Falls and Bleeds in Relation to the Use of Drugs as Quality Indicators for Medication Associated Harm in Iceland

Working title:

Proposal to measure severe and avoidable medication associated harm in Iceland.

Abstract (150 words)

In 2017, the World Health Organisation (WHO) launched its third 5-year global patient safety challenge to improve medication safety. The aim is to reduce severe and avoidable medication related harm by 50%, globally within 5 years. The objective of this proposal is to construct quality indicators which can be used to measure severe and avoidable medication associated harm. It provides opportunity to monitor the impact of the implementation of medication safety improvement work in Iceland as an overarching clinical outcome measure. A severe, avoidable medication-related harm is understood as 1) permanent or transient harm to the patient or necessitates treatment, 2) could be avoided by following current good professional practice and 3) with predominant probability is due to the patient´s medication. Two indicators were defined, bleeding and falls associated with (due to) the use of medication. These are clinically relevant outcomes, are relevant to the definition of "severe avoidable medication related harm", occur frequently in the adult population, and are retrievable from national registries or health care databases of medical records, allowing retrospective outcome extraction and record linkage with redeemed prescriptions, according to pre-specified ATC codes in the National Medicine Registry in Iceland.

1. Background

In 2017, the World Health Organisation (WHO) launched its third 5-year global patient safety challenge to improve medication safety. Its previous two challenges focussed on improving infection control practices and surgical safety. Medication safety is to date the most complex and ambitious campaign launched by the WHO. A framework for action was created based on the gathering of learning from the most advanced health care systems and research evidence. Health care systems globally are encouraged to focus on three priority actions: transitions of care, polypharmacy and high-risk situations. The aim of the campaign is *to reduce severe and avoidable medication related harm by 50%, globally within 5 years by addressing harm resulting from errors or unsafe practices due to weaknesses in health systems* (WHO 2017). A whole systems approach is recommended to tackle the problem from multiple angles: engaging patients and the public, health care workers, re-designing systems and practices and the medications themselves such as packaging and naming. Success of applying the framework into action requires high level governmental and strategic alignment across the health care system.

Figure 1: WHO Medication Without Harm Strategic Framework (WHO 2018)

2. Introduction

At the end of 2018, Landspítali – The National University Hospital of Iceland (LSH) initiated a year long process of translating the WHO Medication Without Harm strategic framework into the development of a programme for improvement locally. A risk-based analysis (failure mode and effects analysis) of current medication processes, an analysis on the drivers and barriers for improvement, root cause analysis and active staff engagement was conducted including learning from past medication safety improvement projects. A 5-year improvement programme was developed based on the most pressing local needs. This programme has been designed with the following requirements in mind:

- a whole systems approach involving all health care providers
- a structured and scientifically rigorous approach that promotes sustained action
- clinical leadership and ownership on the frontline
- an “all hands on deck” approach with change implemented from the bottom-up
- strong governance, oversight and high level investment

In early 2020, a national steering committee was formed and the design and testing of improvements on the clinical frontline was initiated.

3. Objective

The purpose of this proposal is to set the stage for measuring the impact of the strategic framework of the WHO Medication Without Harm Project in Iceland. This will be started by developing a portfolio of two quality indicators, which can be used to measure severe and avoidable medication related harm at baseline and downstream following the implementation of the medication safety improvement work in Iceland.

4. The Medication Safety Improvement Programme in Iceland

The improvement programme in Iceland focuses on three action areas as recommend by the WHO: improving medication safety during transitions of care, in polypharmacy and in high-risk situations.

a. Improving medication safety during transitions of care

An estimation of over 50% medication error rates occurs when patients move between healthcare services following hospitalisation or outpatient visits (Garfield, 2009). This has a more significant impact on older adults who experience serious consequences from medication errors, half of which are potentially preventable (Parekh, 2018). Interventions that have been found to reduce error rates during transitions of care are summarised by the WHO, which include structured medication reconciliation, enhanced patient knowledge about medications they should be taking, clear and transparent communication between healthcare professionals, centralised medication information and pharmacists' involvement (World Health Organisation 2019c). Analysis of the risks and problems relating to transitions of care in Iceland revealed that these interventions are not being implemented in standardised ways across sectors, with considerable variation between healthcare professionals and teams. The strategy to improve medication safety during transitions of care in Iceland therefore focuses on these priorities and is summarised in the driver diagram below (Figure 2). An effort has been made to define the approaches of medication reconciliation and medication review in Iceland in a published letter to the Icelandic Medical journal (Sigurðardóttir et al 2021).

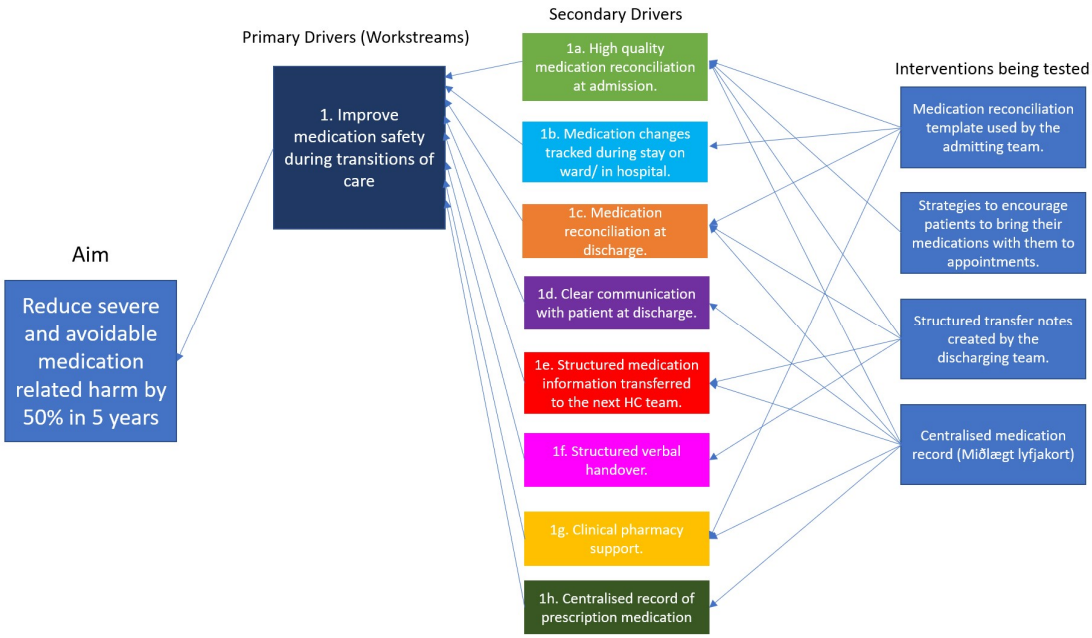

Figure 2. Drivers to improve medication safety during transitions of care in Iceland

b. Improving medication safety in polypharmacy

A growing body of research evidence has associated polypharmacy with adverse health outcomes, especially in older adults (Pazan, 2021). The WHO describes the importance of strengthening the medication review process as a prerequisite for identifying and reducing inappropriate polypharmacy (World Health Organisation 2019b). There are numerous publications indicating that certain medication classes are used extensively in Iceland. These are outlined and referenced later in the

text. Due to limited availability of clinical pharmacy expertise to support the medication review process in the Icelandic healthcare system, strategies for improvement emphasise finding creative solutions to share these resources across healthcare sectors and upskilling other types of healthcare professionals (e.g. doctors, pharmacists working in commercial pharmacies and pharmacy technicians). Evidence-based deprescribing tools and those which assist the practitioners to identify potentially harmful drug interactions will also be made available. The improvement of health literacy of the public will likewise play an important role in reducing inappropriate polypharmacy as well as strengthening laws and regulation on the use of automated drug renewals and multi dose dispensing systems. The strategy for improving medication safety in polypharmacy is summarised in Figure 3 below.

Figure 3. Drivers to improve medication safety in polypharmacy in Iceland

c. Improving medication safety in high risk situations

Not all medications have the potential to cause severe harm and vulnerable patients are at higher risk of serious consequences of medication errors. The WHO recommends healthcare systems to prioritise their efforts to safeguard specific patient groups and create safer processes in the use of high-risk medications (World Health Organisation 2019a). The results of the risk-based analysis of medication preparation, dispensing and administration processes on inpatients wards at LSH in 2019 revealed that there are no standardised processes for implementing extra safeguards for high risk medications such as independent double checking between different healthcare professionals. Inadequate patient identification practices persist resulting in patient misidentification when medications are administered in hospital despite the presence of guidelines. Electronic medication prescribing and administrative systems lack the necessary safeguards to prevent errors from high-risk medications and there is considerable variation in the way in which healthcare professionals and teams work. Furthermore, quality indicators published internationally indicate that sales of opioids and benzodiazepines are highest in Iceland compared to other Nordic countries (Editorial Group for NOMESCO Health Statistics, 2020). The priorities for Iceland relating to improving medication safety

in high-risk situations therefore focus on the safe use of high risk medications according to the APINCHS acronym (Australian Commission on Safety and Quality in Health Care, 2019) and strengthening of the medication review process supported by trained pharmacists. A summary of the strategy is summarised in Figure 4.

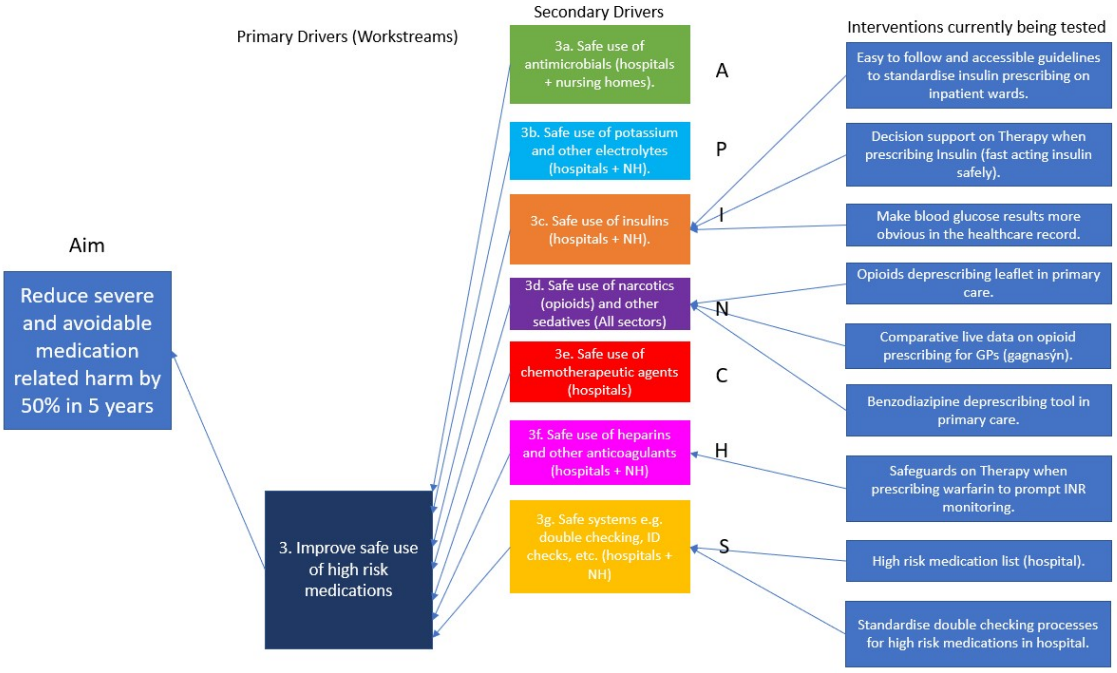

Figure 4. Drivers to improve medication safety in high risk situations in Iceland

5. Methodology to measure improvement of medication safety in Iceland

A working group was appointed by the WHO Medication Without Harm national steering committee to explore and define potential indicators that can be utilized to measure the outcome of improvement programme in Iceland.

Group membership:

- Guðrún Stefánsdóttir, Team Leader PhV and Bioequivalence Assessment, Icelandic Medicines Agency (Lyfjastofnun) (Chair and Lead)
- Kristján Linnet, Pharmacist, Development Centre for Primary Care (Þróunarmiðstöð íslenskrar heilsugæslu)
- Anna Bryndís Blöndal, Pharmacist, Development Centre for Primary Care (Þróunarmiðstöð íslenskrar heilsugæslu)
- Aðalsteinn Guðmundsson, Consultant Geriatrician, LSH
- Jóhann M. Lenharðsson, Head of Supervision and Quality of Healthcare, Directorate of Health (embætti landlæknis)
- Védís Helga Eiríksdóttir, Project Manager, Health Information, Directorate of Health (embætti landlæknis)
- Birna Björg Másdóttir, Project Manager, Health Informatics Department (Hagdeild), LSH
- Amelia Samuel, Quality Lead, Quality Department, LSH (Project Manager)

The working group convened in May 2020 to determine the potential quality indicators for the improvement programme in Iceland. The WHO did not define "severe, avoidable medication-related harm", but instead put the task at national level, as a relevant definition needs to be adapted to the national context.

The group first defined the level of harm, what is avoidable and what constitutes medication related harm. Definitions from Denmark and the United Kingdom were then reviewed and compared with existing situations in Iceland. Population, medications and situations were then mapped to fit these definitions. Current research on medication related harm pertaining to transitions of care, polypharmacy and high-risk medications were then reviewed. A consensus was reached by the working group, taking into consideration the availability of data in the country, size and characteristics of the Icelandic population. ICD-10, ATC and NOMESCO codes were adapted from the Danish specification. Some ICD-10 codes were eliminated due to irrelevance to the Icelandic context and other ICD-10 codes on bleeding were added based on learning taken from concurrent research on the validation of specificity of diagnostic codes in Iceland (Ingason 2021) and research evidence relating to harm due to the use of anti-thrombotics (Sennesael 2017).

Three independent reviewers were chosen by the National Steering Committee to provide expert advice on the development of the indicators:

1. Einar Stefán Björnsson, Professor at the University of Iceland School of Medicine and Chief Physician at LSH
2. Ólafur Helgi Samúelsson, Consultant in Geriatric Medicine at LSH
3. Members of the Hospital Falls Committee at LSH
    a. Bergþóra Baldursdóttir, Chair, Specialist in Geriatric Physiotherapy and Project Manager for Falls Prevention at LSH
    b. Konstantín Shcherbak, Consultant in Geraitric Medicine at LSH

6. Definition of Medication Related Harm in Iceland

A severe, avoidable medication-related harm, is understood as a:

- *1) permanent or transient harm to the patient or necessitates treatment*
- *2) could be avoided by following current good professional practice*
- *3) with predominant probability is due to the patient´s medication*

1) *permanent or transient harm to the patient or necessitates treatment*: The harm is fatal, life-threatening, causes hospitalization, necessitates treatment for example in the emergency room or causes significant impairment e.g. incapacity to work or increased care needs. The severity of harm is assessed according to the WHO classification for patient safety: descriptions of harm severity (WHO 2009).

2) could be avoided by following current good professional practice: Good professional practice means the best current treatment or care for an individual patient, that can be expected by a healthcare professional under the given circumstances. The harm can occur due to errors or deviations from the rules adopted, for example guidelines, and may cover all phases of medication e.g. prescribing, dispensing, administering and monitoring. The errors can both be at an individual level or due to system failures. This also includes the WHO definition of medication errors (WHO 2016).

3) with predominant probability is due to the patient´s medication: The harm must consist of a well-defined medical condition or a known medication-related phenomenon. The harm may be due to one or more medications which the patient has received and there is a significant probability that it is related to the medication, although could also be explained by disease or other drugs. The likelihood is at least "possible" according to the WHO definition of causality: (WHO-UMC 2013)

7. Proposed Quality Indicators as Clinical Outcome Measures for Severe and Avoidable Medication Related Harm

The following quality indicators, which can be used to measure severe and avoidable medication related harm as clinical outcome measures, are proposed:

1. Emergency department attendances or hospitalisation of patients 18 years and over due to bleeding events and the use of antithrombotics, NSAIDs, Aspirin, Bisphosphonates, SSRs and SNRIs (adapted from the Danish specification).

2. Emergency department attendances or hospitalisation of patients 65 years and over due to falls and the use of at least one falls risk increasing drugs (FRIDs) (adapted from the Danish specification).

3. Emergency department attendances or hospitalisation of patients 65 years and over due to falls and the use of ≥5 concurrent medications that includes at least one FRID.

The working group concluded that adults taking a range of medications that result in emergency department attendances or hospitalisation due to falls or bleeding would be the most meaningful quality indicators of severe and avoidable medication related harm in Iceland.

The prevalence of ADR-related hospitalisations due to anti-thrombotics is potentially high (van der Hooft 2008) and the risk of hospitalisation due to falls is increased with polypharmacy (Zaninotto et al 2020) (Morin et al 2019). These events can be retrievable from Icelandic registries, they are potentially preventable (Sennesael et al 2018) (de Jong et al 2013) and impact can be measured within the timeframe of the improvement campaign (five years). The working group concluded that these are clinically relevant outcomes, in alignment with the definition of "severe avoidable medication related harm", occur frequently in the adult population, are registered in national databases and/or hospital medical records and can be matched with the National Medicine Registry in Iceland (Lyfjagagnagrunnur embætti landlæknis), which uses the ATC coding system making it possible to extract data retrospectively and set a baseline.

In Denmark, the draft quality indicators for severe and avoidable medication related harm were defined as emergency department visits or hospitalisation due to bleeds, falls and constipation associated with the use of a range of medications (Nielson et al 2019). Constipation was considered to be difficult to measure in Iceland and draw conclusions due to the lack of data (coded) and a small size of the population in comparison to Denmark. The group decided to adapt the Danish specifications for bleeding events and falls due to similarities in the healthcare systems and populations. This was in order to make the outcomes of the project more comparable to other countries and creates ongoing opportunities to share learning internationally. An additional falls quality indicator associated with polypharmacy and FRIDs is also proposed. Furthermore, there will be ongoing collaboration with current researchers relating to the validation of specificity of diagnostic codes for bleeding events in Iceland.

At later stages, unplanned hospitalisation and re-admission in people over the age of 65 years taking ≥5 medications could be considered as a quality indicator. This is because people who are 65 years and over are more likely to be taking multiple medications (Morin et al 2017) and more likely to be admitted and re-admitted to hospital due to adverse drug reactions (ADRs) (van der Hooft et al 2008). There is also evidence that the prevalence of polypharmacy and use of inappropriate medications is high in older adults admitted to LSH (Sigurdardottir 2011).

It is worth noting that in addition to these proposed overarching clinical outcomes of falls and bleeds due to medications, the group will explore the use of established surrogate measures in the duration of this improvement campaign. These include a combination of locally developed quality indicators and ones that were already published providing comparative data internationally (Editorial Group for NOMESCO Health Statistics, 2020) (OECD, 2019). Examples of these include:

i. Evidence of structured medication reconciliation for patients within 24 hours of admission to hospital (locally developed indicator)
ii. Proportion of patients 75 years and over who are taking more than 5 medications concurrently (an OECD – Health Care Quality and Outcomes (HCQO) indicator)
iii. Long term use of benzodiazepines and related drugs in ≥65 years of age (Number DDDs per individual) (OECD HCQO indicator)
iv. Any anticoagulating drug in combination with an oral NSAID (OECD HCQO indicator)
v. Sales of opioids (NOMESCO Nordic Health and Welfare Statistics)
vi. Proportion of blood glucose results that are within range for inpatients with diabetes (locally developed indicator)

Monitoring polypharmacy is recognised in the WHO's third Global Patient Safety Challenge: Medication without Harm as a way of identifying people at risk of medicine-related harm and who may benefit from a medicines review. (WHO 2019b) A detailed list of other surrogate measures and their relationship to the improvement programme and proposed clinical outcome measures are included in Appendix A. Outcome measures published in (current) clinical research that were reviewed for this proposal are summarised in Appendix B.

1. Draft Specification for Data Extraction and Analysis

a. Quality indicator and outcome measure on preventable bleeding events due to the use of medication (similar to the Danish specification)

Medication ATC codes:

- Every drug against thromboembolic diseases (ATC code B01)
- NSAIDs (ATC code M01A)
- Aspirin (ATC code N02BA)
- Bisphosphonates (ATC code M05BA)
- SSRIs (ATC code N06AB)
- SNRIs (ATC codes N06AX16 and N06AX21)

Clinical outcome ICD-10 Codes:

Gastrointestinal bleeds:

- Ulcer of esophagus (K22.1)
- Gastro-esophageal laceration-hemorrhage syndrome (K22.6)
- Gastric ulcer (K25)
- Acute gastric ulcer with hemorrhage (K25.0)
- Acute gastric ulcer with perforation (K25.1)
- Acute gastric ulcer with hemorrhage and perforation (K25.2)
- Acute gastric ulcer without hemorrhage or perforation (K25.3)
- Chronic or nonspecific gastric ulcer with hemorrhage (K25.4)
- Chronic or unspecified gastric ulcer with perforation (K25.5)
- Chronic or nonspecific gastric ulcer with hemorrhage and perforation (K25.6)
- Chronic gastric ulcer without hemorrhage or perforation (K25.7)
- Gastric ulcer, unspecified as acute or chronic, without hemorrhage or perforation (K25.9)
- Duodenal ulcer (K26)
- Acute duodenal ulcer with hemorrhage (K26.0)
- Acute duodenal ulcer with perforation (K26.1)
- Acute duodenal ulcer with hemorrhage and perforation (K26.2)
- Acute duodenal ulcer without hemorrhage or perforation (K26.3)
- Chronic or nonspecific duodenal ulcer with bleeding (K26.4)
- Chronic or unspecified duodenal ulcer with perforation (K26.5)
- Chronic or nonspecific duodenal ulcer with bleeding and perforation (K26.6)
- Chronic duodenal ulcer without hemorrhage or perforation (K26.7)
- Duodenal ulcer, unspecified as acute or chronic, without hemorrhage or perforation (K26.9)
- Peptic ulcer, site unspecified (K27)
- Acute gastroduodenal ulcer with hemorrhage (K27.0)
- Acute peptic ulcer, site unspecified, with perforation (K27.1)
- Acute gastroduodenal ulcer with hemorrhage and perforation (K27.2)
- Acute peptic ulcer, site unspecified, without hemorrhage or perforation (K27.3)
- Chronic or nonspecific gastroduodenal ulcer with hemorrhage (K27.4)
- Chronic or unspecified peptic ulcer, site unspecified, with perforation (K27.5)
- Chronic or nonspecific gastroduodenal ulcer with hemorrhage and perforation (K27.6)
- Chronic peptic ulcer, site unspecified, without hemorrhage or perforation (K27.7)
- Peptic ulcer, site unspecified, unspecified as acute or chronic, without hemorrhage or perforation (K27.9)
- Gastrojejunal ulcer (K28)
- Acute gastrointestinal ulcer with hemorrhage (K28.0)
- Acute gastrojejunal ulcer with perforation (K28.1)
- Acute gastrointestinal ulcer with hemorrhage and perforation (K28.2)
- Acute gastrojejunal ulcer without hemorrhage or perforation (K28.3)
- Chronic or nonspecific gastrointestinal ulcer with hemorrhage (K28.4)
- Chronic or unspecified gastrojejunal ulcer with perforation (K28.5)
- Chronic or nonspecific gastrointestinal ulcer with hemorrhage and perforation (K28.6)
- Chronic gastrojejunal ulcer without hemorrhage or perforation (K28.7)

- Gastrojejunal ulcer, unspecified as acute or chronic, without hemorrhage or perforation (K28.9)
- Acute hemorrhagic gastritis (K29.0)
- Acute hemorrhagic duodenitis (K298A)
- Angiodysplasia of colon (K55.2)
- Other vascular disorders of intestine (K55.8)
- Vascular disorder of intestine, unspecified (K55.9)
- Acute anorectal hemorrhage (K62.5)
- Ulcer of anus and rectum (K62.6)
- Ulcer of intestine (K63.3)
- Nonspecific bleeding from the bowels (K638C)
- Hematemesis (K92.0)
- Melena (K92.1)
- Nonspecific gastrointestinal bleeding (K92.2)
- Esophageal varices (I85.0)

Intracranial hemorrhage:

- Subarachnoid hemorrhage (I60)
- Acute hemorrhagic duodenitis (I60.0)
- Nontraumatic subarachnoid hemorrhage from middle cerebral artery (I60.1)
- Nontraumatic subarachnoid hemorrhage from anterior communicating artery (I60.2)
- Nontraumatic subarachnoid hemorrhage from posterior communicating artery (I60.3)
- Nontraumatic subarachnoid hemorrhage from basilar artery (I60.4)
- Nontraumatic subarachnoid hemorrhage from vertebral artery (I60.5)
- Nontraumatic subarachnoid hemorrhage from other intracranial arteries (I60.6)
- Nontraumatic subarachnoid hemorrhage from unspecified intracranial artery (I60.7)
- Other nontraumatic subarachnoid hemorrhage (I60.8)
- Nontraumatic subarachnoid hemorrhage, unspecified (I60.9)
- Stroke (I61)
- Nontraumatic intracerebral hemorrhage in hemisphere, subcortical (I61.0)
- Nontraumatic intracerebral hemorrhage in hemisphere, cortical (I61.1)
- Nontraumatic intracerebral hemorrhage in hemisphere, unspecified (I61.2)
- Nontraumatic intracerebral hemorrhage in brain stem (I61.3)
- Nontraumatic intracerebral hemorrhage in cerebellum (I61.4)
- Nontraumatic intracerebral hemorrhage, intraventricular (I61.5)
- Nontraumatic intracerebral hemorrhage, multiple localized (I61.6)
- Other nontraumatic intracerebral hemorrhage (I61.8)
- Nontraumatic intracerebral hemorrhage, unspecified (I61.9)
- Other non-traumatic intracranial hemorrhage (I62)
- Nontraumatic subdural hemorrhage (I62.0)
- Nontraumatic extradural hemorrhage (I62.1)
- Nontraumatic intracranial hemorrhage, unspecified (I62.9)
- Late consequences of stroke (I69.1)
- Late consequences of subarachnoid hemorrhage (I69.0)
- Focal traumatic brain injury (S06.3)
- Epidural hemorrhage (S06.4)
- Traumatic subdural hemorrhage (S06.5)

- Traumatic subarachnoid hemorrhage (S06.6)

Other bleeding events:

- Conjunctival hemorrhage (H11.3)
- Retinal hemorrhage (H35.6)
- Vitreous hemorrhage (H43.1)
- Hemothorax (J94.2)
- Hemarthrosis (M25.0)
- Recurrent and persistent hematuria (N02)
- Recurrent and persistent hematuria with minor glomerular abnormality (N02.0)
- Recurrent and persistent hematuria with focal and segmental glomerular lesions (N02.1)
- Recurrent and persistent hematuria with diffuse membranous glomerulonephritis (N02.2)
- Recurrent and persistent hematuria with diffuse mesangial proliferative glomerulonephritis (N02.3)
- Recurrent and persistent hematuria with diffuse endocapillary proliferative glomerulonephritis (N02.4)
- Recurrent and persistent hematuria with diffuse mesangiocapillary glomerulonephritis (N02.5)
- Recurrent and persistent hematuria with dense deposit disease (N02.6)
- Recurrent and persistent hematuria with diffuse crescentic glomerulonephritis (N02.7)
- Recurrent and persistent hematuria with other morphologic changes (N02.8)
- Recurrent and persistent hematuria with unspecified morphologic changes (N02.9)
- Postmenopausal bleeding (N95.0)
- Bleeding from airways (R04)
- Epistaxis (R04.0)
- Hemorrhage from throat (R04.1)
- Hemoptysis (R04.2)
- Hemorrhage from other sites in respiratory passages (R04.8)
- Hemorrhage from respiratory passages, unspecified (R04.9)
- Nonspecific urinary hemorrhage (R31)
- Hemorrhage, not elsewhere classified (R58)

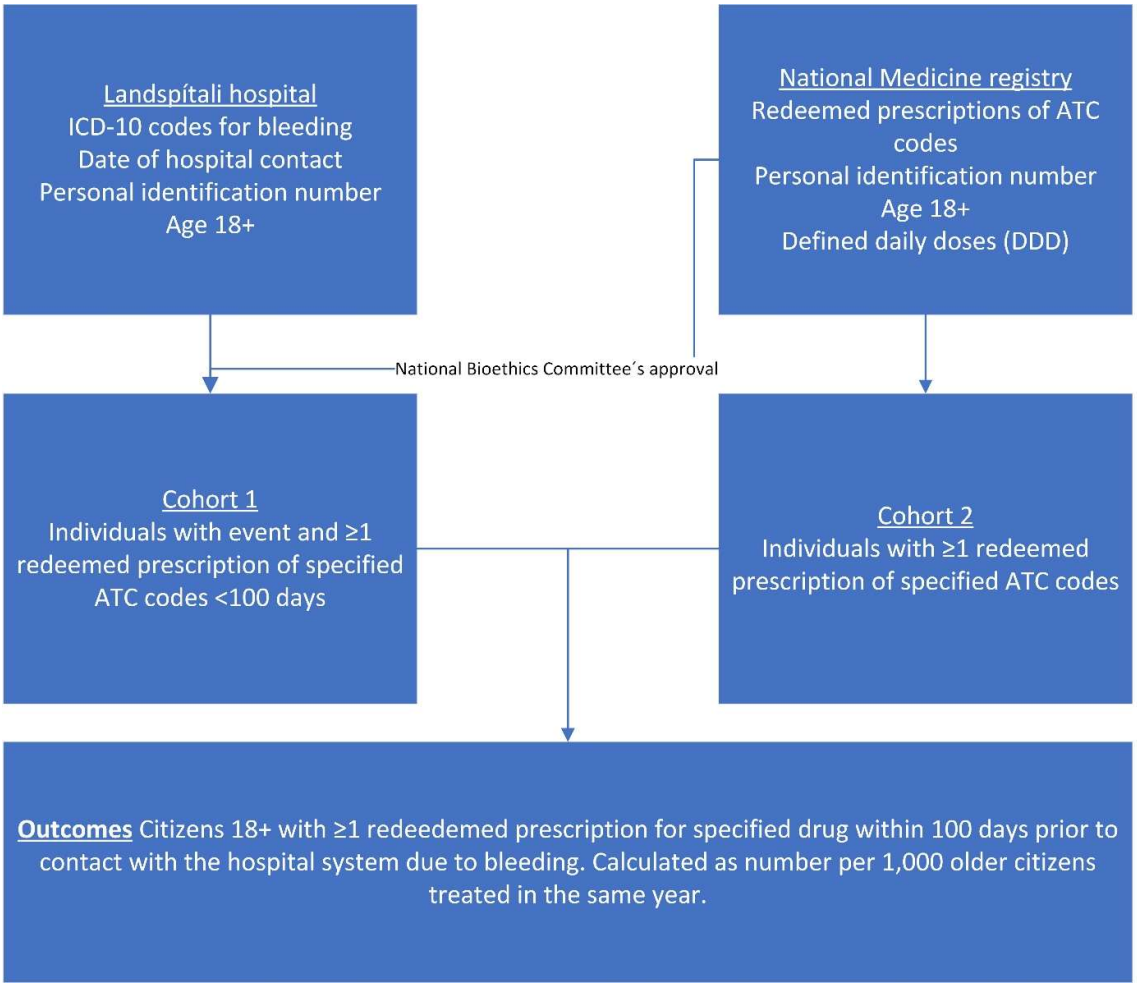

Figure 5. Data extraction and analysis plan for preventable bleeding due to medication

Inclusion criteria for bleeding events (nominator)

Citizens who are 18+ years of age at first contact to the hospital.

The first contact to hospital is acute and where one or more diagnostic codes for bleeding are used.

Visit to the emergency department or hospital stay.

Citizens with at least one prescription redeemed for the listed medicines ATC codes in the 100 days prior to the event.

Inclusion criteria for denominator

Citizens 18+ years of age with at least one prescription redeemed for the listed medicines ATC codes in the year of evaluation.

Number of bleeding events

Adult citizens (18+) with hospital visit as a result of bleeding. Calculated as absolute number per 1,000 of the overall older population per year.

b. Quality indicators and outcome measures on preventable falls due to medication (similar to the Danish specification)

Medication ATC codes:

- Antidepressants (ATC code N06A)
- Antipsychotics including lithium (ATC code N05A)
- Benzodiazepines (ATC codes N05BA, N05CD, N03AE and N05CF)
- Sedative antihistamines (ATC codes N05BB01, N07CA02, R06AA02, R06AA04, R06ADO2, R06AE03 and R06AE05)
- Opioids (ATC code N02A – excluding N02AJ07 and ATC codes R05DA, N07BC, R05FA, N01AH and A07DA02)
- Antiepileptics (ATC code N03)
- Migraine drugs (ATC code N02C)
- Antiarrhythmics (ATC code C01B)
- Antianginal (ATC code C01D)
- Antihypertensives (ATC code C02)
- Diuretics (ATC code C03)
- Betablockers (ATC code C07)
- Calcium antagonists (ATC code C08)
- Ace-inhibitors and ATII-antagonists (ATC code C09)
- Insulines (ATC code A10A)
- Sulfonylurea (ATC code A10BB)*
- Alfa-blockers (ATC code G04CA)*
- Anticholinergics (ATC code N05CM05 (scopolamine), S01FA04 (cyclopentolathýdróklóríð), G04BD10 (darifenacin) , R06AD02 (Promethazinum), G04BD07 (Tolterodinum), R06AE05 (Meclozinum), N05BB01 (Hydroxyzinum), R06AA02 (Diphenhydraminum)) G04BD07-11 (Antimuscarinic for overactive bladder and urge incontinence)*

**Additional codes not reflected in the Danish specification, which are supported by STOPPFalls criteria (Seppala et al, 2020)*

Clinical outcome using NOMESCO codes:

- E00 Fall on same level
- E01 Fall from lesser height
- E02 Fall from greater height
- E03 Fall from unspecified height
- E08 Fall, other specified
- E09 Fall, unspecified

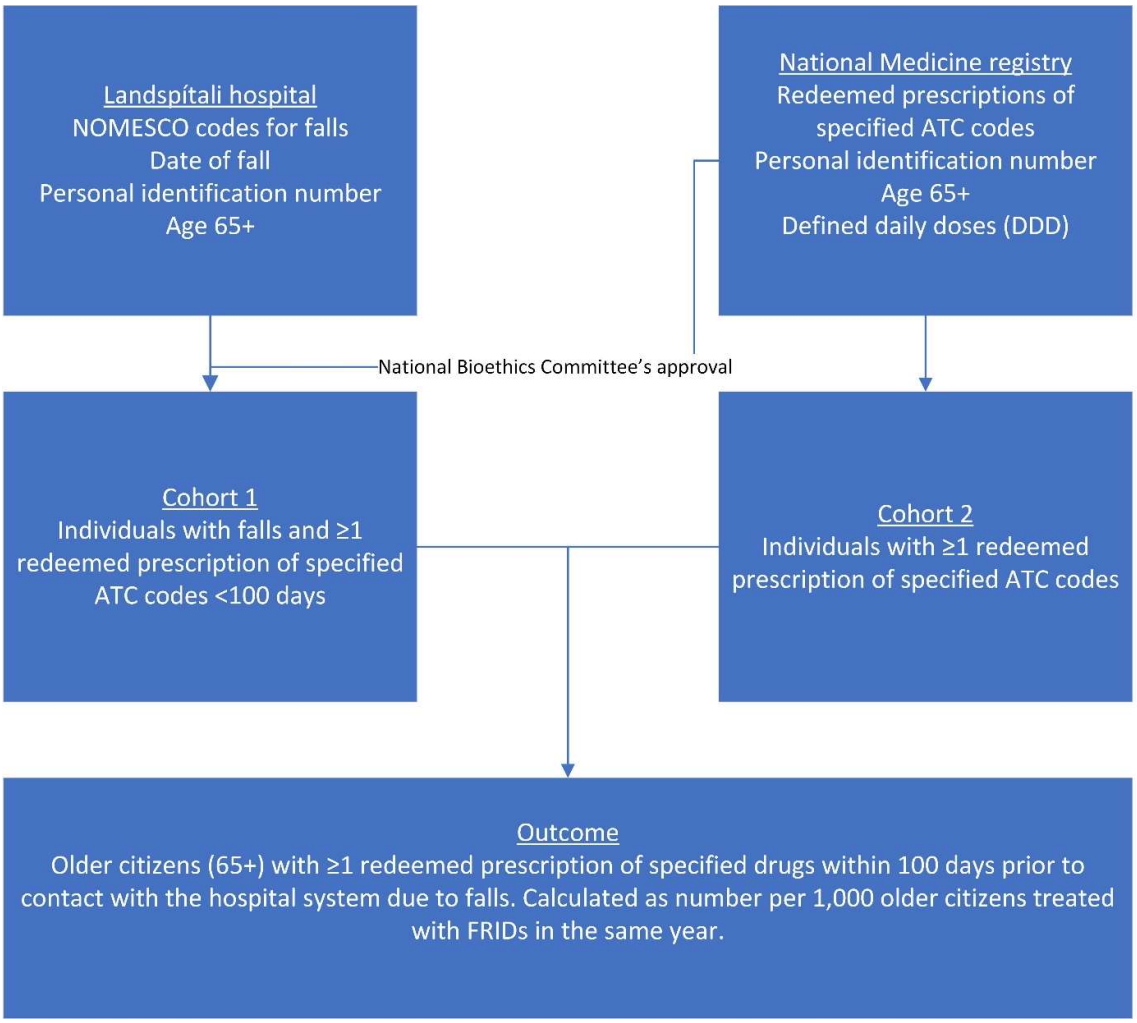

Figure 6. Data extraction and analysis plan for preventable falls due to medication

Inclusion criteria for falls (nominator)

Citizens who are 65+ years of age at first contact to the hospital.

The first contact to hospital is acute and where one or more diagnostic codes for falls are used.

Emergency room stay where the duration of stay is ≥4 hours or hospital admission.

Citizens with at least one prescription redeemed for the listed medicines ATC codes in the 100 days prior to the event.

Inclusion criteria for denominator

Citizens 65+ years of age with at least one prescription redeemed for the listed medicines ATC codes in the year of evaluation.

Number of Falls

Older citizens (65+) with hospital visit as a result of falls. Calculated as absolute number and number per 1,000 of the overall older population per year.

c. *Falls and the concurrent use of ≥5 medications that includes at least one fall risk increasing drug (FRIDs) for older citizens (65+).*

Medication ATC codes:

- Antidepressants (ATC code N06A)
- Antipsychotics including lithium (ATC code N05A)
- Benzodiazepines (ATC codes N05BA, N05CD, N03AE and N05CF)
- Sedative antihistamines (ATC codes N05BB01, N07CA02, R06AA02, R06AA04, R06ADO2, R06AE03 and R06AE05)
- Opioids (ATC code N02A – excluding N02AJ07 and ATC codes R05DA, N07BC, R05FA, N01AH and A07DA02)
- Antiepileptics (ATC code N03)
- Migraine drugs (ATC code N02C)
- Antiarrhythmics (ATC code C01B)
- Antianginal (ATC code C01D)
- Antihypertensives (ATC code C02)
- Diuretics (ATC code C03)
- Betablockers (ATC code C07)
- Calcium antagonists (ATC code C08)
- Ace-inhibitors and ATII-antagonists (ATC code C09)
- Insulines (ATC code A10A)
- Sulfonylurea (ATC code A10BB)
- Alfa-blockers (ATC code G04CA)
- Anticholinergics (ATC code N05CM05 (scopolamine), S01FA04 (cyclopentolate hydrochloride), G04BD10 (darifenacin) , R06AD02 (promethazine), G04BD07 (tolterodine), R06AE05 (meclozine), N05BB01 (hydroxyzine), R06AA02 (diphenhydramine)) G04BD07-11 (Antimuscarinic for overactive bladder and urge incontinence)

Clinical outcome using NOMESCO codes:

- E00 Fall on same level
- E01 Fall from lesser height
- E02 Fall from greater height
- E03 Fall from unspecified height
- E08 Fall, other specified
- E09 Fall, unspecified

Polypharmacy:

- Polypharmacy ≥5 medications
- Hyperpolypharmacy ≥10 medications

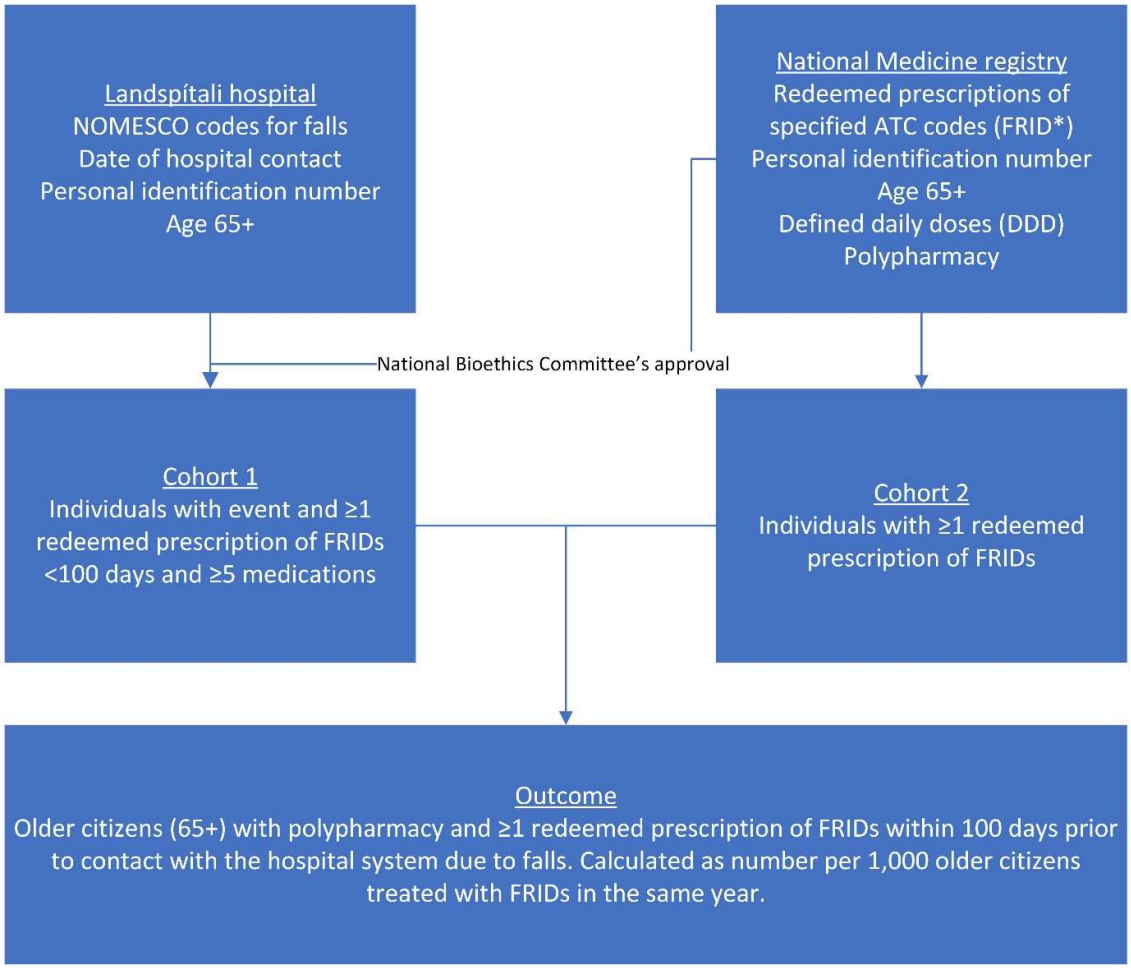

Figure 6. Data extraction and analysis plan for preventable falls due to FRID medication and polypharmacy

Inclusion criteria for falls (nominator)

Citizens who are 65+ years of age at first contact to the hospital due to fall.

The first contact to hospital is acute and where one or more diagnostic codes for falls are used.

Hospital stay where the duration of stay is ≥4 hours.

Citizens with at least one prescription redeemed for the listed medicines ATC codes and ≥5 concurrent medications in the 100 days prior to the event.

Inclusion criteria for denominator

Citizens 65+ years of age with at least one prescription redeemed for the listed medicines ATC codes in the year of evaluation.

Number of Falls

Older citizens (65+) with hospital visit as a result of falls. Calculated as absolute number and number per 1,000 of the overall older population per year.

2. Project Roadmap and Timescales

The project roadmap and timescales are detailed in Appendix C.

Baseline data for five years will be extracted from January 2017 to December 2021 and analysed as a pilot to determine relevance and accuracy of the proposed quality indicators. Learning from the pilot analysis of quality indicators in Denmark will also be reviewed and resources required to manage ongoing data extraction and analysis in Iceland will be determined. A new proposal for extracting and linking data retrospectively (if necessary) and prospectively until 2026 will be created and submitted to the bioethics committee for approval.

The immediate goal for this proposal is that by September 2022, a detailed specification for data extraction and analysis of a suite of national quality indicators for medication safety in Iceland will be ready and resources identified to carry out the task.

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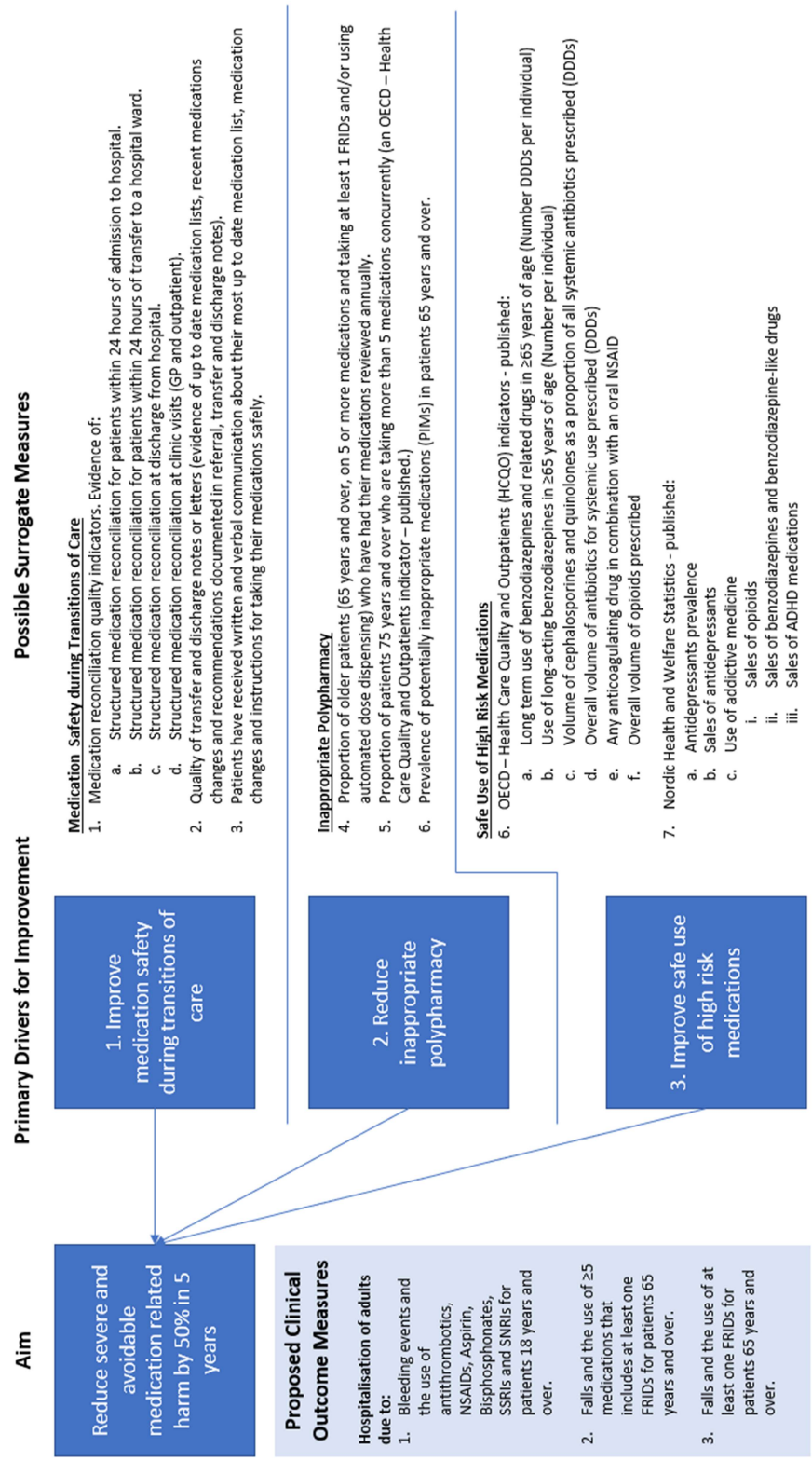
Appendix A – Summary of Proposed Clinical Outcome Measures and Surrogate Measures for Avoidable Medication Related Harm in Iceland



Appendix B – Summary of reviewed clinical research relating to medication safety in transitions of care, polypharmacy and high risk situations

Study	Population	Intervention	Outcome Measure
Medication related harm resulting in hospitalisation			
Harholt et al 2010	Adverse Drug Reactions (ADR) related hospitalisation in patients ≥60 years between 1981 - 2007 in the Netherlands.	--	Incidence rate of ADR related hospitalisations per 10,000 older persons.
Van der Hooft 2008	ADR-related acute admissions to hospitals for all patients registered with 150 general practitioners throughout the Netherlands in 2003.	--	Prevalence of ADR acute admissions.
Transitions of Care			
Redmond et al 2018	25 studies (RCTs) published up to January 2018 involving 6995 participants in 8 countries, which mainly included older people prescribed multiple medications.	Medication reconciliation at care transition (in hospital or immediately related settings) – 23 studies were primarily pharmacy delivered, one was an electronic reconciliation tool and one medical record changes.	Medication discrepencies, preventable adverse drug events (PADEs), ADEs, unplanned rehospitalisation, hospital utilisation (composite measure of emergency department and rehospitalisation).
Kwan et al 2013	18 studies: all from hospitals in the United States and Canada	Hospital based medication reconciliation	Clinically significant discrepencies: unintended medication discrepencies at transitions of care post hospital discharge or unplanned hospital readmission within 30 days.
Polypharmacy			
Pazan et al 2021	Narrative review of definitions, epidemiology and consequences of polypharmacy in older adults (65+ years, studies published between		Pre-frailty and frailty; mortality; hospitalisation (any hospitalisation, unplanned, re-hospitalisation, all-cause and fracture specific admission to hospital, emergency department

	November 2015 – November 2020)		re-visit); falls; decline in cognitive function, cognitive impairment.
Zaninotto 2020	6220 participants aged 50+ in England who were hospitalised due to a fall between 2012 – 2018.	--	Prevalence of people admitted to hospital due to a fall comparing those taking no medications, 1-4 medications, 5-9 medications (polypharmacy) and 10+ medications.(heightened polypharmacy).
Chen et al 2019	13 studies – permanent residents of residential aged care facilities in Australia (nursing homes or long term care facilities)	Residential Medication Management Reviews and general practitioners' acceptance of pharmacists' recommendations to resolve medication related problems.	Drug Burden Index (DBI), reduction of high risk medications prescribed, lower anticholinergic burden (ACB), medication appropriateness index (MAI).
Morin 2019	49,609 cases of older adults (≥70 years) in Sweden who had an incident non-elective admission due to a fall between 1 January and 31 December 2013.	Exposure to multiple prescription drugs (≥4 is polypharmacy) during 7 days preceding the index date.	Fractures due to falls and fractures due to falls in addition to the use of fall-risk increasing drugs and chronic multimorbidity.
High Risk Medications following the APINCHS acronym (Australian Commission on Safety and Quality in Health Care, 2019)			
van der Hooft 2008	ADR-related acute admissions to hospitals for all patients registered with 150 general practitioners throughout the Netherlands in 2003.	--	The ADRs that most frequently caused hospitalisations were gastro-intestinal bleeding with anti-thrombotics, bradycardia/hypotension with cardiovascular drugs and neutropenic fever with cytostatics. Incidence rate of ADR-related hospitalisations per drug group was highest for anti-thrombotics and anti-infectives.
Tamma et al 2017	Adult inpatients receiving systemic antibiotic therapy.	--	Antibiotic associated ADEs (30 days after antibiotic initiation)

			including *C diff* and MDRO infections (90 days after antibiotic initiation)
Cousins et al 2011	16,600 reported incidents that affected patients in the United Kingdom involving insulin between November 2003 and November 2009.	--	Hospitalisation due to hypoglycaemia; hyperglycaemia or hypoglycaemia in hospital.
Tilly et al 2017 (report that cites research findings)	Older adults in the United States (≥65 years)	--	„Opioid use disorder“ (dependence, overdose), opioid side effects and opioid use disorder related hospitalization, use of emergency departments, death, falls
Sennesael 2017	Patients admitted to hospital with a thrombotic or bleeding event while under DOAC (n =46) or VKA (n = 43) (median age 79 years) between July 2015 to January 2016 in Belgium (2 teaching hospitals)		Bleeds as ADRs associated with the use of VKA anticoagulants; thrombotic events and bleeds for DOACs caused by medication errors (emergency hospital admission).

Appendix C – Roadmap and timescales for Measuring Impact of WHO lyfjameðferð án skaða

Step	Current Status	22. maí 2020	29. maí 2020	5. júní 2020	12. júní 2020	19. júní 2020	26. júní 2020	Summer Break	14. ágúst 2020	21. ágúst 2020	28. ágúst 2020	4. september 2020	11. september 2020	18. september 2020	25. september 2020	2. október 2020	9. október 2020	16. október 2020	23. október 2020	30. október 2020	6. nóvember 2020	13. nóvember 2020	20. nóvember 2020	27. nóvember 2020	4. desember 2020	11. desember 2020	18. desember 2020	Christmas Break	Janúar 2021	Febrúar 2021	Mars 2021
1. Define „severe and avoidable medication related harm"	Complete	x																													
2. Draft indicators	Complete			x					x	x	x	x									x	x									
3. Investigate availability of data	Complete				x	x	x		x	x	x	x									x	x									
4. Analyse how to extract data	Complete												x	x	x	x	x	x	x	x			x	x	x	x					
5. Draft proposed measures and data extraction	Complete																										x				
6. Update National Steering Committee	Cancelled due to pandemic																x	x	x	x											
7. Proposal to National Steering Committee for approval	Complete																												x		
8. Proposal to independent reviewers	Complete																														x

Step	Current Status	apríl 2021	maí 2021	júní 2021	Summer Break	Summer Break	september 2021	október 2021	nóvember 2021	desember 2021	janúar 2022	febrúar 2022	Mars 2022	apríl 2022	maí 2022	júní 2022	Summer Break	Summer Break	september 2022
9. Revise proposal	Complete		x	x			x	X											
10. Submit proposal to ethics committee for approval	In progress								x	X	x								
11. Request access to data from Landspítali and Embætti Landlæknis	Pending										x								
12. Extract pilot data	Pending											x							
13. Analyse pilot data	Pending												x						
14. Create plan for permanent data extraction	Pending													x	x				
15. Approval by national steering committee	Pending															x			
16. Form permanent team to carry out data extraction plan	Pending																		x

Annex 1 – Icelandic definition of severe avoidable medication related harm

Lyfjatengt heilsutjón sem koma hefði mátt í veg fyrir er:

- *1) varanlegt heilsutjón, tímabundið eða krefst meðferðar*
- *2) og hægt hefði verið að koma í veg fyrir með góðum starfsháttum*
- *3) og miklar líkur eru á að sé lyfjatengt*
- 1) *varanlegt heilsutjón, tímabundið eða krefst meðferðar*. Heilsutjónið er lífshættulegt, leiðir til eða lengir sjúkrahúslegu, þarfnast meðferðar t.d. á bráðamóttöku, veldur fötlun t.d. óvinnufærni, aukinni umönnunarþörf eða leiðir til dauða. Alvarleiki heilsutjóns er metinn yfir meðallagi samkvæmt skilgreiningu WHO: https://www.who.int/bulletin/volumes/96/7/17-199802/en/
- *2) og hægt hefði verið að koma í veg fyrir með góðum starfsháttum*. Með góðum starfsháttum er átt við bestu meðferð sem völ er á og ætlast má til af heilbrigðisstarfsmönnum við tilgreindar aðstæður. Heilsutjónið getur orðið vegna mistaka eða frávika frá viðurkenndum starfsháttum og nær yfir öll stig lyfjameðferðar þ.e. ávísun, afgreiðslu, lyfjagjöf og eftirfylgd. Mistök og frávik frá viðurkenndum starfsháttum geta verið bæði einstaklingsbundin og kerfistengd. Þetta felur í sér skilgreiningu WHO á mistökum við lyfjameðferð. *WHO Medication errors: Technical series on safer primary care, 2016, ISBN 978-92-4-151164-3*
- *3) og miklar líkur eru á að sé lyfjatengt.* Heilsutjónið verður að vera skilgreinanlegt sjúkdómsástand eða þekkt afleiðing lyfjanotkunar. Heilsutjónið getur verið af völdum eins eða fleiri lyfja og verulegar líkur eru á að það sé vegna lyfjanna en ekki sjúkdóma eða annarra efna. Líkur teljast að lágmarki "mögulegar" samkvæmt skilgreiningu WHO fyrir orsakasamband. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf