

BMJ Open Adverse Drug reactions in an Ageing PopulaTion (ADAPT) study protocol: a cross-sectional and prospective cohort study of hospital admissions related to adverse drug reactions in older patients

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ABSTRACT

Introduction Older people experience greater morbidity with a corresponding increase in medication use resulting in a potentially higher risk of adverse drug reactions (ADRs). The aim of this study is to determine the prevalence and characteristics of ADR-related hospital admissions among older patients (≥65 years) and their associated health and cost outcomes.

Methods and analysis The proposed study will include a cross-sectional study of ADR prevalence in all patients aged ≥65 years admitted acutely to a large tertiary referral hospital in Ireland over a 9-month period (2016–2017) and a prospective cohort study of patient-reported health outcomes and costs associated with ADR-related hospital admissions. All acute medical admissions will be screened for a suspected ADR-related hospital admission. A number of validated algorithms will be applied to assess the type, causative medications, preventability and severity of each ADR. ADRs will be determined, using a consensus method, by an expert panel. Patients who provide consent will be followed up 3 months post-discharge to establish patient-reported health outcomes (health service use, health-related quality of life, adherence) and costs associated with ADR-related hospital admissions. A random sample of patients admitted to hospital without a suspected ADR will be invited to take part in the study as a control group.

Ethics and dissemination Ethical approval was obtained from Beaumont Hospital Ethics Committee. Findings will be disseminated through presentations and peer-reviewed publications.

INTRODUCTION

An adverse drug reaction (ADR) has been defined as ‘an appreciably harmful or unpleasant reaction resulting from an intervention relating to the use of a medicinal product’.¹ ADRs are common and result in significant morbidity, mortality and increased healthcare costs.² Studies in general adult populations have indicated that 5%–7% of all hospitalisations are due to ADRs, with over half of these judged to be preventable, and

Strengths and limitations of this study

- This study will provide detailed information on the prevalence and characterisation of adverse drug reactions (ADRs) in a large older population
- There have been no long-term follow-up studies of older patients with ADR-related hospital admissions and a range of risk factors, health outcomes and costs will be assessed
- ADR determination in older populations is challenging and there is a risk of misclassification; a multifaceted review of each suspected ADR will be undertaken as well as independent review by an expert panel
- A number of patients may not have the capacity to complete the health outcome measures

that 3%–6% of ADRs are fatal or have serious health consequences.^{3–5} Healthcare costs attributable to ADRs have been estimated to be 5%–9% of total inpatient costs per annum.⁶ Older people experience greater morbidity with a corresponding increase in medication utilisation resulting in a higher risk of ADRs.⁷ Ageing is also associated with a variety of physiological changes affecting the pharmacokinetics and pharmacodynamics of medications, which may increase the potential for drug toxicity and ADRs.⁸ Therefore, older people are potentially at an increased risk of ADR-related hospital admissions and many of these ADRs may be preventable.⁹ Studies have indicated that more than half of hospital admissions for ADRs are preventable with only 19%–28% of ADRs causing hospital admission in older patients considered unavoidable.^{4,9}

Two systematic reviews of international studies have suggested a median ADR-related hospital admission rate of 10% and 11%,

respectively, in those aged ≥ 65 years.^{10 11} One of these systematic reviews reported a wide variation in the overall ADR prevalence rate between studies ranging from 5.8% in 1756 older Italian patients to 46.3% in a smaller Belgian study.^{9 11 12} This wide variation in reported prevalence rates may be due, in part, to different admission settings (geriatric unit versus accident and emergency (A&E)) and differences in study methods used to define and identify ADRs.¹³ Differences in prescribing practices and available medications across regions may also contribute to this wide variation.¹⁴ In Ireland, studies to date have included relatively small numbers of patients and were conducted over short time periods.^{15 16}

ADRs are difficult to identify in older populations and patients often present acutely with symptoms that are highly prevalent in people with multiple comorbidities, for example, dizziness, delirium or falls.¹³ Current hospital reporting systems significantly under-report the incidence of ADRs and provide unreliable estimates of ADR-related hospital admissions in older populations.^{17 18} A systematic review found a median ADR under-reporting rate of 94% across 39 studies.¹⁹ To accurately detect ADRs, a number of methods are required including an in-depth medical record review and a causality assessment between the drug and the adverse clinical event.²⁰

Several factors have been reported to contribute to the increased incidence of ADRs in older populations. These include increasing age, polypharmacy, multimorbidity, prior ADR and dementia in the acute setting.^{11 21} There is some evidence that potentially inappropriate prescribing, identified by the STOPP tool, is associated with an increased risk of ADRs and hospitalisation in older people.^{22 23} Errors in medication administration and autonomous modification of medication schedules have also been reported to contribute to ADRs.²⁴ However, predictive risk factors for ADRs in older populations are still poorly understood. Current validated risk prediction tools have focused mainly on ADRs occurring in the hospital setting and do not include a comprehensive list of risk factors, such as functional and social factors, which may contribute to ADR-related hospitalisation.^{25 26}

Few studies have investigated patient outcomes and costs associated with ADR-related hospital admissions. There is some evidence that ADRs related to hospital admissions are associated with higher subsequent health services utilisation and costs.²⁷ Previous studies have found that those presenting with an ADR have a longer median hospital stay and a higher rate of subsequent outpatient health service use than those without ADRs.^{27 28} A study in Canada found that hospital admissions due to ADRs in older patients cost an estimated US\$35.7 million annually.²⁹ Few studies have examined the physical and psychological morbidity associated with ADRs in older populations, as well as the cost of ADRs and subsequent medication management.

Given the limited number of prospective studies of ADR-related hospital admissions in older populations, there is a need to establish the prevalence of ADRs in

older people and to obtain a greater understanding of the risk factors, health outcomes and costs associated with ADR-related admissions. This will inform the development of policies and interventions focused on improving medication management in older people and identify where resources can be most effectively used to reduce older peoples' risk of ADRs and associated morbidity and costs.

Aims and objectives

The aim of this study is to determine the prevalence and characteristics of ADR-related hospital admissions among older patients (≥ 65 years) and their associated health and cost outcomes. The specific objectives are:

- ▶ To determine the prevalence of ADR-related hospital admissions among older patients (≥ 65 years)
- ▶ To examine the type and range of drug classes involved in ADR-related hospital admissions
- ▶ To determine the causality, preventability and severity of each ADR
- ▶ To identify the risk factors associated with ADR-related hospital admissions
- ▶ To examine patient discharge outcomes and the length of hospital stay of ADR-related hospital admissions
- ▶ To establish patient-reported health outcomes associated with ADR-related hospital admissions (health service use, health-related quality of life (HRQOL) and medication adherence)
- ▶ To establish the associated costs of ADR-related hospital admissions

METHODS

Study design

The proposed study will include a cross-sectional study of ADR prevalence in all patients aged ≥ 65 years admitted acutely to a large tertiary referral hospital in Ireland over a 9-month period (2016–2017) and a prospective cohort study of patient-reported health outcomes and costs associated with ADR-related hospital admissions.

Observation period

The study recruitment period is from 27 November 2016 to 27 August 2017. A sample of ADR and non-ADR patients who provide informed consent will be followed up 3 months post-discharge from hospital to establish patient-reported health outcomes and costs associated with ADR-related hospital admissions.

ADR screening

A cross-sectional study of all acute admissions through the Emergency Department, Outpatients Department, and direct acute admissions to the hospital wards will be undertaken. All admitted patients will be screened for a suspected ADR-related hospital admission within the first 36 hours of admission by the research team (Specialist Registrar in Geriatric Registrar (CCu), two hospital pharmacists (CW and CB)) using a previously validated

screening process.^{4 30} An acute admission is defined as the acceptance of the care of a patient for admission to an acute bed within the hospital under a named treating clinician or surgeon. Patients transferred from other hospitals will be excluded.

An ADR is defined as 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.'¹ The screening approach incorporates a multifaceted review by the research team of each admitted patient to assess the likelihood of an ADR being a reason for admission in the context of the patient's medication, clinical condition, medical history, comorbidities and investigation results. Where an ADR is suspected or where the medication history is unclear or incomplete, a full medication reconciliation will be completed. A number of independent sources will be consulted to verify the patient's medication history, including the patient's self-reported medication list, pharmacist medication list and general practitioner (GP) medication list. A current medication list will be established, including a list of all recently discontinued or short-course medications. Depending on the nature of the clinical presentation, further enquiry into the patient's past medication usage with their pharmacist and/or GP may be made, as some ADRs can present some time after discontinuation of the medication. Enquiry will also be made about the use of over-the-counter (OTC) medications and herbal preparations as part of the medication reconciliation process. Adherence to each medication will also be assessed by patient self-report and consolidation between patient self-report and pharmacist dispensing record will be undertaken, where possible.

The research team will electronically record details of the nature of the suspected ADR, suspected medications and relevant clinical information, comorbidities and investigation results required for suspected ADR determination. In cases where the admission diagnosis and the presence of an ADR is uncertain, the patient's clinical course and investigation results will be followed up by the research team until a diagnosis is made or the patient is discharged.

In order to determine whether the admission is due to an ADR, a reliable assessment of the relationship between drug administration and the adverse clinical event is required in terms of causality, preventability and severity.^{31 32} The research team will apply a number of decision aids and validated algorithms to assess the type, causative medication, preventability and severity of each ADR. The research team will categorise the suspected ADRs as either type A (dose dependent and predictable from the known pharmacology) or type B (idiosyncratic, no clear dose/response relationship and not predictable from the known pharmacology) according to the Rawlins and Thompson classification system.³³ ADR causality will be determined by the research team applying the WHO

criteria, Naranjo criteria and Liverpool Algorithm.³⁴⁻³⁶

The Hallas criteria will be used to categorise the avoidability/preventability of the ADRs as definitely avoidable, possibly avoidable or unavoidable.³⁷ ADR severity will be classified as mild, moderate or severe using the Hartwig severity assessment scale.³⁸ The research team will also assess if the ADR was due to a known drug interaction as outlined in the Summary of Product Characteristics (SmPC). The details of medications will be recorded using the WHO Anatomical Therapeutic Chemical (ATC) codes. The nature of the reaction will be reported using Medical Dictionary for Regulatory Activities terminology.³⁵

Participant recruitment

All patients with a suspected ADR and admitted to hospital during the 9-month study recruitment period will be asked by the research team to take part in a prospective cohort study investigating medication management in older populations. Patients with a suspected ADR are eligible to take part in the prospective cohort study if they are aged ≥ 65 years and English speaking. Patients will be asked by the research team to provide informed consent: (i) to complete a baseline questionnaire measuring their health service use, health-related quality of life (HRQOL) and medication adherence, prior to hospital admission; (ii) to be contacted 3 months post-discharge by the research team to complete a follow-up questionnaire including the same measures; and (iii) for the research team to link their prescription dispensing information per the Health Services Executive (HSE) Primary Care Reimbursement Services (PCRS) pharmacy claims database to the information they provided in their questionnaire and their hospital medical record (for General Medical Services (GMS) patients only). The GMS scheme is means tested and provides individuals with free or substantially subsidised healthcare and prescription medications.³⁹ It is estimated that over 97% of those aged ≥ 70 years nationally avail of the scheme.⁴⁰ The HSE-PCRS pharmacy claims database provides details on monthly dispensed medications for each individual within the GMS scheme. Prescription medications are coded using the ATC classification system and strength, quantity, method and unit of administration of each drug dispensed are available.⁴¹

A random sample of patients, who are determined by the research team not to have a suspected ADR on screening and who are admitted to hospital during the 9-month study recruitment period, will also be invited to take part in the follow-up study. This cohort of non-ADR patients will be asked to provide informed consent to complete the same questionnaire measures at baseline and follow-up as the ADR cohort, with linkage to their prescription dispensing information, as a comparison control group. Control patients are eligible to take part in the prospective cohort study if they are aged ≥ 65 years, English speaking and prescribed at least one medication. Patients will be randomised to the control group from the hospital admission list, which details patients'

chronological order of hospital admission on each day for those aged ≥ 65 years, using randomisation software <http://www.randomization.com>. These randomised patients will be invited to take part in the study as control patients. If a control group patient is subsequently determined to have a suspected ADR, an additional patient will be randomised and invited to take part in the study instead. Patients with a suspected ADR and control patients are ineligible to take part in the prospective cohort study if they are <65 years, non-English speaking or terminally ill.

Screening of acute admissions for suspected ADRs and initial medication review may include unconscious patients, patients with intellectual, visual or hearing impairments or acquired brain injury. If the patient is deemed unable to provide informed consent due to illness severity or physical or cognitive impairment, the patient's next of kin will be asked to provide assent to take part in the study. Patients may be deemed temporarily unable to provide informed consent or permanently unable to provide informed consent (such as in the case of advanced dementia). The medical and nursing teams managing and providing the patient's care will be able to identify those patients who are incapable permanently of providing informed consent and will be able to provide the research team with an estimation regarding recovery and improvement for those temporarily unable to provide informed consent. For patients deemed permanently unable to provide informed consent, the patient's next of kin will be asked to give assent to provide the same information and answer an abbreviated questionnaire to the best of their ability, as described above for patients who are able to give informed consent. The selection of the study cohort is shown graphically in [figure 1](#).

Sample size

Approximately 3500 hospital admissions will be reviewed for a suspected ADR during the 9-month study period (2016–2017). It is estimated that 350 participants (approximately 10% of the 3500 hospital admissions) will have an ADR during the study period. This number provides an estimate of the prevalence of ADRs within $\pm 1\%$ precision. A further 350 participants who are determined not to have an ADR (control group) will also be recruited to take part in the study. The 700 participants will be invited to complete a baseline and a follow-up questionnaire 3 months post-discharge. We anticipate a 50% response rate (approximately $n=350$ participants; 175 ADR cohort, 175 non-ADR cohort).

Risk factors associated with ADRs

[Table 1](#) provides an overview of the measures to be collected as part of the ADR determination process and potential risk factors for ADRs. The potential risk factors for ADRs, based on previous systematic reviews, are categorised as: (i) medication-related risk factors; (ii) disease-related risk factors; (iii) functional ability-related risk factors; (iv) medication adherence-related risk factors;

and (iv) patient-related risk factors.¹¹ Medication-related risk factors include the types and number of medications that patients are prescribed, potentially inappropriate medication and drug/drug interactions. Potentially inappropriate prescribing will be assessed using the STOPP and START screening tools; STOPP consists of a set of inappropriate combinations of medicines and diseases that should be avoided or stopped and START is a set of recommended treatments for given conditions.⁴² Drug/drug interactions will be assessed per using SmPC documents. Disease-related risk factors include certain diagnoses, for example, impaired renal function and the patient's comorbidity burden. Patient comorbidity will be measured based on the patient's hospital record (Charlson comorbidity index).⁴³ Delirium will be assessed using the 4AT on hospital admission, a sensitive and specific screening tool for assessing delirium in older inpatients, including those with probable dementia.⁴⁴

Functional ability-related risk factors include measures of frailty, falls and mobility. A recent systematic review of the diagnostic accuracy of instruments to identify frailty in older populations recommended the use of more than one test to identify frailty in routine care.⁴⁵ Frailty will be assessed at baseline on hospital admission using three different validated measures for all patients with a suspected ADR and control patients; the Triage Risk Screening Tool,⁴⁶ PRISMA-7⁴⁷ and FRAIL.⁴⁸ Patients will be asked to self-report if they have fallen within the last year, their level of mobility (use of walking aids) and physical fitness, any unintentional weight loss in the previous 6 months and any problems in daily life due to poor vision and/or hearing. Medication adherence risk factors include medication adherence and medication management techniques. Adherence to each prescribed medication will be estimated at hospital admission for all patients with an ADR and control patients, by confirming patient self-reported medication list with the community pharmacy dispensing record, where possible. Patients will also be asked questions about their medication management including use of blister packs and pill organisers. Patient-related risk factors include age, gender, smoking status and alcohol usage. Patients' medical card (GMS) status (ie, access to free medical care based on means testing) will be recorded from patient's medical record and used as a proxy for socioeconomic status.

Outcomes

Main outcome—ADRs

The main outcome will be the prevalence and characterisation of ADRs in all patients aged ≥ 65 years admitted acutely to a large tertiary referral hospital in Ireland. Suspected ADR-related hospital admissions, as determined by the research team, will be reviewed using a one round questionnaire consensus method by an expert panel consisting of a senior clinical pharmacist, a clinical pharmacologist and a consultant geriatrician. The panel will establish a suspected ADR as a 'true ADR' if the reason for hospital admission is consistent with the

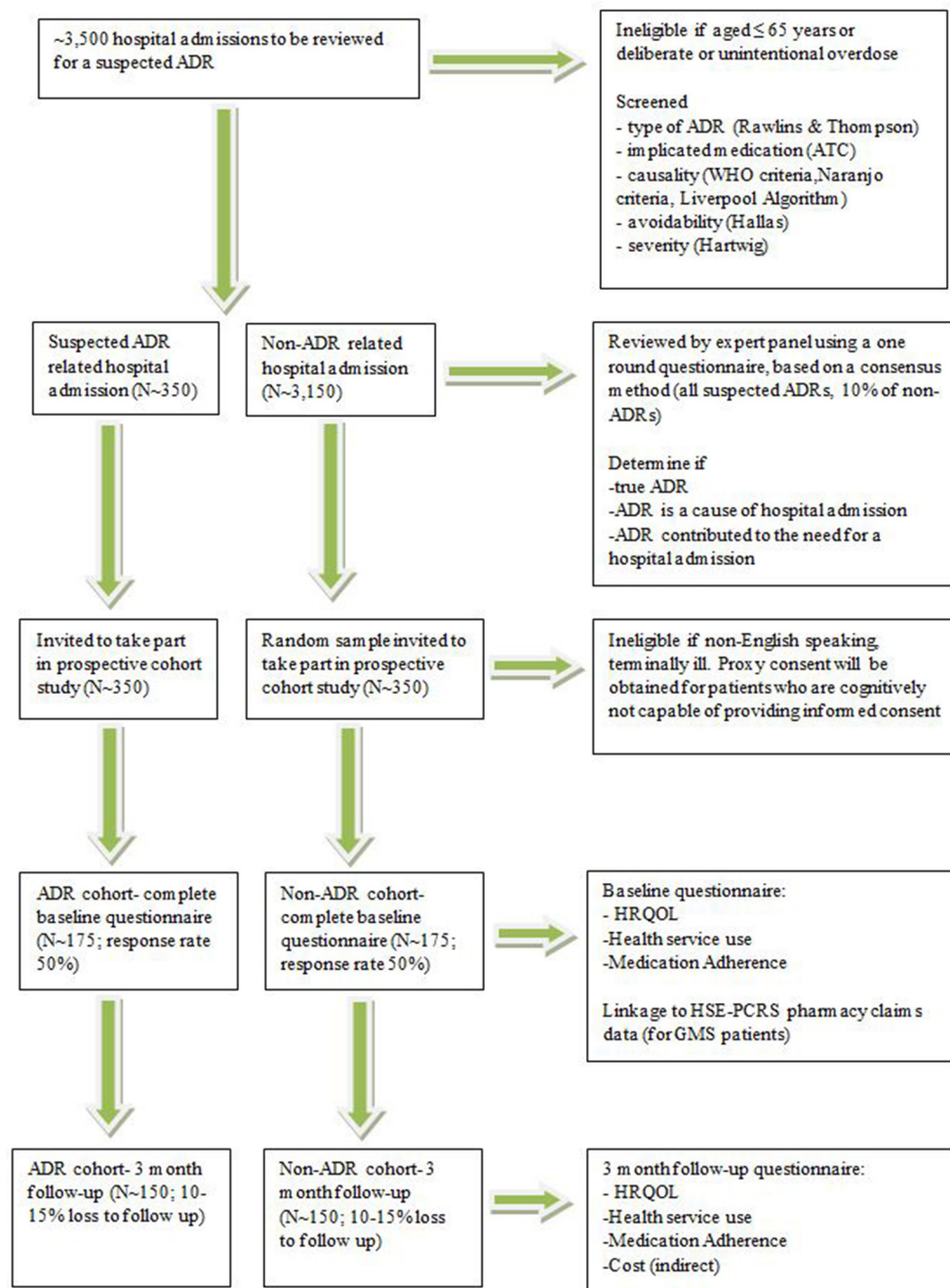


Figure 1 Description of study cohort. ADR, adverse drug reaction; GMS, General Medical Services; HRQOL, health-related quality of life; HSE-PCRS, Health Services Executive Primary Care Reimbursement Services.

known adverse effect profile of the drug (according to the SmPC), if there is a temporal relation with the start of drug therapy and if, after appropriate investigations, other causes are excluded as in previous ADR research studies.⁴

Each member of the panel will independently review the information provided on the nature of the ADR, suspected medications, OTC medications, patient's clinical conditions, medical and prescription drug history and results of clinical and laboratory investigations (table 1). Each member of the panel will rate their confidence that: (i) the suspected ADR is a 'true ADR'; (ii) the ADR is a cause of hospital admission; and (iii) the ADR contributed

to the need for hospital admission on a scale of 1 (definitely not) to 5 (definitely). For each suspected ADR, the median and IQR will be calculated for each scale and consensus will be defined as ≥ 4.0 for each scale.²¹⁻⁴⁹ Where consensus has not been reached on a suspected ADR, the panel will meet and discuss these individual suspected ADRs to achieve consensus. To ensure suspected ADRs were not missed, a random sample (10%) of non-ADRs will be analysed by the panel using patient case notes.²³

Secondary outcomes

Secondary outcomes include: (i) health service use; (ii) HRQOL; (iii) adherence to medication; and (iv)

Table 1 Measures and risk factors to be collected as part of the ADR determination process

Measures	Description of measures
Medications	
Types of medications	ATC code, medication recently commenced (or not), self-medicated (or not), PRN (or not), short course (or not), details of recently discontinued medications, over-the-counter medications and allergies and sensitivities
Number of medications	Number of medications prescribed
Potentially inappropriate medication	Application of the STOPP and START potentially inappropriate prescribing screening tools ⁴²
Drug/drug interactions	Drug interactions assessed using Summary of Product Characteristics documents
Disease	
Presenting issues	Description of presenting symptoms
Diagnosis	Diagnosis on admission (ICD-10)
Comorbidities	Charlson comorbidity index
Delirium	4AT screening tool for assessing delirium in older patients ⁴⁴
Functional ability	
Frailty	Triage Risk Screening Tool, ⁴⁶ PRISMA-7 ⁴⁷ and FRAIL ⁴⁸
Falls	Fallen in the past year (yes/no), fallen more than once in the past year (yes/no), number of falls
Mobility	Use of walking aid or device when crossing a room (yes/no) or when outside (yes/no). Type of walking aid or device
Physical fitness	Self-reported physical fitness (0, very bad; 10, very good)
Weight loss	Self-reported unintentional weight loss in the previous 6 months (yes/no)
Vision	Encounter problems in daily life due to poor vision (yes/no)
Hearing	Encounter problems in daily life due to poor hearing (yes/no)
Medication taking behaviour	
Adherence	Self-reported adherence for each prescribed medication on hospital admission and consolidation between patient self-report and pharmacist dispensing record will be undertaken, where possible
Medication management	Use of blister pack (or not), use of pill organiser (or not) and fills own pill organiser (or not)
Patient sociodemographics	
Age	Date of birth
Gender	Male/female
Smoking status	Current smoker, former smoker (pack year history)
Alcohol usage	Drinks alcohol (yes/no), no of units per week
Medical card	Yes/no

Medications will be coded using the WHO ATC classification system .

Blister pack is a preformed plastic packaging for medication by pharmacist.

ADR, adverse drug reaction; ATC, Anatomical Therapeutic Chemical; ICD-10, International Statistical Classification of Diseases and Related Health Problems-10th Revision.

ADR-related costs. [table 2](#) describes the health and cost outcomes associated with ADR-related hospital admissions.

Health service use

Health service use will be measured for all patients with an ADR and control patients using patients' hospital medical records. For all patients with an ADR and control patients, the duration of their hospital stay (number of days) and their status at discharge (eg, home, long-term

care, death) will be recorded based on their hospital record ([table 2](#)).

Health service use will also be measured by participant self-report using questionnaires for patients with an ADR and control patients who consent to take part in the study on medications management in older populations. Participants will be asked to complete a baseline questionnaire measuring the number of: (i) GP visits; (ii) out of hours GP services; (iii) hospital visits—A&E

Table 2 Health and cost outcomes and covariates associated with ADR-related hospital admissions

Measures	Description of measures	Method of data collection
Health service use—outcome		
Duration of hospital stay	Number of days	Hospital medical record
Status at discharge	Eg, home, long-term care, death	Hospital medical record
Health services	General practitioner visits, accident and emergency visits, outpatient visits, hospitalisations, use of therapies (eg, physiotherapy, occupational therapy), use of services (eg, dietician, optician, chiropody, pharmacy), public health nurse, day care centre and use of respite care (in the previous 3 months)	Baseline and 3-month follow-up questionnaire
Home help	Receipt of home help (yes/no), hours per week of paid home help and unpaid home help, source of unpaid home help (eg, spouse/partner, children, etc.)	Baseline and 3-month follow-up questionnaire
Home help activities	Types of activities received help with in the previous month (eg, walking, getting dressed, bathing, etc.) and source of help (eg, home help, spouse/partner, neighbour)	Baseline and 3-month follow-up questionnaire
HRQOL—outcome		
EQ-5DL	EQ-5DL is a generic measure of health for clinical and economic appraisal	Baseline and 3-month follow-up questionnaire
Self-rated health	Self-reported health compared with others of same age	Baseline and 3-month follow-up questionnaire
Groningen Frailty Index	Measures the loss of functions and resources in four domains: physical (mobility functions, multiple health problems, physical fatigue, vision, hearing), cognitive (cognitive dysfunction), social (emotional isolation) and psychological (depressed mood and feelings of anxiety)	Baseline and 3-month follow-up questionnaire
Functional ability	Falls, mobility, physical function, weight loss, hearing and vision (see table 1 for details of measures)	3-month follow-up questionnaire only (baseline collected on hospital admission; table 1)
HADS	Hospital Anxiety and Depression Scale (HADS) measures anxiety and depression	Baseline and 3-month follow-up questionnaire*
PSS-4	Perceived Stress Scale (PSS-4) measures the perception of stress	3-month follow-up questionnaire only*
ICECAP-O	The ICEpop CAPability measure for Older people (ICECAP-O) measures well-being defined in a broader sense and includes measures of attachment, security and independence	3-month follow-up questionnaire only*
Adherence to medication—outcome		
PDC	The proportion of days covered (PDC) for each drug class	HSE-PCRS pharmacy claims data (GMS patients only)
MARS-5	Medication Adherence Report Scale (MARS-5) is a self-report measure of intentional and unintentional adherence to medication	Baseline and 3-month follow-up questionnaire
Medications	Number of medications and types of medication	HSE-PCRS pharmacy claims data (GMS patients only)
Cost—outcome		
Investigations	As required (eg, blood pressure, pulse, HbA1c, glucose, international normalised ratio, creatinine, urea)	Hospital medical record
Procedures	As required (eg, ECG, imaging, endoscopy)	Hospital medical record
Healthcare therapies and services	Details of therapies (eg, physiotherapy) and services (eg, chiropody) provided during hospital admission	Hospital medical record

Continued

Table 2 Continued

Measures	Description of measures	Method of data collection
Productivity	Had to stop or reduce amount of time working and/or attending social activities because of health problems in the previous 3 months. Family member or friend had to stop or reduce or change amount of time working because of participant's health problems in the previous 3 months	3-month follow-up questionnaire only
Carer allowance	Receipt of State Carer's Allowance or Carer's Benefit to provide care for participant (yes/no) and participant's relationship with person receiving allowance or benefit (eg, spouse/partner, children, not related)	Baseline and 3-month follow-up questionnaire
Covariates		
Additional sociodemographic information		
Ethnicity	Irish or other	3-month follow-up questionnaire only
Children	Yes/no, number of daughters and sons	3-month follow-up questionnaire only
Education	Level of education (eg, primary to post-graduate)	3-month follow-up questionnaire only
Marital status	Single, married, cohabiting, etc.	3-month follow-up questionnaire only
Occupational status	Employed, retired, looking after family/home, etc.	3-month follow-up questionnaire only
Living arrangements	With whom participant lives (eg, partner, children, live one)	3-month follow-up questionnaire only
Type of accommodation	Type of accommodation participant lives in (eg, house, sheltered accommodation, nursing home)	3-month follow-up only
Deprivation	Deprivation score of the electoral division the participant lives in based on the Small Area Health Research Unit national deprivation indexes	Baseline questionnaire
Health Insurance	Health insurance status (yes/no)	Baseline questionnaire
Additional morbidity information		
Morbidity	Diagnosed with any new medical conditions since baseline (past 3 months)	3-month follow-up questionnaire only
Comorbidity	RxRisk-V is an algorithm that classifies prescription drug fills into chronic disease classes	HSE-PCRS pharmacy claims data (GMS patients only)
Social and personal support		
LSNS-6	The Lubben Social Network Scale (LSNS-6) is a composite measure of family and friends networks, for use with older people, which asks patients how many people they have contact with and how often	3-month follow-up questionnaire only
BRS	Brief Resilience Scale (BRS) measures participant ability to recover/bounce back from stressful events	3-month follow-up questionnaire only*
Medication taking support and beliefs		
ADQ	Adherence Determinants Questionnaire (ADQ) subscale—Support/Barriers to medication taking	Baseline and 3-month follow-up questionnaire
BMQ	Beliefs about medication questionnaire (BMQ) consists of two scales assessing patients' beliefs about the necessity of prescribed medication for controlling their disease and their concerns about potential adverse consequences of taking it	Baseline and 3-month follow-up questionnaire*

*will not be assessed for participants with proxy consent

visits, hospital inpatient (including duration of stay) and outpatient visits; (iii) use of therapies (eg, physiotherapy, occupational therapy); (iv) use of services (eg, dietician, optician, hearing, pharmacy); (v) public health nurse; and (vi) use of day care centres and respite care in the previous 3 months.³⁶ Participants will also be asked details about their use of home help, including number of hours per week (paid/unpaid), source of home help (eg, spouse/partner) and type of activities with which they receive help. Participants will be asked to answer the same questions again 3 months post-discharge (table 2).

Health-related quality of life

Participants' overall HRQOL will be assessed by the EQ-5DL and by self-reported health compared with others of the same age at baseline and 3 months post-discharge using questionnaires.^{50 51} Physical, cognitive, social and psychological functional ability will be assessed by the self-report using the Groningen Frailty Index.⁵² Participants will also be asked at 3 months post-discharge to self-report if they have fallen within the last 3 months, their level of mobility (use and type of walking aids) and physical fitness, any unintentional weight loss in the previous 3 months and any problems in daily life due to poor vision and/or hearing (baseline measures will be collected on hospital admission; table 1). Psychological well-being will be assessed using the Hospital Anxiety and Depression Scale at baseline and 3 months post-discharge.⁵³ Well-being in general will be measured 3 months post-discharge only and will be assessed using the ICEpop CAPability measure for Older people and the Perceived Stress Scale (table 2).^{54 55} Psychological well-being and well-being in general will not be assessed in the abbreviated questionnaire for participants with proxy consent.

Adherence to medication

Participants' adherence to medication will be measured at baseline and 3 months post-discharge using two methodologies: (i) the proportion of days covered (PDC) from pharmacy claims data for the year previous to participants' date of admission and 3 months post-discharge for GMS patients; and (ii) the Medication Adherence Report Scale, a five-point self-assessment scale that assesses both intentional and unintentional non-adherence.⁵⁶ The PDC is calculated as the sum of the days supplied for each medication divided by the number of days in the study period.^{57 58} Changes in the number of medications prescribed and types of medications will be recorded between the two time periods (table 2).

Costs

Both direct and indirect costs will be estimated in order to assess the total economic burden of ADR-related hospital admissions. Direct medical costs include inpatient hospital admissions (diagnostic related groups and length of stay), investigations and procedures performed and healthcare services, for example, physiotherapy provided during hospital admission (table 2). Health service use in general

and use of home help will be measured at baseline and 3 months post-discharge for patients who provide consent to take part in the study on medications management in older populations, as described above. Indirect costs include lost productivity due to absenteeism from work/social commitments and formal and informal care from family and friends, and these will be measured by participant self-report in the follow-up questionnaire (table 2).

Covariates

A number of sociodemographic factors, as described above, will be recorded at hospital admission for all patients with an ADR and control patients. For patients who consent to take part in the study on medications management in older populations, additional sociodemographic information will be obtained including participant's ethnicity, number of children, education, marital status, occupation status and living arrangements and health insurance status. Participants' addresses will be geocoded to determine which electoral divisions (EDs) they live in. Participant deprivation will be estimated as the deprivation score of the ED in which the patient lives based on the Small Area Health Research Unit national deprivation index (table 2).⁵⁹

Additional information on participant morbidity will be obtained by participant self-report in the follow-up questionnaire. Participant comorbidity will also be assessed and validated for GMS patients by applying the RxRisk-V instrument to HSE-PCRS pharmacy claims data for the year previous to the participant's date of admission and the 3 months post-discharge. The RxRisk-V is an algorithm that classifies prescription drug fills into chronic disease classes based on the WHO ATC classification system and was developed specifically for older populations (table 2).⁶⁰

Participants' social support network will be measured 3 months post-discharge using the Lubben Social Network Scale: a composite measure of family and friends networks, for use with older people, which asks patients how many people they have contact with and how often. Participant's resilience (or ability to bounce back after difficult times) will be measured 3 months post-discharge according to the Brief Resilience Scale (table 2).⁶¹ Resilience will not be measured for participants with proxy consent.

Support and barriers to medication taking and participants' beliefs about their medications will be assessed using the Adherence Determinants Questionnaire subscale and Beliefs about Medicines Questionnaire (BMQ), respectively, at baseline and 3 months post-discharge.^{62 63} The BMQ comprises two five-item scales assessing patients' beliefs about the necessity of prescribed medication for controlling their illness and their concerns about the potential adverse consequences of taking it (table 2).⁶³ The beliefs and preferences of older patients regarding their medication have been shown to be associated with medication adherence.⁶⁴ BMQ will not be assessed for participants with proxy consent.

Data analysis

Prevalence and characteristics of ADR-related hospital admissions

Descriptive statistics will be used to summarise the results on the prevalence of ADRs, the different types of ADRs and their various classifications (eg, preventability, severity), as well as the various drug classes involved in ADRs. Descriptive statistics will include calculating and presenting rates, means (SD), medians (IQR) or percentages and frequencies, as appropriate, with 95% CIs. For proportions, the χ^2 test will be used to compare between different types and classifications of ADRs.

Risk factors associated with ADR-related hospital admissions

The distribution of medication-related risk factors, disease-related risk factors, functional ability-related risk factors, medication adherence-related risk factors and patient-related risk factors will be compared between patients with an ADR and non-ADR-related hospital admission using relative risks (RR) and risk differences (RD). Multivariate binomial models will be used to estimate adjusted RR and RD (logit and identity link used, respectively) with 95% CIs for associations between all risk factors and ADR versus non-ADR-related hospital admissions. The risk factors for ADRs will initially be examined univariately and any at $p < 0.10$ will be considered in a multivariate model. The predictive discrimination of the optimum models for ADR versus non-ADR-related hospital admissions will be assessed using receiver operating characteristic curves to produce estimates of the areas under the curves (c-statistics) and 95% CIs.

Secondary health outcomes associated with ADR-related hospital admissions

Descriptive statistics including medians (IQR), means (SD) and proportions will be used to summarise health outcomes (health service use, HRQOL, adherence), differences in health outcomes (baseline and 3-month follow-up) and covariates for ADR-related hospital admissions and non-ADR-related hospital admissions and the various types and classifications of ADR-related hospital admissions.

Log-linear and logistic regression models will be used to examine the association (unadjusted and adjusted) between ADR-related hospital admissions, the different types of ADRs and their classifications, on patient discharge outcomes and duration of hospital stay, health service use, HRQOL and medication adherence (baseline and 3-month follow-up), while controlling for covariates (eg, sociodemographics, morbidity). Covariates that are associated with individual outcomes at the $p < 0.10$ level will be included in multivariate models. For the final multivariate models, a p value < 0.05 will be considered statistically significant.

Costs associated with ADR-related hospital admissions

Unit costs per hospital inpatient stay, investigations and invasive procedures, GP visits, paid home help and so on are available through the HSE and the National Centre

for Pharmacoeconomics. Diagnosis-related group costs from the Healthcare Purchasing Office will be used to estimate hospital-based costs and costs for GP visits will be sourced from the Irish College of General Practitioners.⁶⁵ These unit costs will be used to calculate total and average costs for patients with an ADR-related hospital admission and those without an ADR-related hospital admission. Costs will also be calculated per ADR classification (eg, severity, preventability).

Unit costs for indirect costs (eg, loss of productivity) will be calculated using consolidated salary scales available from the Department of Health and Central Expenditure Evaluation Unit.⁶⁶ The association (unadjusted and adjusted) between ADR-related hospital admissions and indirect costs will be examined using the gamma distribution while controlling for covariates (eg, sociodemographics, morbidity).⁶⁷

Analysis will be performed using Stata V.14.0 (StataCorp). Findings will be published at an aggregate level.

ETHICS AND DISSEMINATION

Ethical approval

This research study was approved by Beaumont Hospital Ethics (Medical Research) Committee (Ref:16/49).

Dissemination

Dissemination will take place via peer-reviewed publications, presentations at national and international conferences, professional networks and through exchanges with relevant policy makers and healthcare practitioners, patients, family members and service users.

STRENGTHS AND LIMITATIONS

This study will provide detailed information on the prevalence and characterisation of ADRs in a large older population. There have been no long-term follow-up studies of older patients with ADR-related hospital admissions and this study will assess a range of health and cost outcomes. This study has a number of limitations. The determination of ADR prevalence includes a multifaceted review of each suspected ADR including clinical judgement and chart review, the application of a number of decision aids and validated algorithms as well as independent review by an expert panel using a consensus method. However, ADR determination in older populations is challenging and there is a risk of misclassification, given that older people often have several comorbidities and disabilities and are prescribed numerous medications.

A number of measures in the study are based on patient self-report and patient recall may be inaccurate. Where feasible, information on health outcomes will be taken from other sources (eg, HSE-PCRS pharmacy claims database for adherence). The application of all of the STOPP and START criteria to patients with an ADR-related hospital admission and control patients will not be possible, due to a lack of information on the specific

duration of patient's medication usage prior to hospital admission. However, these criteria will be applicable for GMS patients, who provide consent, derived from their HSE-PCRS pharmacy claims data. Diagnostic and laboratory data will also be available to support the application of these criteria, which is generally not available in the community setting.

The study has estimated a 50% response rate for patients with an ADR-related hospital admission and control patients consenting to take part in a prospective cohort study investigating medication management in older populations. In order for this study to accurately measure ADR-related health and cost outcomes in older populations and reduce research bias, the study population needs to include participants who may not have the capacity to give informed consent due to cognitive impairments or severity of illness. Previous research on the hospitalisation of older people in Ireland has indicated that the prevalence of dementia is 25% in those admitted to hospital.⁶⁸ Participants will be offered the possibility of completing the questionnaire measures in person or by phone and, where feasible, a proxy (next of kin, person closest to the patient) will be sought to provide assent to take part in the study. However, it is likely that a number of patients will not have the capacity to complete the questionnaire measures and the proposed response rate is overestimated and the analyses for some associations of interest will be underpowered. While we aim to adjust for a number of covariates, it is also possible that there may be other unknown or unmeasured covariates.

Due to the difficulty in determining causality of ADRs immediately, it is possible that patients with a suspected ADR, as determined by the research team and are invited to take part in the prospective cohort study, will be determined not to have a 'true ADR' after expert panel review (figure 1). However, the expected numbers are likely to be small and, therefore, unlikely to impact on the overall study size.

CONCLUSIONS

This study will provide important estimates of the occurrence of ADR-related hospital admissions in older populations, the risk factors associated with ADRs and an assessment of the health and cost outcomes associated with ADR-related hospital admissions. This study will provide information which will be of benefit to the public, healthcare professionals and policy makers and will inform service planning, methods of reducing future ADRs and improving medication management in older populations.

Contributors CaC, CC, DW and KB conceived and designed the study. CaC drafted the manuscript. CC, CB, CW, AH, DW and KB provided expertise in their respective fields, all critically reviewed the manuscript and approved the final version of the manuscript for submission.

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