEEN THE STOPP AND START CRITERIA VERSIONS 1 AND 2

Benoit Boland, Olivia Dalleur and Stefanie Thevelin conceptualised and designed the study, performed data collection and data analysis. Leila El Mounaouar performed data collection and data analysis. Séverine Henrard and Stefanie Thevelin performed the statistical analysis. Stefanie Thevelin drafted the initial manuscript and all authors critically revised and approved the final manuscript.

CHAPTER 2.2: MEDICATION-RELATED PREFERENCES OF OLDER PEOPLE WITH MULTI-MORBIDITY AND POLYPHARMACY: PROTOCOL FOR A SCOPING REVIEW

Stefanie Thevelin, Olivia Dalleur, Anne Spinewine and Kristie Weir conceptualised and designed the study. Stefanie Thevelin and Kristie Weir designed the search strategy, performed the selection of studies and will perform data extraction of included studies.

APPENDIX 3: CHANGES IN STOPP/START V_2 COMPARED WITH STOPP/START V_1

Changes in STOPP/START v_1 versus STOPP/START v_2 criteria [1,2]	
STOPP criteria v_1 REMOVED from STOPP criteria v_2	
A	**Cardiovascular system**
A5	Non-cardioselective beta-blocker with Chronic Obstructive Pulmonary Disease (COPD) (risk of bronchospasm).
A8	Calcium channel blockers with chronic constipation (may exacerbate constipation).
A9	Use of aspirin and warfarin in combination without histamine H2 receptor antagonist (except cimetidine because of interaction with warfarin) or proton pump inhibitor (high risk of gastrointestinal bleeding).
A10	Dipyridamole as monotherapy for cardiovascular secondary prevention (no evidence for efficacy).
A13	Aspirin with no history of coronary, cerebral or peripheral arterial symptoms or occlusive arterial event (not indicated).
A14	Aspirin to treat dizziness not clearly attributable to cerebrovascular disease (not indicated).
B	**Central nervous system and psychotropic drugs**
B10	Phenothiazines in patients with epilepsy (may lower seizure threshold).
C	**Gastro-intestinal system**
C1	Diphenoxylate, loperamide or codeine phosphate for treatment of diarrhoea of unknown cause (risk of delayed diagnosis, may exacerbate constipation with overflow diarrhoea, may precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognised gastroenteritis).
C2	Diphenoxylate, loperamide or codeine phosphate for treatment of severe infective gastroenteritis i.e. bloody diarrhoea, high fever or severe systemic toxicity (risk of exacerbation or protraction of infection).
F	**Urogenital system**
F5	Selective alpha-blockers in males with frequent urinary incontinence, i.e. one or more episodes of incontinence daily (risk of urinary frequency and worsening of incontinence).
F6	Alpha-blockers with long-term urinary catheter *in situ* i.e. more than 2 months (drug not indicated).
	Drugs that adversely affect those prone to falls (≥ 1 fall in the past 3 months)
H3	First-generation antihistamines (sedative, may impair sensorium).
H5	Long-term opioids in those with recurrent falls (risk of drowsiness, postural hypotension, vertigo).
I	**Analgesic drugs**
I3	Long-term opioids in those with dementia unless indicated for palliative care or management of moderate/severe chronic pain syndrome.
NEW STOPP criteria v_2	
A	**Indication of medication**
A1	Any drug prescribed without an evidence-based clinical indication.
A2	Any drug prescribed beyond the recommended duration, where treatment duration is well defined.
B	**Cardiovascular system**
B1	Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit).

B4	Beta-blocker with bradycardia (< 50/min), type II heart block or complete heart block (risk of complete heart block, asystole).
B5	Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem).
B9	Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).
B10	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of or lack of efficacy with other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people).
B11	ACE inhibitors (ACEI) or Angiotensin receptor blockers (ARB's) in patients with hyperkalaemia.
B12	Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K^+ should be monitored regularly i.e. at least every 6 months).
B13	Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina (risk of cardiovascular collapse).
C	**Antiplatelet/anticoagulant drugs**
C4	Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy).
C5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin).
C6	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (No added benefit from dual therapy).
C7	Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects).
C11	NSAID with concurrent antiplatelet agent(s) without proton pump inhibitor (PPI) prophylaxis (increased risk of peptic ulcer disease).
D	**Central nervous system and psychotropic drugs**
D2	Initiation of tricyclic antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).
D3	Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).
D8	Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).
D9	Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non- pharmacological treatments have failed (increased risk of stroke).
D11	Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).

D12	Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).
D13	Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy).
E	**Renal system**
E2	Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m^2 (risk of bleeding).
E3	Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m^2 (risk of bleeding).
E5	Colchicine if eGFR < 10 ml/min/1.73m^2 (risk of colchicine toxicity).
E6	Metformin if eGFR < 30 ml/min/1.73m^2 (risk of lactic acidosis).
F	**Gastrointestinal system**
F4	Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate > 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate > 1800 mg/day; no evidence of enhanced iron absorption above these doses).
G	**Respiratory system**
G4	Non-selective beta-blocker (whether oral or topical for glaucoma) with a history of asthma requiring treatment (risk of increased bronchospasm).
G5	Benzodiazepines with acute or chronic respiratory failure i.e. pO_2 < 8.0 kPa ± pCO_2 > 6.5 kPa (risk of exacerbation of respiratory failure).
H	**Musculoskeletal system**
H7	COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke).
H8	NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease).
H9	Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture).
I	**Urogenital system**
I2	Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope).
	Endocrine system
J2	Thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure).
J6	Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).
	Drugs that predictably increase the risk of falls in older people
K4	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).
	Analgesic drugs
L3	Long-acting opioids without short-acting opioids for breakthrough pain (risk of persistence of severe pain).
N	**Antimuscarinic/anticholinergic drug burden**
	Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity).

CHANGED STOPP criteria v_1 versus STOPP criteria v_2		
	Cardiovascular system	
	STOPP v_1	**STOPP v_2**
A2-B7	Loop diuretic for dependent ankle oedema only i.e. no clinical signs of heart failure (no evidence of efficacy, compression hosiery usually more appropriate).	Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).
A4-B8	Thiazide diuretic with a history of gout (may exacerbate gout).	Thiazide diuretic with current significant hypokalaemia (i.e. serum K^+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na^+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).
A6-B3	Beta-blocker in combination with verapamil (risk of symptomatic heart block).	Beta-blocker in combination with verapamil or diltiazem (risk of heart block).
	Antiplatelet/anticoagulant drugs	
	STOPP v_1	**STOPP v_2**
A12-C1	Aspirin at dose > 150mg day (increased bleeding risk, no evidence for increased efficacy).	Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).
A11-C2	Aspirin with a past history of peptic ulcer disease without histamine H2 receptor antagonist or PPI (risk of bleeding).	Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer).
A15-C8	Warfarin for first, uncomplicated deep venous thrombosis for longer than 6 months duration (no proven added benefit).	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months (no proven added benefit).
A16-C9	Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration (no proven benefit).	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months (no proven added benefit).
A17-C3	Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder (high risk of bleeding).	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).
E5-C10	Warfarin and NSAID together (risk of gastrointestinal bleeding).	NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in

		combination (risk of major gastrointestinal bleeding).
	Central nervous system and psychotropic drugs	
	STOPP v_1	**STOPP v_2**
B7-D5	Long-term (i.e. > 1 month), long-acting benzodiazepines e.g. chlordiazepoxide, flurazepam, nitrazepam, chlorazepate and benzodiazepines with long-acting metabolites e.g. diazepam (risk of prolonged sedation, confusion, impaired balance, falls).	Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).
B8-D10	Long-term (i.e. > 1 month) neuroleptics as long-term hypnotics (risk of confusion, hypotension, extra-pyramidal side effects, falls).	Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extrapyramidal side effects, falls).
B9-D6	Long-term neuroleptics (> 1 month) in those with parkinsonism (likely to worsen extra-pyramidal symptoms)	Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extrapyramidal symptoms).
B13-D14	Prolonged use (> 1 week) of first generation antihistamines i.e. diphenydramine, chlorpheniramine, cyclizine, promethazine (risk of sedation and anti-cholinergic side effects).	First-generation antihistamines (safer, less toxic antihistamines now widely available).
	Cardiovascular system ➔ Renal system	
	STOPP v_1	**STOPP v_2**
A1-E1	Digoxin at a long-term dose > 125µg/day with impaired renal function (eGFR < 50ml/min - increased risk of toxicity).	Digoxin at a long-term dose > 125µg/day if eGFR < 30 ml/min/1.73m^2 (risk of digoxin toxicity if plasma levels not measured).
	Gastro-intestinal system	
	STOPP v_1	**STOPP v_2**
C4-F2	PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks (earlier discontinuation or dose reduction for maintenance/prophylactic treatment of peptic ulcer disease, oesophagitis or GORD indicated).	PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).
B4, B5, C5, F3 ➔ F3	• TCA's with constipation (likely to worsen constipation). • TCA's with an opiate or calcium channel blocker (risk of severe constipation). • Anticholinergic antispasmodic drugs with chronic constipation (risk of exacerbation of constipation) • Bladder antimuscarinic drugs with chronic constipation (risk of exacerbation of constipation).	Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation).

	Respiratory system	
	STOPP v_1	STOPP v_2
D3-G3	Nebulised ipratropium with glaucoma (may exacerbate glaucoma).	Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).
	Musculoskeletal system	
	STOPP v_1	STOPP v_2
E1-H1	Non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent histamine H2 receptor antagonist, PPI or misoprostol (risk of peptic ulcer relapse).	Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).
E2-E3 ➔ H2	NSAID with moderate-severe hypertension (moderate: 160/100mmHg – 179/109mmHg; severe: ≥180/110mmHg) (risk of exacerbation of hypertension).	NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).
E7 ➔ H4-H5	Long-term corticosteroids (> 3 months) as monotherapy for rheumatoid arthritis or osteoarthritis (risk of major systemic corticosteroid side-effects).	• Long-term corticosteroids (> 3 months) as monotherapy for rheumatoid arthritis (risk of systemic corticosteroid side-effects). • Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).
E8-H6	Long-term NSAID or colchicine for chronic treatment of gout where there is no contraindication to allopurinol (allopurinol first choice prophylactic drug in gout).	Long-term NSAID or colchicine (> 3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).
	Urogenital system	
	STOPP v_1	STOPP v_2
F1-2-4 ➔ I1	• Bladder antimuscarinic drugs with dementia (risk of increased confusion, agitation). • Bladder antimuscarinic drugs with chronic glaucoma (risk of acute exacerbation of glaucoma). • Bladder antimuscarinic drugs with chronic prostatism (risk of urinary retention).	Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).

	Endocrine system	
	STOPP v_1	**STOPP v_2**
G1-J1	Glibenclamide or chlorpropamide with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).	Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).
UNCHANGED STOPP criteria v_1-v_2		
	Duplicate drug classes	
J-A3	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).	
	Cardiovascular system	
A3-B6	Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).	
A7-B2	Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).	
	Central nervous system and psychotropic drugs	
B1,B2,B3, B6-D1	Tricyclic antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).	
B11-D7	Anticholinergics/antimuscarinics to treat extra-pyramidal side effects of neuroleptic medications (risk of anticholinergic toxicity).	
B12-D4	Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. serum Na^+ < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).	
	Gastrointestinal system	
C3-F1	Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).	
	Musculoskeletal system ➔ renal system	
E6-E4	NSAID's if eGFR < 50 ml/min/1.73m^2 (risk of deterioration in renal function).	
	Respiratory system	
D1-G1	Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).	
D2-G2	Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).	
	Musculoskeletal system	
E4-H3	Long-term use of NSAID (> 3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief).	
	Endocrine system	
G2-J3	Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).	
G3-J4	Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence).	
G4-J5	Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).	
	Drugs that predictably increase the risk of falls in older people	
H1-K1	Benzodiazepines (sedative, may cause reduced sensorium, impair balance).	

H2-K2	Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).
H4-K3	Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg (risk of syncope, falls).
	Analgesic drugs
I1-L1	Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed).
I2-L2	Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).
START criteria v_1 REMOVED from START criteria v_2	
F	**Endocrine system**
F1	Metformin with type 2 diabetes mellitus +/− metabolic syndrome (in the absence of renal impairment, i.e. serum creatinine > 150 µmol/l, or estimated GFR < 50 ml/min/1.73 m^2).
F3	Aspirin for primary prevention of cardiovascular disease in diabetes mellitus.
F4	Statin therapy for primary prevention of cardiovascular disease in diabetes mellitus.
NEW START criteria v_2	
A	**Cardiovascular system**
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.
C	**Central nervous system & eyes**
C3	Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).
C4	Topical prostaglandin, prostamide or beta-blocker for primary open-angle glaucoma.
C5	Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.
C6	Dopamine agonist (ropinirole or pramipexole or rotigotine) for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.
E	**Musculoskeletal system**
E4	Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).
E5	Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout.
E7	Folic acid supplement in patients taking methotexate.
G	**Urogenital system**
G1	Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.
G2	5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.
G3	Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis.

H	**Analgesics**	
H1	High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.	
H2	Laxatives in patients receiving opioids regularly.	
I	**Vaccines**	
I1	Seasonal trivalent influenza vaccine annually.	
I2	Pneumococcal vaccine at least once after age 65 according to national guidelines.	
CHANGED START criteria v_1 versus START criteria v_2		
	Cardiovascular system	
	START v_1	**START v_2**
A1-A1	Warfarin in the presence of chronic atrial fibrillation A1.	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.
A2-A2	Aspirin in the presence of chronic atrial fibrillation, where warfarin is contraindicated, but not aspirin.	Aspirin (75 mg – 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.
A3-A3	Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm.	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.
A4-A4	Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg.	Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently > 90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.
A5-A5	Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is > 5 yrs.	Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.
A8-A7	Beta-blocker with chronic stable angina.	Beta-blocker with ischaemic heart disease.

References

1. Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther* 2008;46(2):72-83. [published Online First: 2008/01/26]
2. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44(2):213-8. doi: 10.1093/ageing/afu145 [published Online First: 2014/10/18]

APPENDIX 4: TOPIC GUIDE MIXED METHODS STUDY PATIENT EXPERIENCE

Introduction

Thank you for agreeing to participate in this interview. Like many seniors, you take multiple medications for different diseases. Some medications are prescribed by the GP, some by specialists or following a hospitalization. Sometimes during the hospitalization, the doctor or pharmacist and you, take the time to review all your medications. Together with you they check if there are medications that should be stopped, if medications are missing, if doses are suitable, if all medications work well together and if the treatment is in line with your preferences. This is called a medication review. As you know, at the moment we are undertaking the OPERAM project that compares different methods of medication review in seniors. Therefore, we are interested in your personal experience and thoughts on these medication changes and how it was discussed with you during your recent hospitalisation. As a patient, you know best how these medication review services should be designed to help you. The results of this research may help to improve these services for caring for people like you.

Our discussion will not take more than 1 hour. Everything you say here will remain strictly anonymous. If you agree, I will record the interview, to transcribe your remarks as accurately as possible. Do you agree?

You don't need to answer questions where you're uncomfortable with and you can withdraw from the interview whenever you wish. There are no right or wrong answers, we are interested in your personal opinion.

Do you have any questions before we begin? Can you confirm that you are happy for the interview to be recorded?

Icebreaker

a) What is your general opinion about the fact that the physician or the pharmacist reviews the medication during hospitalisation (stop, start, changes of medication)?

b) May I ask you to think about your recent hospitalisation, during which some medication changes were proposed. Could you tell me which medication changes were proposed/implemented during your hospitalisation? (*if the patient does not remember, explain the changes*)

If the medication changes are unclear or seem unimplemented: ask to see the medication box or list to ensure you are aware which medications the patient is actually taking.

Patient experience of and attitudes towards medication changes (perceived utility, barriers, facilitators)

1. What do you think about the medication changes (*refer to the proposed medication changes*) proposed by the physician or the pharmacist?

Prompts*:

- How do you feel (physically) about these medications changes?
- How did you experience these medication changes?
- What is good about these changes (i.e. satisfaction, advantages, as compared to the situation before hospitalisation)?
- What is not good about these changes (i.e. fear, difficulties, discomfort, annoyance)?

Patient experience of and perspectives on decision-making regarding medication changes (shared-decision making)

2. During your hospitalisation, the following medication changes were proposed (*remind the changes*). Could you tell me how these medication changes were proposed to you?

Prompts*:

- Who presented these changes to you? (physician, pharmacist?)
- In which context did it happen? (time taken for discussion, location, at discharge, other people involved?)

3. What kind of information did you receive about these medication changes?

- To what extent have you understood the proposed medication changes?
- To what extent are you satisfied or not about the information you have received?
- When we propose to start, stop or change a medicine, there are often advantages and disadvantages to consider. To what extent were these advantages and disadvantages of medication changes discussed with you/your family?
- In an ideal world, how would you have liked to be informed about the medication changes?

4. When deciding to change a medication, there are 3 possible ways to proceed. It is either the doctor that decides alone, or it is the patient that takes the decision alone or it is a shared decision. How was the decision of changing your medication taken during your hospitalisation?

Prompts*:

- Was there something that helped you in deciding on medication changes?

- Was one of your family members or a carer involved in the discussion?
  - If yes: did they help you to make decisions on your treatment? How do you feel about that?
  - If no: would you have preferred someone to be present?
- To what extent were you satisfied or not with your involvement in decision-making?
  - Would you have liked to participate more? Not participate?
  - If the patient did not participate: what kept you from being involved in the decision?
- In an ideal world, how would you have liked that the decision making on medication changes occurred?
- How do you see your role as a patient in making decisions about your medications?

5. Taking into account what is important to patients, their preferences and needs is an essential part of reviewing the medication.

- For you, what is important that your medications do to you?
- People like you taking multiple medications, have shown to distinguish between four care goals regarding their medications: living as long as possible, reducing/eliminating symptoms and side effects (e.g. dizziness, shortness of breath, constipation), maintaining independence (e.g. living alone, getting dressed, washing) and reducing/eliminating pain. Could you explain me which care goals you expect from your medications? (*use Outcome Prioritisation Tool as visual aid and ask the patient to prioritize the four care goals*)
- To what extent were your preferences discussed when the medications changes were proposed?

- To what extent did you feel listened to and understood concerning your preferences for medications?
- To what extent do you think your current medications allow you to reach (*cite the care goals prioritized by the patient*)?

Transition and continuity

6. When you are hospitalised, the hospital informs your GP about the medication changes.

- Since your hospitalisation, did you talk about the changed medications with your GP or pharmacist?
- How did it go? What was his/her opinion about the proposed changes?

Suggestions for improvement

7. As a patient, you know best how these medication review services should be designed to help you. If you should help researchers to improve the medication review service for people like you, what would be your suggestions?

Prompts*:

- What was good about how the medication review process was delivered?
- What needs to be improved?

8. Would you like to add something else to everything we have discussed here today?

Questionnaire: Beliefs about medicines questionnaire (BMQ)

Explain the BMQ questionnaire and let the patient complete it (*if not possible, read the questions out loud*). Invite the patient to comment out if he/she wishes while completing the questionnaire (*keep on recording the interview*). Introduce the questionnaire as follows:

- We would like to ask you questions about your personal opinion regarding medicines in general (BMQ-General) and medicines prescribed for you (BMQ-Specific).
- The following affirmations are opinions of other people about their medication.
- Please, thick to what extend you agree or not to these affirmations.
- There are no correct or wrong answer. We are interested by your personal opinion.

APPENDIX 5: NHS PATIENT EXPERIENCE FRAMEWORK[1]

NHS

NHS Patient Experience Framework

In October 2011 the **NHS National Quality Board (NQB)** agreed on a working definition of patient experience to guide the measurement of patient experience across the NHS. This framework outlines those elements which are critical to the patients' experience of NHS Services.

- **Respect for patient-centred values, preferences, and expressed needs,** including: cultural issues; the dignity, privacy and independence of patients and service users; an awareness of quality-of-life issues; and shared decision making;
- **Coordination and integration of care** across the health and social care system;
- **Information, communication, and education** on clinical status, progress, prognosis, and processes of care in order to facilitate autonomy, self-care and health promotion;
- **Physical comfort** including pain management, help with activities of daily living, and clean and comfortable surroundings;
- **Emotional support** and alleviation of fear and anxiety about such issues as clinical status, prognosis, and the impact of illness on patients, their families and their finances;
- **Welcoming the involvement of family and friends,** on whom patients and service users rely, in decision-making and demonstrating awareness and accommodation of their needs as care-givers;
- **Transition and continuity** as regards information that will help patients care for themselves away from a clinical setting, and coordination, planning, and support to ease transitions;
- **Access to care** with attention for example, to time spent waiting for admission or time between admission and placement in a room in an in-patient setting, and waiting time for an appointment or visit in the out-patient, primary care or social care setting.

This framework is based on a modified version of the Picker Institute Principles of Patient-Centred Care, an evidence based definition of a good patient experience. When using this framework the NHS is required under the Equality Act 2010 to take account of its Public Sector Equality Duty including eliminating discrimination, harassment and victimisation, promoting equality and fostering good relations between people.

DH Department of Health

Reference

1. NHS England. NHS Patient Experience Framework. 2015 [Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215159/dh_132788.pdf accessed July 2019].

APPENDIX 6: MEDLINE (OVID) SEARCH STRATEGY SCOPING REVIEW (04/2019)

#	Search Statement	Results
1	exp polypharmacy/	4379
2	exp inappropriate prescribing/	2584
3	exp deprescription/	206
4	exp "drug utilization review"/	4208
5	polypharmacy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	8450
6	(multiple adj2 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2178
7	(multiple adj2 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	384
8	(multiple adj2 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	41965
9	(many adj2 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1421
10	(many adj2 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1719
11	(many adj2 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	9789
12	(inappropriate adj4 prescription*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1010
13	(inappropriate adj4 prescribing).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word,	3646

	rare disease supplementary concept word, unique identifier, synonyms]	
14	deprescri*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	529
15	(discontinu* adj4 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4263
16	(discontinu* adj4 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	116
17	(discontinu* adj4 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	8373
18	(reduc* adj4 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	8063
19	(reduc* adj4 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1332
20	(reduc* adj4 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	27821
21	(stop* adj4 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2005
22	(stop* adj4 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	198
23	(stop* adj4 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2768
24	(cease adj4 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word,	44

	organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
25	(cease adj4 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5
26	(cease adj4 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	60
27	(medication* adj4 cessation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1211
28	(medicine* adj4 cessation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	69
29	(drug* adj4 cessation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1943
30	(taper* adj4 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	385
31	(taper* adj4 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	6
32	(taper* adj4 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	318
33	(withdraw* adj4 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1936
34	(withdraw* adj4 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	121
35	(withdraw* adj4 drug*).mp. [mp=title, abstract, original title, name of substance	9287

	word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
36	(refus* adj4 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	374
37	(refus* adj4 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	58
38	(refus* adj4 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	309
39	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	67251
40	(start* adj4 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1820
41	(start* adj4 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	557
42	(start* adj4 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3774
43	(commenc* adj4 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	183
44	(commenc* adj4 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	37
45	(commenc* adj4 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	316
46	(initiat* adj4 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word,	1799

	organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
47	(initiat* adj4 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1072
48	(continu* adj2 medication*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1703
49	(continu* adj4 medicine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1716
50	(continu* adj4 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	8301
51	(initiat* adj4 drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4547
52	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51	25151
53	(medication* adj4 review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4466
54	(medicine* adj4 review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5145
55	(drug* adj4 review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	17849
56	(medication* adj4 evaluation*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1331
57	(medicine* adj4 evaluation*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1952

58	(drug* adj4 evaluation*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	98765
59	(medication* adj4 assessment*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1683
60	(medicine* adj4 assessment*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1489
61	(drug* adj4 assessment*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	6379
62	(prescription* adj4 review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	908
63	(prescription* adj4 evaluation*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	518
64	(prescription* adj4 assessment*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	418
65	(polypharmacy adj4 review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	88
66	(polypharmacy adj4 evaluation*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	15
67	(polypharmacy adj4 assessment*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	43
68	53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67	137685
69	exp aging/	234602
70	geriatrics/	29166

71	(old* adj3 people).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	31817
72	(old* adj3 person*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	14411
73	elder*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	250172
74	(old* adj3 adult*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	84070
75	(old* adj3 patient*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	136593
76	senior*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	37424
77	frail*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	22583
78	geriatric*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	96672
79	aging*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	329183
80	ageing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	39072
81	exp chronic disease/ or exp multiple chronic conditions/	254840
82	multimorbid*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism	3958

	supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
83	multi-morbid*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	644
84	(multiple adj2 chronic adj2 condition*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1327
85	(multiple adj2 chronic adj2 disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	523
86	(multiple adj2 comorbid*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3411
87	(multiple adj2 condition*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5684
88	(multiple adj2 illness*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	696
89	(multiple adj2 disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	13638
90	(comorbid adj2 disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2851
91	(multiple adj2 chronic adj2 illness*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	140
92	69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91	1092311
93	(patient* adj4 preference*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare	21320

	disease supplementary concept word, unique identifier, synonyms]	
94	(patient* adj4 priorit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4880
95	(patient* adj4 goal*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	11730
96	(patient* adj4 perspective*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	15616
97	(patient* adj4 belief*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4347
98	(patient* adj4 value*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	54178
99	(treatment* adj4 preference*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4790
100	(treatment* adj4 priorit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2587
101	(treatment* adj4 goal*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	13912
102	(care adj4 goal*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	6254
103	(patient adj4 decision*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	10773
104	(stated adj2 preference*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word,	831

	organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
105	(preference adj2 weight*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	407
106	(best adj2 worst adj2 scaling).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	177
107	tradeoff*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	6105
108	trade-off*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	20338
109	(willingness adj2 to adj2 accept).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	18
110	(willingness adj2 to adj2 pay).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	431
111	WTP.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1577
112	(multi-attribute adj2 utility).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	172
113	(standard adj2 gamble).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	830
114	(choice adj2 model*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2244
115	(discrete adj2 choice*).mp. [mp=title, abstract, original title, name of substance word,	1864

	subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
116	DCE.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5220
117	(decision adj2 analysis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	6574
118	MCDA.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	486
119	(analytic adj2 hierarchy adj2 process).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	629
120	(visual adj2 analogue adj2 scale).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	22270
121	(conjoint adj2 analysis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	719
122	(contingent adj2 valuation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	676
123	(guttmann adj2 scale).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1
124	(semantic adj2 differential adj2 technique).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	88
125	(direct adj2 rating).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	58

126	exp patient preference/	7083
127	exp patient-reported outcome/	2995
128	exp patient participation/	23714
129	(patient* adj4 choice*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	18703
130	exp Withholding Treatment/	14573
131	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 130	300285
132	exp Health Priorities/	10383
133	exp Goals/	15623
134	exp Social Values/	19463
135	93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 132 or 133 or 134	281482
136	92 and 131 and 135	926
137	limit 136 to english language	840

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2013–2014	Master of Science in Clinical Pharmacy, International Practice & Policy University College London, United Kingdom
2011–2013	Master of Science in Hospital Pharmacy Inter-university programme (Ghent University, University of Louvain, University of Antwerp, University of Brussels), Belgium
2006–2011	Master of Science in Pharmaceutical Care Ghent University, Belgium

PROFESSIONAL EXPERIENCE

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July 2013 – September 2013	Hospital Pharmacist AZ Sint-Lucas, Ghent
January 2013 – June 2013	Locum pharmacist Coop group, Ghent
September 2011 – January 2013	Hospital Pharmacist Trainee AZ Sint-Lucas, Ghent

LIST OF PUBLICATIONS AND COMMUNICATIONS

Scientific publications in relationship with this thesis

Thevelin S, Spinewine A, Beuscart JB, Boland B, Marien S, Vaillant F, Wilting I, Vondeling A, Floriani C, Schneider C, Donzé J, Rodondi N, Cullinan S, O'Mahony D, Dalleur O. Development of a standardised chart review method to identify drug-related hospital admissions in older people. British Journal of Clinical Pharmacology. 2018; 84(11):2600-2614.

Thevelin S, Mounaouar LE, Marien S, Boland B, Henrard S, Dalleur O. Potentially inappropriate prescribing and related hospital admissions in geriatric patients: A comparative analysis between the STOPP and START criteria versions 1 and 2. Drugs & Aging. 2019; 36(5):453-459.

Scientific publications not included in the thesis manuscript

Beuscart JB, Pont LG, Thevelin S, Boland B, Dalleur O, Rutjes AWS, Westbrook JI, Spinewine A. A systematic review of the outcomes reported in trials of medication review in older patients: the need for a core outcome set. British Journal of Clinical Pharmacology. 2017; 83(5):942-952.

Beuscart JB, Dalleur O, Boland B, Thevelin S, Knol W, Cullinan S, Schneider C, O'Mahony D, Rodondi N, Spinewine A. Development of a core outcome set for medication review in older patients with multimorbidity and polypharmacy: a study protocol. Clinical Interventions in Aging. 2017; 12:1379-1389

Beuscart JB, Knol W, Cullinan S, Schneider C, Dalleur O, Boland B, Thevelin S, Jansen PAF, O'Mahony D, Rodondi N, Spinewine A. International core outcome set for clinical trials of medication review in multi-morbid older patients with polypharmacy. BMC Medicine. 2018; 16(1):21.

Hansen CR, O'Mahony D, Kearney PM, Sahm LJ, Cullinan S, Huibers CJA, Thevelin S, Rutjes AWS, Knol W, Streit S, Byrne S. Identification of behaviour change techniques in deprescribing interventions: a systematic review and meta-analysis. British Journal of Clinical Pharmacology. 2018; 84(12):2716-2728.

Oral presentations at national and international meetings

Development and validation of a standardised method to identify drug-related hospital admissions in older people. 19èmes Journées d'Automne de la Société Belge de Gérontologie et Gériatrie (SBGG), 21-22 October 2016, Liège, Belgium.

Ma thèse en 180 secondes - 'Le traitement VIP, la solution pour les personnes âgées?' Winner of the UCL university competition and selected for the inter-university finals, 2016 (https://www.youtube.com/watch?v=m7GdwBeMRys).

Seminar drug-related hospital admissions: detection and prevention. 24th congress of the European Association of Hospital Pharmacists (EAHP), 27-29 March 2019, Barcelona, Spain.

Poster presentations at international meetings

Healthcare professionals' knowledge of intravenous fluid treatment. 20th congress of the European Association of Hospital Pharmacists (EAHP), 25-27 March 2015, Hamburg, Germany.

Development and validation of a standardised method to identify drug-related hospital admissions in older people. International Congress of the European Union Geriatric Medicine Society (EUGMS), 5-7 October 2016, Lissabon, Portugal.