BRISMED

Pragmatic Evaluation of Effectiveness and Acceptability of the Bristol Medication Review Toolkit

Trial Protocol

Approvals and IDs	***Reference***
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This protocol has regard for the HRA guidance

NHS
National Institute for Health Research

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TRIAL SUMMARY

Trial Title	Pragmatic Evaluation of Effectiveness and Acceptability of the Bristol Medication Review Toolkit
Short title	BRISMED
Population	Adults (aged ≥18 years) eligible for structured medication review in English general practices contributing data to the Oxford-Royal College of GPs Clinical Informatics Digital Hub (ORCHID)
Trial Design	Pragmatic cluster randomised controlled trial of practice-level intervention, with an embedded mixed-methods process evaluation
Planned Sample Size	Approximately 500 PCNs (~800-900) GP practices (main trial outcome), of which 56 practices (28 intervention and 28 control) will also take part in the mixed methods process evaluation
Duration of trial intervention delivery	12 months (April 2024 to March 2025)
Follow up	3 months (April-June 2025)
Trial Period	30 months (October 2023- March 2026) The end date for the study is 31st March 2026

Objectives of the main trial	Outcomes of the main trial	Objectives of the process evaluation
• Successful implementation of the Bristol Medication Review (BRISMED) Toolkit in general practices • Comparison of clinical effectiveness of the BRISMED Toolkit with usual care, alongside an evaluation of the cost implications • Assessment of acceptability to, and experience of, patients and practitioners	Primary outcome: Rate of Potentially Inappropriate Prescribing, (PIP) at 12 months Secondary outcomes: • Number of medicines at 12 months • Treatment burden (MTBQ) at 12 months • Medication Regimen Complexity Index at 12 months • Medication adherence at 12 months • All-cause adverse drug reactions (ADRs) over the past 12 months • Health service utilisation (GP consultations and unplanned hospitalisation) over the past 12 months • NHS costs (sum of GP prescribing, consultations, and hospital use) Outcomes will be determined using anonymised routine	• Qualitative and quantitative assessment of practitioner/patient views/experience of medication reviews in both trial arms. • Identification of possible mechanisms and contextual factors behind treatment outcomes in both trial arms. • Assessment of acceptability, implementation and scalability of the BRISMED Toolkit.

	electronic health record (EHR) data through ORCHID	

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NIHR Health Service and Delivery Programme National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton, SO16 7NS Telephone: 023 8059 5586 Fax: 023 8059 5639 Email: htaoas@southampton.ac.uk	Grant funding NIHR ref. 154205 £905,737.43
University of Bristol Research and Enterprise Development 3rd Floor, Senate House Tyndall Avenue Bristol, BS8 1TH Tel: 0117 928 8676 Email: red-office@bristol.ac.uk	Sponsorship

History of version changes and amendments- Study protocol

Version No.	Version Date	Pages	Description of change
V2.0	14/03/2023	3 20	The Trial Summary has been amended as requested by the HRA to clarify that the end date of the study is 31st March 2026 Section 5.2.6 Sampling and consent for observation of medication review has been updated to confirm that when not in use at sites, audio-recording devices will be locked in a filing cabinet/cupboard or desk draw.
V3.0		26	Clarification that we are randomising at PCN level rather than GP site level within the main text of the protocol and the trial flow diagram Replacement of the original model with a graphically designed, more 'professional'-looking version. Minor editing to 'BRISMED Toolkit', 'BMR Model' and 'Accurx' to ensure accuracy and consistency of use of appropriate terminology throughout the protocol Addition of 2 new references corresponding to clarifying information in the main text related to the sample size calculation Removal of 1 surplus reference

			As agreed with our Trial Steering Committee, we have specified an additional analyses of the primary outcome (i.e. a subgroup analysis of patients receiving ≤6 regular medicines).

LIST OF CONTENTS

LIST OF ABBREVIATIONS/TERMS

Accurx	Informatics tool used by GP practices for SMS
ADR	Adverse Drug Reaction
AE	Adverse Event
BMR	Bristol Medication Review Model
BNF	British National Formulary
BRISMED	Acronym for the toolkit and trial described in this protocol
CAPC	Centre for Academic Primary Care
CaRE	Consultation and Relational Empathy questionnaire
CAG	Confidential Advisory Group
CCA	Cost Consequence Analysis
CCG	Clinical Commissioning Group
CI	Chief Investigator
CollaboRATE	Patient-reported measure of shared decision making
COM-B	Theoretical model of behaviour change
CPPE	Centre for Pharmacy Postgraduate Education
CRF	Case Report Form
CRN	Clinical Research Network
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
DQIP	Data-Driven Quality Improvement in Primary Care study
ED	Emergency Department
EMIS Web	Clinical computer system used by GP practices
EQ-5D-5L	EuroQol validated questionnaire on 5 domains of quality of life
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations 2018
GP	General Practitioner
HCP	Health Care Professional
HEAP	Health Economics Analysis Plan
HRA	Health Research Authority
HS&DR	Health Services and Delivery Research
HTA	Health Technology Assessment
ICB	Integrated Care Board
ICC	Intraclass correlation coefficient
IMD	Index of Multiple Deprivation (area measure of socioeconomic status)
IMPPP	RCT of complex medication optimisation intervention for polypharmacy
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
IT	Information Technology
ITT	Intention to Treat analysis strategy
MRCI	Medication Regimen Complexity Index
MTBQ	Multimorbidity Treatment Burden Questionnaire
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NSAIDs	Non-steroidal anti-inflammatory drugs
OID	Organisation Information Document (sponsor/practice agreement)

ORCHID	Oxford-Royal College of GPs Clinical Informatics Digital Hub
OPTION	Observing PaTient Involvement in decisiON making questionnaire
PAG	Patient Advisory Group
PCN	Primary Care Network
PI	Principal Investigator
PINCER	Pharmacist-led Information teChnology intervention for medication Errors
PIL	Participant Information Leaflet
PIP	Potentially inappropriate prescribing
PPG	Patient Participation Group
PPI	Patient and Public Involvement
QOF	Quality Outcomes Framework (NHS Payment-for-Performance system)
RCT	Randomised Controlled Trial
RCGP	Royal College of General Practitioners
R&D	Research and Development
RDSF	Research Data Storage Facility
REC	Research Ethics Committee
RPS	Royal Pharmaceutical Society
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAR	Serious Adverse Reaction
SLA	Service Level Agreement
SMR	Structured Medication Review
SMS	Short Message Service (text messaging system used by mobile phones)
SOP	Standard Operating Procedure
STOPP/START	Validated set of potentially inappropriate prescribing indicators
SUSAR	Suspected Unexpected Serious Adverse Reaction
SystmOne	Clinical computer system used by GP practices
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UoB	University of Bristol
VAS	Visual Analogue Scale

STUDY PROTOCOL

1.0 Plain English Summary

At a medication review a patient meets with a GP or pharmacist to discuss the medicines they are using. Medication reviews are important to check that the medicines a patient is taking are the right ones for their conditions. Reviews also check that the medicines are being used in a safe and effective way. Medication reviews are part of normal health care for people taking medicines long-term, but research shows that medication reviews do not always improve care. Also, patients do not always feel that their views are considered when decisions to change their medicines are made. The National Institute for Health and Care Excellence (NICE) gives advice and guidance to the NHS. NICE has said better medication reviews are needed, and many doctors, pharmacists and patients agree.

To improve medication reviews, researchers at the University of Bristol have developed the “Bristol Medication Review Toolkit”. Doctors, pharmacists, patients and researchers worked together to develop this toolkit. The toolkit gives doctors and pharmacists advice about how to do a medication review. It also gives patients advice about how to get the most from their review.

We now want to find out if giving GP practices the Bristol Medication Review (BRISMED) Toolkit improves the patient’s experience of medication review and leads to more appropriate prescribing. We also want to find out if patients, doctors and pharmacists find the toolkit easy to use.

The project has three parts:

1. We will give the Bristol Medication Review Toolkit to around 400 GP practices across the UK, and give advice on how to use it. We will speak to patients, GPs and pharmacists to make sure the Toolkit is as useful as possible, and that practices know how to use it properly.

2. Over one year, we will compare medication use in the GP practices that are using the BRISMED Toolkit with GP practices that are not using it. We will collect information recorded by doctors and pharmacists in GP practice computer systems. We want to find out if medicines are being used safely, and other things like the number of medicines being given to patients. We will also look for any other changes in the use of health services (for example, hospital admissions).

3. We will interview patients, doctors and pharmacists about their views and experiences of medication reviews. We will ask some doctors and pharmacists about their experience of using the BRISMED Toolkit. A survey will be sent to some patients to find out about their experiences of their medication review. We will also audio-record some medication reviews, survey GP practices, and collect information from their computer systems, to find out how practices do medicine reviews, with and without the Toolkit.

The results will help us find the best way to carry out medication reviews in the future. This will help ensure medicines are used in a safe and effective way. It will also make sure patients are fully involved in discussions about their medicines. If the toolkit is found to be helpful and easy to use, it will be simple to make it available to all GP practices in the future. We will share our findings with doctors, pharmacists, NHS managers and policymakers (who decide what health services are provided), other researchers, patients and members of the public. Patients and members of the public have helped

with the design of the research and with the Toolkit we are testing. They will also help carry out the research and share our findings in ways that everyone can understand.

2.0 Background and rationale

2.1 Background

Medicines are a key intervention used by health services, and many patients have complex multi-drug regimens[1]. Used appropriately, this can improve clinical outcomes[2], but there are risks of adverse consequences (e.g. hazardous prescribing[3], reduced quality of life[4]). Medicines optimisation aims to ensure safe and effective medicines use[5], with medication reviews a critical part of the process. Reviews are defined by NICE as “a structured critical examination of a person’s medicines” aimed at agreeing therapeutic objectives, optimising medication impact, reducing drug harms and cutting waste[6] and form part of current NHS policy[7].

Review structure/content varies depending on the clinical information available and degree of patient involvement[8]. Clinical guidelines vary in how they recommend reviews are conducted: the WHO and Scottish polypharmacy guidance describes a 7-step model[9,10] and Welsh guidance recommends the NO TEARS model[11]; neither are underpinned by robust evidence of effectiveness. Guidance from the Royal Pharmaceutical Society[12] and NICE[6], and the 2020 NHS England contract[7], do not specify a particular approach. A survey of usual medication review practices in 25 GP surgeries (part of our ongoing IMPPP primary care polypharmacy trial, NIHR 16/118/14[13]) found >80% GPs and a third of pharmacists received no training in medication review. Around half of practices had no specified review model/template or practice policy. A systematic review by Huiskes found isolated medication reviews, as advocated by current policy, lacked standardisation and had minimal impact on outcomes[14]. A recent evaluation of implementation of NHS England’s national policy of Structured Medication Reviews (SMR) found them not to be patient focused with pharmacists lacking necessary expertise[15].

In summary, medication reviews are a critical part of practice, but there is no established approach, no consistency, insufficient training, and poor evidence of effectiveness. New evidence is needed to inform the delivery of effective reviews, underpinned by availability of appropriate tools to allow implementation in clinical practice.

2.2 Importance

This proposal is a direct response to Research Recommendation 2.2 of the current NICE Medicines Optimisation guideline NG5 (effectiveness of medication review)[6]. Nearly half of adults take prescription medicines, and a quarter ≥3 medicines[16]. Given reviews are key to optimising medicines delivery, the proposed study is relevant to many patients, with potential to improve treatment effectiveness/safety, thus improving morbidity, mortality and quality of life. High prescribing rates persist[17], so this issue will be of sustained future interest. The research also aligns with current NHS policy and contractual arrangements[7]. As such, delivering more effective reviews can potentially achieve savings (e.g. through fewer medication harms) whilst minimally impacting existing resources. Current policy and practice lacks evidence; the proposed research addresses this knowledge gap by building on existing work we have conducted to develop a review model. Using a pragmatic, real-world evaluation, the research findings will be generalizable and readily implemented in practice.

2.3 Need for research

Medication reviews can improve specific clinical outcomes in certain patient groups (e.g. diabetes[18], heart failure[19]). Some complex interventions (e.g. combining informatics and education) may reduce problematic prescribing[20,21].

However, a 2017 systematic review by Huiskes found isolated medication reviews had minimal impact on clinical outcomes and no effect on quality of life, concluding such reviews should not be part of standard care[14]. We recently updated this literature review[22]. Using a similar search strategy to Huiskes, we searched MEDLINE and Embase databases for randomised controlled trials of interventions which aligned with the NICE guideline definition of medication review. We excluded reviews targeting a specific therapeutic area, with narrow focus (e.g. adherence only), that excluded direct patient participation, or that formed part of a complex intervention or co-intervention. We found 28 trials, with moderate overall bias. Evidence was limited that medication reviews improve key clinical outcomes[22]. Huiskes attributes the lack of apparent effectiveness in part to insufficient standardisation of reviews and differing review objectives[14]. Our own work also found patient centredness lacking in a third of studies[22].

Madden et al also found current SMR policy lacked patient focus and necessary training, with reviews consequently failing to meet policy objectives[15].

In consultation with an expert working group, we used our findings to develop the comprehensive Bristol Medication Review (BMR) Model[22], incorporating key components identified in the literature and emphasising patient-centredness; this empowers patients, and is deemed key to medicines optimisation[12] and improving patient satisfaction and treatment adherence[23]. The structure aligns with familiar traditional consultation frameworks (e.g. Calgary-Cambridge approach[24]) with a flexible design allowing for the contrasting approaches of doctors and pharmacists[25] and being better suited to the complexity of clinical practice[26]. The model, accompanying guidance and example questions provide an easy-to-use resource, aiming to support development of knowledge/skills, facilitate planning and delivery of reviews[27], and to address recognised barriers to implementation (e.g. complexity, poor layout of materials, lack of evidence)[28].

3.0 Aims and objectives

3.1 Aim

The aim of this project is to address the research question “how does the Bristol Medication Review (BRISMED) Toolkit compare with standard general practice care, in terms of clinical effectiveness, and acceptability to patients and practitioners?”

3.2 Objectives

The three core study objectives are

1) successful implementation of the BRISMED Toolkit in general practices
2) comparison of clinical effectiveness of the BRISMED Toolkit with usual care, alongside an evaluation of the cost implications
3) assessment of acceptability to, and experience of, patients and practitioners.

To meet Objective 1, we will provide access to the BRISMED Toolkit, including the BMR Model and other supporting resources, through an easy-to-use website. Implementation and adoption will be evaluated by monitoring access to the website, using coded data extracted from the GP clinical systems, and from surveys and qualitative work with patients and clinicians.

For Objective 2, we will conduct a pragmatic, cluster randomised trial. Key clinical outcomes will align with those recommended by NICE, and will primarily be assessed using routine electronic health records, alongside some additional patient reported measures. Health economic evaluation will be conducted in the form of a cost consequence study.

To address Objective 3, a mixed-methods process evaluation will be undertaken in parallel with the main trial, including a range of observations, interviews and surveys with patients and clinicians.

4.0 Study design and setting

This study is a large, pragmatic randomised controlled trial, evaluating a practice-level intervention. Usual care for medicines optimisation is constantly changing and many local primary care systems have already implemented review models, often in highly heterogeneous or untested ways. This makes it difficult to implement a narrowly-defined intervention as part of a typical clinical trial. There is also no existing review model in widespread use we can readily adapt. The study will thus evaluate whether flexible implementation of a new toolkit of medication review resources (the BRISMED Toolkit), leads to improvements in care. The study will involve randomising GP practices to intervention plus usual care or usual care at the level of Primary Care Networks (PCNs). Quantitative analysis of prescribing metrics and health service utilisation will be captured remotely using routine data, with a mixed-method process evaluation providing detailed, contextualised insights into practitioner and patient views/experiences. Outcomes have been selected to capture key aspects of medicines use (e.g. safety, adherence, treatment burden, service use) as per previous research[22] and as recommended by NICE[6].

4.1 P.I.C.O.

4.1.1 Population

The population under study in the main trial analysis will include approximately 8 million patients registered with around 800-900 GP England practices contributing to the secure data processing environment of the nationally representative Oxford-Royal College of GPs Clinical Informatics Digital Hub (ORCHID) [29]. By using this large dataset, we can ensure our study is inclusive and will be generalizable to the wider UK population. Although most long-term prescribing occurs in adults, medication reviews are conducted in patients of all age, and given the practice-level nature of the intervention, it is not possible to restrict use of the BRISMED Toolkit to a particular age group or patient subgroup. However, the main trial analysis will be limited to adults (≥18 years). Adult (≥18 years) patients from a smaller subset of 56 of the original practices will be included in the process evaluation.

4.1.2 Intervention

Provision of the BRISMED Toolkit, comprising the BMR model and supporting materials for guidance, training and implementation.

4.1.3 Comparator

Usual clinical care (likely to be highly heterogenous but most patients will receive some sort of annual review).

4.2 Outcomes

4.2.1 Primary trial endpoint/outcome

- Rate of potentially inappropriate prescribing, (PIP) (proportion of patients in each practice triggering at least one PIP criteria at 12 months).

4.2.3 Secondary outcomes (main analysis)

- Number of long-term medicines currently used at 12 months
- Medication Treatment Burden (measured using MTBQ) at 12 months

- Medication Regimen Complexity Index at 12 months
- Medication adherence at 12 months
- All-cause adverse drug reactions (ADRs) over the past 12 months
- Health service utilisation (GP consultations/unplanned hospitalisation over the past 12 months)
- NHS costs (sum of GP prescribing, consultations, and hospital use)

Prescribing and health service utilisation data will be captured anonymously from routinely collected electronic health records available via the ORCHID network.

4.2.4 Secondary outcomes (process evaluation analysis)

- Post-review patient experience (measured within 2-weeks)
    - Shared decision making (CollaboRATE)
    - Empathy (CaRE)
    - Confidence in clinician/reviewer (5-point Likert scale)
    - Overall satisfaction (5-point Likert scale)
- Quality of life (measured at between 3-9 months)
    - EQ-5D-5L
    - EQ-VAS

We cannot capture patient-reported outcomes using routine data, so we will obtain data on patient/practitioner care experience, plus quality of life in a subset of patients within the 56 practices participating in the process evaluation.

5.0 Trial eligibility criteria for practices

General practices using EMIS or SystmOne clinical systems, and contributing to the secure data processing environment of the nationally representative Oxford-Royal College of GPs Clinical Informatics Digital Hub (ORCHID), will be eligible to participate in the trial. Practices will only be included if they have not explicitly opted out of participating in the BRISMED study.

A subset of 56 practices (28 from each trial arm) will be recruited to the embedded mixed-methods process evaluation. Practices will be eligible to participate in the process evaluation if they have Accurx text messaging technology with ability for bulk text messaging enabled. This technology will be required for administration of patient surveys. All 56 practices conducting research activities as part of the process evaluation will be asked to complete the Organisation Information Document (OID), which is being used as the research agreement between the practice and the sponsor e.g. the University of Bristol.

5.1 Participant population

5.1.1 Main trial population

All patients aged ≥18 years who have not registered with their practice an opt-out of sharing data outside of the practice for purposes of research or planning, will be included in the main trial analysis. Patient consent to participate in the main trial will not be specifically sought since this is a practice-level intervention and practices already contribute anonymised routine data to the ORCHID network.

5.1.2 Process evaluation population

Within the 56 practices participating in the process evaluation, all adult patients (aged ≥18 years) receiving a structured medication review during four 2-week blocks within the 12-month intervention period will be sent a patient-experience questionnaire, and all adult patients receiving a review within the 12-month intervention period will be sent a quality of life questionnaire. Additionally, a smaller number of patients will be purposefully sampled and invited to provide consent to participate in an interview.

5.2 Recruitment procedures

5.2.1 Practice recruitment for the main trial

We will randomly sample 500 PCNs (i.e. approximately 800-900 practices) from the larger network of practices contributing data to ORCHID (>1800 practices), and randomly allocate half to intervention or control. Practices have already agreed to share anonymous data with the ORCHID network, but will be allowed to opt out of specifically participating in the BRISMED trial if they wish. The ORCHID network will liaise with intervention practices in order to “push out” the intervention and promote adoption. Practices will be asked to implement the intervention as they see fit. This is designed to reflect “real world” practice, acknowledging not all intervention practices may fully engage. The additional workload for practices is low, as the intervention aligns strongly with usual care and requires minimal if any additional resource.

5.2.2 Recruitment of practices for the process evaluation

A subset of 56 practices will be recruited to participate in the process evaluation detailed below. These practices will be purposively sampled across PCNs in both trial arms in relation to list size, performance on the national GP Patient Survey, availability of practice-based pharmacist, training status, and socioeconomic status to ensure maximum variation. Principal Investigators at practices agreeing to participate will be required to sign an OID, as detailed earlier, and complete Good Clinical Practice training if they have not already done so.

5.2.3 Identification and recruitment of clinicians for interview

We will interview up to 22 GPs and clinical pharmacists across the 56 practices participating in the process evaluation once they have completed conducting reviews in the trial.

Identification

Clinicians will be identified through the practice research lead. Purposive sampling varying by clinician characteristics (age (decades), gender, ethnicity) and practice characteristics (list size, practice area-level deprivation) will be used to capture maximum variation in views and experiences.

Invitation

Individual GPs and pharmacists will be approached via email about the study by the research lead in the practice. An electronic invitation letter and participant information sheet will be attached to the email.

Recruitment

Individuals who are interested in participating will be asked to complete a brief online survey to capture age range, gender and ethnicity (to facilitate purposive sampling across all potential participants), along with an electronic consent form. Participants will then be contacted by the research team to proceed with the interview.

5.2.4 Identification and recruitment of patient participants for interview

We will interview up to 22 patients within one month of review completion.

Identification

Patients will be identified as those confirming on their patient-experience survey (see Process Evaluation; Patient Experience Survey below for details of this survey) they would be willing to be interviewed. Responses to this survey will provide us with additional sampling details, including age, gender, ethnicity, highest level of education, and total number of medicines. The survey will also

collect contact details to enable the researchers to provide an invitation letter, participant information sheet and consent form.

Invitation

Invitations will be sent to patients who have already expressed an interest in being interviewed, and who are purposefully sampled for interview (based upon survey their response) to ensure maximum variation amongst interviewees.

Recruitment

A participant invitation letter, information sheet and consent form will be provided to patients via email or post based upon the type of contact details provided by the patient within the patient-experience survey. Individuals still wishing to take part having received further information will be asked to contact the research team to arrange a date for interview.

5.2.5 Consent processes for qualitative interviews

All potential participants will be provided with a study information sheet (electronic for clinicians; paper and electronic for patients) and further questions invited. The voluntary nature of participation in the study will be made clear in information given to participants. Potential participants will be asked to complete a written (electronic or paper) consent form in advance of the interview. Interview participants will be additionally asked to provide verbal confirmation they are still happy to proceed before taking part in telephone or online interviews, which will be audio recorded immediately prior to the interview.

The researchers will convey to participants via the information sheet and consent form that their participation in the research study is voluntary and that they can withdraw at any time, that they are not obliged to answer any question they feel uncomfortable with, and that the interview can be terminated at their request at any time. This will also be verbally conveyed at the point of obtaining verbal consent.

All participants will be assured of the confidentiality of the data collected and will be asked for permission to publish anonymised quotations from the qualitative interviews. To comply with GDPR and other relevant legislation, only data necessary to the purposes of the research will be obtained and stored. Personal data will not be kept for longer than is required for the purpose for which it has been acquired. Data will be held in compliance with the sponsor's standard operating procedures.

The researcher will arrange the interview at a convenient date and time and place (if an in-person interview is preferable) for the participant. All interviews will be recorded via an audio-recorder (e.g. interviews conducted via video call will not be video recorded).

5.2.6 Sampling and consent for observation of medication review

Audio-recording of medication reviews conducted over a 2-week period will be undertaken in 10 intervention and 5 control practices. Practices will be purposively sampled to reflect variations in patient populations and geography across PCNs. Practices will be provided with an encrypted audio-recorder to record 20 consecutive reviews. Practices will send all patients due to receive a medication review over the 2-week period, a participant information sheet and a printed consent form at least 7-days prior to the review. The patient participant information sheet will encourage the patient to contact a member of the research team if they have any questions. Patients may complete the paper consent form prior to the interview if they wish and bring them to the appointment, or may complete the paper or electronic consent forms with the clinician undertaking the review before proceeding with audio-

recording. At the start of the medication review appointment, the clinician will ask the patient to confirm they are still happy to proceed with audio-recording of their review. If the patient is still willing to participate, the clinician will audio-record their verbal confirmation immediately prior to the review. The clinician will also record the patient's age, sex, ethnicity, postcode, key clinical conditions (based on QOF), medication count, and presence/absence of specific key medications (grouped by BNF category) using an online electronic study report form. This will be explained within the patient participant information sheet. At the end of the medication review before the audio-recorder is switched off, the clinician will ask the patient to confirm for the recording that they still wish for the audio-recording to be used within the research. If the patients withdraws their consent at this point, the clinician will delete the audio recording.
Consent from clinicians for audio-recording of medication review will be sought also. Clinicians at the 15 practices that are participating in this element of the process evaluation will receive an invitation pack via email. The pack will include an invitation to participate, a clinician participant information sheet and a link to an electronic consent form. The clinician will be encouraged to contact the research team if they have any questions.
Clinicians that complete and submit the electronic consent form will be contacted by a member of the research team and be provided with training in Good Clinical Practice for obtaining patient participant consent and how to use the recording device. Training will be provided also around how to complete the electronic and paper consent forms and the electronic study report form. Training will be delivered by the qualitative senior research associate via a 20-minute online meeting using MS Teams.

Clinicians responsible for audio-recording of medication review will be provided with an encrypted audio-recorder and a step-by-step guide detailing how to use the recorder within the review, securely save the recordings after the review and also arrange courier collection for return of the recorder and recordings to the research team at the University of Bristol after the last review has been recorded. Clinicians who are responsible for audio-recording medication reviews at participating sites will be asked to securely store the recording device in a locked filing cabinet/cupboard or desk draw when it is not in used.

6.0 Randomisation

We will randomise by Primary Care Network (PCN) rather than individual practices. This reduces inter-arm contamination risk as practice pharmacists generally work within PCNs, and is something we have successfully done for other trials. Randomisation will be generated using a computer algorithm. At the time of writing, 250 PCNs corresponds to 412 practices (this may vary slightly due to changes in PCN and practice make-up, but is expected to remain around 400-450 practices).

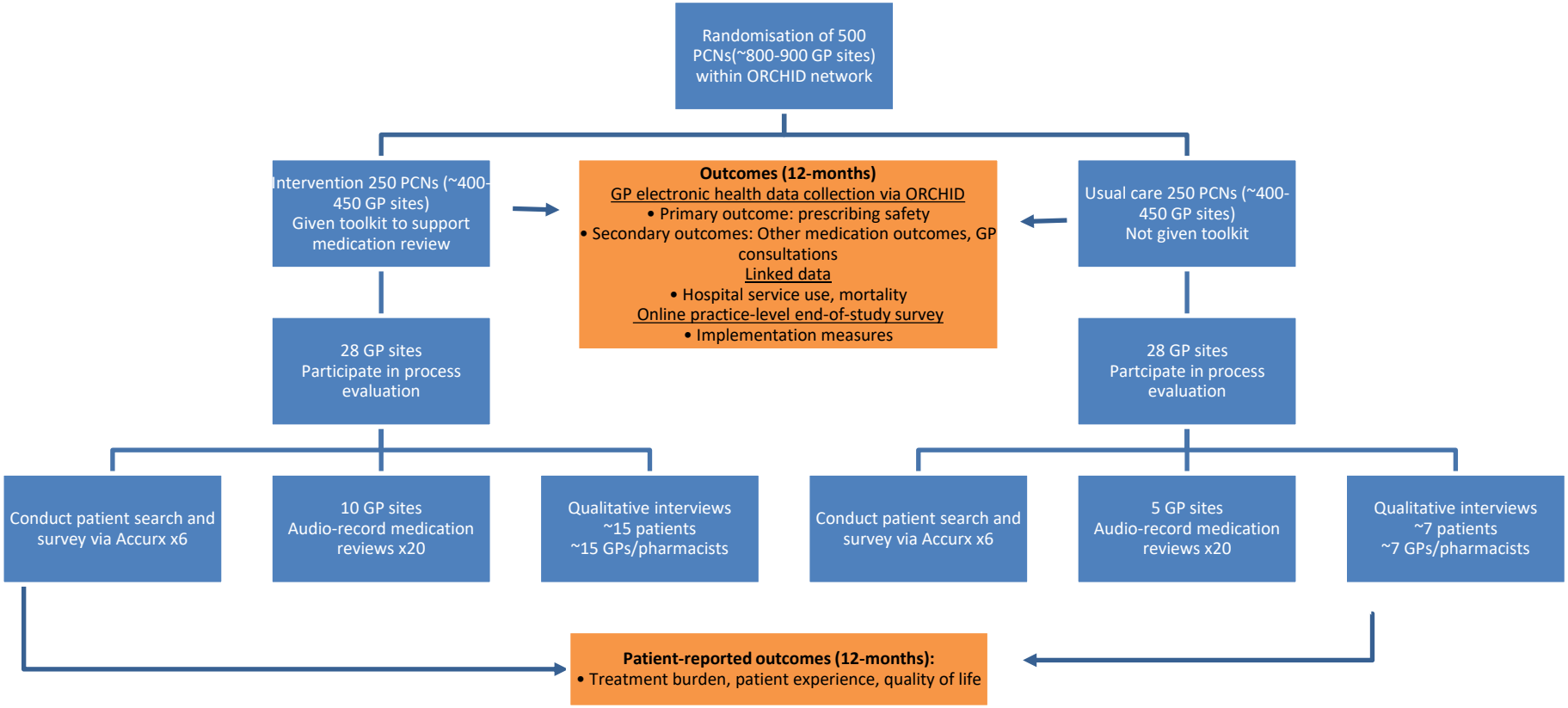
6.1 Allocation concealment

Practices will not be informed of whether they will be in the intervention arm before agreeing to participate.

6.2 Blinding

Practices will be recruited before randomisation. It is not possible to blind practices to randomisation status after randomisation, and although patients could discover which arm their practice has been randomised to, we will not draw attention to this. Analysis will be conducted in a blinded manner.

7.0 Trial flow chart



7.1 Schematic of process evaluation activities at 56 sites

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Intervention delivery period																
Searches & Accurx text messaging of patient experience survey (x4)																
Searches & Accurx text messaging of QoL survey (x2)																
Audio recording of all medication reviews over 2-week period																
Interviews with up to 22 patients across																
Interviews with up to 22 GPs and pharmacists across 56 practices																
Completion of a practice engagement survey																
ORCHID process evaluation data extraction and analysis																

7.2 Ascertainment of outcomes and covariate data collection

The table below details the timing of different outcome measures and the source of data. As a subset of 56 sites will be participating in the mixed-methods Process Evaluation, the number of sites contributing to data collection is detailed in the final column.

Outcome measure	Data source	Study month	Number of sites
Primary outcome			
Potentially inappropriate prescribing	Primary care data via ORCHID	16	~800-900
Medication related measures			
Number of medicines	Primary care data via ORCHID	16	~800-900
Medication regimen complexity	Primary care data via ORCHID	16	~800-900
Medication adherence	Primary care data via ORCHID	16	~800-900
Medication-related (ADR) admissions	NHS Digital	16	~800-900
Rates of medication review	Routine data via ORCHID	16	~800-900
Other health service utilisation			
Unplanned hospital admissions	NHS Digital	16	~800-900
Primary care consultation rate	Primary care data via ORCHID	16	~800-900
Outpatient utilisation data	NHS Digital	16	~800-900
...A&E attendance data	NHS Digital	16	~800-900
Other outcomes			
All-cause mortality	NHS Digital	16	~800-900
Patient reported outcomes			
Medication Treatment burden	Patient survey via Accurx SMS	3,6,9,12	56
Patient experience of review	Patient survey via AccurX SMS	3,6,9,12	56
Quality of life (EQ-5D, EQ-VAS)	Patient survey via AccurX SMS	9,15	56
Other process measures			
Rates of medication review	Primary care data via ORCHID	16	~800-900
Usage of the BRISMED Toolkit & usual care for medication review	Practice survey via REDCap & primary care data via ORCHID	13-14 &16	~800-900

Timepoints for and sources of other covariate data being collection is provided in the table below.

Covariates	Data source	Study month	Number of sites
Main trial analysis			
Patient demographics	Primary care data via ORCHID	16	~800-900
…Common clinical conditions	Primary care data via ORCHID	16	~800-900
…Specific drug classes	Primary care data via ORCHID	16	~800-900
Process evaluation analysis			
Age, sex, ethnicity, education	Patient survey via Accurx SMS	9,15	56
…Common clinical conditions	Patient survey via Accurx SMS	9,15	56
…Specific drug classes	Patient survey via Accurx SMS	9,15	56

Qualitative data collection will be conducted by the qualitative researcher who will lead on the analysis with input from other members of the trial management team. Full details are provided in the Process Evaluation section.

8.0 Intervention design and delivery

8.1 Overview of the intervention

The Bristol Medication Review (BRISMED) Toolkit intervention comprises components designed to facilitate more effective, thorough, and patient-centred medication review. This includes:

- Model (BMR) for delivering a structured medication review
- Guidance on use of the model in clinical practice
- Primer document to empower patients to be more involved in their review
- Training materials for clinicians
- Templates for recording data in GP clinical systems
- Recommendations for practices on implementation

Intervention practices will be provided electronically with the BRISMED Toolkit. It will be left to individual practices how they implement the model (e.g. remote vs in-person; type of clinician conducting review; characteristics of patients invited to review, review frequency). The intervention makes no specific recommendations with respect to case-finding, and so participating sites will continue to identify patients who require a medication review in accordance with local policies. As such, the patients receiving a review as part of the intervention will be the same as those receiving a review as part of usual care.

Drawing on the COM-B model of behaviour change[27], we anticipate achieving change in medication review practice by modifying the capability, opportunity and motivation of clinicians to deliver reviews. *Capability* will be influenced by improving clinicians' knowledge and skills through provision of a clear and comprehensive model for conducting medication reviews alongside relevant training materials. *Opportunity* will be optimised by aligning the intervention to usual practice (with familiarity helping to ensure legitimacy and reduce barriers to adoption), using a model of review which aligns with standard consulting behaviour and is flexible for different clinicians' approaches, providing guidance and recommendations to support practices and PCNs to identify optimal approaches to implementation, and ensuring access to relevant resources (provision of a clinical IT template, primer document, and website providing easy access to supporting materials). *Motivation* will be enhanced through education about the importance of medication reviews, quarterly reminder information sent to intervention practices, continuous professional development (CPD) certificates for completing training, and reimbursement of training time.

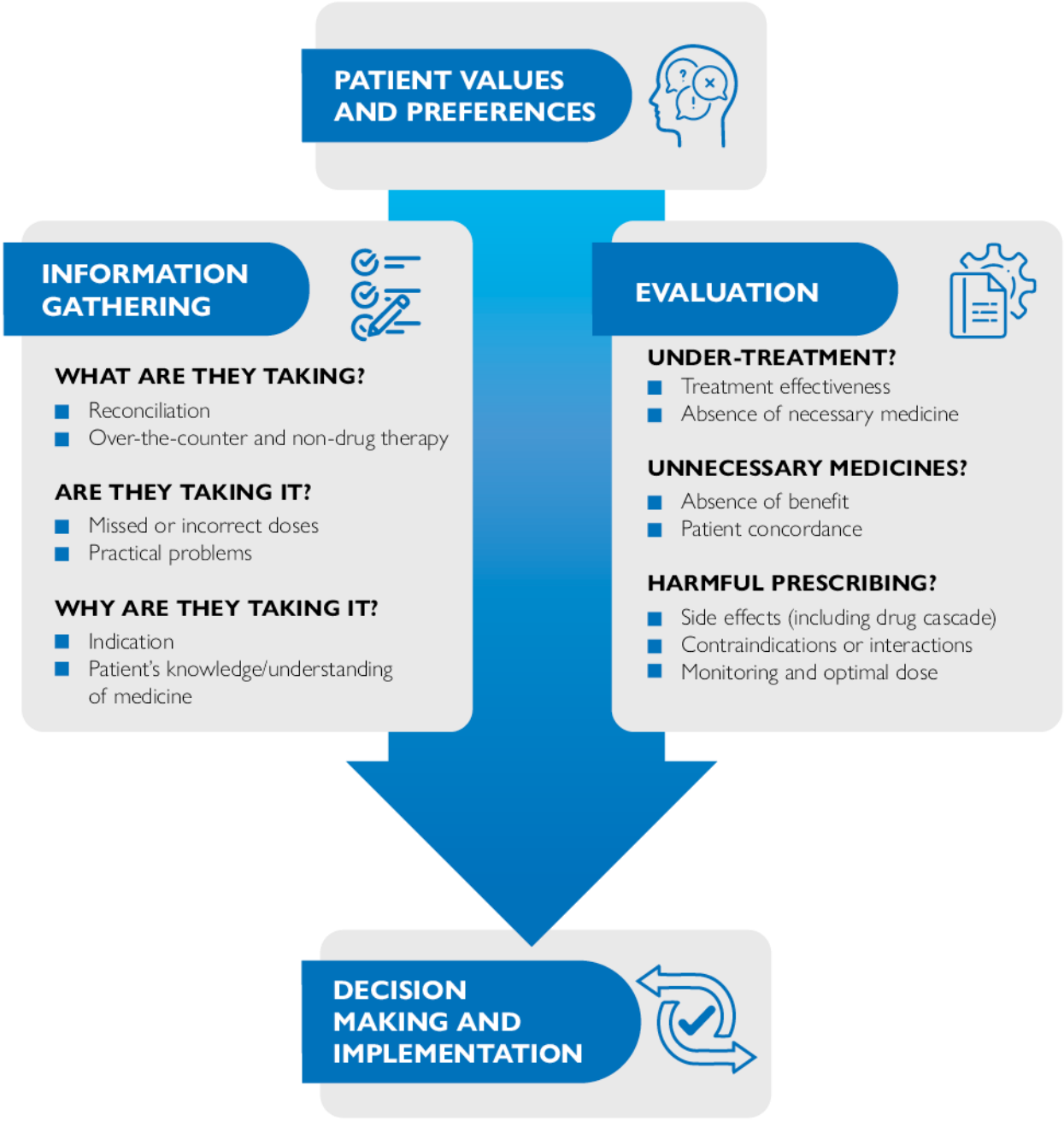
Additional details on the separate BRISMED Toolkit components are provided below.

8.2 Bristol Medication Review Model

The Model (Figure 1) integrates common themes identified through a systematic review of the literature, with a patient-centred approach[22]. The model has a clearly defined start focused on the patient's values and preferences, which continues through the review process. There is an information gathering phase which runs in parallel with an evaluation phase. The former focuses on what is being taken and why (i.e. history taking and reconciliation, assessment of adherence, rationale for treatment), and the latter on the medicines (i.e. undertreatment, overtreatment, harm). These feed through to the final decision making and implementation stage. The model was designed to emphasise patient centredness, a holistic approach, to be more in-keeping with traditional consultation structure and patient expectations, and to be flexible to accommodate differences in approach to

consulting particularly between professions. The BMR Model has received favourable feedback at medicines optimisation training delivered by Price (co-app) to clinicians in our local area.

Figure 1. Bristol Medication Review Model



8.2.1 Clinical guidance

A short guidance document has been developed to facilitate use of the BMR Model. This includes recommendations on use of the model, including a glossary of terms and definitions explaining the

different elements of the model in more detail, and a list of “example questions” suitable for the clinician to ask as part of a patient-facing review. This was published as part of the original model development paper [22].

8.2.2 Primer document

This brief patient leaflet provides information about the upcoming review, and offers the patient an opportunity to reflect on their medications, including any specific problems or particular priorities they may have. In many cases, patients have had little opportunity to prepare for a medication review, and as a consequence the review may be more focused on clinician priorities rather than those of the patient[30]. The primer document helps the patient prepare for and focus the review, as well as gathering information in advance. The BRISMED primer document was developed in consultation with patients as part of other work conducted to understand patients’ perspectives of medication review in primary care [30]. Translation of patient-facing materials will be undertaken.

8.2.3 Training materials

We have developed a training programme in medication review as part of our ongoing IMPPP polypharmacy clinical trial[13]. This includes elements on patient-centred structured medication review, potentially inappropriate prescribing, and common but particularly challenging aspects of prescribing (e.g. deprescribing, non-adherence). Feedback on the training from participating clinicians has shown high satisfaction. We are also able to draw on a range of materials we have developed for training GP trainers and undergraduate students about medication optimisation. These materials will be adapted for the proposed study to include video and written materials for clinicians. The BRISMED Training Programme will be designed to minimise workload for clinicians (e.g., taking a total of 1-hour to complete), comprising six, 10-minute self-directed (e.g. not requiring completion all at once), interactive (e.g. include videos and self-assessment) learning modules which focus on delivery of patient-facing medication review. Clinicians will be able to download a continuous professional development (CPD) certificate following completion of training. The BRISMED Training Programme will be made freely available to clinicians at intervention practices via a designated intervention website (further details of the website are provided within the Intervention Manual; 4.0 BRISMED Training Programme and 6.0 BRISMED website for intervention practices).

8.2.4 Clinical system templates

Clinical templates suitable for use within the two major clinical informatics systems used by GP practices (EMIS, SystmOne) will be developed. These templates will include elements which align with the BMR Model. They will also provide links to training resources and other relevant supporting materials and show automated prescribing safety indicators (e.g. describing potentially inappropriate prescribing) which have been developed for and are widely used within routine general practice [20]. Templates are widely used by practices for recording data as part of a wide range of clinical activities, so clinicians are familiar with using them (further details are provided within the Intervention Manual; 5.0 IT Template).

8.2.5 Implementation recommendations

Recommendations will be provided to practices on how best to implement the review model. This will include advice to practices on how to hold an initial engagement event with clinicians and working with their local Patient Participation Group. Similar materials will be provided to PCNs to promote the work to practices. Most of this guidance has already been developed as part of the original published BMR Model development work[22]. During the initial study set-up period, we will consult clinicians and commissioners through online workshops to identify possible barriers and facilitators to adoption, and

explore how best to enhance practice/practitioner engagement; this will be used to further enhance the recommendations on implementation.

8.3 Delivery of the intervention

The Bristol Medication Review Toolkit intervention will be rolled out simultaneously to the practices randomised to the intervention arm of the study. Practices will access the BMR toolkit, training programme, IT templates, supporting material and implementation recommendations via a designated, easy to use website. The link to the website will be shared with intervention practices only. To access the BRISMED intervention resources via the website, clinicians will be required to log in by selecting their practice name from the drop-down list of intervention sites and entering their name. (see Intervention Manual; 6.0 BRISMED website for intervention practices). Login requests to the website will be captured to enable assessment of usage of these resources at intervention sites as detailed within sections 10.4.1 and 10.4.2 below.

Intervention delivery will take place over a period of 12 months commencing 1st April 2024.

9.0 Usual care comparator

There are no established approaches for undertaking medication review in current UK general practice. The nature of usual care is uncertain, but probably comprises a combination of structured medication reviews delivered by practice-based pharmacists (as part of the NHS England Directed Enhanced Service) and some GPs, alongside brief, opportunistic, largely unstructured medication reviews conducted predominantly by GPs during routine consultations for other purposes. There is variability in training (with many clinicians receiving none), clinical approaches to review, use of templates, and strategies for implementation. Medication reviews are generally recommended to be carried out on a minimum of an annual basis for patient receiving long-term medications.

10.0 Process evaluation

A mixed-method process evaluation will be conducted to understand practitioner/patient views/experience of medication reviews, identify possible mechanisms and contextual factors behind treatment outcomes in both trial arms, and to explore acceptability, implementation and scalability of the BRISMED Toolkit. This will be achieved through: 1) patient surveys to evaluate their experience of the review itself, and then their quality of life; 2) in-depth interviews with practitioners and patients to explore views and experiences of the review in terms of content, delivery and outcomes ; 3) analysis of audio-recording observations of medication reviews to assess treatment fidelity; and 4) quantitative evaluation of practice engagement (a practice-level survey plus routine practice data).

All practices will be asked if they are willing to participate in the process evaluation. Of those who are agreeable, we will recruit a representative sample (see Sampling/Recruitment above for criteria) of 28 intervention practices and 28 control practices to participate in the process evaluation. Stratified sampling will be used to ensure an appropriate range of socioeconomic deprivation (based on practice IMD) and presence or otherwise of a practice pharmacist. IMD is likely to correlate with other important diversity factors such as ethnicity. Practices will be required to have the necessary Accurx text messaging technology with bulk messaging functionality (approximately 70% of all UK practices). Patient surveys will be conducted in all 56 of these practices, but interviews and observations of reviews will only be carried out in a smaller number as detailed below.

10.1 Patient surveys

10.1.1 Searches

Patient surveys will be conducted electronically in all 28 intervention and 28 control practices. Practice administrative staff will conduct searches of the clinical system for patients with a medication review code recorded in a specified time frame as detailed below. A bulk SMS text message will then be sent to the resulting list of patients using the Accurx system. The text message will include a link to an online survey; patients can contact their practice for a paper version if they wish. All GP clinical systems have the necessary functionality to carry out the required searches, and process evaluation practices will have been selected to ensure they have the necessary Accurx technology too. Conducting the searches and text messaging is relatively straightforward, but practice administrative staff will be provided with clear step-by-step instructions to help with the process. Although a relatively quick process, we will limit the number of times it is required to minimise the workload for practices. By using an established technology, we mitigate the risks associated with what is otherwise a relatively novel approach to carrying out this work.

10.1.2 Response rates

Response rates to text messaging surveys can be as low as 10% in eneral population[38], but have been found to be substantially higher (>60%) for those associated with specific clinical care[39]. By ensuring surveys are very short, and it's clear to patients that it relates to a specific aspect of care delivered by their practice, we hope to maximise engagement. Smartphone usage is now widespread even in older patients. We therefore anticipate that response rates will still be reasonable, although will adjust for response bias in subsequent analyses (see 10.2.5 Analysis of survey data below).

10.1.3 Patient experience survey

A patient survey will be sent to all patients who have received a medication review in the previous 2 weeks (i.e. around 15% of reviewed patients). Surveys will be conducted every 3 months during the 12-month intervention delivery period to assess the patient's experience of their review. By using a 2-

week limit, this should improve patient recall, and hopefully improve engagement. By conducting the survey at different time points, we will be able to see if patient experience varies over time (e.g. due to a learning effect or other change in practice). The patient experience survey will be built on existing instruments, including questions on shared decision making (CollaboRATE[41]), empathy (CaRE measure[42]), and both confidence and satisfaction (5-point Likert scales[13]). Patients will additionally be asked whether they are willing to be contacted separately to participate in an interview, as detailed above in section 5.2.4 Identification and recruitment of patient participants for interview. Electronic validation will be used to ensure response completeness in the electronic survey to reduce the risk of missing data.

10.1.4 Quality of life survey

A further patient survey will be conducted at two time points to assess patient quality of life. This will be sent at 9 months to all patients receiving a review in the first 6 months of the intervention delivery period, and at 15 months to all patients receiving a review in the second 6 months of the intervention delivery period. This will provide quality of life measures (EQ-5D, EQ-VAS) and potentially additional relevant measures (e.g. treatment burden) at 3-9 months following the review. Again, we will be able to see if there is change over time between the first and second halves of the intervention delivery period. It is not straightforward to assess QoL at baseline, because it is not possible to know when the medication review will be carried out for a given patient. This prevents us conducting a full cost-effectiveness analysis, although it is still possible to undertake a cost-consequences analysis (see 12.0 Economic evaluation below).

10.1.5 Analysis of survey data

A straightforward analysis will be conducted of findings, comparing outcomes (experience of care, quality of life) between trials arms, adjusting for key patient characteristics and clustering by practice. In particular, we will account for inclusivity and diversity by adjusting for patient factors such as deprivation and ethnicity, in our analyses. Quality of life measures will also be used in the economic evaluation. There is a potential for response bias in survey respondents. We will therefore capture core individual data on respondents in the survey that we predict to be associated with response rates, including age, gender, ethnicity, and education (this will be used as a proxy measure of socioeconomic status), in addition to morbidity status (from a core list of health conditions drawn from the Cambridge Multimorbidity Score), number of repeat medicines, and specific medications classes (based on BNF grouping).

At present, we are not certain whether we will be able to collect individual level data for non-responders: Accurx are currently undertaking development work which may allow this to be done. If available, we will use inverse-probability weighting to adjust for survey response rates. If individual non-response data are not available, we will still be able to get population data at each practice alongside the data from responders, and we use one of a number of alternative methods as summarised by Keeble [DOI: 10.4236/ojepi.2015.53020] to adjust for selection bias as a sensitivity analysis depending on the exact nature of the data available; this will be specified in the Statistical Analysis Plan.

10.2 Qualitative interviews

We will conduct ~22 patient interviews (15 intervention, 7 control) within one month of review completion. Details of the approach for identification, invitation and recruitment are provided earlier. The survey will occur within 2 weeks of the patient's review, and patients will be invited for interview as

soon as possible after this to limit recall bias. Interviews will explore patients' views and experiences of the review in terms of content, delivery and outcomes, including preparedness, patient-centredness, shared decision making and acceptability.

We will also interview ~22 GPs and pharmacists from the 56 process evaluation practices (15 from intervention arm, 7 from control arm) with purposive sampling including for usage of the BRISMED Toolkit in the intervention arm. Interviews will explore practitioners' views/experiences of conducting reviews and identify what drives review content/delivery. Practitioners in the intervention arm will also be asked about their use of the BRISMED Toolkit, how it affected and informed their practice, and how they think it could be implemented nationally. Practitioners will be interviewed once the intervention delivery period has ended, to avoid the interview process influencing their views of the study and intervention.

Interviews will be semi-structured to ensure key areas are discussed, whilst allowing participants to raise issues they consider important. Separate topic guides will be developed in parallel for practitioner and patient interviews, including questions relevant to both interviewee groups, aiding cross-group comparisons. Interviews (~40 mins) will be conducted online or by phone. Data collection and analysis will proceed in parallel, with initial findings informing the focus of later interviews. Data collection will end when saturation is reached[43].

With participant consent, interviews will be audio recorded and transcribed verbatim. Data will be analysed thematically[44] to allow comparisons to be made within and across data sets, permitting identification of key themes, deviant cases, and differences/similarities in the views of patients, GPs and pharmacists. Two researchers will independently code a subset of transcripts, then discuss coding discrepancies to achieve consensus and maximise rigour. Throughout analysis, findings will be presented to the wider research team and PPI advisors to encourage reflection and ensure credibility. NVivo software will be used during data analysis to aid data management and to facilitate electronic coding and retrieval of data.

10.3 Observations of medication review

Audio-recording of reviews will be undertaken in both trial arms to examine how reviews are conducted in practice, including how the BRISMED Toolkit is implemented and affects review content/delivery in intervention practices. This data collection method is less intrusive than in-person observation, so less likely to influence practitioner behaviour. We have successfully used this approach to evaluate reviews as part of our IMPPP polypharmacy trial.

We will ask clinicians to record 20 consecutive reviews conducted over a 2-week period in 10 intervention and 5 control practices (i.e. total 300 reviews); this simplifies logistics as no decisions need taken by the clinicians or research team with respect to which specific reviews should be recorded. We will vary the timing of this activity in different practices, to allow us to examine whether changes in practice occur over the intervention delivery period. From the 300 reviews recorded, we will then purposively sample up to 25 and 15 reviews from intervention/control arms respectively, with a mix of GPs and pharmacists, and within the intervention arm select recordings where the BRISMED Toolkit has been used (identification, recruitment and consent processes are detailed above within Recruitment procedures; Section Sampling and consent for observation of medication review).

Analysis will focus on the content/delivery of reviews, using conversation analysis techniques[45] to explore practitioner and patient interaction. A bespoke observation guide will be co-developed by the

research team and PPI advisors. Specific elements of this guide will focus on person-centred communication and associated behaviours, informed by questions from existing instruments (e.g. SDM-Q9[46], CollaboRATE[41], CaRE[42], 5-item OPTION[40]). When analysed alongside data from the patient/practitioner interviews, this will provide detailed understanding of how reviews are conducted in practice.

10.4 Implementation evaluation

We will assess intervention implementation of the BRISMED Toolkit by examining rates of recorded medication review (including use of the BMR Model) using routine practice data extracted by the ORCHID system, and by distributing a short, practice-level survey to all participating intervention practices once intervention delivery ends. The practice-level survey will be used to capture data related to routinely used practices and processes for the organisation and delivery of reviews (i.e. usual care) including which professionals conduct reviews (e.g. GP, clinical Pharmacist), the mode of delivery of reviews (e.g. in-person, via telephone), type of review (e.g. structured medication review with the patient), content of review (e.g. patient perspectives, safety, medication use considerations) and use of tools or models to support delivery (e.g. Scottish 7-Steps, NO TEARS). Additionally, the practice-level survey administered to intervention practices will capture measures of engagement with the intervention to quantify the nature of implementation (e.g. number/type of clinicians involved, which elements of the BRISMED Toolkit were used). This will help understand differences in outcomes between trial arms.

10.4.1 Assessment of fidelity

The BRISMED Toolkit comprises five key elements (review model, primer document, guidance documents, training materials, IT templates), and it will be possible to quantify usage of these within all the intervention sites. Implementation data for all intervention sites will be collected from several sources. Use of the training materials will be captured through login requests to the website and time spent on the website, providing us insight into which practices have accessed these materials and for how long. We will be able also to quantify use of other BRISMED Toolkit materials on the website by clinicians (e.g. downloads of primer, guidance documents, templates).

The IT templates given to intervention practices will be designed so that data recorded within the template is coded in a specific way within the clinical record (e.g. coded record identifying use of the BRISMED Toolkit). This information will then be extracted alongside other routine clinical practice data through the ORCHID network system. This will be possible in all intervention practices and not just the subset involved in the process evaluation.

Additionally, a practice-level survey will be administered to all intervention practices at the end of intervention delivery. The survey will capture information related to usage of each the five elements of the BRISMED Toolkit and the number and type of clinicians engaging with and using the intervention to support medication reviews.

10.4.2 Analysis and reporting of fidelity

Descriptive analyses will be undertaken to categorise practices according to fidelity/implementation, for different aspects of BRISMED Toolkit usage (i.e. engagement in training, usage of BRISMED online materials and IT templates, responses to practice- level, end-of-study survey). Secondary analyses will then be undertaken to explore how effectiveness varies by degree of fidelity, providing mechanistic insights into intervention efficacy. However, the primary effectiveness analysis will be performed using the ITT principle to preserve randomisation and avoid baseline confounding; this analysis will not adjust for fidelity.

11.0 Statistics and data analysis

11.1 Sample size calculation

Based on baseline pilot data from our IMPPP trial evaluating primary care management of polypharmacy (NIHR ID 16/118/14), and previous data on the prevalence of STOPP/START indicators[31], we expect 40% of patients to be eligible for review, with a primary outcome rate of 20%. Work by Stocks[32] found an ICC of 0.04 for a composite potentially inappropriate prescribing (PIP) indicator in UK general practice. Two other studies using similar outcomes have found ICCs on the GP practice scale ranging from 0.01 to 0.025 [34] [35]. A Cochrane review found a mean risk reduction of 21% in PIP[33]. Based on more conservative values (RR=15%) and using the upper estimate of ICC on the GP practice scale (0.04), 250 PCNs per arm (mean±SD size 20593±15229, with 40% eligible) per arm provides 93.3% power (alpha=5%) to detect a meaningful 15% relative reduction in primary outcome.

We estimate that of those on medications, 76% of individuals will be receiving up to 6 regular medications. This makes no difference to the power we would have to detect an effect within this subgroup.

With practices undertaking 5000 reviews per year (40% review rate from an average of 12514 patients), surveys sent to half of patients receiving a review, and a survey response rate of 10%, we can anticipate ~250 responses to the QoL survey per practice. The coefficient of variation in ORCHID practice list size is around 0.68. The DREAMeR medication review trial found a baseline EQ-VAS of 70 (SD 16)[36], and we estimate an ICC on the GP practice scale of 0.11 [37]. Based on an effect size of 5 points on the EQ-VAS, 28 practices per arm (total 56) will provide us with 80.8% power.

Sample size calculations have been carried out on the PCN scale for the main study which is the unit of randomisation. Sample size calculations for the process evaluation are carried out on the GP practice scale however we will ensure that only one GP practice per PCN can be randomised to the process evaluation to maintain independence within a PCN.

11.2 Progression criteria

A single “stop-go” criterion related to practice recruitment is proposed, prior to intervention roll-out, to mitigate the risk associated with inadequate recruitment:

- ≥380 practices per arm (i.e. >80% power) – proceed with intervention roll-out
- 300-379 practices per arm (i.e. >70% power) – discuss with funder including either proceeding regardless, or extending recruitment for an additional 3 months
- <300 practices – discuss termination of the study with funder, or restricting to the planned process evaluation analyses in the subgroup of 56 practices (this will still provide invaluable data into quality of life, treatment burden and other aspects of patient and clinician experience which will be extremely useful in its own right).

11.3 Statistical analysis plan

The analysis and reporting of this trial will be undertaken in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines, as extended to cluster trials. The statistical analyses will follow a pre-defined Statistical Analysis Plan (SAP) agreed with the TSC and DMC. The main primary

outcome comparative analyses between randomised arms will be conducted on an intention-to-treat (ITT) basis without imputation of missing data.

11.3.1 Preliminary analyses

Descriptive statistics of baseline cluster level and individual level clinical and socio-demographic characteristics will be used to describe the study sample and to ascertain comparability of the randomisation groups.

11.3.2 Main analysis – primary outcome measure

Our primary outcome will be potentially inappropriate prescribing (PIP). This will be a binary variable, including the widely used STOPP/START indicators (these are originally designed for assessing prescribing in the elderly, but many are still relevant to younger patients) and the most frequently occurring age-independent PIP indicators identified from our IMPPP trial. The potentially inappropriate prescribing indicators used in the IMPPP trial are well established and were previously successfully employed in the DQIP trial[21].

The primary analysis will use random effects Poisson regression on the practice scale to explore the rates of potentially inappropriate prescribing indicators within each GP practice at the end of the intervention period by arm using the ITT principle. The random effect will account for clustering by PCN. The number of patients potentially eligible for review at each GP site will be used as the offset term whilst also adjusting for the baseline rates of the outcome. We will determine baseline rates by looking at the electronic prescribing records at each GP site in the 12 months prior to randomisation. This will be a test for superiority focussing on the estimate, 95% CI and p-value from the regression model.

Additional analyses - primary outcome measure

Additional analyses of the primary outcome will include a subgroup analysis of patients receiving ≤6 regular medicines. Methods for subgroup analyses are described in the section below, 11.3.3.

This *a priori* subgroup analysis is proposed as there is evidence from our IMPPP trial that patients with fewer medicines may have greater benefit [currently unpublished], and that interventions focused on narrower aspects of prescribing safety (and thus potentially less complex patients, with fewer morbidities or medicines) show effectiveness [20,21].

11.3.3 Secondary analyses

Analysis of the secondary outcomes will use the same method as for the primary outcome analysis. Subgroup analyses will be undertaken by age, sex, socioeconomic status, medication count, and evidence of implementation within practices (coded record identifying BMR Model). We will not fit different regression models for each subgroup, but instead will add an interaction term to the analysis model to derive the effect size within subgroups; this is more efficient and allows a hypothesis test of effect sizes being different in subgroups.

We will explore analyses on the individual level for the primary and some of the medication-related secondary analyses (e.g. medication count, MRCI). However, this approach is logistically problematic for the analysis of outcomes such as health service utilisation or medication adherence, which might take up to 12 months to become apparent. A considerable (i.e. 12-month) wait would be required after the intervention period ends for all the necessary data to become available. Analysis on the practice scale mitigates this issue.

Our analysis of quality of life and patient experience will be random effects regression models (linear, logistic or Poisson models, as appropriate) for each individual by arm using the ITT principle. A random effect will account for clustering by GP practice. This will be a test for superiority focussing on the estimate, 95% CI and p-value from the regression model.

Missing data is unlikely to be a significant issue for our main analyses, e.g. if a drug or disease is missing in routine data it is generally assumed that this corresponds to its absence rather than a recording omission, and it is generally difficult (and often impossible) to distinguish these two possibilities. Given the nature of routine health record data, other key factors such as age and gender are unlikely to be missing. We will explore the nature of missingness for other patient-level data such as ethnicity and socioeconomic deprivation, and use established approaches such as multiple imputation to address missingness if appropriate.

12.0 Economic evaluation

12.1 Health economic cost consequence analysis

There is a paucity of robust economic evidence on medication reviews; one review study found few trials had included an economic evaluation and those that did were of limited quality[47]. Good economic evidence is crucial to determine if the time, effort and costs involved in conducting a medication review using the BRISMED Toolkit are an appropriate use of limited NHS resources.

The outcomes from improved medications reviews are multiple and include health and non-health benefits which are difficult to reduce to a single measure. In this trial the economic evaluation will be a cost consequence analysis (CCA)[48] which considers all the health and non-health benefits of an intervention, even those which cannot be costed. This is a distinguishing feature from other types of economic analysis. It accepts that different types of benefits cannot be measured using the same units and reports them in a disaggregated form. The initial cost of implementation is compared to subsequent NHS savings and changes in patient reported outcomes. This will provide a table of mean costs and outcomes/effects with incremental differences between the trial arms, including confidence intervals and p values. A CCA will provide a clear descriptive summary that will allow decision makers to form their own opinion on the importance and relevance of the costs and outcomes to their decision-making context. CCAs have been recommended for interventions (such as BRISMED) that have multiple effects[49], and a combination of numerous health and non-health benefits that may be difficult to measure in a common unit[50].

We will record direct costs to the NHS of implementing the BRISMED Toolkit (engagement events, materials, training, staff time to deliver intervention, etc.) as well as indirect (productivity losses, additional GP consultations, unplanned admissions) and intangible costs (quality of life, patient experience). Routine data will allow us to compare costs of long-term medicines and subsequent care use (i.e. GP consultations, admissions, ED visits) between arms. Using CCA will allow us to report other relevant outcome information collected in a subset of patients including duration of medication reviews (audio recordings in 300 patients), and patient experience and quality of life (patient surveys). EQ-5D is the most widely used measure of quality of life, although it is unclear whether it will be sensitive to the effect of medication reviews. We will, however, include EQ-VAS which was found by the DREAMeR study to be impacted by medication review[36].

The approach for dealing with missing data or response bias will reflect that taken for the other statistical analyses mentioned earlier.

In the present study it is not possible to use longer-term economic modelling, firstly as medication reviews will occur multiple times (at least annually) there is a (complex and unpredictable) accumulative effect to consider which would require a longer period of observation. Secondly there is no cost effectiveness outcome in the current study such as an incremental cost effectiveness ratio or net monetary benefit. The reasons for not pursuing a cost effectiveness analysis are three-fold: firstly, in the short-term we are unlikely to see a change in quality of life measures, and therefore we could not justify the additional cost of collecting them beyond baseline; secondly, a cost effective outcome based on cost per incidence of PIP avoided is not a very useful measure for decision makers; thirdly, the intervention involves multiple effects and a combination of health and non-health benefits which are difficult to combine into one single measure. In these cases, the recommended analysis is cost consequences, which is what we are pursuing.

The health economic analyses will follow a pre-defined detailed approach presented in a separate Health Economics Analysis Plan (HEAP).

13.0 Data handling

13.1 Data collection tools

Data for the main analysis will be collected through the ORCHID network. This includes a database of contact details for individual practices participating in ORCHID. The ORCHID database is hosted by the Nuffield Department of Primary Care Health Sciences at the University of Oxford. The network is a resource for UK-wide health research and a Trusted Research Environment (TRE) with expertly curated themed datasets to support health research. The pseudonymised data, extracted by information service providers, are processed within the private and secure network of the Clinical Informatics and Health Outcomes Research Group at University of Oxford under a formal data sharing agreement.

For the purposes of the process evaluation, patient and practice staff contact details in the 56 participating practices needed for day-to-day study management will be entered onto the trial management REDCap database. Other quantitative process evaluation data will primarily be in the form of participant self-report of online questionnaires. These data will be anonymised and entered directly into a REDCap database, held on secure servers at the University of Bristol; equivalent online forms will be developed within REDCap itself. REDCap is a secure web application for building and managing online surveys and databases. REDCap is specifically geared to support online or offline data capture for research studies and operations. The REDCap Consortium, a vast support network of collaborators, is composed of thousands of active institutional partners in over one hundred countries who utilise and support REDCap.

Further data for the qualitative elements of the process evaluation will be collected by the qualitative researcher using a variety of media as detailed elsewhere. Audio recordings will be captured using encrypted recording software/hardware. Transcriptions will be undertaken by a service approved by University of Bristol and transferred in an anonymised format to the institution's secure Research Data Storage Facility (RDSF) for analysis.

13.2 Data handling and record keeping

Anonymous data extracted for the main analysis (including any externally linked data, such as hospital records) will be initially stored and processed within the University of Oxford's systems, in line with standard ORCHID processes. Only once processed, with required data minimisation applied, will any data be transferred to the University of Bristol RDSF for statistical analysis. These data will only be labelled with anonymous identifiers, and will not identify patient, practice or PCN.

Four separate servers will be used to store the main trial analysis data (RDSF), survey data (REDCap), qualitative recordings (RDSF), and any person-identifiable data (REDCap trial management database).

Data will be collected and retained in accordance with the General Data Protection Regulation 2018 (GDPR) (see section *17.6 Data protection and patient* confidentiality for more details) and The University of Bristol, Research Data Service 'Guidance on the Retention of Research Records and Data' (Version 2.0 January 2019) .

In accordance with REC requirements, regulatory authorities including monitors and auditors from NHS Trusts may request access to source data and documents for cross checking. This will be

explained in the participant information sheet and a statement included as part of the written consent form to be signed by the participant.

13.3 Access to data

The Senior IT Manager (in collaboration with the trial manager and Chief Investigator) will manage access rights both to the participant contact data in the trial management REDCap database, to the survey data held in REDCap, and to the main trial analysis data and qualitative data stored in the respective RDSF servers.

Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that once the trial is completed, anonymised trial data will be made available through the RDSF to facilitate sharing with other researchers once appropriate (separate) approvals are in place.

13.4 Archiving

The University of Bristol will be the data custodian for all study data, irrespective of study site. All data will be held in Bristol and will conform to the University of Bristol's data security policy. All data will be held in compliance with GDPR and other relevant legislation. Further details are provided under *17.6 Data protection and patient* confidentiality.

14.0 Safety

Medication review involves starting, stopping and otherwise changing medicines, and there is risk involved in this activity. However, this is a standard part of clinical practice, and we consider the safety risks posed by implementing the BRISMED Toolkit, over usual practice, to be very low. Nevertheless, out of an abundance of caution, we will conduct a pragmatic interim safety analysis, as well as allowing for spontaneous reporting where considered appropriate by the local principal investigator (PI).

14.1 Interim safety analysis

14.1.1 Timing of interim analysis

The safety analysis will be conducted at 3 and 6 months. We have selected these time points as a compromise between providing adequate time for the intervention to have an impact (especially by 6 months), while providing enough time and opportunity (particularly at 3 months) to take action in the unlikely event of discrepancies in potential safety events occurring between the two arms.

14.1.2 Data extraction

It is not feasible to use the ORCHID system or NHS England/digital to extract data for the safety analysis (detailed in 14.1.4 below) prior to the end of the study, so instead this will involve the 56 practices participating in the process evaluation. These practices will conduct a search in their clinical system of patients who have received a medication review in the previous 3 months. As patients will not have provided explicit consent, this search will only be used to generate aggregate patient numbers, and this will be used to assess rates of GP coding of adverse drug reactions, all-cause unplanned hospital admissions, and death between the two trial arms.

We have considered the ability to detect differences between the two arms of the study in these safety outcomes. Using similar numbers to the primary outcome sample size calculation with mean size of these practices 12514 (SD: 8473), 40% eligible and an ICC of 0.10 the table below shows the minimum detectable difference between the arms based on different baseline proportions of these outcomes and a power of 80% or 70%. The ICC uses a higher more conservative estimate than the primary outcome as only the practices within the process evaluation will contribute data to this safety analysis and is on the GP practice scale rather than the PCN scale. In all these cases, the minimum detectable difference is relatively large. We are not powered to detect relatively small differences in adverse event rates, but we anticipate 80% power to detect a ≤10% absolute increase in adverse event rate (assuming a baseline of event rate of ≤10%, and similar ICC and distribution of practice size to the main trial).

Baseline proportion	Detectable difference (80% power)	Detectable difference (70% power)
0.01	0.054	0.045
0.02	0.064	0.054
0.05	0.083	0.072
0.1	0.103	0.090

14.1.3 Categorisation of safety events

For an average practice with list size 10,000, this equates to approximately 1,000 medication reviews being undertaken in a 3-month period. The very nature of medication reviews includes the explicit identification of potential safety concerns, but these numbers make it entirely unfeasible to conduct a formal categorisation of safety events. Local PIs will therefore not be asked to review events to attribute seriousness, intensity, relatedness and expectedness.

14.1.4 Analysis

The analysis of the interim safety measures will use the same approach as the main analysis for the primary outcome measure (section 11.3.2). That is random effects Poisson regression on the practice scale to explore the rates of the safety measures within each GP practice over the first 3 and also the first 6 months. The number of patients potentially eligible for review at each GP site will be used as the offset term.

14.2 Spontaneously reported safety events

If local PIs feel strongly that an event could be related to the use of the BRISMED Toolkit, they will still be able to submit a corresponding spontaneous safety report. Definitions of seriousness, relatedness, expectedness, and intensity are provided in Appendix 2. We note, however, that in our IMPPP study we received no spontaneous reports.

14.2.1 Reporting form

The reporting form for serious adverse events (SAEs) will include full details in medical terms and case description; event duration (start and end dates, if applicable); action taken; outcome; intensity and seriousness criteria; causality (i.e. relatedness to trial/intervention), in the opinion of the PI; and whether the event would be considered expected or unexpected.

14.2.2 Reporting time frames

Local PIs will be required to notify the Sponsor and the central research team of any Serious Adverse Reactions; SAEs which they have assessed as being possibly, probably, or definitely related to the trial intervention or the research process, within 24 hours. Reports should be submitted in accordance with the standard operating procedure of University Hospitals Bristol and Weston, who manage safety reports on behalf of UoB. Those SAEs considered to be a Suspected Unexpected Serious Adverse Reaction (SUSAR) will be reported to the REC within 15 days of the Chief Investigator being made aware, using the relevant HRA report form.

14.2.3 Follow-up of SUSARs

All SUSARs will be actively followed-up by the local PI with follow-up information being provided to the research team using the SAE/SUSAR Follow-up Report Form, until the SUSAR has resolved. The research team will then forward the follow-up report form to the sponsor.

14.3 Data Monitoring Committee

The researchers will collate adverse event data for presentation to the independent Data Monitoring Committee (DMC). This will be done as soon as possible after the interim safety data are collected, at both 3 and 6 months. The DMC will also be presented with all spontaneous SAE reports (whether or not considered to be SUSARs) at all scheduled meetings.

15.0 Trial management

15.1 Day-to-day management

The study will be coordinated and project-managed by DM as chief investigator. RP will provide clinical leadership of the project as deputy chief investigator, and will additionally provide mentorship and support for DM.

A Trial Management Group (TMG), consisting of the applicants and all other researchers will meet monthly throughout the entire duration of the project to ensure smooth progress of the research; these meetings will be held by videoconference.

Additional meetings will be hosted (primarily in Bristol) to support finalising and rollout of the BRISMED Toolkit, planning for data extraction, supporting data analysis, and reporting planning and writing. Some of these meetings will be hosted in-person to facilitate discussions including problem-solving and decision-making.

A Bristol-based trial administrator will support project management, alongside additional administrative staff from the established ORCHID team in Oxford. This will include delivery of remote surveys and undertaking health record data extraction through the ORCHID system.

An appropriately experienced senior research associate will undertake data gathering and analysis for the qualitative elements, with senior methodological support provided by KT. ORCHID-based researchers will undertake health record data curation and management.

A further two Bristol-based research associates will undertake the statistical and economic analyses, with senior support from ML and PM respectively.

15.2 Principal Investigator

Principal investigators (PIs) at each site participating in the process evaluation will be a GP, pharmacist or other clinician with appropriate GCP training. They will be responsible for oversight of research activities being conducted at the site and facilitating the search activity for interim safety reporting purposes.

Because of the practice-level nature of intervention delivery, many of the clinicians who deliver the BRISMED intervention, even in practices signed up for the process evaluation, may not have received GCP training or indeed be fully aware of the nature of the trial. These clinicians will therefore not be expected to be involved in safety reporting, other than in consultation with the local PI.

15.3 Chief Investigator

The Chief Investigator, delegating to the Deputy Chief Investigator where appropriate (e.g. for clinical decisions), will be responsible for:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning intensity, seriousness, causality and expectedness of spontaneously reported SAEs, where it has not been possible to obtain local medical assessment.

- Immediate review of all reportable SAEs including expedited reporting of SUSARS to the Sponsor and REC within required timelines.
- Central data collection of SUSARs and deaths and notifying PIs of SAEs that occur within the trial.
- Ensuring safety reports are prepared in collaboration with appropriate members of the TMG group for the main REC, DMC and TSC.

15.4 Sponsor

The sponsor (University of Bristol) will be responsible for overall oversight of the trial.

15.5 Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial, monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

The TSC will meet on 4 occasions (or more frequently if deemed necessary by the TSC) to provide external oversight, supervision and advice about all aspects of the research.

Membership:

- Dr Deborah McCahon, CI, University of Bristol
- Prof. Nefyn Williams, Independent chair and academic GP, University of Liverpool
- Prof. Alex Bottle, Independent statistician, Imperial College London
- Prof. Simon Fraser, Independent academic GP, University of Southampton
- Prof. David Alldred, Independent academic pharmacist, University of Leeds
- Dr Hayley Gorton, Independent academic pharmacist, University of Huddersfield
- Ms. Mary Mancini, Independent lay member
- Ms. Frances Place, Independent lay member

15.6 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be established consisting of 3 independent academic members, including two statisticians and a clinician with relevant interests. The DMC will meet before each TSC as necessary, as well as at 3 and 6 months to review interim safety reporting data.

In accordance with the Trial Terms of Reference for the DMC, this group will be responsible for assessing safety and efficacy of the trial.

At the first DMC meeting, the committee will agree on its charter of operations and advise on the way safety data should be presented at future DMCs and whether stopping rules for efficacy or safety are required. The DMC will report findings and recommendations to the TSC.

Membership:

- Dr Mariam Molokhia, Independent chair and academic GP, Kings College London
- Dr Matt Barclay, Independent statistician, University College London

- Dr Anower Hossain, Independent statistician, University of Warwick

15.7 Patient Advisory Group (PAG)

Patient input informed the funding application and has already informed the design of this study. Patient input will continue to be essential in terms of intervention development and the trial itself, including ethical issues that may arise as a consequence of an intervention.

To ensure our research is grounded in end user needs, we will recruit a Patient Advisory Group (PAG) to help deliver this research, recruiting PPI advisors from our existing networks (Bristol, South-West, Leeds-Bradford, South Wales, London) to maximise geographical and sociodemographic variation in experiences/views. Advisors will contribute to research conduct and management in five in-person meetings, which will be used to discuss study progress, research delivery and troubleshooting, and interpretation of findings.

PPI co-applicant TY is a service user and will join the Trial Management Group (TMG) to ensure patient priorities are represented with respect to study oversight and decision making; the TMG will meet monthly, and additionally for specific elements of the project. TY has expressed a desire to co-chair PAG meetings with deputy chief investigator RP. TY and RP will facilitate interaction between the PAG and the TMG. As required, PAG members may be co-opted to the TMG to provide specific advice and expertise.

Two independent PPI advisors will support trial oversight as members of the Trial Steering Committee to ensure decisions promote and protect the public interest and produce outcomes that will benefit patients.

A funded PPI&E facilitator will provide practical and moral support, encouragement and guidance and ensure that training and other needs are identified and met. We will give PAG members a “job description” and time/travel expenses. Clear expectations/timeframes for tasks assigned to contributors will be set out, emphasising flexibility and level of involvement, to avoid fatigue/stress. We will offer learning opportunities, including informal in-house small group training, provision of high-quality written materials, and signposting to relevant online resources (NIHR Learn About Research) and training events (People in Health West of England, PHWE).

Advisors will contribute to writing of patient-facing study materials (e.g. participant information sheets, invitation letters), patient experience surveys and qualitative interview topic guides. Materials will be developed through ad hoc online working and in-person meetings. PAG members will also contribute to the in-person expert working group that will co-design and agree the final intervention resources for intervention practices.

We will also engage with Patient Participation Groups (PPGs) to draw on local community expertise/knowledge Most GP practices have a PPG which is a group of patients, carers and GP practice staff who meet to discuss practice issues and patient experience to help improve the service. . We will provide guidance to encourage practices to work with their PPG to identify potential barriers and enablers to intervention adoption. We will work with the National Association for Patient Participation to inform this guidance.

Dissemination to patients, carers and the wider public will be undertaken in close consultation with our PAG members. This will include co-production of press releases and public-facing materials, and identification of methods of public dissemination (e.g. websites, patient/carer workshops, online

information sessions). A study website will be developed, and we will work with the Bristol-based communications officer and use our institutions' social media outlets to update and engage the public during and after the study.

16.0 Monitoring, audit and inspection

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by the Sponsor, the relevant REC and for inspection by other licensing bodies.

16.1 Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations can happen at any time, but they must be adequately documented and reported to the CI and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

16.2 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree:

a) the safety or physical or mental integrity of the subjects of the trial; or

b) the scientific value of the trial

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. They will assess the seriousness of any breach in line with a corresponding SOP.

17.0 Ethical and regulatory considerations

This study will be conducted in accordance with:

- Good Clinical Practice guidelines
- UK Policy Framework for Health and Social Care Research

Any amendments to the trial documents must be approved by the Sponsor prior to submission to the REC.

Before any site can enrol patients into the process evaluation, the CI/PI or designee will obtain confirmation of capacity and capability for each site in-line with HRA processes.

For all amendments the CI/PI or designee will confirm with the Sponsor, the HRA (±REC) and sites' R&D departments that permissions are ongoing.

17.1 Peer review

The proposal for this trial has been peer-reviewed through the NIHR HS&DR peer-review process, which includes independent expert and lay reviewers.

17.2 Research Ethics Committee (REC) review and reports

Before the start of the study, a favourable opinion will be sought from an IRAS Ethics Committee for the study protocol, informed consent forms, topic guides and other supporting documents. NHS HRA approval will be required. Research sites will be practices drawn from across England.

All correspondence with the REC will be retained in the Trial Master File (TMF)/Investigator Site File (ISF). An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will notify the REC of the end of the study and if the study is ended prematurely (including the reasons for the premature termination). Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

GCP training will be carried out by certain staff members depending on their delegated responsibilities within the trial. The level of training required will be determined according to the NIHR Delegation and Training Decision Aid. Informed consent to participate in the trial will be sought and obtained according to GCP guidelines.

17.3 Amendments

The Sponsor will determine whether an amendment is substantial or non-substantial. All amendments will be processed through the HRA and where appropriate the REC. If applicable, other specialist review bodies (e.g. NHS Digital CAG) will be notified about substantial amendments in case the amendment affects their opinion of the study. Amendments will also be notified to NHS R&D departments of participating sites to confirm ongoing capacity and capability to deliver the study.

17.4 Indemnity

The necessary trial insurance is provided by the Sponsor.

17.5 Retention of data

To comply with GDPR and other relevant legislation, personal data will not be kept for longer than is required for the purpose for which it has been acquired. Data will be held in compliance with the Sponsor's standard operating procedures.

17.6 Data protection and patient confidentiality

The University of Bristol will be the data custodian for all study data, irrespective of study site. All data will be held in Bristol and will conform to the University of Bristol's data security policy. All data will be held in compliance with GDPR and other relevant legislation.

Participants' personal identifiers will be stored securely and separately from other trial data (e.g. clinical, questionnaires, qualitative), with these other data identified only using a unique participant code. All personal identifiers will be removed from data and securely destroyed within 3 months of completion of the final analysis.

After the final study analysis is complete, anonymised data from the process evaluation will be uploaded to a 'controlled access' data repository. This will be fully explained in the participant information sheet and participants will be asked to confirm their consent for this as part of the consent process. Data from the main trial analysis will not be stored, as patient's will not have provided consent.

17.6.1 Written data

All data in written form, such as written consent forms which contain participant names will be stored in locked filing cabinets in a secure University office. Personal identifiable paper records (e.g. hard copies of consent forms) will be kept separate from any anonymised paper records (questionnaires).

17.6.2 Electronic data

Electronic data will be stored on a secure password protected University network file-store where access is controlled by use of user accounts and file access control lists. Access will be granted only to those authorised users who require access for the purposes of data management and analysis. Servers providing the system hosting are located in secure data centres within the University of Bristol estate. These buildings are protected by secure automatic locking doors, requiring appropriate University Card (MiFare2) and biometric second factor-controlled access to enter (for limited authorised personnel only) and are monitored by CCTV by University security services. Locations of routers and switches are physically restricted to IT Services staff.

17.6.3 Recorded qualitative data

Audio recordings of participant or health professional interviews, and observations of medication review appointments, will be recorded on encrypted digital recorders which will be locked in a secured cabinet in the relevant local University department. Recordings will be transferred onto UoB servers, and stored in line with other electronic data (see above) as soon as possible after each use.

All recordings will be identified by unique participant identifier only, prior to secure transfer to a University of Bristol approved transcription company or transcriber that has signed the required confidentiality agreements. On receipt, all transcripts will be immediately transferred to a UoB server and stored in line with other electronic data. Participants will be required to consent to the specific

storage of anonymised interview data (transcripts only) on the 'controlled access' data repository. Patient and clinician participants will be offered the option to consent to storage of their audio-recording of the medication review on the 'controlled access' data repository.

17.7 Access to the final trial dataset

Anonymous research data from the process evaluation (but not the main trial analysis) will be stored securely at the University of Bristol and kept for future open access. At the end of the study, members of the TMG will develop a data sharing policy consistent with UoB policy. Requests for access to data must be via written confidentiality and data sharing agreements (DSA) with the CI (or his appointed nominee). A protocol describing the purpose and methods intended must be provided. Requests for data release outside of the planned analyses will be considered by the TSC. As data will be anonymised and identifiers destroyed, future linkage will not be possible.

The DSA will cover limitations of use, transfer to 3rd parties, data storage and acknowledgements. The person applying for use of the data will be scrutinized for appropriate eligibility by members of the research team. All requests will require their own separate REC approval prior to data being released.

17.8 Competing interests

The DMC will be entirely independent of the investigators, with independence as defined by NIHR. The TSC will have 75% of membership independent of the investigators. Competing interests of independent members will be declared directly to NIHR. The following are financial and other competing interests for the chief investigator and other investigators that may be perceived to affect the study:

- Rupert Payne (Deputy CI) holds various grants from NIHR related to polypharmacy, multimorbidity and medicines optimisation. He is consultant editor for the journal Prescriber.

There are no other competing interests.

18.0 Dissemination policy

Our dissemination strategy will be supported by local press offices and communication officers, with policy engagement facilitated through the University of Bristol's PolicyBristol initiative and the host organisation (Bristol, North Somerset and South Gloucestershire, Integrated Care Board) Impact Acceleration Unit. This will aim to maximise impact, with a key focus being on primary care professional and policy engagement.

18.1 Outputs

Our research team has considerable expertise in the presentation of research to a range of audiences, including working with key professional and policy organisations (e.g. RCGP, RPS, NICE) to promote engagement by clinicians and practices. We envisage a range of outputs, most to be produced in the final 6-month dissemination period:

- Free access to the BRISMED Toolkit for practising clinicians (including trainees and students) through a website (including guidance documents, educational materials, IT templates, etc).
- Open access journal publications , including 1) clinical effectiveness, 2) implementation, 3) patient and clinician experience of the intervention, and 4) health economics
- NIHR final report (including executive and Plain English summaries)
- Academic conference presentations (covering same areas as academic papers)
- Printed and electronic promotional material targeting NHS managers, commissioners and policy makers
- Policy briefing documents, drawing upon research findings plus feedback from stakeholder engagement exercise at a national workshop
- Information leaflets and infographics in English language and six of the most frequently encountered non-English main languages for patients about polypharmacy and medication review
- Trial website (providing patient information, and research updates throughout project including final results; this website linked to, but separate from, the BRISMED Toolkit website

18.2 Engagement with stakeholders

We will engage with the following audiences to disseminate findings and optimise impact:

18.2.1 Healthcare professionals

We will work with the Royal College of General Practitioners (RCGP), Royal Pharmaceutical Society (RPS), and Centre for Pharmacy Postgraduate Education (CPPE) to promote the research findings. The RCGP and RPS provide professional representation for over 40,000 practising GPs, and over 40,000 pharmacists, respectively; both have established communication networks including a strong social media presence. The CPPE provides educational solutions for the NHS pharmacy workforce, including those based in general practice. We will liaise with RCGP to contribute to its existing range of tools for supporting practices. All three organisations hold national annual conferences, as we will work with them to identify opportunities for workshops to disseminate findings and discuss implementation strategies.

18.2.2 Commissioners and policymakers

These stakeholders will be invited to two national workshops, and will be influenced by articles in the lay, professional and academic press. We will work with the medicines management teams of local Integrated Care Boards (ICBs) including those for Bristol, Devon and Oxfordshire, to ensure

appropriate engagement with commissioners, with whom we will hold local workshops. We will use our existing networks to engage with other key stakeholders (e.g. NICE, Health Education England, Royal Colleges) to further influence policy. Our final NIHR report will include an executive summary, accompanied by relevant promotional material, targeting NHS managers.

18.2.3 Patients and lay audience

As part of our dissemination process and achieving impact, we consider wider public engagement critical for empowering patients to participate in more effective, patient-centred medication reviews. We will co-produce press releases with PPI members and distribute via print media, websites and relevant patient organisations (e.g. National Association of Patient Participation, Age UK). Design and promotion will be supported by Bristol and Exeter University press offices and our departmental communications teams to maximise impact. We will work with our patient advisory group to identify other methods of public dissemination, and to produce public facing materials including patient information leaflets. Translation of written patient materials will be carried out for the 6 most frequently encountered non-English main languages.

18.2.4 Research participants

A trial website will be developed, and we will utilise our institution social media outlets to update and engage participating practices and the public during and following the study. Research findings and relevant outputs will be made available to all practices, including patient information materials (translated as appropriate) for distribution through patient participation groups, newsletters and other routes.

18.2.5 Academics

Papers will be submitted to high impact medical journals and presented at academic conferences (e.g. Society of Academic Primary Care [SAPC], North American Primary Care Research Group [NAPCRG]). We will also engage with the SAPC Special Interest Group focused on medicines optimisation (chaired by co-lead RP), which acts as a forum for both medical and pharmacy academics in this field. The full project report will be available on the NIHR website and published in the NIHR journal series.

18.3 Adoption/implementation

As discussed above, we will engage with relevant professional and policy organisations to highlight our findings and to promote and disseminate the intervention materials for use in the wider NHS. We will work with stakeholders to understand and overcome potential barriers to adoption. Given the nature of the intervention and that it aligns closely with existing usual practice, we do not envisage the need for any further processes to encourage implementation.

18.4 Further funding/support required

The intervention being proposed is readily scalable, and therefore implementation will not require significant funding. Addition support may be required to ensure materials (e.g. training resources, IT templates) are kept up-to-date, and to maintain online hosting of the relevant resources. We envisage funding for this being relatively small, and delivered through non-research channels (e.g. NHS England, ICBs).

18.5 Possible barriers to adoption

The intervention resources will be made freely and easily available, thus facilitating adoption. Potential barriers to implementation in practice may include acceptability to clinicians and feasibility of use in clinical practice. The process evaluation elements of the research will help us to understand any such potential barriers, and alongside our stakeholder engagement work will be used to help develop solutions to address these.

18.6 Impact

The aforementioned research outputs and dissemination strategy will:

- Potentially provide an effective and acceptable model for the delivery of medication reviews in primary care, with the potential for use by all healthcare professionals with relevant clinical experience in other healthcare settings
- Potentially improve medication safety and effectiveness, as well as patient-centredness, for patients receiving medication reviews
- Potentially reduce use of health services (including fewer prescriptions) and reduce medication waste
- Deliver education and improve awareness around medication reviews
- Provide practical resources to support delivery of medication reviews in practice
- Inform guidance on best practice for medication reviews in primary care
- Inform policy in terms of understanding how best to implement medication reviews in practice, including making effective use of the growing number of practice pharmacists

Irrespective of the main trial findings, we will also gain valuable information about the feasibility of conducting a large-scale pragmatic trial in this highly efficient way, as well as insight into the utility of using bulk text messaging to obtain patient reported experience and outcomes. This will be extremely useful for other researchers in the future. In addition, we will be creating a dataset comprising 300 audio-recordings of medication review. This will be a very valuable resource for future study of patient-clinician interaction in the field of medicines optimisation.

REFERENCES

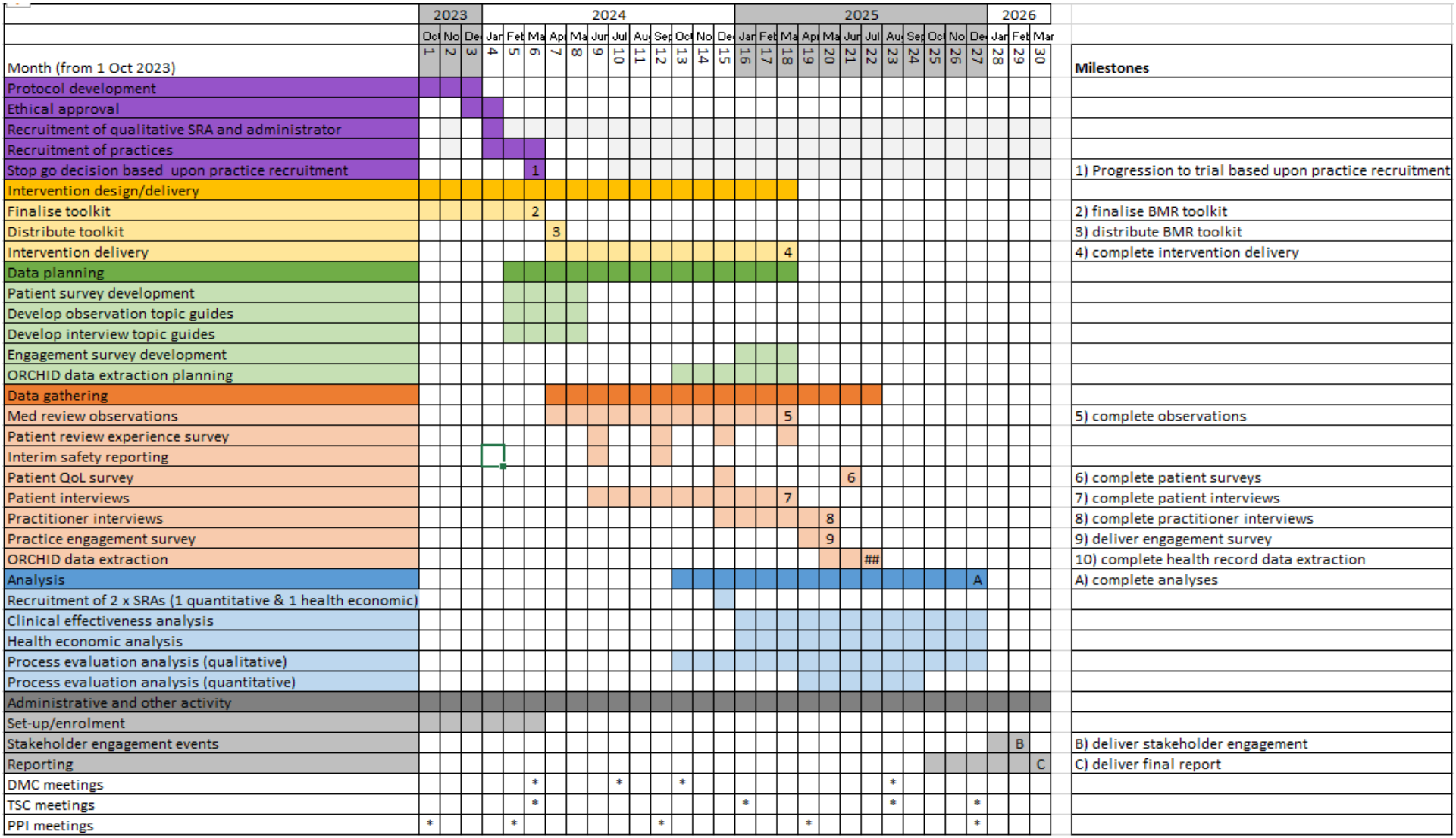
1. Payne RA, et al. Prevalence of polypharmacy in a Scottish primary care population. Eur J Clin Pharmacol. 2014;70:575-81. doi.org/10.1007/s00228-013-1639-9
2. Payne RA, et al. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol. 2014;77:1073-82. doi.org/10.1111/bcp.12292
3. Guthrie B, et al. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. BMC Med. 2015;13:74. doi.org/10.1186/s12916-015-0322-7
4. Montiel-Luque A, et al. Medication-related factors associated with health-related quality of life in patients older than 65 years with polypharmacy. PLoS One. 2017;12:e0171320. doi.org/10.1371/journal.pone.0171320
5. Duerden M, et al. Polypharmacy and medicines optimisation: Making it safe and sound. King's Fund. 2013
6. NICE. Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes. Clinical Guideline NG5. 2015
7. NHS England, Structured medication reviews and medicines optimisation, 2020. https://www.england.nhs.uk/publication/structured-medication-reviews-and-medicines-optimisation/
8. Griese-Mammen N, et al. PCNE definition of medication review: reaching agreement. Int J Clin Pharm. 2018;40:1199-1208. doi.org/10.1007/s11096-018-0696-7
9. World Health Organization. Medication Safety in Polypharmacy: Technical report. 2019;WHO/UHC/SDS/2019.11
10. Scottish Government Polypharmacy Model of Care Group. Polypharmacy Guidance, Realistic Prescribing 3rd Edition, 2018. Scot. Govt.
11. All Wales Medicines Strategy Group. Polypharmacy: Guidance for prescribing. 2014. https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-optimisation/prescribing-guidance/polypharmacy-guidance-for-prescribing/
12. Royal Pharmaceutical Society. Medicines Optimisation: Helping patients to make the most of medicines. Good practice guidance for healthcare professionals in England. 2013.
13. Payne RA, et al. Improving Medicines use in People with Polypharmacy in Primary Care (IMPPP): Protocol for a multicentre cluster randomised trial comparing a complex intervention for medication optimization against usual care [version 1; peer review: awaiting peer review]. NIHR Open Res 2022, 2:54. doi.org/10.3310/nihropenres.13285.1
14. Huiskes VJ, et al. Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials. BMC Fam Pract. 2017;18:5. doi.org/10.1186/s12875-016-0577-x
15. Madden M, et al. Early implementation of the structured medication review in England: a qualitative study. Br J Gen Pract. 2022;72(722):e641-8. doi.org/10.3399/bjgp.2022.0014
16. Health Survey for England 2016: Prescribed medicines. http://healthsurvey.hscic.gov.uk/media/63790/HSE2016-pres-med.pdf
17. NHS Business Services Authority. Prescribing Cost Analysis, England. 2008-2021. https://www.nhsbsa.nhs.uk/statistical-collections/prescription-cost-analysis-england
18. Schindler E, et al. Medication Review by Community Pharmacists for Type 2 Diabetes Patients in Routine Care: Results of the DIATHEM-Study. Front Pharmacol. 2020;11:1176. doi.org/10.3389/fphar.2020.01176
19. Yates L, et al. Evaluation of Pharmacist Medication Review Service in an Outpatient Heart Failure Clinic. J Pharm Pract. 2020;33:820-826. doi.org/10.1177/0897190019842696
20. Avery AJ, et al. A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis. Lancet. 2012;379:1310-9. doi.org/10.1016/s0140-6736(11)61817-5
21. Dreischulte T, et al. Safer Prescribing--A Trial of Education, Informatics, and Financial Incentives. N Engl J Med. 2016;374:1053-64. doi.org/10.1056/nejmsa1508955
22. McCahon D, et al. Development of a model of medication review for use in clinical practice: Bristol Medication Review Model. BMC Medicine 2021;19(1):262. doi.org/10.1186/s12916-021-02136-9

23. Weiss MC, et al. Medication decision making and patient outcomes in GP, nurse and pharmacist prescriber consultations. Prim Health Care Res Dev. 2015;16:513-27. doi.org/10.1017/s146342361400053x
24. Kurtz S, et al. Marrying content and process in clinical method teaching: enhancing the Calgary-Cambridge guides. Acad Med. 2003;78:802-9. doi.org/10.1097/00001888-200308000-00011
25. Duncan P, et al. Barriers and enablers to collaborative working between GPs and pharmacists: a qualitative interview study. Br J Gen Pract. 2020;70:e155-e163. doi.org/10.3399/bjgp20x708197
26. Charlesworth M, et al. An observational study of critical care physicians' assessment and decision-making practices in response to patient referrals. Anaesthesia. 2017;72:80-92. doi.org/10.1111/anae.13667
27. Michie S, et al. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6:42. doi.org/10.1186/1748-5908-6-42
28. Fischer F, et al. Barriers and Strategies in Guideline Implementation - A Scoping Review. Healthcare (Basel). 2016;4:36. doi.org/10.3390/healthcare4030036
29. de Lusignan, et al. The Oxford Royal College of General Practitioners Clinical Informatics Digital Hub: Protocol to Develop Extended COVID-19 Surveillance and Trial Platforms. JMIR Public Health Surveill. 2020;6(3):e19773. doi.org/10.2196/19773
30. McCahon D, et al. Patient perceptions and experiences of medication review: qualitative study in general practice. BMC Prim Care. 2022;23:293. doi.org/10.1186/s12875-022-01903-8
31. Hill-Taylor B, et al. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic & economic impact. J Clin Pharm Ther. 2013;38:360-72. doi.org/10.1111/jcpt.12059
32. Stocks SJ, et al. Examining variations in prescribing safety in UK general practice: cross sectional study using the Clinical Practice Research Datalink. BMJ. 2015;351:h5501. doi.org/10.1136/bmj.h5501
33. Rankin A, et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2018;9(9):CD008165. doi.org/10.1002/14651858.cd008165.pub4
34. Rankin, A., Gorman, A., Cole, J., Cadogan, C.A., Barry, H.E., Agus, A., Logan, D., McDowell, C., Molloy, G.J., Ryan, C. and Leathem, C., 2022. An external pilot cluster randomised controlled trial of a theory-based intervention to improve appropriate polypharmacy in older people in primary care (PolyPrime). *Pilot and feasibility studies*, *8*(1), p.203.
35. Khatter, A., Moriarty, F., Ashworth, M., Durbaba, S. and Redmond, P., 2021. Prevalence and predictors of potentially inappropriate prescribing in middle-aged adults: a repeated cross-sectional study. *British Journal of General Practice*, *71*(708), pp.e491-e497.
36. Verdoorn S, et al. Effects of a clinical medication review focused on personal goals, quality of life, and health problems in older persons with polypharmacy: A randomised controlled trial (DREAMeR-study). PLoS Med. 2019;16(5):e1002798. doi.org/10.1371/journal.pmed.1002798
37. Warren FC, et al. Evaluation of different recruitment and randomisation methods in a trial of general practitioner-led interventions to increase physical activity: a randomised controlled feasibility study with factorial design. Trials. 2014;15(1):1-11. doi.org/10.1186/1745-6215-15-134
38. Marlar J. Using Text Messaging to Reach Survey Respondents. Gallup, Nov 2017. Available at: https://news.gallup.com/opinion/methodology/221159/using-text-messaging-reach-survey-respondents.aspx
39. Pedder H, et al. How do patients respond to text messaging in primary care? NIHR ARC West, Apr 2020. Available at: https://arc-w.nihr.ac.uk/Wordpress/wp-content/uploads/2020/04/Text-messaging-COVID-rapid-review.pdf
40. Elwyn G, et al. Shared decision making: developing the OPTION scale for measuring patient involvement. Qual Saf Health Care. 2003;12(2):93-99. doi.org/10.1136/qhc.12.2.93
41. Barr PJ, et al. The psychometric properties of CollaboRATE: a fast and frugal patient-reported measure of the shared decision-making process. J Med Internet Res. 2014;16(1):e2. doi.org/10.2196/jmir.3085
42. Mercer SW, et al. The consultation and relational empathy (CARE) measure: development and preliminary validation and reliability of an empathy-based consultation process measure. Fam Pract. 2004;21(6):699-705. doi.org/10.1093/fampra/cmh621

43. Saunders B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. Quality & Quantity 2018;52(4):1893-907. doi.org/10.1007/s11135-017-0574-8
44. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77-101. doi.org/10.1191/1478088706qp063oa
45. Antaki C. Six Kinds of Applied Conversation Analysis. In: Antaki C. (eds) Applied Conversation Analysis. Palgrave Advances in Linguistics. Palgrave Macmillan, London. 2011. pp1-14. doi.org/10.1057/9780230316874_1
46. Kriston L, et al. The 9-item Shared Decision Making Questionnaire (SDM-Q-9). Development and psychometric properties in a primary care sample. Patient Educ Couns. 2010;80:94–9. doi.org/10.1016/j.pec.2009.09.034
47. Zermansky AG, Silcock J. Is Medication Review by Primary-Care Pharmacists for Older People Cost Effective? Pharmacoeconomics. 2009;27:11–24. doi.org/10.2165/00019053-200927010-00003
48. Coast J. Is economic evaluation in touch with society's health values? BMJ 2004;329:1233. doi.org/10.1136/bmj.329.7476.1233
49. Drummond MF, et al. Methods for the economic evaluation of health care programme. Fourth ed. 2015. Oxford University Press.
50. NICE. How NICE measures value for money in relation to public health interventions. Local government briefing. NICE, 2013. Available at: https://www.nice.org.uk/Media/Default/guidance/LGB10-Briefing-20150126.pdf

APPENDICES

Appendix 1: Trial Gantt chart



Appendix 2. Definitions of safety terms

Serious adverse events

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence in a participant subject to the BRISMED intervention, not necessarily caused by or related to the intervention or research processes, that:

- results in death
- is life-threatening (i.e. participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires or prolongs inpatient hospitalisation
- results in persistent or significant disability/incapacity
- is otherwise considered medically significant by the investigator

Other 'important medical events', will be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Relatedness

A Serious Adverse Event (SAE) judged by the investigator as having a reasonable causal relationship to the intervention (i.e. possibly, probably or definitely related) will be considered to be a Serious Adverse Reaction (SAR). The relationship between the intervention and the occurrence of each adverse event will be assessed and categorised as follows:

- **Not related:** Temporal relationship of onset of event, relative to intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
- **Unlikely to be related:** Temporal relationship of onset of event, relative to intervention, is unlikely; it is likely another cause by itself explains the occurrence of the event.
- **Possibly related:** Temporal relationship of onset of event, relative to intervention, is reasonable but event could have been due to another equally likely cause.
- **Probably related:** Temporal relationship of onset of event, relative to intervention, is reasonable and the event is more likely explained by the intervention than any other cause.
- **Definitely related:** Temporal relationship of onset of event, relative to intervention, is reasonable and there is no other cause to explain the event.

Definition of "intervention"

For the purposes of the definition of relatedness, the term "intervention" is further defined as any clinical element of the BRISMED medication review process, which results in a change to the medication at that time. For the avoidance of doubt:

1. In general, the elements of the intervention that are not immediately related to clinical care (e.g. training, informatics tool) are NOT considered to be the "intervention" for the purposes of safety reporting. However, should a clinician feel strongly that one of these other elements was directly and causally related to the adverse event, then it can be reported as "related"
2. A "change" to medication may include dose or formulation change, drug substance change, starting a new drug, or stopping an old drug.

3. The absence of a review is NOT considered to be an “intervention”. This includes a failure to attend a scheduled review by a patient. As a consequence, it is not possible for a control practice to have a “related” adverse reaction.
4. The failure during a BRISMED medication review to change a medication (as defined by point 2 above) which is felt to be causally related to the event, will be considered to be “related”, unless there is documented evidence as part of the BRISMED review of agreement with the patient over appropriate actions to mitigate the risk, irrespective of whether or not that resulted in a change in medication.

Note that this definition, including the four points of clarification above, are based on our IMPPP study, and recommendations from its TSC and DMC, which felt there was a need for a pragmatic definition which facilitated consistency in reporting across practices, and accounted for the potential for substantial clinical nuance when judging whether the failure to change a medication could have been reasonably foreseen to lead to harm.

Expectedness

Adverse reactions assessed as related to the intervention (possibly, probably, definitely) will be considered as either expected or not expected.

Adverse events will be considered as expected in the following circumstances:

- An adverse drug reaction, where all the following criteria are met:
    - Consistent with the WHO definition of ADR: a response to a medicine which is noxious and unintended, and which occurs at doses normally used in humans
    - Listed in British National Formulary (BNF) as a common or very common
    - The drug has, as part of the BRISMED intervention been
        - Started, or
        - increased in dose, or
        - affected as part of a drug-drug interaction by a change (started, stopped, dose increased, dose decreased) in another drug, where that potential interaction is listed in the BNF
    - The intensity (see below) of the reaction is no greater than that expected by the clinician
- Worsening of the clinical indication of a drug, where all the following criteria are met:
    - The indication is listed in the BNF (both licensed and unlicensed indications)
    - The drug has, as part of the BRISMED intervention, been stopped or decreased in dose, or affected as part of a drug-drug interaction (see above)
    - The intensity of the deterioration in clinical indication is no greater than that expected by the clinician
- An adverse change in patient behaviour, considered by the GP to be consistent with that expected as a direct consequence of the BRISMED intervention (for example, a decrease in medication adherence following an increase in medication burden)

Adverse events not meeting the above definition will be considered unexpected. For example:

- An adverse drug reaction not listed in BNF, or considered uncommon or rare in the BNF
- A worsening of the clinical indication despite a clinically appropriate change in drug (e.g. myocardial infarction despite an increase in statin dose)

Intensity

It is important to record intensity because in some expected events the intensity could become greater than expected, resulting in the event being defined as unexpected, and this may change the reporting requirements.

The assessment of intensity will be based upon the investigators clinical judgement using the following definitions:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.