HRA PROTOCOL COMPLIANCE DECLARATION

This protocol has regard for the HRA guidance and order of content

FULL STUDY TITLE

Implementation of a medicine management plan (MMP) to reduce medication-related harm (MRH) in older people post-hospital discharge: a randomised controlled trial.

SHORT STUDY TITLE

Reducing medication-related harm (MRH) in older people

PROTOCOL VERSION NUMBER AND DATE: Version 9: 12.01.22

RESEARCH REFERENCE NUMBERS

IRAS Number:	305313
SPONSOR:	University of Sussex
FUNDER:	ARC Kent Surrey and Sussex (ARC KSS)

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:

.....

Date:
...../...../.....

Name:

Dr Anthony Walsh

Position:

Research governance officer, Research and Enterprise Services, University of Sussex

Chief Investigator:

Signature:
.....

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...../...../.....

Name:

Dr Khalid Ali, MBBS, FRCP, MD

Position:

Senior lecturer in Geriatrics, Brighton and Sussex Medical School

LIST OF CONTENTS

LIST OF ABBREVIATIONS

ADE	Adverse Drug Event
AE	Adverse Event
ADR	Adverse Drug Reaction
AHSN	Academic Health Science Networks
ARC KSS	Applied Research Collaboration Kent, Surrey & Sussex
BGS	British Geriatrics Society
CI	Chief Investigator
DMS	Discharge Medicines Service
GCP	Good Clinical Practice
GP	General Practitioner
HWBH	Healthwatch Brighton and Hove
MMP	Medicines Management Plan
MRH	Medication-Related Harm
NHS	National Health Service
PCIE	Public and Community Involvement and Engagement Committee
PI	Principal Investigator
PIS	Participant Information Sheet
R&D	Research & Development
RCT	Randomised Control Trial
REC	Research Ethics Committee
RPM	Risk Prediction Model
RPT	Risk Prediction Tool

SOP	Standard Operating Procedure
U3A	University of the Third Age
UPIN	Unique Participant Identification Number
WHO	World Health Organisation

KEY STUDY CONTACTS

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Committees	**Study advisory committee:** Mrs Frances McCabe Dr Katherine Morley Lisa James Lisa Devine Professor Graham Davies Dr Rebekah Schiff Professor Tischa van der Cammen

	Public and Community Involvement and Engagement (PCIE) committee: Mrs Victoria Hamer Ms Barbara Odell Mrs Frances Finbarr-Sexton **National adoption committee:** Liz Butterfield Dr Nikesh Parekh Ms Neveen Sorial Nora Davies Mr Erik Kihlstrom

STUDY SUMMARY

Study Title	Implementation of a medicine management plan (MMP) to reduce medication-related harm (MRH) in older people post-hospital discharge: a randomised controlled trial
Internal ref. no. (or short title)	Reducing medication-related harm (MRH) in older people
Study Design	Randomised Controlled Trial
Study Participants	Older people >65 years who are due to be discharged from hospital
Planned Size of Sample (if applicable)	682 participants
Follow up duration (if applicable)	8 weeks
Planned Study Period	18 months
Research Question/Aim(s)	To assess the clinical and cost effectiveness of a risk prediction tool (RPT)-informed Medicine Management Plan (MMP) linked to the NHS Discharge Medicine Service (DMS) compared to the NHS DMS alone in reducing MRH in the 8 weeks post-hospital discharge.

FUNDING

FUNDER	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
Applied Research Collaboration Kent, Surrey, and Sussex (ARC KSS)	£74,479

ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor is the University of Sussex represented by Dr Anthony Walsh. The University of Sussex is overseeing the conduct of this research study in compliance with MHRA and GCP regulations. The University of Sussex will assume overall responsibility for the initiation and management of the study. The study is funded by ARC KSS.

The study funder has not and will not have input into the study design, conduct, data analysis and interpretation, manuscript writing, or dissemination of results. The chief investigator and study research team have developed the study design, and will be responsible for the study conduct, data collection, data analysis and interpretation, manuscript writing, and dissemination (writing study report, and submission to scientific conferences, and scientific journals). The sponsorship committee at Sussex University has provided input into the study documents, and that input has been included into the final study documents.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Study advisory committee:

- Mrs Frances McCabe. Board director at Healthwatch Brighton and Hove. Lead of the Hospital Discharge Project. Chair of the study advisory committee.
- Dr Katherine Morley. Research Leader at RAND Europe. Senior statistician, supporting data interpretation, and currently working on the British Geriatrics Society (BGS) funded study, "Developing an implementation pathway for reducing the risk of medication-related harm in older people post-hospital discharge".
- Lisa James. Senior program manager at Kent, Surrey and Sussex Academy of Health Sciences Network (KSS AHSN). Study intervention co-lead. Co-applicant.
- Lisa Devine. Program manager at KSS AHSN. Study intervention co-lead. Co-applicant.

- Professor Graham Davies. Professor of Pharmacy at King's College London (KCL). Collaborator. Chair of data monitoring committee. Involved in original PRIME study and co-author in some of its publications.
- Dr Rebekah Schiff. Consultant geriatrician at Guy's and St Thomas' NHS Foundation Trust. Collaborator. Member of study advisory committee. Involved in original PRIME study and co-author in some of its publications.
- Professor Tischa van der Cammen. Professor of Geriatrics at Delft University. Collaborator, committee member of study advisory committee. Involved in original PRIME study and co-author in some of its publications.

Public and Community Involvement and Engagement (PCIE) committee:

- Mrs Victoria Hamer. Honorary Patient and Public Involvement (PPI) Fellow, Centre for Public Engagement (CPE) Faculty of Health, Social Care and Education, Kingston and St George's Joint Faculty, University of London. Lead. Expert patient. Formerly consultee as PPI on original PRIME study.
- Ms Barbara Odell. Secretary of Brighton and Hove branch of the University of the Third Age (U3A). Collaborator.
- Mrs Frances Finbarr-Sexton. Carer for family member. Collaborator.

National adoption committee:

- Liz Butterfield. Specialist Pharmacist at Airedale Telemedicine Hub. Clinical Lead in Medicines Optimisation at KSS AHSN. Collaborator. Chair of the National Adoption committee.
- Dr Nikesh Parekh. GP. He was the PRIME Clinical Trial Fellow, and co-author on all its publications. Collaborator. Member of the National Adoption committee.
- Ms Neveen Sorial. Principal Pharmacist at Brighton and Hove CCG. Responsible for the strategic development and implementation of medicines optimisation services across Brighton and Hove CCG. Collaborator. Member of the National Adoption committee.
- Nora Davies. External partnership project developer (Innovation & Business Partnerships) at University of Sussex. Manager of 'Ageing Well: Changing the Conversation' platform, collaborator. Member of the National Adoption committee.
- Mr Erik Kihlstrom. UK Ambassador of the 'Ageing 2.0' Brighton and London Chapters. Former Interim Director of the Government-led £98 million Healthy Ageing Industrial Strategy Challenge Fund. Collaborator. Member of the National Adoption committee.

KEY WORDS: medication, harm, older people, risk, prediction, model.

STUDY FLOW CHART

See appendix for a schematic overview of the participant's journey through the study.

See appendix for a timeline providing an overview of the study management.

STUDY PROTOCOL

Implementation of a medicine management plan (MMP) to reduce medication-related harm (MRH) in older people post-hospital discharge: a randomised controlled trial.

1 BACKGROUND

Medication Without Harm is the World Health Organisation's (WHO) Third Global Patient Safety Challenge. It aims to "reduce the level of severe, avoidable harm related to medication by 50% over 5 years, globally" (1). Medication-related harm (MRH) includes harm from adverse drug reactions (ADR), non-adherence and medication errors (2).

In a large, prospective UK study of 18,820 patients, the prevalence of an ADR-related admission was 6.5% with the average age of 76 years old and an estimated cost of £466 million annually (3). A large, retrospective study of adverse events (AE) across 58 US hospitals identified 5077 cases of inpatient admissions in the over 65s from 99,628 emergency department visits with half occurring in those older than 80 (4). A meta-analysis shows elderly patients are 4 times more likely to be admitted with an ADR compared to younger patients (5). In a systematic review of MRH in older adults, between 17-51% patients' experience MRH within 30 days post-discharge (2). Our study team have shown that in the 8 weeks following hospital discharge, 37% of over 65s experienced MRH with an estimated cost of £400million annually (6).

Factors contributing to MRH in older people include multimorbidity and polypharmacy (7), age-related changes in pharmacokinetics and pharmacodynamics (8) and medication non-adherence (9). Transition of care at hospital discharge is high-risk for occurrence of MRH with multiple contributory factors: the impact of acute illness, an inpatient stay and patient deconditioning (10), medication discrepancies at admission or discharge (11), patient/carer education on the discharge medication regimen and use of new medications (12), and poor communication between secondary and primary care (13,14).

The WHO identifies three key target areas to protect patients from MRH: high-risk situations, polypharmacy and transitions of care (1). The WHO defines high-risk situations as certain clinical circumstances in which the impact of MRH may be greater; this includes elderly individuals and those with hepatic or renal impairment. Discharge of an elderly individual is an especially high-risk situation encompassing many factors that may lead to MRH.

The NHS Discharge Medicines Service (DMS) is a newly-commissioned community pharmacy service aimed to reduce avoidable post-discharge MRH based on an initiative led and delivered by the Academic Health Science Networks (AHSNs). The DMS is a system of communication allowing hospital pharmacists to refer patients to community pharmacists to ensure they receive adequate support post-discharge. The evidence has been informed by multiple studies showing reduced readmission rates and shorter hospital stays (15–18).

Although effective, patient selection in the NHS DMS is based on hospital pharmacist judgement and not on any evidence-based risk stratification data (19). NHS England support risk stratification using risk prediction models (RPMs) in identifying individuals who will derive the most benefit from target interventions (20). Risk stratification is increasingly important in a healthcare system challenged by an ageing population (21) with an increasing prevalence of healthcare use due to MRH (22).

Six prior RPMs exists; McElnay (23), the BADRI Model (24), the GerontoNet ADR risk score (25), Trivalle (26), the PADR-EC score (27), and the ADRROP prediction scale (28). These RPMs do not predict the risk of MRH occurring in the post-discharge period. No impact studies of these tools have been published. They predict the risk of inpatient ADR/ADE (24–26,28) or risk of an unplanned admission being due to ADR/ADE (23,27).

The PRIME model has been developed and internally validated as the first RPM to predict the absolute risk of an older person experiencing MRH in the 8-week post-discharge period (29). It was developed though a large multicentre, prospective observational cohort study. The PRIME model consists of eight variables routinely collected in hospital (age, gender, antiplatelet drug, sodium level, antidiabetic drug, past ADR history, number of medicines, and living alone). This tool considers demographic, medical and social factors in predicting the absolute risk of MRH. The PRIME tool calculates risk of definite MRH; MRH that was classified as 'probable' or 'possible' was excluded.

Currently, there are no tools in clinical practice to target interventions to high-risk patients in the community following hospital discharge. The PRIME model is the first RPM able to predict risk of MRH in older adults in the community in the 8 weeks post-discharge.

2 RATIONALE

Medication-related harm (MRH) for this study will include adverse drug reactions, medication errors, and a failure to take/receive medication, either following non-adherence or a failure in the supply chain.

The WHO identifies transition of care as a key area in which it is necessary to protect patients from harm (1). Previous interventions in the post-discharge period have been ineffective (30–33). The evidence-based NHS DMS has been shown to decrease readmission rate and shorten length of hospital stay (15–18). Patient selection is based on hospital pharmacist judgement and not on any evidence-based risk stratification data (19). Clinical judgement alone is not sufficient in predicting MRH in older patients (34).

NHS England recognises risk stratification using RPMs can target those at greatest risk and those who are most likely to derive benefit from intervention (20). The PRIME tool is the first tool to predict absolute risk of MRH in the 8 weeks post-discharge period and is a better predictor than clinical judgement (34). The medicine management plan was developed through a study funded by the British Geriatrics Society (BGS) led by Dr Frances-Ann Kirkham and Dr Khalid Ali in consultation with patients, carers and healthcare professionals.

The PRIME team in collaboration with AHSN-KSS will implement a risk-stratification approach linked with the NHS DMS. The study will recruit patients aged 65 and older discharged from 4 acute hospital trusts. The control arm will consist of NHS DMS care only. The intervention arm will consist of NHS DMS with a specific medicines management plan (MMP). The MMP will be as follows:

1. A copy of the discharge summary
2. Specific education about possible medication-related harm from the discharge medications. Education will be delivered by the ward pharmacist and / or the ward doctor at the point of discharge.
3. Clear guidance on who to contact (their GP or their community pharmacist) if they experience any MRH.

4. The name and contact of the community pharmacist will be provided by the ward pharmacist.

5. A copy of the percentage/ probability of harm from medication calculated using the PRIME study RPT, and presented as a visual analogue scale will be offered to patients and (if available) their carers. *See Appendix for document.*

3 THEORETICAL FRAMEWORK

Current risk stratification in clinical practice for MRH in older adults is based on clinical judgement. Clinical judgement is not useful in predicting MRH (34). Currently, MRH risk prediction tools are not routinely used in clinical practice, as existing tools have not been assessed for impact and implementation (35). The PRIME tool has been transparently developed and validated. The MMP has been developed with consultation from patients and carers. To satisfy the next stage of risk-prediction model creation, the impact of the tool will be assessed on a new sample of individuals. Targeted interventions at high-risk individuals may be a clinically and cost-effective solution in reducing rates of MRH in older adults.

4 RESEARCH QUESTION/ AIM

4.1 Primary Research Question

Will a Medicines Management Plan linked to the NHS DMS be more effective than the NHS DMS alone in reducing rates of MRH?

4.2 Objectives

I. To measure and compare the rates of MRH in the two groups.

II. To measure the costs of delivering the intervention and any associated MRH-related service use in the two groups across the 8-week study period. To perform modelling to provide national cost estimates.

III. To undertake a process evaluation.

4.3 Outcome

A clinical, economic and service evaluation of NHS DMS alone compared to a MMP linked with the NHS DMS in reducing MRH

5 STUDY DESIGN AND METHODS OF DATA COLLECTION AND DATA ANALYSIS

Participants will be recruited across 4 sites: Royal Sussex County Hospital in Brighton, Ashford and St Peter's Hospital in Ashford, Medway Hospital in Kent, and Royal Devon Hospital in Exeter. The proposed study is a Randomised Control Trial (RCT), as patients will be randomised into either the NHS DMS alone (control arm/standard care), or RPT-stratification plus MMP linked to the NHS DMS (intervention arm).

Sample size/power details

In determining the sample size, let the proportion of subjects developing MRH when given the standard care be p_1, while the proportion of subjects developing MRH among those put through intervention arm be p_2. Common measures for comparing whether the two proportions are statistically significantly different are:

1. Difference, $\delta = p_1 - p_2$
2. Odds-ratio, $\Psi = \frac{p_1/(1-p_1)}{p_2/(1-p_2)}$

Then the two equivalent hypotheses for evaluating whether the two proportions are different are H_0:δ=0 and H_0:Ψ=1. The values of Ψ close to 1, indicate no difference and those further from 1 are the ones that specify differences that may be clinically important. The sample size formula can be expressed so that the only parameters needed are the prevalence of MRH in the population receiving standard care and odds-ratios and there is no need to directly incorporate δ in calculations. In this case Ψ is the fixed parameter and sample size can be calculated for various values of prevalence. The advantage of using the odds-ratios as fixed is that it is straightforward to define clinically important differences from a range of admissible values. Once desired value of odds-ration is selected, the corresponding values of δ (defining clinically important difference), can be computed for the observed prevalence value.

The choice of the value of odds-ratio to use is based on the range of values of odds-ratios that normally show up as significant in statistical analyses. As it is not expected that the two arms of the study would be dramatically different, we recommend the choice of medium values of odds-ratios.

A systematic review of MRH in older adults found that between 17% and 51% of patients experience MRH within 30 days of hospital discharge. In the UK, approximately 28% of older adults (≥65 years) use health services due to MRH within the 8 weeks following hospital discharge (6). Therefore, our choice of the prevalence to use in the sample size calculation is limited to MRH rates between 20% - 40%. In particular, we take the prevalence of MRH among the group under standard treatment to be 35% and an odds-ratio of 1.6 is considered large enough to result in a clinically important difference in MRH rates between arm 1 and arm 2. These choices of p_1 and odds-ratio corresponds to δ=0.098.

To determine the required sample size to estimate a difference δ that is clinically relevant, the method of Fleiss, Tytun, and Ury (53) was used. This method has been implemented in the function "bsamsize" given in R package "Hmisc" (54). To calculate sample size using this method, one needs to provide the following parameters: the prevalence of MRH among people given standard treatment (p_1) and among people given the new care/intervention ($p2$), odds-ratio (Ψ), the statistical power we wish to achieve, and the margin of error.

We found that a sample size of n=682 (341 subjects on each arm) will be required to detect δ=0.098 (i.e., odds-ratio=1.6), with 80% statistical power, and a 5% margin of error, if we assume that the prevalence of MRH among those on standard treatment is 35%.

5.1 CLINICAL EFFECTIVENESS

Baseline Data Collection

The baseline data collected and methodology will correspond to that of the original PRIME Study (36). Consenting participants (and participants consenting through their consultee) will have baseline data collected by a trained research nurse.

Demographic (age, gender, ethnicity), clinical (discharge diagnosis, co-morbidities, renal function, electrolytes, hepatic function), and social indicator data (living arrangements and care package on discharge) will be collected. Admission and discharge medication data (drug name, frequency, dosage) and use of compliance aids will be collected and coded using the WHO-ATC code (37). The above are routine clinical data, and so can be collected directly from the hospital notes.

Validated tools will be used to collect data on comorbidities, nutritional status, physical function and cognitive function. The Charlson Comorbidity Index (CCI) which predicts 10-year survival in patients based on age and co-morbid status will be collected by the research nurse (38). The Malnutrition Universal Screening Tool (MUST) score is a nutritional screening tool routinely used on elderly care wards to stratify and manage overall risk of malnutrition (39). The Barthel ADL Index is a validated scale used to measure performance in activities in daily living (ADL) (40). Barthel's Index, MUST and Abbreviated Mental Test Score (AMTS) will be collected from patients' notes only.

Data collection will take place using a form designed to be scanned into an electronic database. At the point of data collection, each participant will be allocated a unique participant identification number (UPIN). Data will be anonymised prior to upload to the electronic database. The anonymised data base will be stored on NHS and University Computers. Hard copy non-anonymised data will be stored in locked cabinets in each respective study site with access provided to the CI and each respective PI only. Hard copy data will be destroyed in compliance with local protocol at 3 years.

Follow up Data Collection

The research pharmacist will conduct a telephone interview and GP records review after eight weeks post-discharge for every participant. The phone interview with study participants will take form 5 minutes to 30 minutes depending on the amount of information study participants have to share with the pharmacist around your medications. A standardised questionnaire will determine whether the patient has experienced MRH. Suspected ADRs, medication adherence, and primary/secondary care usage will be explored. MRH severity will be assessed using the Morimoto scale (45). If an ADR is suspected, causality will be assessed using the Naranjo algorithm (46). Medication adherence will be assessed using the Morisky scale (47).

Participants re-admitted within the study time frame will be reviewed prospectively to ascertain MRH as the primary end-point. They will not re-enter the study as new participants.

Statistical Analysis Plan

In the PRIME study (29), eight risk factors for medication-related harm (MRH) were identified: gender, age, past adverse drug reactions, antiplatelet drug, antidiabetic drug, living alone after discharge, Sodium level (mmol/L) and total number of medicines at discharge. These variables will be explored further in the proposed study. The univariate summaries of these variables will be provided and compared between participants in the control arm and participants in the intervention arm.

Baseline characteristics of participants included in the study will be analysed (using aggregated data and for data stratified by certain demographic characteristics) for descriptive purposes only.

Important variables known to be associated with MRH will also be described by randomisation groups. These variables will be taken into account in the analysis by fitting one multivariable logistic regression incorporating these variables to the data.

5.2 ECONOMIC

Economic Evaluation

The economic analysis will adopt the perspective of health and personal social services. Resources involved in delivering the interventions will be gathered prospectively. A researcher will observe the RNs and pharmacists involved in undertaking risk assessments and creating Medicines Management Plans in order to establish the time involved. Initially, time measurements will be obtained for a random sample of 25 participants with the sample being increased if high variability is observed. As in the original PRIME study, service use associated with incidents of medication-related harm will be collected retrospectively from three sources: phone interviews with participants, GP records and hospital records, including A&E attendance, hospital re-admissions, outpatient, GP, community care and social care. Costs of service use and the intervention will be based on validated national sources (PSSRU; National Reference costs) (49). Costs will be compared between groups and modelled to provide national estimates (50).

5.3 PROCESS

Process Evaluation

This work package will include data collection and analysis from qualitative focus group interviews of researchers and service providers based on the need to investigate the acceptance and use of the study processes in both the control and the intervention arms. The evaluation will explore the context of implementation of the proposed intervention in the four study sites: Royal Sussex County Hospital in Brighton, Ashford and St Peter's Hospital in Ashford, Medway Hospital in Kent, and Royal Devon Hospital in Exeter. The focus of interviews will be based on previous studies of new ways of working to enhance medicines management that sought to include practitioner understanding in the adoption (51), and the development of recommendations to inform the scaling and sustainable roll-out of the protocol in further study in practice. Normalisation process theory enables learning about the use of a new tool within existing practices and shapes learning about the organisational receptivity.

Interviews:

It is known that pharmacy interventions with older people increase safety (52), and the interview schedule /topic guide in the proposed study will investigate the context, perceived outcomes, and delivery of the study intervention by interviewing healthcare providers in hospital and the community (a group of doctors, pharmacists, nurses, and commissioners). There is a background knowledge associated with the benefits of using PRIME-RPT that will be shared with the PCIE group. The results of the process evaluation will be discussed with the PCIE committee.

Sampling:

Purposive sampling will include where possible a matched sample of 6-9 interviews in each site (Brighton, Ashford, Exeter and Kent) including service providers, and researchers: study nurses and pharmacists, geriatricians, senior operational managers and in addition external stakeholders in CCGs and potentially in community services or primary care. It is assumed that each context will have a variation in organisational form but also similarities in relation to best practices in discharge management and medicines management. Process evaluation will include this variance in relation to individual sites. Links with the CCGs will be facilitated by Neveen Sorial, a member of the National Adoption committee in the study.

Data collection:

Focus group interviews with researchers and service providers will be undertaken by Zoom/MS Teams and are expected to last 45-60 minutes and will be based on a semi structured interview topic guide. The meetings will be audio/ video recorded and notated with key quotations italicized by the RA. The trial coordinator will set up the interviews on behalf of the process evaluation team, at the convenience of both parties.

Analysis:

SFD and the research associate will undertake a framework analysis, by initially coding the data from interviews/ focus groups and forming the basis of the key themes. This initial framework will be shared with the research team (the study advisory committee, the PCIE committee, and the National Adoption committee) and when the framework is agreed the data will be charted for the purpose of synthesis. The synthesis will form the basis of a site report and this can be compared with the achievement of recruitment targets and protocol in each setting with draft recommendations drawn up to shape the learning about the processes used to normalise the use of the study processes (PRIME-RPT, NHS DMS, and medicine management plan).

Timeline:

The initial meeting with the 4 sites will include discussion about the process evaluation – identifying key stakeholders who are responsible for the study. Data collection will take place midway through the project and the analysis will align to the final study report led by Dr Khalid Ali (KA).

6 STUDY SETTING

This is a multicentre study across 4 hospitals: Royal Sussex County Hospital, Medway Maritime Hospital, Royal Devon and Exeter NHS Foundation Trust and Ashford and St Peter's Hospital.

In each hospital, patients aged 65 and older due for discharge in 48 hours will be approached by a research nurse. This is appropriate research setting to acquire a sample representative of our target population.

Study participants will be followed up for 8 weeks post-discharge.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

7.1.1 Inclusion criteria

- Patients must be over the age of 65 years at the time of recruitment, admitted to an acute Elderly Care or General Medical Ward,
- Patients to be identified when they are likely to be discharged within 48 hours.
- Patients need to be registered with a General Practitioner within the areas covered by the recruiting hospitals.
- Informed written consent must be provided from patients with capacity OR personal consultees acting on behalf of patients without capacity

7.1.2 Exclusion criteria

- Patients lacking capacity and have no consultee to advise
- Patients that are transferred to other acute healthcare trusts (but excluding step down or intermediate care facilities)
- Patients who have a short life expectancy, due to a terminal illness
- Patients who are unable to read/speak/understand English

7.2 Sampling and Recruitment

7.2.1 Sampling technique

After enrolment, participants will be randomised to either the intervention or group receiving standard treatment: a 1-to-1 ratio stratified by site, with allocations permuted between blocks. The randomisation sequence will be created using the R software package (54): “randomizeR”, a program that generates randomized equi-probable sequences through a procedure called Permuted Block Randomization (PBR) with block constellation. The parameters involved include: the block constellation, the number of treatment groups (in our case, 2), and the vector of the ratio (which in our case is a vector with two elements, which are both 1’s).

7.2.2 Recruitment

In each hospital, the research nurse will approach patients aged 65 years and over about to be discharged in the next 48 hours. We are confident that in each of the 4 hospital sites, six patients can be recruited each week in view of the ease of screening and recruiting study participants. At this rate, 24 patients can be recruited weekly from the 4 hospital sites, equating to 96 patients per month. Consequently, we will be able to recruit 684 patients to the study from the 4 sites in approximately 7.5 months. Our sample size is 682 patients. The research nurse and trial pharmacist will work in collaboration with hospital and primary care clinical teams (GPs and community pharmacists) and the DMS service teams to ensure study recruitment and data collection is achieved according to time and target.

Recruitment targets will be monitored closely by the study advisory committee. In addition, we do have a contingency plan to open 1-2 additional sites if recruitment from the initial 4 sites is not achieving the target of 96 patients per month. The risk-assessment strategy described below will enable us to accomplish our target in the proposed timeline. *(See Table 1 in Appendix)*

7.3.1 Sample identification

The research nurse will visit the elderly care and general medical wards daily and will liaise with the medical team to identify those eligible participants. The clinical team will inform potential participants about the study, and if they express an interest in taking part, the research nurse will approach them. The research nurse will approach patients aged 65 years and older who are due to be discharged from the acute Care of the Elderly and General Medicine wards and fit inclusion/exclusion criteria.

7.3.2 Consent

The research nurses will be trained on requesting consent from potential participants. The participant will be provided with a participant information sheet and the research nurse will explain the study to them. They will be given the opportunity to ask questions, and the time to consider their participation up until the point of discharge. Informed written consent will be sought.

If a potential participant lacks capacity to consent, a family member/friend/carer will be asked to act as a personal consultee and to support the potential participant taking part in the study. If the potential participant regains capacity prior to discharge, they will be invited to take part in the study. It is important to include those who lack capacity, as we do not wish to exclude those who are most likely to experience MRH i.e. those most vulnerable due to frailty and/or cognitive limitation. If a potential participant lacks capacity and a suitable personal consultee is not available, they will not be included in the study.

Continued consent will be assumed throughout the 8-week study period. There will only be a maximum of three points of contact with the research team; firstly, on joining the study, secondly at the end of the 8-week study period and, thirdly, in the case that they are re-admitted within the 8 weeks.

Participants with capacity will be asked to provide a family member/relative/friend to contact, in case that they lose their capacity if they are re-admitted or at the 8-week phone call. This will be needed in case that the family member/relative/friend needs to be contacted, to act as a consultee to consent for the patient who has lost capacity for continued participation. The patient will be withdrawn if there is no consultee, if the consultee decides to withdraw the individual from the study or if the participant themself wishes to be withdrawn. For participants who lack capacity, a phone call or Zoom interview will be conducted with their carers/consultees.

8 ETHICAL AND REGULATORY CONSIDERATIONS

Following acceptance of the University of Sussex sponsorship committee, the study will be submitted to a national ethics committee. After securing ethics approval, the study will be undertaken.

8.1 Assessment and management of risk

The chief investigator Dr Khalid Ali (KA) will be working closely with the study core team, to ensure that the study participants are appropriately recruited to the study, and remain anonymous, and that the medicines they are taking are safe and monitored during their participation in the study.

If any member of the study team encounters safeguarding concerns for any of the participants, then the GP and hospital consultant will be informed as well as safeguarding teams in the hospital or the community.

If new information relevant to continued participation becomes available during the study period, then the study team will send this information to the participant through their preferred choice (email or post). We consider this an unlikely possibility; this study trials a one-off intervention rather than a continuous one, and there will be no interim analyses. Other possible risks and strategies to manage them are discussed in *Table 1*, attached to the *Appendix*.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from an NHS REC for the study protocol, informed consent forms and other relevant documents.

As per HRA guidance:

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- All correspondence with the REC will be retained.
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the study.
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

As per HRA guidance:

- Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.
- For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments

As per HRA guidance:

- If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.
- If applicable, other specialist review bodies need to be notified about substantial amendments in case the amendment affects their opinion of the study.
- Amendments also need to be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site.

8.3 Peer review

The study has been peer reviewed by Sheffield Hallam University represented by Dr Sally Fowler-Davis, University of Surrey represented by Professor Heather Gage, and by Professor Tischa van der Cammen from Delft University.

8.4 Patient & Public Involvement

The Acceptability of Research

MRH predominately affects older people, as well as their carers. The study Public and Community Involvement and Engagement (PCIE) committee consists of an older person with links to the University of the Third Age (U3A) – a learning cooperative for those in later life, a carer for an older adult, and an expert patient.

Mrs Victoria Hamer will lead the PCIE committee. She has been involved with the PRIME study since 2014 by providing comments. Mrs Hamer has the right expertise to lead the PCIE committee; she is an expert patient and a lay member of the University of Sussex, University of Brighton, Sussex Partnership NHS Foundation Trust, University Hospitals Sussex NHS Foundation Trust (UHSussex): Joint Multi-disciplinary Pre-Sponsorship Review Panel. Ms Victoria Hamer and the PCIE Committee will review Participant Information Sheets and Consent Forms. Five lay members will be invited to the PCIE committee from those involved in the BGS-funded study, 'Developing an implementation pathway for reducing the risk of MRH in older people post-hospital discharge', as well as new members via the ENRICH platform, U3A and HWBH.

The BGS funded study directly engaged with individuals with lived experience including both patients and carers to help co-develop the medicine management plan that is to be used in this study.

Mrs Frances McCabe will lead the Study Advisory Committee. She is chair for Healthwatch Brighton and Hove (HWBW), an organisation that represents people who use health and social care services in Brighton and Hove. In addition, she led the Hospital Discharge Project which involved volunteers ringing recently discharged patients, checking in on them and signposting them to additional services as required. Her involvement in this study will help us ensure that we keep the community at the centre of our research.

PCIE activities started on 27th April 2021 with a talk from Dr Ali to 'Ageing 2.0' and 'Ageing Well: Changing the Conversation' audience to explain the study to members of the public.

A short video explaining the study will be available on KSS-CRN and 'Ageing Well: Changing the Conversation' websites for potential study participants, and their carers. This will be a 3-minute introduction to the study, which will be developed in collaboration with Impact Acceleration Award (IAA) team. Queries will be answered by the trial coordinator and chief investigator.

The Design of the Research

Patient and public involvement was sought in proposal development:

Dr Khalid Ali engaged with University of the Third Age (U3A) members, emailed study summary, and presented on September 15th 2020 to the group. The group responses informed the study design in relation to timing of recruitment and engagement with carers.

Interview questions for service providers and researchers involved in the process evaluation component of the study will be shared by the PCIE committee.

Undertaking of the research

When a patient lacks capacity to consent to participate in the proposed study, a family member/relative/friend will be invited to act as a personal consultee with support provided from the research nurse, and where appropriate from the PI and chief investigator.

Direct access phone line (in working hours) and email contact will be provided by the research nurse and study coordinator to respond to PCIE committee members outside of planned formal meetings. Technical support for virtual meetings will be provided by the Trial Co-ordinator.

Analysis of Results

Results from the process evaluation will be shared with the PCIE committee. This framework will be shared with the PCIE committee, as well as the study advisory and National Adoption committee, to inform the final shape of the framework.

Plans for Dissemination of Findings

Once the study findings are released, the PCIE committee will collaborate with the National Adoption committee to support initiatives to translate the study results into practice; such collaboration will be informed by listening to people affected by challenges from their medicines.

Mrs Frances McCabe has existing links with East and West Sussex Healthwatch and UK-wide. These links will disseminate study activities via webinars, newsletters, and web pages. HWBH has links with commissioners of Adult Health and Social Care in Brighton and will use them to lobby for implementation of study findings.

For the study results, a short report / summary will be developed using plain English language, and will be posted on KSS-CRN, ENRICH and 'Ageing Well: Changing the Conversation' platforms.

8.5 Protocol compliance

As per HRA guidance:

- Accidental protocol deviations will be adequately documented on the relevant forms by the research nurse and reported to the Chief Investigator and Sponsor immediately.
- Deviations from the protocol which are found to frequently recur are not acceptable, and will be immediately dealt by the chief investigator in consultation with the study advisory committee.

8.6 Data protection and patient confidentiality

All investigators and study site staff must comply with the requirements of the Data Protection Act 2018 and the UK General Data Protection Regulation (GDPR) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Data will include written, recorded or MS Teams/ Zoom interviews and will be handled as secure information throughout the study.

The study will involve the collection of personal data following voluntary and informed written consent (section 7.3.2). Consenting participants will have data recorded on a paper data collection form. The form will be scannable for automatic transcription onto the electronic database. Data will be de-identified at transcription with each participant being allocated a Unique Patient Identifier Number (UPIN). The electronic data will be encrypted; the decryption key will only be available to direct members of the study team. The original identifiers will only be accessible through the hard copies. Hard copies will be stored in a secure location at the Research and Development Department at each centre. The hard copy data will be destroyed after a maximum of 3 years after the study has ended. Following hard copy destruction, the pseudo-anonymised data will be completely anonymised. The data custodian is the University of Sussex.

8.7 Indemnity

Indemnity regulations that the University of Sussex operate will be applicable to the study conduct, analysis, and dissemination.

8.8 Access to the final study dataset

Only the study research team will have access to the anonymised final study dataset. The dataset may be used for secondary analysis. This is addressed in the information sheets and consent forms.

9 DISSEMINATION POLICY

9.1 Dissemination policy

Both protocol and the study results paper will be submitted for publication to an open-access journal to maximise reaching a wide audience. The protocol will be published within 3 months of the study starting and the study results paper, as well as being presented at scientific conferences, will be published within 18 months of the study starting.

At study completion, the data will be analysed and the final study report will be prepared by Dr Khalid Ali (KA). All publications from this study will acknowledge that the work was supported through funding provided by NIHR ARC-KSS.

The academic community will be informed about the study through the research team links with the KSS-CRN, the National Ageing Research Network, and the BGS. The chief investigator (CI) is the ageing specialty lead in KSS-CRN and well placed to report study outputs to the national and international scientific community. Dissemination activities will be supported by University of Sussex Impact Acceleration team (through study collaborator Nora Davies).

The study participants, the KSS academic community, the national aging speciality group and the care home community (via the Enabling Research in Care Homes (ENRICH) platform) will be notified of study updates with a newsletter every 4-months. During the study, if new information relevant to continued participation becomes available during the study period, then the study team will send this information to the participant through their preferred choice (email or post). We consider this an unlikely possibility; this study trials a one-off intervention rather than a continuous one, and there will be no interim analyses.

The findings will be disseminated in collaboration with several organisations: the Brighton and London Chapters for ''Ageing 2.0; the Ageing Well: Changing the conversation platform''; the KSS AHSN and national AHSN network; the National Medicine Optimisation Network; the KSS Chief Pharmacy network; the KSS Medicine Safety Network and the NHS Improvement Patients Safety Collaborative Medicine Safety Programme. Additionally, the study team have connections with Healthwatch Brighton & Hove and the U3A group.

The service evaluation of the proposed study will provide knowledge of the enablers and barriers to scale up the study regionally and nationally. The National Adoption committee will work with Policy@Sussex and the ARC-KSS to continue to build awareness about the study and its findings. To sustain the impact of the study beyond the life of the study itself, we will continue working with the study partners, their organisations and commissioning groups in Sussex and nationwide to lobby for wider national implementation of the study findings.

9.2 Authorship eligibility guidelines and any intended use of professional writers

All reports or scientific output resulting from the study will follow scientific guidance for authorship rules. The study team will write all scientific output, and no use of professional writers will be used.

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11 APPENDICES

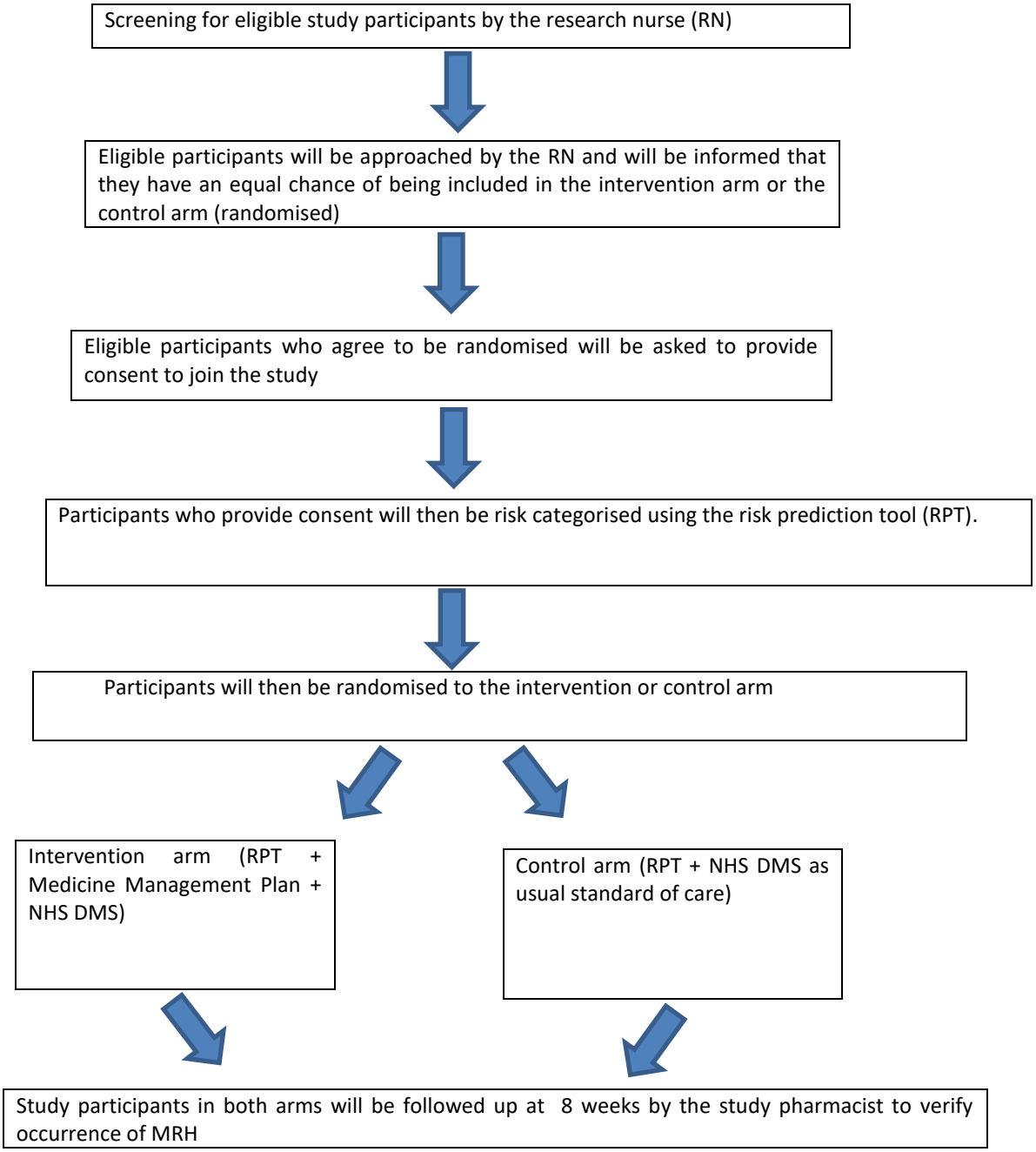
11.1 Appendix 1- Required documentation

- CVs of Chief Investigator (KA) and co-applicants
- GCP certificates of Dr Khalid Ali
- Study flowchart
- Screening log template document
- IRAS form
- Patient Information Sheet & Patient Consent Form
- Consultee Information Sheet & Consultee consent Form
- UHSussex GDPR leaflet

11.2 Appendix 2 – Schedule of Procedures (Example)

- Study Management Timeline
- Table 1: Possible risks and management strategies
- Medicine Management Plan

11.2 Implementation of a risk prediction tool to reduce medication-related harm (MRH) in older people post-hospital discharge – Flow Chart.



Study Management Timeline

Start date: 1st February 2022.

Duration: 18 months.

End date: 1ST JULY 2023

Activity	Responsibility	Timing
Training of study pharmacists across the 4 sites	Dr Jennifer Stevenson	Training provided in first 4 weeks following study approval On-going support will be provided throughout, especially in verifying MRH when unclear.
Training of research nurses across the 4 sites on consenting mechanisms, inclusion and exclusion criteria, data collection and documentation.	The study coordinator	Training provided in first 4 weeks following study approval
PCIE review of documents prior to ethics approval	PCIE committee led by Victoria Hamer	Within 2 months of sponsorship
Ethics approval	The CI	Within 2 months of sponsorship
Preparation and submission of interim reports to the sponsor (University of Sussex) and funder (ARC KSS)	The CI and study coordinator	As required
Study oversight meetings to ensure recruitment and data capture is on target	The study advisory committee led by Frances McCabe	3-monthly
Study newsletter	The CI and study coordinator	4-monthly
On-going PCIE committee meetings	The PCIE committee led by Victoria Hamer	4-monthly
On-going National Adoption committee meetings	The National Adoption committee led by Liz Butterfield	4-monthly
Publication of protocol in open access journal	The CI	Within first 3 months
Publication of study findings	The CI	Within 18 months

Plain English Summary

Hospital discharge is a high-risk situation for experiencing medication-related harm (MRH). This may be due to side effects, consequences of not taking the medication, or medication errors.

Older people at the point of discharge are at higher risk of medication-related harm (MRH). This is due to underlying health conditions, being on multiple medications, and changes in the way the body handles medication with older age.

1 in 3 adults aged 65 and over experience medication-related harm (MRH) in the 8 weeks post-discharge, with half of these episodes being potentially preventable (Parekh et al, 2018). Our research team developed a Risk Prediction Tool (RPT) which is the first objective approach to predict the absolute risk of an older adult experiencing MRH in the 8 weeks post-discharge (Parekh et al, 2020). This absolute risk is presented as a numerical score (percentage). NHS England (2015) acknowledged that risk-prediction tools can help in targeting appropriate interventions to those at the greatest risk of harm, and these high-risk groups are the ones most likely to benefit from such interventions.

Our current study aims to reduce medication-related harm in older people after a hospital stay by improving the medicines information that a patient or their carer receives on discharge. Participants will have an equal chance of being allocated to the intervention group (additional information about their own risk and medications plus exchange of information between hospital pharmacists and community pharmacists) or to the usual care group (exchange of information between hospital pharmacists and community pharmacists). All study participants will have their risk related to their medicines calculated using the RPT.

The study period is 8 weeks, and will take place across multiple hospital sites. At the end of the 8 weeks, study participants or their carers will be interviewed over the phone by the study pharmacist to identify if they have experienced MRH. If study participants were re-admitted to hospital in the 8-weeks period after joining the study, they will be assessed to check if the subsequent admission was due to MRH.

Table 1: **Possible risks and management strategies**

Possible risk	**Plan to manage risk**	**Study member/ team managing risk**
Delay in securing ethics approval	Early ethics approval submission as soon as the funding decision is known	Chief Investigator (CI) Dr Khalid Ali.
Not recruiting to time and target	Opening additional study sites: Princess Royal Hospital, Haywards Heath, and St Thomas', SouthamptonHospital with funding from Impact Acceleration Award (IAA). Royal Devon Hospital in Exeter is a study site and this makes the study eligible for adoption into the national portfolio of ageing research studies.	CI and study advisory committee, and the PCIE committee
Study nurses and trial pharmacists' familiarity with the study recruitment procedures	Training and supervision delivered on a regular basis. Two pharmacists providing cross cover for data collection in each study site.	Jennifer Stevenson, CI and Trial coordinator.
Loss to follow up in study participants	Regular updating of CRF for study participants	DMS team, Trial coordinator, and study advisory committee
Coordination between clinical teams and research team	The service evaluation work package	Professor Sally Fowler-Davis and CI.

Generalisability of study results	National scaling up of the study findings	National Adoption committee, and service evaluation package