CompreHensive geriAtRician-led MEdication Review: CHARMER

Work Package 4: Definitive trial

Version	3.2
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Sponsor	University of Leicester
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Study registration	ISRCTN13248281
NRES #	N/A

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1 Administrative Information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol template Version 4. It describes the CHARMER definitive study, sponsored by University of Leicester and co-ordinated by NCTU.

It provides information about procedures for entering participants into the study, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, study population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the study; replication of key aspects of study methods and conduct; and appraisal of the study's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the study. Sites entering participants for the first time should confirm they have the correct version through a member of the study team at NCTU.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials [1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of NCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The study will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, and the UK Policy Framework for Health and Social Care Research, and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and NCTU.

Participating sites will inform NCTU as soon as they are aware of a possible serious breach of compliance, so that NCTU can fulfil its requirement to report the breach, if necessary, within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the study, or
- The scientific value of the study.

1.2 Sponsor

University of Leicester (UoL) is the study sponsor and has delegated responsibility for the overall management of the CHARMER definitive study to the Chief Investigator and NCTU. Queries relating to sponsorship of this study should be addressed to the Chief Investigator or via the Study Sponsor contact details included at the beginning of this document.

1.3 Structured Study Summary

Primary Registry and Study Identifying Number	ISRCTN13248281
Date of Registration in Primary Registry	21/07/2023
Secondary Identifying Numbers	• Identifiers assigned by the sponsor: 0920 • IRAS number: 323504 • NIHR: 200874
Source of Monetary or Material Support	NIHR Programme Grants for Applied Research
Sponsor	University of Leicester rgosponsor@le.ac.uk
Contact for Public Queries	CHARMER.study@le.ac.uk
Contact for Scientific Queries	Professor David Wright D.J.Wright@leicester.ac.uk CHARMER.study@le.ac.uk
Short Title or Acronym	CHARMER
Scientific Title	Stepped wedge design definitive study, with internal pilot, of a hospital-based behaviour change deprescribing intervention to estimate effectiveness, cost-effectiveness, and safety.
Countries of Recruitment	England
Health Condition(s) or Problem(s) Studied	Patients who are over 65 and prescribed at least one potentially inappropriate medicine where the likely harms outweigh the benefits.
Intervention(s)	The CHARMER intervention comprises multiple components delivered to geriatricians and pharmacists to target their key barriers and enablers to proactive deprescribing with the intention that this will increase deprescribing.
Key Inclusion and Exclusion Criteria	**Hospitals** Acute hospital sites will be selected from those that have expressed an interest in being a part of the CHARMER

	research programme. Our sampling will also consider diversity in the hospital's patient population to explore whether any behaviour change arising from the CHARMER intervention is acceptable to a diverse patient population, including ethnicity and deprivation.
	
	Inclusion Criteria:
	
	• Hospital willing and able to adopt intervention into routine care
	• Older people's medicine service with at least one inpatient ward on which to conduct the CHARMER study (the study ward(s)). The participating ward(s) would be required to meet the following criteria:
	  o the majority of patients have a minimum length of stay of 3 days
	  o the average total monthly throughput across participating ward(s) of approximately 120 patients have at least one geriatrician (consultant or specialist registrar) and one ward-based pharmacist working on them
	  o electronic prescribing system implemented on the study ward(s)
	• A minimum of one geriatrician *and* one pharmacist willing to be recruited to receive the intervention.
	• Named clinician willing and appropriate to take Principal Investigator responsibility
	• Suitably trained staff available to recruit patients and enter data
	• Hospital has e-prescribing system
	• Hospital has availability of suitably trained project manager
	
	Exclusion:
	
	• Hospitals without a ward-based pharmacy service
	• Mental health hospitals
	• Wards that primarily host patients who are medically fit for discharge but awaiting discharge care packages
	• Hospitals without an e-prescribing system
	
	Practitioners
	
	Inclusion Criteria:

	• Consultant Geriatrician or Specialist Registrar and appropriately qualified Pharmacist working across Older People's Medicine wards Exclusion Criteria: • Less than 0.3 FTE of ward-based time **Patients** All patients under the care of a participating geriatrician (Steps 1-4 only) and receiving treatment on the study ward(s) within the study window (February 2024 to July 2025) will be included. Only patients that are discharged from hospital and who did not pass away during admission will be included.
Study Type	Stepped Wedge Trial with internal pilot.
Date of First Enrolment	February 2024
Target Sample Size	Twenty-four hospitals will be recruited to the trial for a total of 21 months, with twenty completing a period of control (minimum 3 months) and intervention (minimum 3 months) according to a stepped wedge design. The remaining four will be randomised to replace sites if they withdraw once the trial begins and will otherwise remain in control for the duration of the trial.
Outcomes	**Primary outcome measure:** • Readmission to hospital 90 days post-discharge **Patient Oriented Outcomes:** • Mortality • Number of hospital stays post discharge • Quality of Life • Satisfaction with deprescribing • Medication related side-effects **Process Outcomes:** • Number of regularly prescribed medicines at point of leaving the ward • Number of prescribed medicines for 'when required use' at point of leaving the ward • Number of prescribed medicines that are stopped

	• Number of prescribed medicines with dosage reduced • Number of stopped medicines that are re-started within three months of discharge **Economic Outcomes:** • Costs associated with the intervention (cost associated with intervention; secondary care costs; primary care costs (in subsample) • Cost-effectiveness (cost per re-admission avoided) • Cost per Quality Adjusted Life Year (QALY) (sub-sample)

1.4 Roles and Responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the Trial Master File for current lists.

1.4.1 Protocol Contributors

Name	Affiliation	Role
Prof David Alldred	University of Leeds	Co-Investigator and Work Package 4 Co-Lead
Prof Debi Bhattacharya	University of Leicester	NIHR PGfAR CHARMER Co-Principal Investigator
Dr Allan Clark	University of East Anglia	Statistician
Dr Jackie Martin Kerry	University of Leicester	Process Evaluation Lead & Programme Manager
Amber Hammond	University of East Anglia	Trial Coordinator
Dr Sion Scott	University of Leicester	Study Behavioural Scientist
Dr Erika Sims	University of East Anglia	Research Lead, Norwich Clinical Trials Unit
David Turner	University of East Anglia	Health Economist
Prof David Wright	University of Leicester	NIHR PGfAR CHARMER Co-Principal Investigator Work Package 4 Co-Lead

1.4.2 Role of Study Sponsor and Funders

Name	Affiliation	Role
Dr Cat Taylor	University of Leicester	Head of Research Governance (Sponsor)
Zaynab Manea	NIHR	Funder Representative

1.4.3 Study Team

Name	Affiliation	Role and responsibilities
Prof David Alldred	University of Leeds	Co-Chief Investigator and Work Package 4 Co-Lead
Prof Debi Bhattacharya	University of Leicester	NIHR Co-Chief Investigator Behavioural Science Expertise
Dr Allan Clark	University of East Anglia	Study Statistician
Antony Colles	University of East Anglia	Data Management Lead
Janet Gray		PPI Advisory Group Member
Shelby Carr	University of East Anglia	Trial Assistant
Caitlin Pearce	University of East Anglia	Trial Assistant
Dr Jackie Martin-Kerry	University of Leicester	Process Evaluation Lead & Programme Manager
Amanda Edmondson	University of Leicester	Research Assistant (process evaluation)
Elizabeth Bywater-Florance	University of Leicester	Research Associate (process evaluation)
Amber Hammond	University of East Anglia	Trial Coordinator

Dr Sion Scott	University of Leicester	Study Behavioural Scientist
Dr Erika Sims	University of East Anglia	Research Lead – Norwich CTU
David Taylor		PPI Advisory Group Member
David Turner	University of East Anglia	Health Economics
Prof Miles Witham	Newcastle University	Academic geriatrician
Prof David Wright	University of Leicester	NIHR Co-Principal Investigator Co-Chief Investigator Work Package 4 Co-Lead Clinical Trialist

1.4.4 Programme Management Group

Name	Affiliation	Role and responsibilities
Prof Debi Bhattacharya	University of Leicester	NIHR Co-Chief Investigator
Prof David Wright	University of Leicester	NIHR Co-Chief Investigator
Dr Sion Scott	University of Leicester	Study Behavioural Scientist
Dr Martyn Patel	Norfolk and Norwich University Hospital NHS Foundation Trust	Consultant Geriatrician
Prof Miles Witham	Newcastle University	Academic geriatrician

Prof David Alldred	University of Leeds	Co-Chief Investigator
Dr Allan Clark	University of East Anglia	Statistician
David Turner	University of East Anglia	Health economist
Erika Sims	University of East Anglia	Research lead – CTU
Amber Hammond	University of East Anglia	Trial Coordinator
Martin Pond	University of East Anglia	Head of data management
Dr Victoria Keevil	Cambridge University hospital NHS Foundation Trust	Academic geriatrician
Dr Jackie Martin Kerry	University of Leicester	Process Evaluation Lead & Programme Manager
Bethany Atkins	University of Leicester	Research Associate
Dr Jo Taylor	University of York	Co-Investigator (qualitative)
Janet Gray		PPI Advisory Group
David Taylor		PPI Advisory Group

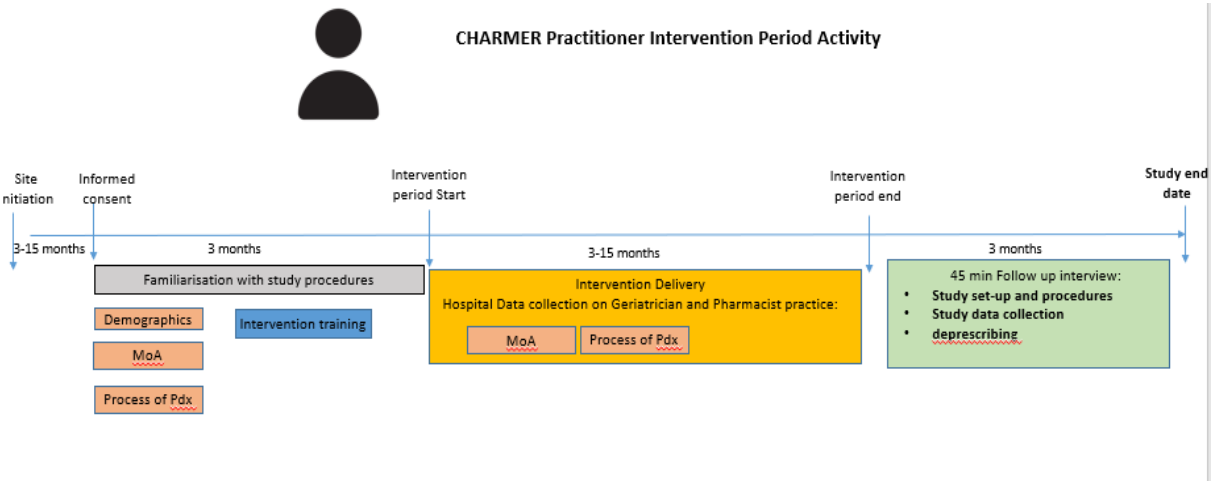
1.4.5 Programme Steering Committee

Name	Affiliation	Role and responsibilities
Professor Adam Gordon		Chair

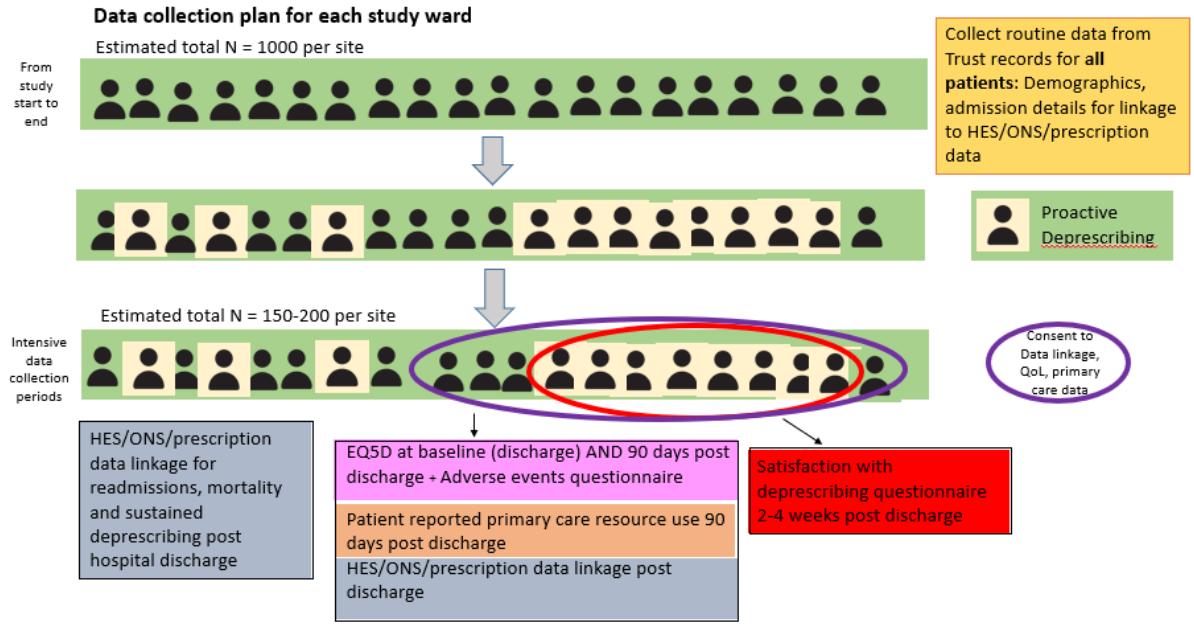
Richard Cattell	NHS England and NHS Improvement	Deputy Chief Pharmaceutical Officer
Professor Richard Emsley	Kings College London	Professor Medical Statistics and Trial Methodology
Rebecca Harmston		PPI member
Alan Brown		PPI Member
Dr Lynsay Matthews	University of Glasgow	Research Fellow in behavioural medicine
Professor Dyfrig Hughes	Bangor University	Professor of Pharmacoeconomics
Professor Debi Bhattacharya	University of Leicester	Chief Investigator
Matthew Hammond	University of East Anglia	Deputy Director Norwich Clinical Trials Unit
Dr Allan Clark	University of East Anglia	Senior Statistician
Julie Dawson	Norfolk and Norwich University NHS Foundation Trust	Lead NHS Trust representative
Amber Hammond	University of East Anglia	Trial Coordinator
Zaynab Manea	NIHR	Funder representative
Dr Jackie Martin-Kerry	University of Leicester	Programme Manager

2 Study Diagram

Practitioner flow



Patient flow



3 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
BCT	Behaviour Change Technique
CI	Chief Investigator
CRF	Case Report Form
EQ-5D-5L	Euroqol Health related quality of life questionnaire
GCP	Good Clinical Practice
HIE	Health Innovation East
HRA	Health Research Authority
ICH	International Conference on Harmonisation
MoA	Mechanism of Action Questionnaire
NCTU	Norwich Clinical Trial Unit
PDx	Proactive deprescribing
PI	Principal Investigator
PID	Participant Identification Number
PIS	Participant Information Sheet
PMG	Programme Management Group
PROMS	Patient Reported Outcome Measures
PRUK	Pharmacy Research UK
PSC	Programme Steering Committee
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
R&D	Research and Development

REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SSA	Site Specific Approval
SMT	Study Management Team
TMG	Trial Management Group
ToR	Terms of Reference
TSC	Study Steering Committee
UEA	University of East Anglia
UoL	University of Leicester

4 Glossary

PDx – Proactive Deprescribing:

As we get older, our bodies are less able to handle some medicines. Medicines that were once effective and safe may not have as much benefit and may have an increased chance of causing harm. In our previous research we asked older people and their carers about their thoughts on stopping these medicines. They told us that they would like these medicines reviewed by doctors in hospital during their stay and for those no longer needed or that could cause harm to be stopped. This is called 'proactive deprescribing' and is different to stopping a medicine after harm has occurred.

5 Introduction

5.1 Background and Rationale

Approximately 50% of older people are prescribed one or more medicines where the risk of harm outweighs the chances of benefit. This predisposes them to adverse outcomes including morbidity, hospitalisation, and mortality [3]. There is an expectation from patients and carers that prescribed medicines have been reviewed for appropriateness and any inappropriate medicines stopped [4]. The research team's PRUK-funded evaluation of 2,039 hospitalised older patients prescribed 24,552 pre-admission medicines established that most medicines are only stopped after they have caused harm, i.e., reactive deprescribing [5]. For example, stopping a blood pressure medication after it has caused a fall due to dizziness. This means that those medicines prescribed to over 50% of patients where the likelihood of future harm outweighs any benefits are not being stopped [5].

In response to the alarming statistics regarding avoidable harm from inappropriately prescribed medication, there has been a global drive to increase proactive deprescribing (PDx) to reduce medicine-related harm. PDx is the process of healthcare practitioners and patients/informal carers (e.g. family members) working together to identify and safely discontinue medicines where the likelihood of future harm outweighs any benefits. PDx is central to both the World Health Organisation Global Patient Safety Challenge: Medication Without Harm [6], and to achieving the UK government's vision of addressing NHS overprescribing to ensure that "patients get the medicines they need and stop taking those that no longer benefit them" [Secretary of State for Health and Social Care] [7].

PDx is a complex behaviour commencing with a full medication history through to deprescribing a medicine, documenting and then monitoring the patient. Figure 1. Summarises the six steps of the PDx process.

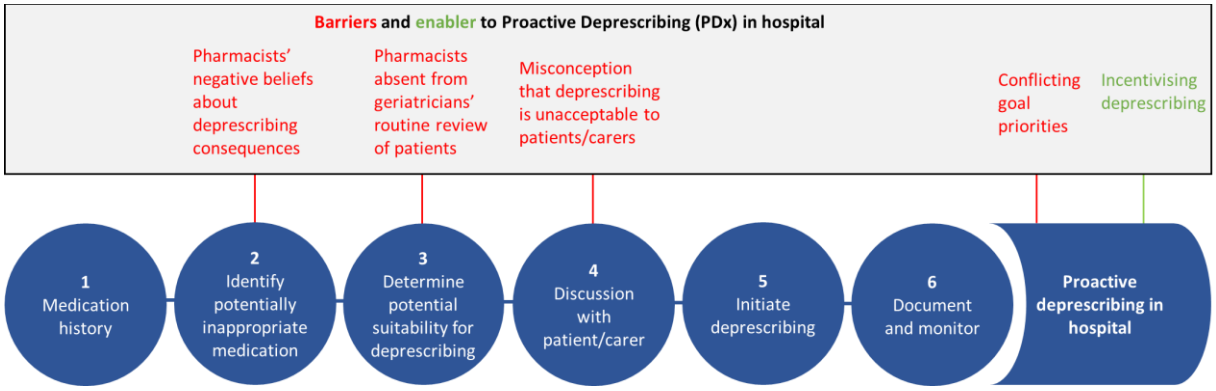


Figure 1. A model for supporting proactive deprescribing by geriatricians and pharmacists in hospital

A 2018 systematic review of existing hospital deprescribing interventions found limited, if any, impact on the primary outcome measure of potentially inappropriate medication [8]; this may be attributable to interventions not targeting the barriers and enablers of PDx in this setting [8, 9]. Using theory to underpin the design of an intervention focused on behaviour change may enhance the likelihood of implementation and effectiveness of the intervention [10].

Patients have communicated an expectation that the responsibility for initiating PDx discussions in hospital lies with the prescriber rather than the patient or carer [4]. The research gap that needs addressing is therefore targeting prescriber behaviour to increase the proportion of PDx opportunities that are identified and discussed with patients. Prescribers have recognised the scope for several professional groups working in hospital to contribute to PDx; however, there was consensus that overall responsibility should rest with senior doctors, which aligns with the patient perspective [11]. The generalist role of geriatricians was perceived to align well with PDx as this requires a holistic evaluation of all prescribed medicines. Figure 1 provides in its grey layer, four barriers and one enabler to PDx [11].

The CompreHensive geriAtRician-led Medication Review (CHARMER) intervention is designed to equip NHS geriatricians and pharmacists to work with older adults and friends/relatives in hospital to deprescribe unnecessary or harmful medicines. CHARMER is underpinned by behaviour change theory and has been developed in partnership with geriatricians, pharmacists and other NHS hospital staff involved in its implementation with oversight from a team of Patient and Public Involvement (PPI) members (1,2). The intervention comprises five components:

- Localised hospital action plan for implementing the CHARMER components for PDx
- Pharmacist workshop
- Weekly pharmacist and geriatrician proactive deprescribing briefing
- Generic pre-prepared videos of geriatricians navigating deprescribing consultations
- Benchmarking reports on PDx activities

The intervention is designed to address the barriers and enablers to PDx. The decision regarding whether PDx is appropriate will remain as a partnership between the patient, prescriber and if appropriate, also the carer, based on both the clinical picture and individual preference. Because the intervention targets geriatricians and pharmacists, as such all patients admitted to an intervention ward could be exposed to the effects of the intervention by virtue of being under the care of a recipient of the intervention.

In line with MRC guidance for the development and evaluation of complex interventions the intervention and trial were feasibility tested. Based on the learnings in the feasibility study we were able to:

Intervention

- Revise the intervention package protocol
- Categorise the intervention and research acceptability and safety
- Refine the fidelity framework

Trial design

- Refine data collection processes
- Understand site readiness processes and make additional changes to support sites
- Confirm that there were sufficient number of patients appropriate for PDx

- Confirm participation and attrition rates
- Confirm feasibility of recruitment processes, and make changes where appropriate
- Confirm the suitability of the outcome and process measures
- Confirm safety monitoring process
- Confirm processes for the process evaluation

5.2 Objectives

The aim of this definitive study with internal pilot is to estimate effectiveness and cost-effectiveness of the CHARMER intervention to enhance proactive deprescribing within the hospital setting.

Trial design

The objectives for the internal pilot are to ensure sufficient patient enrolment rate to achieve the target sample size. The pilot will be evaluated according to the following criteria to enable the trial to continue beyond the pilot phase:

- An average of 200 patients per hospital enrolled over 3 months (green)
- An average of 150-199 patients per hospital enrolled over 3 months (amber)
- Below an average of 150 patients per hospital enrolled over 3 months (red)

If the above is green, proceed with definitive trial.

If the above is amber, proceed with definitive trial if appropriate solutions are identified.

If the above is red, in consultation with the Programme Steering Committee, make a decision regarding whether to proceed.

The objectives for the main trial, with respect to the CHARMER intervention, are to:

- Estimate effectiveness
- Estimate cost-effectiveness
- Describe safety

The process evaluation is intended to:

- Describe the dose, reach and fidelity of the intervention
- Identify any unintended consequences of the intervention
- Investigate the mechanisms of impact of the intervention

- Identify any adaptations made to the intervention and how these affect the impact of the intervention
- Identify barriers and enablers to intervention delivery
- Explore factors that influence the extent to which the intervention addresses the barriers and enabler to PDx
- Describe the perceived effectiveness of intervention components from patient, consultee, pharmacist, and physician perspectives
- Explore barriers and enablers to the intervention package being continued beyond the trial context and implemented in other hospitals
- Refine the logic model

5.3 Study Overview

This is a stepped wedge design trial to be performed across acute hospitals in England.

6 Site Selection

The study sponsor (University of Leicester: UoL) has overall responsibility for site and investigator selection and has delegated this role to the CI and NCTU.

Hospital recruitment

24 hospitals across England will take part providing anonymised routine data for approximately 1000 patients each. We will recruit hospitals via the CRN and have obtained expressions of interest during WP3 to minimise time to start in WP4. According to the stepped wedge design all participating hospitals will begin the trial at the same time in a control phase. We will step hospital sites into the intervention implementation at 3-month intervals (five hospitals every three months) to ensure sufficient capacity of the research team to appropriately support each site. Each site will therefore take part in the study for a total of 21 months (including follow up period).

Should the number of patients enrolled into the trial be lower than anticipated, the additional sites may be randomised and/or the duration of the trial may be extended.

6.1 Site/Investigator Eligibility Criteria

We have secured expressions of interest from 45 eligible hospitals through activities associated with Work Packages 1,2 and 3 of the CHARMER research programme. All hospitals have indicated a desire to participate in this definitive study.

To participate in the CHARMER definitive study, investigators and study sites must fulfil the following eligibility criteria:

Hospitals

Acute hospitals will be selected from those that have expressed an interest in participating in the CHARMER research programme. We will sample to represent diversity in hospitals' patient population to explore whether any behaviour change arising from the CHARMER intervention is acceptable to a diverse patient population.

Hospitals fulfilling the following inclusion criteria are eligible:

- Older people's medicine service with at least one inpatient ward on which to conduct the CHARMER study (the study ward). The participating ward(s) would be required to meet the following criteria:
    - the majority of patients have a minimum length of stay of 3 days
    - the average total monthly throughput across participating ward(s) of approximately 120 patients have at least one geriatrician (consultant or specialist registrar) and one ward-based pharmacist working on them
    - electronic prescribing system implemented on the study ward(s)
- Hospital willing and has the capability and capacity to implement all components of the CHARMER intervention
- Able to provide a 0.2 FTE project/transformation/quality improvement manager or similar to oversee implementation of the CHARMER intervention over a 14-week period (3-month set-up and 2 weeks post intervention roll-out)
- Named clinician willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff e.g., CRN research nurses, available to recruit patient and personal consultee participants and enter required data

Exclusion:

- Wards that primarily host patients who are medically fit for discharge but awaiting discharge care packages
- Hospitals without a ward-based pharmacy service
- Mental health hospitals

Practitioners

Inclusion Criteria:

- Consultant Geriatrician/Specialist Registrar and Specialist Medical Pharmacist (appropriately skilled) working across Older People's Medicine wards

Exclusion Criteria:

- Less than 0.3 FTE of ward-based time

Hospital sites fulfilling eligibility criteria will be issued with the CHARMER Definitive study Site File and a pack of documentation needed by the Research and Development Department (R&D) of their Trust to enable the Trust to provide confirmation of capacity and capability to undertake the study.

6.1.1 Principal Investigator's (PI) Qualifications and Agreements

The PI(s) must be willing to sign an investigator statement to comply with the study protocol (confirming their specific roles and responsibilities relating to the study, and that their site is willing and able to comply with the requirements of the study). This includes:

- Confirmation of appropriate qualifications
- Agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site
- Maintaining documented evidence of all staff at the site who have been delegated study related duties

6.1.1.2 Resourcing at Site

The PI should demonstrate ability to recruit sufficient practitioner participants. The PI should also demonstrate that their hospital has one or more wards of sufficient ward size and patient turnover. They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the study (21 months) to enable them to conduct the study properly and safely. Sites will be expected to complete a delegation of responsibilities log and provide staff contact details. The site should have sufficient data management resources to allow prompt data return to NCTU.

The site must be able to provide a project manager, who could be the PI, for 14 weeks to manage implementation of the intervention prior to the intervention commencing.

6.2 Site Approval and Activation

We will provide the CHARMER handbook, developed for the definitive study, to the project manager and PI. The handbook comprises instructions for how to deliver the trial and CHARMER intervention in accordance with the approved research ethics and governance processes.

On receipt of the signed PI statement, approved delegation of responsibilities log and staff contact details, the study manager or delegate will notify the PI in writing of the plans for site initiation. Sites will not be permitted to begin any study procedures until a letter for activation has been issued. The Study Manager or delegate will be responsible for issuing this after Sponsor Green Light to begin process has been completed.

The site must conduct the study in compliance with the protocol as agreed by the Sponsor and HRA, and which was given favourable opinion by the Research Ethics Committee (REC). The PI or delegate must document and explain any deviation from the approved protocol and communicate this to the study team at NCTU.

6.3 Study Design

We will undertake the internal pilot study over the first three months of the trial at all 24 sites (20 sites required plus 20% allowance for site withdrawal) and the definitive study at 20 of these sites. Each site will be in the trial for 21 months with a minimum of three months as a control site, three months for CHARMER intervention implementation and three months for follow-up post implementation.

The CHARMER intervention will be compared to standard care at the sites during the control phase because this is the most effective way to evaluate the intervention and CHARMER intervention processes.

The hospital will identify one or more wards to be included in the study. Their selection will be informed by a range of factors including, the number of beds, average length of stay, pharmacy service provision and number of geriatricians providing services on the ward(s).

During the intervention implementation period, a project manager will be recruited to help implement the CHARMER intervention. Geriatricians and pharmacists will also be recruited and those consenting will receive the CHARMER intervention package, designed to address the barriers and enablers to PDx in hospitals. They will also complete questionnaires and participate in interviews. All participating staff will complete a consent form that covers all activities.

During both intervention and control phases, routine health data (primary reason for admission, medication data) will be collected for all patients at each site receiving treatment on a study ward and a subset of patients will be consented for additional data, e.g. health related quality of life.

Within the process evaluation, we will engage with a wide range of stakeholders including primary care practitioners, who whilst not directly involved in delivering/receiving the CHARMER intervention, may experience its effects by virtue of their patients receiving care from clinicians exposed to the intervention.

6.4 Participants

6.4.1 Eligibility of Staff Participants

All sites

Staff involved with delivering the CHARMER intervention and/or trial delivery will be eligible to participate in the trial and process evaluations.

Practitioners will be eligible if they are a geriatrician or pharmacist (appropriately skilled) at an intervention site. They will be excluded if they have less than 0.3 FTE of ward-based time as this will provide insufficient exposure to the intervention components.

Primary care staff will be eligible if they have a prescribing role and have at least one patient in the CHARMER definitive study at one of the intervention hospitals.

6.4.2 Identification and Recruitment of Staff Participants

Staff identification

At each site, the PI will act as a gatekeeper and will identify one or more Older People's Medicine wards to be included in the study plus at least one geriatrician and one pharmacist working on the intervention ward. They will also identify suitable staff members to form the intervention delivery team and trial delivery team.

During the control period, the PI will identify suitable staff members to form the trial delivery team.

Staff recruitment

At each site, during the 3-month intervention implementation period, the PI, supported by the project manager, will recruit eligible geriatricians, pharmacists, research nurses, and trial delivery team staff by email, supported by the study team. The email will include a brief account of the study and invitation text and an attached Participant Information Sheet (PIS) (Documents 24, 31, 33, 36). A link to an online consent form (Documents 25, 32, 34, 37) will be included in the PIS to ensure that the practitioners who consent have accessed the PIS to learn more about the study and what taking part involves. The PIS signposts potential participants to the contact details of a member of the study team for further information or to ask questions.

Staff wishing to participate, having read the PIS, will complete an electronic consent form hosted on REDCap.

Geriatrician and pharmacist potential participants will be invited to consent to the following (Document 25):

- Short demographics questionnaire (see 6.6.1)
- Completing the Mechanism of Action questionnaire and Practitioner Deprescribing Process Questionnaire
- Taking part in an interview with a member of the CHARMER research team about their experience of being involved in the study (a purposive sample of practitioners, 20-30 pharmacists and 20-30 geriatricians, will be interviewed)

PIs and project managers will be invited to consent to the following (Document 34, 37):

- Delivering the intervention components and recording three of the intervention components (pharmacist workshop, geriatrician video huddle, action plan launch). The PI/project manager will use NHS Trust compliant recording software.
- Taking part in an interview with a member of the CHARMER research team about the intervention delivery processes and events and setting up the study. Some PIs will be asked to take part in a second interview after the active study window period.

Ageing research specialist staff will be invited to consent to the following (Document 32):

- Taking part in an interview with a member of the CHARMER research team about their experiences of CHARMER trial delivery and processes.

Staff will not be able to participate in the study without completing and signing the consent form.

Primary care staff

Site staff will notify GP practices by letter (Document 22) if one or more of their patients have consented to participate in the CHARMER definitive study (intervention period) and had a medicine stopped in hospital. Staff with a prescribing role (GPs, PCN pharmacists and practice nurses) who have at least one patient participating in the CHARMER definitive study will be eligible to participate. We will contact primary care staff either electronically (email) or by post. An invitation letter (Document 23) will be accompanied by a PIS (Document 29) and consent form (Document 30) to complete if they are interested in participating in an interview. A member of the CHARMER research team will also follow up by telephone to check that the letter/email has been received and provide more information about the study if requested. Primary care staff will not be able to participate in an interview without completing and signing the consent form (Document 30).

Primary care teams within regional Research Delivery Networks (RRDNs) will also support the process of identifying and engaging with practice staff who could participate in a focus group or interview. They will do this through email and meetings with practice staff.

6.4.3 Eligibility of Patient Participants (Intervention and Control Periods)

The following relates to all study sites:

Entry into the study cohort

The intervention is being delivered to practitioners, thus all patients under the care of a participating geriatrician on the study ward during the intervention period will be exposed to the effects of the practitioner behaviour change intervention. Based on a previous similar study, we anticipate that it will not be practicable to approach sufficient patients/consultees to seek consent for access to routine health data [33]. In a previous study, from 220 patients on the ward during a two-week period for 64 patients (29.1%) required data could not be collected due to neither patients nor consultees being available to be approached for consent prior to discharge. Reasons for inability to approach were patients being discharged before consent could be sought and patient/consultee not at the bedside. We anticipate that 70% patient/consultees approached for consent will be unachievable as the aforementioned study was resourced with a member of research staff dedicated to seeking consent from patients/consultees every day for a minimum of 8 hours during the study period. We will therefore enter into the study all patients receiving care on the study ward during the study (control and intervention phase) for **routine health data collection including linkage to external datasets** unless patients or consultees refuse consent/assent when approached or choose to opt out their data being used for research. Informed consent will not be sought (Document 7-8).

Enhanced data collection

A subset of patients under the care of a participating geriatrician from the study cohort will be approached to consent to the following prior to their discharge from the study ward (document 10, 14):

- Additional patient reported outcomes – EQ5D-5L (validated); Adverse Drug Events questionnaire (bespoke, non-validated)
- Patient reported primary care utilisation data
- Data linkage of patient reported outcomes and primary care outcome data to routinely held data from the site and held by NHS England

6.4.3.1 Recruitment of Patient Participants

We will seek informed consent from patients or assent from consultees (Document 10,14) if appropriate for enhanced data collection study activities detailed above. Informed consent and consultee assent will be written and collected face to face wherever possible. Should participating hospital site infection rates preclude this e.g., patient isolation or limitations on visitors due to covid 19, local hospital procedures for virtual consent will be used. Virtual consent will comprise of verbal consent over the phone or by video call (e.g. 'WhatsApp, 'Teams' or 'FaceTime' according to local procedures). Sites using virtual consent will be asked to store details of the procedure in the local

investigator site file and written informed consent or consultee assent will be collected when it becomes practically possible to do so.

Patients approached for participation in the enhanced data collection study activities will be provided with a (PIS) (Document 9) and given time to read it fully. A suitably trained and authorised individual will discuss the study with the patient. The patient's capacity to understand the information provided will be assessed during this discussion. The capacity assessment process will include the provision of study information in a way that is suitable and accessible to the potential participant's level of understanding. In order to assess capacity, the assessor should determine that the person has understood and retained that information by asking questions about the study and activities participants will be asked to undertake.

All questions will be addressed by suitably trained site staff and if the participant is willing to participate and understands what is required, written (or, if required, virtual) informed consent will be obtained. During the consent process it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the study, at any time and for any reason, without incurring any penalty or affecting their treatment.

Patients admitted to hospital wards may regain capacity as the reason for their admission improves. Should a patient subsequently regain capacity during their stay on the ward, attempt(s) will be made to obtain their consent to complete the study activities.

However, should a suitably trained and authorised delegate assess a patient as unlikely to regain capacity an attempt will be made to identify a friend or relative who may know the patient's wishes to act as personal consultee and if identified, two attempts made on separate occasions, to contact the personal consultee. If a suitable personal consultee cannot be contacted, for patients who are identified as being discharged to a care home, a professional consultee will be identified from whom assent can be sought. To be included in the enhanced data collection part of the study, patients without capacity must have a personal or professional consultee who is able and willing to provide advice and assent on their behalf (Document 11, 12).

Consent/assent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the PIS and the participant/consultee will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use.

6.4.3.2 Recruitment to Process Evaluations

For patient participants providing informed consent, at the time of consent into the CHARMER definitive study for completion of activities for enhanced data collection, patient participants will be asked to consent to participating in an interview study (Document 10). Those who provide consent may be contacted by the CHARMER process evaluation team to arrange an interview. Only patients recruited in the second enhanced data collection month (post-intervention implementation) will be contacted to be interviewed (or to provide written feedback if preferred).

Consultees will be approached to express interest in participating in an interview (Document 11, 12). Those who consent may be contacted by the CHARMER process evaluation team to arrange an interview (Document 13). Those who do not provide informed consent will not be able to take part in any interviews. Only consultees recruited in the second enhanced data collection month (post-intervention implementation) will be contacted to be interviewed.

6.5 Screening Procedures

Staff Participants:

Written informed consent to enter the study will be obtained from practitioner (geriatrician and pharmacist) participants (Document 24) for staff participants involved in the process evaluation at all sites. This will take place only after explanation of the aims, methods, benefits, and potential hazards of the study and **BEFORE** any study-specific procedures.

Patients:

All patients receiving care on the study ward(s) and under the care of participating geriatrician(s) during the study will be enrolled in the study cohort. All patients enrolled will be given an opt-out leaflet (Document 08) explaining how their data will be collected without consent and how they can opt-out of this if they wish. Written (or if required, virtual) informed consent (Document 10) (or consultee assent (Document 14)) for enhanced data collection activities will be obtained from patient participants or their consultees (if appropriate), after explanation of the aims, methods, benefits, and potential hazards of the study and **BEFORE** any enhanced data collection study procedures.

6.5.1 Concomitant Care

All patients will receive treatment as usual in addition to any PDx initiated by the Practitioner through participation in CHARMER.

6.5.2 The Intervention

The CompreHensive geriAtRician-led Medication Review (CHARMER) intervention comprises six Behaviour Change Techniques (BCTs) designed to address geriatricians' and pharmacists' five barriers and one enabler to PDx. Health Innovation East (HIE) will work with participating sites to help implement the CHARMER intervention. They will meet with sites weekly during this phase to solve any ongoing issues with implementation and gather data ahead of the intervention phase. The six *BCTs* have been operationalised into the following five components of the intervention:

Component 1: Hospital action plan for proactive deprescribing

The CHARMER team have produced a guide for sites to use to plan the implementation of the other four components of the intervention. The project manager will complete a form to describe how the

implementation will happen and organise a launch of the action plan that describes the focus on PDx at the hospital, and this will be recorded and provided to the CHARMER team.

Component 2: Pharmacist workshop

This up to one-hour workshop comprises activities to encourage pharmacists to consider the pros and cons of proactive deprescribing. The role of the project manager/PI is to organise and facilitate the workshop(s), which can be delivered online (e.g. via Teams) or face-to-face up to four weeks before the intervention start date. The workshop(s) can be integrated into an existing (e.g. lunch time learning session) or new in-person or virtual meeting. The workshop will be recorded by the project manager and the recording provided to the CHARMER team.

Component 3: Weekly pharmacist and geriatrician proactive deprescribing briefing

This component comprises a weekly in-person briefing between pharmacists and geriatricians to discuss proactive deprescribing proposals. The role of the intervention delivery team is to reconfigure pharmacists' working patterns/tasks and reach a mutually agreeable time for pharmacists and geriatricians to attend a weekly briefing.

Component 4: Videos of geriatricians navigating deprescribing consultations

This video highlights geriatricians successfully navigating challenging deprescribing consultations. The role of the intervention delivery team is to organise a meeting in which all geriatricians at the hospital can watch and discuss the video. The video and discussion can be integrated into an existing (e.g., lunch time learning session) or new in-person or virtual meeting up to four weeks before the intervention start date. The session will be recorded by the project manager and provided to the CHARMER team.

Component 5: Benchmarking reports on proactive deprescribing activities

Weekly reports on proactive deprescribing activities allow hospitals to monitor and benchmark their progress with other hospitals.

6.6 Protocol Intervention Discontinuation

Sites will confirm willingness to participate in the study.

Site Withdrawal

Hospitals will be able to withdraw from the study at any time. If a hospital chooses to withdraw from the study, all data collected up until the point of withdrawal will be retained and routine data will still be requested for patients included up to this point from NHS England. Should a site randomised to Steps 1 to 4 withdraw completely, a reserve site collecting baseline data will be approached and randomly allocated to switch to a subsequent intervention step. Should a site randomised to receive intervention withdraw from the intervention but wish to remain in the study, this would be permitted. In this scenario, a reserve site collecting baseline data will be approached and randomly allocated to switch at a subsequent intervention step.

Recruited practitioners will be advised of site withdrawal; however, due to the nature of the CHARMER intervention, it would not be possible to reverse any practitioner PDx behaviour change arising from exposure to the CHARMER intervention.

Practitioner Withdrawal

Participating practitioners will be free to withdraw from the study at any time, without providing a reason, by informing a member of the research team. If practitioner participants choose to withdraw during the study, any data they have already contributed as participants will continue to be used. Potential participants will be fully informed of this eventuality in the PIS.

If it is feasible to do so and the study can progress as planned, we will work with the relevant Principal Investigator to recruit a replacement practitioner if one withdraws. If this is not possible e.g., study is nearing completion, we will continue the study with the remaining practitioners.

Patient Withdrawal

All patients under the care of a participating geriatrician on the study ward(s) during the active study window will have routine clinical data collected from the site and linked to health-related datasets held by NHS England subject to section 251 approval from the Confidentiality Advisory Group (CAG). All patients retain the right to opt out of their data being used for research and any patients who have already opted out using the National Data Opt Out will be excluded from the data collection. All data collected up to the point of data opt out will be retained.

Patients may consent (or a consultee may provide advice if the patient is assessed as not having capacity to provide informed consent) to provide responses to patient reported outcomes (PROMS) at baseline and at follow-up, to data collection from the patient's GP to data linkage of PROMS and GP held data to routine data collected from site and data held by NHS England and/or to follow up interview. As participation in the study is entirely voluntary, the participant (or their consultee if relevant) may choose to discontinue completing the questionnaires at any time without this affecting their current or future care. Although not obliged to give a reason for discontinuing to complete the questionnaires, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights. All data collected up to the point of withdrawal from the study will be retained.

6.6.1 Loss to Follow-Up

Practitioners

As Practitioners are employed by the participating sites, it is not anticipated that significant loss to follow-up will occur. Should staff changes occur during the intervention period, if feasible, a suitably qualified practitioner replacement will be approached for consent to take part in the study.

Patients

Due to the short duration of the follow-up period, 3 months (90 days) following discharge, the likelihood of drop-out is minimal. However, as participants will be followed up in the community post discharge, there is a potential for loss to follow-up. Participants who agree to complete the study questionnaires will be asked to provide contact information to which they can be contacted at 3 months follow-up time point – telephone, postal address and/or email. Patients who do not respond to contact requests to complete follow-up questionnaires by phone will be considered as lost to follow-up for the purposes of questionnaire completion. However, clinical data will still be collected from patient records. Data will be retained for analysis.

6.7 Outcomes/Evaluation

The outcomes have been selected following feasibility testing and are in line with our revised logic model (Document 39).

6.7.1 Evaluation of Trial Design

6.7.1.2 Outcome Measures

The CHARMER intervention is targeting practitioners to facilitate them in delivering proactive deprescribing, therefore any intervention effects will be experienced by all patients under the care of intervention practitioners. Routine hospital data as outlined in tables A, B and C will therefore be collected for all patients on study wards to evaluate the effects of the practitioner behaviour change intervention on patient care.

From our feasibility study findings, we estimate that 10% of patients on study wards or consultees will provide written (or, if required, virtual), informed consent for additional patient reported outcome data. Consent will be sought by research nurses or members of the healthcare team with the relevant training in obtaining informed consent for research purposes. Any patients deemed inappropriate by the healthcare team such as those lacking capacity or near end of life will not be approached.

Tables A, B and C provide the outcomes to be collected, how they will be collected and when they will be collected.

Enhanced data collection window: 6-week period occurring once during the control phase and once during the intervention phase where additional, detailed data collection will take place including any medicines stopped in hospital.

Follow up study window: Period during which no new patients may enter the study cohort, ongoing data collection for all patients already in the study cohort.

Table A Patient orientated outcomes to be collected:

Outcome Definition	**Data source/measure**	**Frequency of collection**	**Method of collection**
All Patients on study ward(s) during the study			
Mortality* The death of a patient for any reason	Death certificate data from the ONS	Once at the end of the study	Routine hospital data
Number of Hospital Stays* The number of planned and unplanned admissions and re-admissions to hospital for treatment or monitoring health.	HES Admitted Patient Care dataset from NHS England	Once at the end of the study	Routine hospital data
Patients providing consent/Consultee assent to additional study data collection			
Satisfaction with deprescribing process (Document 16, 17)	An11-item questionnaire capturing satisfaction with the procedures associated with any medicines that may have been stopped	Once, before discharge (for patients who have had a medicine stopped in hospital) in the end of the second	Patient/consultee reported. Undertaken with a research nurse/suitably trained member of the healthcare team at the bedside pre-discharge

	during the hospital stay.	enhanced data collection period	
Medication related adverse events (Document 18)	A 19-item questionnaire to capture presence or absence of symptoms and primary care resource use in the one month prior to assessment.	Once at 90 days (+/- 2 weeks)post discharge	Patient/ Carer reported. Undertaken with a research nurse/suitably trained member of the healthcare team by telephone at 12 weeks post-discharge or via post.
Health related Quality of Life (Document 19)	Questionnaires – EQ-5D-5L	Twice – at discharge **and** at 90 days (+/- 2 weeks) post discharge	Patient or consultee reported. Undertaken with a research nurse/suitably trained member of the healthcare team at the bedside pre-discharge and by telephone/post at 12 weeks post-discharge.

Table B Process outcomes to be collected

Outcome Definition	**Method(s) of collection**	**Frequency and time point of collection**	**Routinely collected or patient/consultee reported**

All Patients on study ward(s) during enhanced data collection study window (Document 4)			
Number of regularly prescribed medicines on leaving the study ward(s) The number of medicines that a patient has been prescribed for regular use when discharged from hospital.	Site Medical Record	Once, at the point of discharge	Routine hospital data
Number of prescribed medicines for when required use on leaving the study ward(s) The number of medicines that a patient has been prescribed for when required use when discharged from hospital.	Site Medical Record	Once, at the point of discharge	Routine hospital data
Number of prescribed medicines that are stopped The number of medicines that have been discontinued during study window AND while patient is on study ward(s)	Site Medical Record	Once, at the point of discharge	Routine hospital data
Number of prescribed medicines with dosage reduced The number of medicines which have had the dosage reduced during study window AND while patient is on study ward(s)	Site Medical Record	Once, at the point of discharge	Routine hospital data

Number of stopped medicines that are re-started The number of medicines that were discontinued during study window AND while patient is on study ward(s) that are subsequently restarted during follow up	Community pharmacy dispensed medicines submitted to NHSBSA, dataset from NHS England	Once at 90 days (+/- 2 weeks) post discharge	Routine primary care data

Table C Economic outcomes to be collected

Outcome Definition	**Method(s) of collection**	**Frequency of collection**	**Routinely collected or patient/consultee reported**
All Patients on study ward(s) during study			
Length of hospital stay for index admission Number of admissions, A&E, and outpatient attendances in follow-up period	Site Medical Record Routine data	At discharge from hospital End of study	Routine hospital data NHS England
Cost/resource use for intervention	Fidelity framework/expert-opinion/study records	During active study periods	Collected as part of study.
Patients providing consent/Consultee assent to additional study data collection			
Number of Primary Care Consultations The number of consultations with General Practitioners or Practice Nurse for treatment or monitoring health	Telephone questionnaire for subset of patients providing consent	Once at 90 days (+/- 2 weeks) post discharge	Patient/consultee reported

EQ-5D-5L	Baseline face-to-face, telephone at 90 days (+/- 2 weeks)	Twice, baseline and 90 days (+/- 2 weeks)	

6.7.1.3 Data Regarding Study Procedures

Quantitative

We will characterise participating hospitals in terms of their infrastructure pertaining to medicines management and the care of older adults by asking PIs to complete a hospital site profile questionnaire to capture the following at all sites at the study start and following implementation of the CHARMER intervention (Document 3):

- IT maturity
- Any medicines optimisation initiatives implemented in the hospital in the previous five years or planned for implementation within the next two years.
- Number and total FTE of geriatricians and pharmacists
- Number and total FTE of geriatricians and pharmacists providing a service on medicine for older people's wards
- Number and total FTE of research staff with a remit to support ageing research at each site

To characterise recruited practitioners at sites, we will collect the following information using an electronic practitioner demographics questionnaire: professional group, age, gender, ethnicity, years in practice and job role. We will also ask recruited practitioners to document any previous education or training relevant to proactive deprescribing.

To characterise the patient population on study wards during the definitive study, site staff will collect information for all patients on study wards during the study in an Enrolment Log. This will capture the following information: age, sex, ethnicity, admission date, discharge date, and death during admission if applicable. A subset of patients on the study ward during both the control and intervention phases of the study will also have details of medicine on admission and discharge from the study ward captured.

Qualitative data collection for trial evaluation

We will ask research and development staff to complete a short (5 minute) questionnaire (Document 38) after capacity and capability has been confirmed at the site, to understand what went well with approval processes, which parts of the process took the most time.

To understand trial processes and any recruitment variation we will undertake 30-minute interviews with ageing specialty research staff (research nurses). We will aim to interview ageing speciality research staff (up to one per hospital for up to 30 minutes) (Document 32) to understand their experiences of the CHARMER trial in terms of set up and recruitment.

6.7.1.4 Data Analysis

The purpose of quantitative data analysis is to determine whether the desired impact on the primary outcome measure was achieved and to describe the effect on secondary outcome measures. We will additionally describe activity achieved within the intervention and control arms to inform the process evaluation. For analysis of qualitative data please see Section 6.8.

Characterising and Comparing Sites

We will characterise the participating hospitals and practitioners using descriptive statistics for data from the hospital site profile questionnaire (Document 3) and practitioner participant data collection form (Document 4). We will visually compare these data with data captured from NHS Improvement's hospital provider level benchmarking tool 'model hospital' regarding the number and cost of staff on medicine for older people's medicine wards. We will visually compare the demographic characteristics of patients between all study wards of the participating hospitals to explore whether they are comparable. We will also explore the completeness of data collection at each site and how data was captured at sites. For the sample of patients in the study cohort from whom consent is obtained either from the patient or consultee for additional non-routine data to be collected, we will visually compare the demographic characteristics of this group with the wider study cohort. This will establish whether the sub-set of patients for whom additional data are collected, are a good representation of the patient cohort in the study. We will explore reasons for any identified differences with the hospital research team and discuss with the CHARMER team PPI members, strategies for addressing any differences.

Evaluating Outcomes

We will calculate the proportion of patients for whom outcome data are available at all data collection time points and the completeness of these data.

6.7.2 Process Evaluation

We will follow the UK Medical Research Council guidance for designing and conducting process evaluations of complex interventions [23, 24, 25, 26] to describe implementation of the CHARMER intervention in the trial. We will undertake the process evaluation using a range of techniques including collection of quantitative data, focused video-based ethnography, and semi-structured interviews with key stakeholders for each site. This will be informed by our fidelity framework.

6.7.2.1 Quantitative Data

We will collect data as per the fidelity framework developed in the feasibility study. This will be in undertaken in all sites by the project manager or PI completing a short checklist about the implementation of the intervention including:

- Duration of the pharmacist workshops at each site, and whether it is delivered as intended

- Frequency and average duration of pharmacist/geriatrician PDx briefings during the intervention period, and who attended
- Number of times the geriatrician videos are viewed
- Structure and planning of action plan to implement the other components of the intervention and whether this is adhered to
- Number of times the benchmarking reports are viewed, and by whom, and timing.

Quality and completeness of all other planned data collection will be reviewed by the research team.

Questionnaires

We will use the Mechanism of Action questionnaire (Document 27) planned to model the intervention's mechanisms of action. We will ask all participating practitioners to complete the questionnaire at baseline and then again after receiving the intervention package. This will enable identification of any targeted barriers/enabler that the intervention failed to address and help explain how the intervention works (or does not work) in changing PDx.

We will also use a Practitioner Deprescribing Process Questionnaire (Document 28) that we will ask all participating practitioners to complete.

We will also ask the project manager at each site to complete a short survey to identify common barriers and enablers for successful implementation of the intervention. This will help us understand whether the intervention can be continued beyond the trial context and implemented more widely.

6.7.2.2 Qualitative Data

We will explore the following:

- The theory of the intervention to see whether it impacts PDx and how it does this
- How the intervention is implemented and whether sites make any adaptations to enhance the intervention's effectiveness
- The fidelity of the intervention (quality and consistency of delivery of the intervention)
- How much of the intervention was delivered (dose)
- Reasons recorded in practitioner notes for not transitioning from a PDx proposal
- Whether the intervention reached the target audience (reach)
- The context the intervention was delivered in, considering system-level and individual-level contextual factors that either hinder or support delivery of the intervention
- The acceptability of the intervention to all stakeholders
- Factors that influence the extent to which the intervention addresses the barriers and enabler to PDx
- The perceived effectiveness of intervention components from patient, consultee, pharmacist, and physician perspectives
- Barriers and enablers to the intervention package being continued beyond the trial context and implemented in other hospitals

6.7.2.2.2 Video Recordings of Intervention Team and Practitioners

We will view recordings of implementation of some of the intervention components at each site to evaluate intervention delivery for both the intervention delivery team, and geriatricians and pharmacists. We will follow guidance on using focused ethnography within health care settings [27, 28] to understand how the CHARMER intervention is implemented in the context of sites.

The project manager at each site will arrange for the following activities to be audio-visually recorded: pharmacist workshop, geriatrician video huddle, and action plan launch. An experienced qualitative researcher from the CHARMER team will view the intervention recordings in terms of how the event was delivered and whether it was delivered as intended. We will also observe how geriatricians and pharmacists engage with the intervention components. The researcher will make detailed notes about how the intervention was delivered at each site to assess the fidelity of the training delivery. We will record structured and detailed field notes based on the intervention fidelity framework for analysis, with analysis beginning as soon as data has been collected. Detailed descriptions of the site settings, activities, communication, body language, barriers, and facilitators within the study setting, will be noted, aiming to identify similarities and differences at each site and how this influences intervention delivery. These descriptions can also be used to focus interviews after the intervention period to explore particular aspects of intervention delivery that were noted during the observations. A thick description will seek to interpret and explore the impact of behaviours and context on the outcomes of the intervention.

6.7.2.2.3 Interviews with PIs, Project Managers, Practitioners, Health Innovation East, Patients and Consultees

We will undertake semi-structured interviews with key stakeholders to explore the intervention delivery, receipt, and impact of the PDx intervention (Document 5).

PI/Project Manager Interviews

We will aim to schedule interviews with either the PI or project manager at all sites, depending on who was most involved in the implementation activities. We will undertake interviews for up to 60 minutes aiming to explore how the intervention was implemented and whether the components were delivered, and any adaptations of the intervention and why these were made. We will be flexible in timing of the interviews, and these will be conducted by telephone or online, shortly after the implementation of intervention components has been completed at each site, to ensure that members can recall detail about the delivery. Topic guides have been developed to structure the interviews and ensure we can explore key aspects of intervention delivery and receipt.

Practitioner Interviews

We aim to interview a sample of participating geriatricians and pharmacists (40-60 in total across sites) for up to 60 minutes by telephone, or via an online platform such as Microsoft Teams.

The baseline Mechanism of Action (MoA) responses will be used to identify geriatricians and pharmacists who have reported at least one barrier to proactive deprescribing that the CHARMER intervention is aiming to address. Of these we will identify participants who, after CHARMER exposure, reported that the barrier(s) to proactive deprescribing were addressed, and some who did not appear to have their barrier(s) addressed by CHARMER, by using the follow-up post intervention MoA responses. This will allow us to sample a range of participants reflecting both impact and no impact of the CHARMER intervention to better understand why and how the intervention has acted on practitioners.

We will ask participating practitioners about their thoughts on the acceptability of the intervention and how it was delivered, as well as their experiences of having conversations with patients about their medicines and any resultant PDx activities. We will also explore the perceived efficacy of each BCT and their operationalisation as an intervention package, and any adaptations of the intervention that were made at sites. We will ask questions to determine any contextual information at sites that either hindered or enhanced the success of the intervention to increase PDx. We will seek to understand any unintended consequences of the intervention. We will explore whether patient or consultee awareness of the PDx intervention had any impacts such as patients requesting PDx discussion or asking whether their practitioner had received the training. We will also seek comments for refinement as necessary.

Patient and Consultee Interviews/Written Feedback

We will seek feedback on the PDx experience from a sample of patients and consultees. We will purposively recruit 20-30 patients and consultees using maximum variation sampling, aiming to achieve variation in age, location (site), sex, ethnicity, number of medicine(s) stopped whilst in hospital and types of medicines they are/were prescribed. Based on learnings from the feasibility study, we will offer patients and consultees the following options of how they provide this feedback: via either a telephone or online (e.g. Microsoft Teams, Zoom) interview, or completion of written feedback by completing a hard copy form with reply paid envelope provided, or completing the form online, received via email. We will contact patients and consultees within 1 week after the patient has been discharged from hospital to either arrange an interview or post the form to them, to ensure that the discussion about their hospital stay is timely/recent and they can recall what happened during their stay. We will aim to seek feedback from patients and consultees at two time points, 1-2 weeks after hospital discharge and 3 months later to seek their feedback on how their medicine changes in hospital have been managed by primary care.

For interviews, experienced qualitative researchers will undertake these by telephone with patients and consultees who have consented to take part in an interview. We will use semi-structured interviews to explore patients' and consultees' experience of study participation including their experience of the service received as a result of the practitioner PDx intervention. We will specifically ask participants questions about their views on the acceptability of their PDx experience including how they experienced any conversations about PDx and their experiences about how their medicines were

managed whilst in hospital. We will also specifically ask for details of any adverse outcomes thought to be associated with the service. Where PDx has occurred, we will also explore whether the PDx decisions have been implemented by primary care after the patient's discharge from hospital.

To enable the discussion of PDx decision by primary care we will ask these patients and consultees to have a second interview or complete a second form approximately 2-3 months after their discharge from hospital. We will specifically ask patients and consultees about their experience since the first interview/form completion. We will not seek to discuss the hospital admission but will focus on their experiences of how their medicines have been managed by primary care since hospital discharge. This will include asking whether the decisions made in hospital are maintained, and if not, what the reasons for this are. We will ask patients and consultees about any appointments they have had with their primary care team and how their experience of these has been and how their medicines have been managed.

Primary Care Stakeholders

We will seek to interview a sample of primary care stakeholders with a prescribing role who have a patient within the definitive study (Document 5). This will include between 10-15 primary care stakeholders (GPs, Primary Care Network or GP practice pharmacists, and nurses with prescribing roles), to explore what happens after the patient is discharged from hospital. We will explore the primary care stakeholders' experiences, whether any PDx decisions are implemented by primary care and whether there are any unintended consequences of PDx. Interviews will be offered by telephone or online platform such as Teams and will last up to 30 minutes; focus groups will be online and up to 60 minutes.

Health Innovation East

Health Innovation East (HIE) are an organisation that provide support to sites in the implementation phase of CHARMER. HIE staff routinely meet with staff participating in CHARMER throughout the three-month implementation phase. We will invite HIE staff to participate in an interview at the end of each intervention implementation phase (four interviews in total), for up to 60 minutes each, by telephone or via an online platform such as Microsoft Teams. HIE staff will be provided with a participant information sheet offering detailed information about the study and what is involved in participation (Document 40). Those who express an interest in participation will be asked to complete an online consent form (Document 41) to participate in an interview. We will ask participating HIE staff about their experience of having conversations with staff about CHARMER. We will ask questions to determine any contextual information about sites that either hindered or enhanced the success of the implementation of the intervention. A topic guide (Document 05) has been developed to structure the interviews and ensure we can explore key aspects of implementation of the intervention.

Table D Process Evaluation Summary:

Component	**Exploring**	**Data collection/ method of assessing**	**Participants/ sites**
Intervention dose (amount of the intervention delivered and received) and fidelity (quality and consistency of delivery of the intervention)	• Was the planned intervention fully delivered? If not, why? • Which intervention components were delivered? • Was sufficient time provided for the intervention to be fully delivered? • Quality of facilitation (where relevant)? • Did all participating practitioners receive all relevant components of the intervention as intended? **Component-specific:** • How were benchmarking reports received (mode and timing) and were they accessed? • Content (of benchmarking reports) in terms of data quality and number of hospitals?	**Recordings** of intervention implementation **Interviews** **Quantitative** metrics of engagement with intervention content e.g., number of times intervention videos viewed	Recordings at **all sites** during implementation period of: • Pharmacist workshop • Geriatrician videos • Action plan launch PI or project manager (dependent on who took more of a role in implementation) Participating practitioners (at a sample of sites).

	• Existing pharmacist and geriatrician relationships and working patterns? (briefings) • Experience levels of geriatricians and pharmacists?	**Checklists (implementation; post-implementation)**	All sites.
Intervention reach (the extent to which the target audience comes into contact with the intervention) and maintenance	• Did all participating practitioners take part in the relevant intervention components? If not, why? • How many relevant intervention components were received by participating practitioners (i.e. did pharmacist receive all intended components)? • Is the intervention maintained over time?	**Interviews** **Recordings** of intervention implementation **Quantitative** metrics of engagement with intervention content e.g., who engages with the intervention dashboard; number of briefings held; **Checklists (implementation; post-implementation)**	PI or project manager (dependent on who took more of a role in implementation) Participating Practitioners (sample) All sites Data obtained by UEA data team (dashboard access) Capture details on implementation activities and also maintenance of intervention

Adaptations of the intervention	• Did sites make any adaptations to the intervention to assist its delivery? If, yes what were the adaptations? • Why were the adaptations made? • How did adaptations impact the intervention?	**Recordings of implementation** **Interviews**	Recordings at **all sites** during implementation period of: • Pharmacist workshop • Geriatrician videos • Action plan launch PIs or project manager Participating Practitioners (sample)
Deprescribing experience	• Was the intervention acceptable (to all stakeholders)? • Were there elements of the intervention for practitioners that were more difficult? • Were practitioners engaged with the intervention or only certain components of the intervention? • Did patients find their medicine management in hospital acceptable? • How many patients had medicines stopped and how many had discussions?	**Recordings** of intervention implementation	Recordings at **all sites** during implementation period of: • Pharmacist workshop • Geriatrician videos • Action plan launch

	• How did participating practitioners find the experience of proactive deprescribing after receiving the intervention? • How did primary care prescribing stakeholders find the process of managing patients' medicines after discharge (including communication between hospital and primary care)?	**Interviews** **Patient/consultee satisfaction with deprescribing questionnaire**	PIs or project manager Participating Practitioners Patients – how they experienced deprescribing and other medicines management in hospital etc. (interview or form) Consultees (interview or form) Primary care stakeholders (with participating patients discharged from participating wards). Patients/consultees during active data collection period
Unintended consequences of intervention	• Were there any unexpected consequences as a result of the intervention? If so, what were these and why/how did they happen?	**Interviews**	PIs Participating Practitioners (sample) Patients how did they experience med management in hospital etc. (interview or form)

			Consultees (interview or form) Primary care stakeholders (with patients discharged from participating wards)
Explore theory of intervention and how it impacts proactive deprescribing behaviour	• Did the intervention exert its effects via the intended mechanisms of action? • Are there other mechanisms of action? • Are there other barriers that the intervention did not address?	**Mechanism of action questionnaire** **Practitioner deprescribing process questionnaire** **Interviews**	Participating practitioners –all Participating practitioners –all PIs Participating Practitioners (sample)
Contextual factors (individual and/or system level at each site that influenced delivery of the intervention; e.g., organisational, cultural, technological,	• Were there any intervention delivery team factors (e.g., skills, enthusiasm, organisation) that impacted the intervention? • How did participating Practitioners feel about proactive deprescribing? • Were there systems in place that hindered or supported proactive deprescribing (e.g. electronic vs paper-based records; size of hospital/ward; staffing models)?	**Quantitative data (mediation analysis)** • number and FTE of staff– geriatricians, pharmacists (both in the Older People's Medicine speciality and overall); ageing speciality research staff; intervention delivery team • demographic data for Practitioners at each site	All sites – site profile questionnaire and practitioner demographics questionnaire

physical contextual factors.)	• Were the participants different at each site (participating Practitioners, patients etc)? • Were there any events or initiatives at the site that had an impact on the intervention? • Level of management/ organisational support for geriatricians and pharmacists to participate in CHARMER? • Patient population at sites (e.g. frailty) • PI characteristics (presence on study ward, engagement, enthusiasm, professional role).	(professional group, age, gender, years in practice and job role). • any previous education or training relevant to proactive deprescribing) for all recruited Practitioners • any medicines optimisation initiatives implemented in the hospital in the previous five years or planned for implementation within the next two years • IT maturity of site • demographic details of patients and consultees to see if any variation between sites **Recordings** of intervention implementation	Recordings at all sites during implementation period of: •Pharmacist workshop •Geriatrician videos •Action plan launch

		Interviews **Site survey to explore barriers and enablers**	PI or project manager (dependent on who took more of a role in implementation) Participating practitioners (sample). Patients – how did they experience their medicine management in hospital etc Consultees Health Innovation East
Contamination effects	• Did awareness of the intervention have unintended impacts? For example, did patients during the control/baseline period request more proactive deprescribing discussions/medication reviews because they were aware of the trial? • *Did practitioners change their behaviour during the baseline period because of awareness of the proactive deprescribing intervention being implemented at other sites?*	**Interviews**	PIs Patients and consultees (interview or form)

6.8 Data Collection and Analysis for all Qualitative Data (Process Evaluations)

All interviews will be digitally recorded, transcribed verbatim by a UoL approved transcriber and pseudonymised, with each participant allocated a Participant ID. Transcripts and observation field notes will be analysed using framework analysis [29] supported by NVivo software [30]. This will involve reading transcripts, and field notes several times to enable familiarisation with the data; we will use codes refined from the feasibility study as well as adding codes inductively as the analysis progresses. Themes will be refined through discussion with the wider team. We will also use Co-Pilot, an artificial intelligence (AI) software as a team member to provide another perspective on data analysis. We will use several test transcripts to see how Co-Pilot performs and aligns with other team members' coding. We will document any discrepancies between AI and human coding to refine the process. Co-Pilot is secure and University of Leicester approved for analysis and covered by institutional and MS365 data protection agreements.

Once this has been completed, we will also map codes to the Theoretical Domains Framework (TDF) and the Normalisation Process Theory (NPT) framework to understand barriers and enablers of implementing the CHARMER intervention.

We will triangulate the Mechanism of Action questionnaire (Document 27) and Practitioner deprescribing process questionnaire (Document 28) findings with the interviews, observation notes and fidelity data to understand the impact of the intervention on PDx. We will use the data to identify any moderators of intervention fidelity e.g., poor engagement from geriatricians or pharmacists during the briefings.

6.8.1 Evaluate Mechanism of Action

We will ask participating geriatricians and pharmacists to evaluate the extent to which the key behavioural determinants were addressed by the intervention using the Mechanism of Action questionnaire (Document 27) developed in WP2. Within this we will additionally ask them in interviews to describe any local changes they introduced to overcome context specific barriers (adaptations) and any which were used to enhance the effectiveness of the CHARMER intervention.

6.9 Participant Assessments and Timeline

6.9.1 Practitioner Participant Assessments

Practitioners providing informed consent for the study will be requested to complete the following assessments:

Demographics questionnaire – (Document 26)

This will include gender, age at consent date, ethnicity, occupational group, job role, years in role, previous training, or education relevant to proactive deprescribing and an email address for direct communication during the study.

Mechanism of Action questionnaire (Document 27)

The Mechanism of Action Questionnaire was tested in CHARMER WP3. This questionnaire aims to assess the extent to which the intervention acts via the intended mechanisms of action and facilitates PDx. We will ask all participating practitioners to complete the questionnaire at baseline and then again after receiving the intervention package. This will enable identification of any targeted barriers/enabler that the intervention failed to address.

Practitioner PDx process questionnaire (Document 28)

We will ask all participating practitioners to complete the practitioner deprescribing process questionnaire at baseline and then again after receiving the intervention package. This will explore the processes that practitioners undertake when proactively deprescribing for older people in hospital.

Patient Participant Assessments

Patients providing informed consent or Consultees providing assent on a patient's behalf will be requested to complete the following questionnaire assessments:

EQ-5D-5L (Document 19) (EuroQol five dimension, 5 level questionnaire [17]) is a validated health related quality of life questionnaire. The measure comprises five questions or dimensions: Mobility, Self-Care, Usual Activities, Pain/discomfort and Anxiety/Depression and a visual analogue scale (0 to 100), which is used as a quantitative measure of overall health status.

Satisfaction with Deprescribing Questionnaire (Document 16-17) is a bespoke designed 11 item questionnaire to capture patient satisfaction with the procedures associated with any medicines that may have been stopped during the hospital stay. This will be collected from patients who have provided informed consent/consultee assent during the second enhanced data collection period (post-intervention implementation) and who have had a medicine stopped only. This will be collected prior to hospital discharge.

Adverse Drug Event Questionnaire (Document 18) is a bespoke designed 19 item questionnaire to capture patient reported symptoms over a 1-month period adapted from Schoenmakers et al (2017) [31].

6.9.2 Participant Routine Data

Routine data collected as part of the patient's inpatient stay will be collected from site health records for all patients. This will include:

Age, sex, ethnicity, admission date, discharge date, and death during admission if applicable (Document 4). Routine data (prescriptions in primary care, secondary care resource use and mortality

records) held by NHS England will be collected at end of the follow up period (3 months post discharge) using data linkage (subject to section 251 approval from the Confidentiality Advisory Group, participant informed consent or consultee assent).

For a 6-week period during the control phase and a 6-week period during the intervention phase at each site additional data will be captured for all patients receiving care from a geriatrician on the study ward during that time. The additional routine data collected for these patients will include medicines on admission and at discharge, deprescribing taking place during their stay on the study ward, usual place of residence and reason for admission.

Timelines are shown for study activities described - hospital and Practitioner activities in Table E, and for patient activities in table F.

Table E Hospital and Practitioner Activities

Hospitals/Staff	Study period						
Study Timepoint	Control Phase (3 -15 months)			Intervention Implementation (3 months)	Intervention Phase (3-15 months)		End of Study
Site Profile Questionnaire	x				x		
Consent of Geriatricians and Pharmacists	x						
Mechanism of Action/Process of Deprescribing Questionnaire				x	x		
Intervention implementation/training for geriatricians and pharmacists				x			
Intervention Delivery					x	x	x
Observations				x			
Interviews (PI, project manager)				x			x
Interviews (geriatricians, pharmacists)					x		x
Interviews (primary care)					x	x	x

Interviews (Health Innovation East)				x				

Table F Patient Activities

Patients	Study Period		
Study Timepoint	Entire study (21 months)	Enhanced data collection window (3 months)	Follow-up study window (3 months after hospital discharge)
Consent		X	
EQ-5D-5L		X	X*
Satisfaction with Deprescribing Questionnaire		X**	
Adverse drug events questionnaire			X*
Secondary Care Routine data collected from patient notes	X	X	
NHS England held HES, Mortality, Prescription data Collection			X
Telephone or online interviews/feedback form			X**
Patient reported Primary Care service use			X

*Completed by completing form by telephone or via post **Completed only by a sample of patients recruited during second enhanced data collection window

6.9.3 Study Closure

The end of the study is defined as 3 months following receipt of data held by NHS England linked to Study collected data and anonymised, to allow for data cleaning activities to be completed.

6.10 Sample Size

A stepped wedge design with a baseline step with all hospitals receiving the control followed by four separate steps, each randomising five hospitals to switch from control to intervention would have 89.5% power to detect a difference of 16.7% to 13.7% of three-month re-admission rates assuming a 5% level of significance and an ICC of 0.05 and 200 participants per hospital per step. The total sample size will be 20,000 participants across 20 sites; an additional four sites will be recruited and remain in the baseline phase unless they are required to replace any sites that withdraw during the trial. This is similar, but slightly smaller, to the difference seen in the MedSafer study [32].

For the enhanced data collection period where medication changes are recorded in hospital then if the sites collect data on 60 participants in a one month period within the control phase and a one month period within the intervention then the study would have 99.99% power to detect an average change of 0.5 medications between the control and intervention phase, assuming a standard deviation of 1.5 medications, a 5% level of significance and a ICC of 0.05.

We will undertake the internal pilot over the first 3 months of the trial at all 24 sites and will evaluate the pilot according to the following criteria to enable the trial to continue beyond the pilot phase:

- An average of 200 patients per hospital enrolled over 3 months (green)
- An average of 150-199 patients per hospital enrolled over 3 months (amber)
- Below an average of 150 patients per hospital enrolled over 3 months (red)

If the above is green, proceed with definitive trial.

If the above is amber proceed with definitive trial if appropriate solutions are identified.

If the above is red, in consultation with the Programme Steering Committee make a decision regarding whether to proceed.

6.11 Data Collection, Management and Analysis

6.11.1 Data Collection Methods

Questionnaire data from Practitioners and Patient Participants, and Routine Data from Sites (Document 2)

Each Practitioner and Patient Participant will be given a unique study Participant Identification Number (PID). Data will be collected at the time-points indicated in the Study Timeline (Table E&F).

The preferred method of data collection is direct online entry of data onto the central database, stored on servers based at NCTU by members of the CHARMER Definitive study team working within each research site. Data may be entered onto paper Case Record Forms (CRFs) prior to entry onto the database (but this is not an essential step). Staff will receive training on data collection and use of the online system.

Data collection, data entry and queries raised by a member of the CHARMER Definitive study team will be conducted in line with the NCTU and study specific Data Management Standard Operating Procedure.

Identification logs, screening logs and enrolment logs will be kept at the study site in a locked cabinet within a secured room.

Participant identifiable data for patients providing consent or consultee assent will be stored on a Participants Database to enable patients to be contacted by site staff or central study team staff for the purpose of contacting participants for completion of questionnaires by telephone; and the central study team for the purpose for sending newsletters during the study. There will be a clear logical separation of participant identifiable data from the study data. Identifiable data for patients who are not approached for consent or consultee assent will be stored at the hospital site only and will not be stored on Norwich CTU servers.

Clinical study team members will receive study protocol training. All data will be handled in accordance with the Data Protection Act 2018.

NHS England held routine data

Outcome data will be obtained from NHS England via the Hospital Episode Statistics Admitted Patient Care, Outpatients, Accident and Emergency, Office of National Statistics Mortality Records and Prescribing Datasets for all patients receiving care on study wards during the active study window unless they opt out. An application for section 251 approval from the Confidentiality Advisory Group (CAG) will be made for the transfer of patient identifiers from each site to a data safe haven approved by NHS England for data linkage, where the patient could not be approached for informed consent prior to discharge. Subject to HRA approval an application via the Data Access Request service (DARS) will be made to NHS England for the named datasets.

Once approved, CHARMER study data containing the Participant PID number will be transferred to NHS England by the CHARMER Data Management team at NCTU.

Patient identifiers requested by NHS England (e.g., NHS Number, Date of Birth, Gender, postcode) will be transferred to the data safe haven at The Norfolk and Norwich University Hospital NHS Foundation Trust (NNUH) from all sites. Subject to a data processing agreement between the site and NNUH, this will be transferred for data linkage to NHS England by NNUH via a secure N3 connection.

The research team at Norwich CTU will not have access to any identifiable information without patient consent.

All identifiers will be removed by NHS England after data linkage and prior to transfer of the data back to NCTU for analysis.

Qualitative Data Collection

Qualitative data collected for the trial and process evaluation is described in section 6.8.

6.11.2 Data Management

Data will be entered under the participant's PID number onto the central database stored on the servers based at NCTU. Access to the database will be via unique, individually assigned usernames and passwords, and only accessible to members of the CHARMER Definitive study team at NCTU, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected physically and environmentally in accordance with University of East Anglia's General Information Security Policy 3 (GISP3: Physical and environmental security).

The database and associated code have been developed by NCTU Data Management, in conjunction with the CHARMER Definitive study team. The database software provides several features to help maintain data quality, including maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the study the database will be retained on the servers of NCTU for on-going analysis of secondary outcomes.

The identification, screening, and enrolment logs, linking participant identifiable data to the pseudonymised ID numbers, will be held locally by the study site. This will either be held in written form in a locked filing cabinet or electronically on secure site systems. After completion of the study the identification, screening and enrolment logs will be stored securely by the sites for 6 years unless otherwise advised by NCTU.

6.11.3 Non-Adherence and Non-Retention

Intervention fidelity will be evaluated during the process evaluation. Should Practitioners trained in the intervention leave during the intervention delivery period, a replacement Practitioner may be recruited to take their place.

In line with usual patient care, participant adherence to prescribed medication is not being evaluated.

6.11.4 Statistical Methods

Internal Pilot

During the initial baseline period of the stepped wedge the number of patients on which re-admission rates would be available will be monitored to assess if the assumptions of the sample size require adjustment.

Main effectiveness analysis

The primary analysis will be using intention-to-treat and we will use a pre-specified statistical analysis plan agreed prior to analysis. Baseline characteristics will be summarised in each arm to check for balance between groups. Analysis will be at the patient level and include data from all patients.

Unplanned readmission at 3 months will be compared between the treatment and control periods using a logistic mixed regression model with hospital included as a random effect, and fixed factors will include randomisation arm and time period. If a significant number have more than one readmission, then a Poisson or Negative binomial model will be used as a secondary analysis. The assumptions of the models will be checked and if appropriate a Generalised Estimating Equation approach will be used if the random effect is not normally distributed, or a non-parametric bootstrap approach will be used if the individual level residuals are not normally distributed. If appropriate, multiple imputation will be used to account for missing data. A sensitivity analysis will adjust for relevant baseline characteristics e.g. QoL, number of pre-admission medicines.

The number of medications stopped in the enhanced period will be compared between the control and intervention using a linear mixed model including hospital as a random effect, and fixed factors will include randomisation arm and time period.

The proportion of patients per arm where a pre-admission medicine is PDx will be compared using logistic regression, the same model as above. It is unlikely that there will be significant missing data for this outcome as it is routinely collected data.

The QoL measures will be compared between the control and intervention using a linear mixed model including hospital as a random effect, and fixed factors will include randomisation arm and time period. If appropriate, we will use imputation to account for missing data.

A full statistical analysis plan (SAP) will be written prior to the start of any data analysis. As the SAP will be more detailed any discrepancies in the analysis between the SAP and the protocol, the SAP will take priority.

Health Economics

We will undertake a within trial economic evaluation from the NHS perspective to estimate whether PDx is cost-effective.

We will include in the evaluation, resources associated with providing the PDX intervention. This would include staff time required for activities such as attending workshops, watching video material, attending briefings, preparing an action plan, and preparing benchmarking reports. We will also investigate the effects that the intervention may have on resource use associated with NHS inpatient admissions in the follow-up period, as well as medicines use. For the consented sub-sample, we will also collect data relating to HRQoL (EQ-5D-5L) and primary care contacts.

Resource use data collection has been informed by lessons learnt from the feasibility study. The occurrence of activities related to the intervention, such as attendance at workshops, will be recorded by means of the fidelity framework conducted as part of the process evaluation. The resource implications of these events will be costed by means of information obtained from the fidelity framework as well as additional insights gained from aspects of the feasibility study, e.g., qualitative work. Where necessary, additional work will be carried out to elicit further information required to cost the intervention. For example, eliciting expert opinion on the typical time required for deprescribing activities.

In terms of NHS resource use we will obtain data from NHS England related to inpatient admissions, A&E, outpatient attendances, and prescribing data. Additionally, data relating to the initial (recruitment) inpatient stay will be obtained from study sites. The feasibility study indicated that primary care related resource use would be difficult to collect by the methods originally planned, namely either interviews with GPs or general practice patient records review, without adding substantially to the burden of the study. For this reason, a bespoke section was added to the drug adverse event questionnaire to collect details of participant primary care use at the 90-day follow-up telephone interview. The proposed questions have been shared with the trial management team and PPI members for comment. This data would be collected from the consented sub-study only. Resources identified will be combined with appropriate unit costs data, e.g., NHS reference costs (11), to estimate the mean overall cost in each study-arm. This will enable an estimate of any differences in the cost of the de-prescribing group compared to usual care.

The primary health economics analysis will be a cost-effectiveness study using the study's primary outcome of re-admissions in the 90-day follow-up period. As part of the study we will collect measures of HRQoL using EQ-5D-5L(3)(5) (4). These will be collected in the consented sub-sample at baseline and at 90 days post-discharge, either by self-report or proxy response. This measure can be used to estimate quality adjusted life years (QALY), enabling the mean difference in QALY scores to be estimated (incremental effect). This will be carried out in the consented sub-sample and will be presented as a sensitivity analysis. As part of the analysis, we will explore whether it is sensible to use these values to impute QALY scores for the whole sample, if carried out this will also be presented as an additional sensitivity analysis.

If the intervention arm is both less expensive e.g., due to lower medication or re-admissions costs, and more effective than usual care in terms of the primary outcome of re-admissions at 90 days then it would be said to dominate usual care and would be the preferred option. If neither the intervention nor the usual care is clearly preferred; we will estimate incremental cost-effectiveness ratios (ICERs) in terms of cost per re-admission prevented(12). The associated level of uncertainty will be characterised by estimating cost-effectiveness acceptability curves (CEACs). Sensitivity analysis will also be undertaken to assess the robustness of results to changes in key assumptions. In line with the outcome analysis, all analyses will be conducted on an intention-to-treat basis. Appropriate actions will be taken where there is missing data, for example imputing data by means of multiple imputation. As part of the health economic analysis a health economics analysis plan (HEAP) will be written, in consultation with the CI and trial statistician and shared with team members.

We will construct a health economic model to explore the effects of long-term changes in prescribing costs and mortality. The exact form of this model will be established in consultation with other

members of the research team, as a clinical input to this process would be vital. A priori, we would expect this to take the form of a Markov model estimating cost per quality adjusted life year.

6.11.4.1 Outcomes

The number of eligible participants will be summarised per month and per site and presented as the median and interquartile range. The reasons for withdrawal/non-participation will be summarised.

The comparison of the recruitment bias will be based by comparing the demographic data of consenters and non-consenters using appropriate summary statistics (e.g., mean, or median) depending on the distribution and type of outcome. No formal hypothesis test will be undertaken but the summary statistics compared informally as it is the size of the potential bias that is important and not the p-value.

The proportion of patients who report each outcome at each timepoint will be summarised per group and overall, with 95% confidence intervals provided. The reasons for missing/incomplete data will be tabulated when known.

The distribution of each outcome measure, and the change in outcome measure, will be assessed using histograms and summary statistics to assess is the outcome has any a) ceiling or floor effects; or b) lack of sensitivity to change, that is the standard deviation of the outcome measure is close to zero.

6.12 Data Monitoring

6.12.1 Data Monitoring Committee

The Programme Steering Committee will act as the Data Monitoring Committee for this trial.

6.12.2 Interim Analyses

No interim analyses are planned.

6.12.3 Data Monitoring for Harm

The outcome variables, deaths and hospital readmissions will be used as safety measures. As the outcome data for death and hospital readmission will be received from NHS England held datasets at the end of the study after last patient has completed the trial, it will not be possible to apply the findings to the intervention during the project. Therefore, no monitoring for harm activities will be undertaken.

6.12.3.1 Adverse Event Reporting

Adverse events (serious or non-serious) will not be collected for this study.

This is a low-risk intervention. Reviewing medications to identify those which could be deprescribed is an activity which is undertaken in routine care. The intervention being evaluated is designed to support and overcome barriers experienced by health professionals to deprescribing in older people's medicine wards but not to direct the decision to deprescribe. The decision regarding whether to proactively deprescribe will remain a clinical decision based on a partnership between the patient,

prescriber and if appropriate, also the carer based on both the clinical picture and individual preference.

6.12.3.2 Incident Reporting

Following deprescribing, it is possible that incidents may occur which may be related to the deprescribing activity. This could include, but not be limited to:

- Complaints from patients/carers in relation to the discussion/decision to deprescribe
- Complaints from primary care professionals in relation to the decision to deprescribe
- Any other incidents which the reporting person thinks may be due to the deprescribing activity.

Patients, carers, and GPs will be provided an email address and a telephone number to which they can report any concerns or incidents (Document 22). New incidents will be reviewed on a weekly basis by a lead clinician, and cumulatively by the Programme Management Group to identify potential commonalities. Incidents will be reported back to the site PI for quality improvement purposes.

6.12.3.2.1 NCTU Responsibilities

NCTU will collate incidents and keep investigators informed of any safety issues that arise during the course of the study.

6.12.4 Quality Assurance and Control

6.12.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the CHARMER Definitive study are based on the standard NCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the study and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on the rights and safety of participants; project concept including study design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the study is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the study related activities are fulfilled.

6.12.4.2 Central Monitoring at NCTU

NCTU staff will review data for errors and missing key data points. The study database will also be programmed to generate reports on errors and error rates. Essential study issues, events, and outputs, including defined key data points, will be detailed in the CHARMER Definitive study Data Management Plan.

6.12.4.3 On-site Monitoring

The frequency, type, and intensity of triggered on-site monitoring will be detailed in the CHARMER Definitive study Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a study site inspection by any regulatory authority, NCTU must be notified as soon as possible. Given the low-risk nature of the intervention, only triggered onsite monitoring will be undertaken.

6.12.4.3.1 Direct Access to Participant Records

Participating investigators must agree to allow study related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other study related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the study.

6.12.4.4 Study Oversight

Study oversight is intended to preserve the integrity of the study by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to study groups; adherence to study interventions and policies to protect participants, including reporting of harms; completeness, accuracy, and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent study oversight complies with the NCTU study oversight policy.

In multi-centre studies this oversight is considered and described both overall and for each recruiting centre by exploring the study dataset or performing site visits as described in the CHARMER Definitive study Quality Management and Monitoring Plan.

6.12.4.4.1 Study Team

The Study Team (SMT) will be set up to assist with developing the design, co-ordination, and day to day operational issues in the management of the study, including budget management. The membership, frequency of meetings, activity (including study conduct and data review) and authority will be covered in the SMT terms of reference.

6.12.4.4.2 Programme/Trial Management Group

A Programme/Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination, and strategic management of the study. The membership, frequency of meetings, activity (including study conduct and data review) and authority will be covered in the TMG terms of reference.

6.12.4.4.3 Independent Programme Steering Committee

The Independent Programme Steering Committee (PSC) is the independent group responsible for oversight of the CHARMER WP4 (Definitive Trial), will take on responsibilities of a Trial Steering Committee in order to safeguard the interests of study participants. The PSC provides advice to the CI, NCTU, the funder and sponsor on all aspects of the study through its independent Chair. The membership, frequency of meetings, activity (including study conduct and data review) and authority will be covered in the PSC terms of reference.

6.12.4.4.5 Study Sponsor

The University of Leicester is the study sponsor. The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the study. The Sponsor is responsible for ensuring that the study meets the relevant standards and makes sure that arrangements are put and kept in place for management, monitoring and reporting. The University of Leicester has delegated some Sponsor activities to the CI and NCTU, these are documented in the Delegation of Activities.

7 Ethics and Dissemination

7.1 Research Ethics and Health Research Authority Approval

Before initiation of the study at any clinical site, the protocol, all informed consent forms, and any material to be given to the prospective participant will be submitted to the relevant REC and to HRA for approval. Any subsequent amendments to these documents will be submitted for further approval.

The rights of the participant (patient and practitioner) to refuse to participate in the study without giving a reason must be respected. After site initiation, clinical decision making in the best interest of the patient remains in the hands of the treating clinician. After site initiation the participants must remain within the study for the purpose of follow up and data analysis according to the intervention or control arm to which their site has been allocated. However, the participant remains free to change their mind at any time about the protocol and follow-up without giving a reason and without prejudicing their employment status (practitioner) or clinical care (patient).

7.2 Competent Authority Approvals

This is not a Clinical Study of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is not required in the UK.

7.3 Other Approvals

Documentation will need to be submitted to the R&D Department at each NHS Site in order to gain confirmation of capacity and capability prior to the study being initiated at that site. Confirmation from the site will take the form of a site agreement signed by both the Sponsor/NCTU and the relevant site.

A copy of the local R&D approval and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the co-ordinating centre before participants are randomised to the study.

The protocol has received formal approval and methodological, statistical, clinical, and operational input from the NCTU Protocol Review Committee.

7.4 Amendments

Amendments to the Protocol and other documents (e.g., changes to eligibility criteria, outcomes, sample size calculations, analyses) will be agreed by the PMG. Such amendments will be forwarded to the Sponsor for review and approval for submission to the Health Research Authority or Ethics Committee for approval. Once the amendment has been categorised it will be sent to relevant sites for consideration in accordance with standard HRA processes and timescales. Amendments must not be implemented until all relevant regulatory approvals have been received, that sites have either confirmed acceptance or, no objection has been received within the defined timescale, and where applicable, Sponsor Green Light has been issued. Notification will be sent by NCTU to study personnel to confirm when an amendment can be implemented.

7.5 Confidentiality

Any paper copies of personal study data will be kept at the participating site in a secure location with restricted access. Following consent, identifiable data will be kept on the study database to allow authorised members of the study team to contact patients in order to arrange appointments/assessments or to send study progress updates in the form of a newsletter. Only authorised study team members will have password access to this part of the database. This information will be securely destroyed 6 years after the end of the study

Confidentiality of patient's personal data is ensured by not collecting patient names on CRFs and limiting access to personal information held on the database at NCTU. At study enrolment the patient will be issued a participant identification number, and this will be the primary identifier for the patient, with secondary identifiers of year of birth and initials.

The patient's consent form will carry their name and signature. These will be kept at the study site, with a copy sent to NCTU for monitoring purposes. This copy will be destroyed once checks are complete. Consent forms will not be kept with any additional patient data.

7.6 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the study.

7.7 Indemnity

The University of Leicester insurance and indemnity will apply for the design of the study protocol and the management of the study. If a patient participant wishes to make a complaint about any aspects of the way they have been treated or approached during the study, the standard National Health Service complaint system will be available to them. Staff participants must seek advice from their employing organisation.

7.8 Finance

The CHARMER Definitive study is fully funded by a National Institute of Health Research Programme Grant for Applied Research grant number [NIHR200874]. It is not expected that any further external funding will be sought.

7.9 Archiving

The investigators agree to archive and/or arrange for secure storage of CHARMER Definitive study materials and records for 6 years after the close of the study unless otherwise advised by the NCTU.

7.10 Access to Data

Requests for access to study data will be considered, and approved in writing where appropriate, after formal application to the SMT. Considerations for approving access are documented in the SMT Terms of Reference. Applications approved by the PMG will be submitted to the PSC for awareness.

7.11 Publication Policy

7.11.1 Study Results

A Publication Policy has been agreed by co-applicants and NCTU for the CHARMER Programme Grant. This is available from the Trial Manager or CI. Authorship will be in line with International Committee of Medical Journal Editors recommendations. The results of the study will be disseminated regardless of the direction of effect.

7.11.2 Reproducible Research

The intention is to publish this protocol. As the results of this study will be used to inform the definitive study (WP4), the study dataset will be made available at the end of the definitive trial subject to approve by CI and Sponsor.

8 Ancillary Studies

No Ancillary studies are planned at this time.

9 Protocol Amendments

Protocol Main Trial CHARMER_v1.0_20230511 – amendment progressed to update patient PIS and protocol to clarify virtual consent process.

Protocol Main Trial CHARMER_v1.1_20230623 – amendment progressed to update patient PIS to reflect collection of A&E/outpatient data from NHS England, to correct small typographical errors, update CHARMER team roles and sample sizes.

Protocol Main Trial CHARMER_v2.0_20231023 – amendment progressed to include additional datasets from NHS England for the health economic analysis. In addition average monthly patients was increased from 100 to 120, Health Innovation East involvement was included, and minor staff updates/typographical updates were corrected.

Protocol Main Trial CHARMER v2.1_20240415 – amendment progressed to remove 'medically fit for discharge' clause unintentionally left from the CHARMER feasibility protocol.

Protocol Main Trial CHARMER_v3.0_20241018 – amendment progressed to remove 20 patient medication review left from the feasibility study, clarification that the PSC will act as the DMC for this trial, increase of enhanced data collection period from 4 weeks to 6 weeks, inclusion of Health Innovation East process evaluation interviews

10 References

1. Chan AW, Tetzlaff JM, Altman DG et Al. SPIRIT 2013 Statement: Defining Protocol Items for Clinical Studys. *Ann Intern Med* 2013; 158:200-207.

2. Chan AW, Tetzlaff, Gotzsche et Al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; 346: e7586.

3. Gallagher, P., et al., Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. Eur J Clin Pharmacol, 2011. 67(11): p. 1175-88.

4. Scott, S., et al., Attitudinal predictors of older peoples' and caregivers' desire to deprescribe in hospital. BMC Geriatr, 2019. 19(1): p. 108.

5. Scott, S., et al., Deprescribing admission medication at a UK teaching hospital; a report on quantity and nature of activity. Int J Clin Pharm, 2018. 40(5): p. 991-996.

6. World Health Organization. Global Patient Safety Challenge: Medication Without Harm. WHO Global Patient Safety Challenge 2017 12 September 2020]; Available from: http://apps.who.int/iris/bitstream/10665/255263/1/WHO-HIS-SDS-2017.6-eng.pdf?ua=1&ua=1.

7. Department of Health and Social Care. Matt Hancock orders review into overprescribing in the NHS. 2018; Available from: https://www.gov.uk/government/news/matt-hancock-orders-review-into-over-prescribing-in-the-nhs.

8. Thillainadesan, J., et al., Impact of Deprescribing Interventions in Older Hospitalised Patients on Prescribing and Clinical Outcomes: A Systematic Review of Randomised Trials. Drugs Aging, 2018. 35(4): p. 303-319.

9. Hansen, C.R., et al., Identification of behaviour change techniques in deprescribing interventions: a systematic review and meta-analysis. Br J Clin Pharmacol, 2018. 84(12): p. 2716-2728.

10. Albarracín, D., et al., A test of major assumptions about behavior change: a comprehensive look at the effects of passive and active HIV-prevention interventions since the beginning of the epidemic. Psychol Bull, 2005. 131(6): p. 856-97.

11. Scott, S., et al., Development of a hospital deprescribing implementation framework: A focus group study with geriatricians and pharmacists. Age Ageing, 2019. 49(1): p. 102-110.

12. Taché, S.V., A. Sönnichsen, and D.M. Ashcroft, Prevalence of adverse drug events in ambulatory care: a systematic review. Ann Pharmacother, 2011. 45(7-8): p. 977-89.

13. Council., M.R., Developing and evaluating complex interventions. 2006.

14. Moore, G.F., et al., Process evaluation of complex interventions: Medical Research Council guidance. Bmj, 2015. 350: p. h1258.

15. Lewis, M., et al., Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back! Pilot Definitive study, 2021. 7(1): p. 40.

16. Charlson, M., et al., Validation of a combined comorbidity index. J Clin Epidemiol, 1994. 47(11): p. 1245-51.

17. Herdman, M., et al., Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research, 2011. 20(10): p. 1727-1736.

18. Grewal, I., et al., Developing attributes for a generic quality of life measure for older people: preferences or capabilities? Soc Sci Med, 2006. 62(8): p. 1891-901.

19. Ware, J.E., Jr., SF-36 health survey update. Spine (Phila Pa 1976), 2000. 25(24): p. 3130-9.

20. Campbell, N.C., et al., Designing and evaluating complex interventions to improve health care. Bmj, 2007. 334(7591): p. 455-9.

21. Bikker, A.P., et al., Conducting a team-based multi-sited focused ethnography in primary care. BMC Med Res Methodol, 2017. 17(1): p. 139.

22. O'Mahony, D., et al., STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing, 2015. 44(2): p. 213-8.

23. Craig P, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ2008;337: a165

24. Moore G, et al. *Process evaluation of complex interventions: UK Medical Research Council (MRC) guidance.* London: MRC Population Health Science Network; 2014.

25. Skivington K, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance BMJ 2021; 374: n2061 doi:10.1136/bmj.n2061

26. Skivington K, *et al.* Framework for the development and evaluation of complex interventions: gap analysis, workshop and consultation-informed update. Health Technol Assess 2021;25(57)

27. Bikker, A., *et al.* Conducting a team-based multi-sited focused ethnography in primary care. BMC Med Res Methodol 2017 **17,** 139 https://doi.org/10.1186/s12874-017-0422-5

28. Morgan-Trimmer, S., Wood, F. Ethnographic methods for process evaluations of complex health

behaviour interventions. Trials 2016 **17,** 232. https://doi.org/10.1186/s13063-016-1340-2

29. Braun, V., Clarke, V.: One size fits all? What counts as quality practice in (reflexive) thematic

analysis? Qual. Res. Psychol. (2020). https://doi.org/10.1080/14780887.2020.1769238

30. QSR International Pty Ltd. (2020) NVivo (released in March

2020), https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home

31. Schoenmakers T, et al Evaluation of Potentially Drug-Related Patient Reported Common

Symptoms Assessed During Clinical Medication Reviews: A Cross-Sectional Observational Study. Drug

Saf 2017. 40: 419-430

32. McDonald, E.G et al The MedSafer Study – Electronic Decision Support for Deprescribing in Hospitalized Older Adults A Cluster Randomizsed Clinical Trial (2022). https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2788297

33. Scott S, et al Attitudinal predictors of older peoples' and caregivers' desire to deprescribe in hospital. BMC geriatrics. 2019 Dec;19(1):1-1

12 Principal Investigator Compliance Statement

Principal Investigator agreement to confirm adherence to the protocol, the UK Policy Framework for Health and Social Care Research and GCP.

CHARMER Definitive study

Comprehensive Geriatrician Led Medication Review – Work Package 4 - Definitive study

I, [Insert investigator name], confirm:

1. that [insert name of site] site is willing and able to comply with the requirements of the CHARMER Definitive study;
2. that I regularly treat the target population and believe the site has the potential for recruiting the required number of suitable subjects within the agreed recruitment period (figures included in the study recruitment plan);
3. that I have sufficient time to properly conduct and complete the study within the agreed study period;
4. that I have supplied an up-to-date curriculum vitae, GCP certificate and/or other relevant documentation requested by NCTU, to demonstrate that I am qualified by education, training, and experience to assume responsibility for the proper conduct of the study at this study site;
5. that I am thoroughly familiar with the appropriate use of the investigational products as described in the protocol, in the current Investigator Brochure (if applicable), in the product information and in other information sources provided by NCTU;
6. that I have an adequate number of qualified staff and adequate facilities available for the foreseen duration of the study to conduct the study properly and safely;
7. that I will maintain a signature and delegation log of appropriately qualified persons to whom I have delegated study related duties which includes confirmation that each member of staff is appropriately trained (including GCP) for the roles allocated to them, and will ensure this is made available to NCTU in a timely manner on request;
8. a research CV for each member of staff on the delegation log will be stored in the site file according to site policy;
9. that I take responsibility for ensuring all staff delegated study related duties are adequately informed about the protocol, the investigational product and their study related duties and functions, and that I will continue to take responsibility for regularly updating them as new information becomes available;
10. that the [insert name of site] site has sufficient resources to manage data generated by the study to allow prompt and complete data and query return to NCTU;
11. that I am aware of, and will comply with, the principles of GCP as given in the CHARMER Definitive study protocol compliance statement and the applicable regulatory requirements, and that a record of my GCP training is accessible and described on my current curriculum vitae;
12. that a record of GCP training is accessible for all staff delegated responsibilities in relation to the CHARMER Definitive study and who are named and approved on the site signature and

delegation of responsibilities log and that individual training evidence will be saved in the site file, for all staff, according to trust policies;

13. that I will permit routine and for-cause monitoring and auditing by NCTU, and inspection by the appropriate regulatory authorities, including the provision of direct access to source data and other participant notes and files as required; and
14. that I agree to archive and/or arrange for secure storage of CHARMER Definitive study materials and records for a minimum of six years after the close of the study unless otherwise advised by the NCTU.

Agreement: Principal Investigator

Name	[insert name]
Signature	[insert wet signature]
Date	[insert date]

(Please return a copy of this signed agreement (only pages 75 and 76) to the CHARMER Definitive study to NCTU at charmer.trial@uea.ac.uk)