Improving Medicines use in People with Polypharmacy in Primary Care

Pilot/Main Trial Protocol

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This protocol has regard for the HRA guidance

NHS
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TRIAL SUMMARY

Trial Title	Improving Medicines use in People with Polypharmacy in Primary Care	
Short title	IMPPP	
Trial Design	Three phase study: 1. Development Phase: mixed methods study in two Scottish health boards including qualitative and epidemiological components and intervention design and refinement. 2. Pilot/Optimisation phase: pilot feasibility study in 5 general practices in Bristol to optimise the intervention. 3. Evaluation phase: multicentre cluster randomised controlled trial (RCT). ***NB. This protocol addresses phases 2 and 3 only***	
Trial Participants	Patients presenting in primary care and community settings with polypharmacy	
Planned Sample Size	37 general practices	
Treatment duration	6 months	
Follow up	6 months	
Planned Trial Period	Nov 2019 to May 2023	
	Objectives	Outcome measures
	Optimisation/Pilot Phase: To optimise the implementation of the intervention for use in the NHS in England in a pilot-feasibility study	
	Main trial Phase: • To evaluate the clinical effectiveness and cost-effectiveness of the intervention in a cluster randomised controlled trial • To examine the implementation of the intervention in the trial using a mixed methods process evaluation	Primary outcome: The primary outcome is the mean number of PIP indicators triggered per patient at 6 months following the pre-review eligibility check Secondary outcomes: • Patient experience • Health service utilisation • Patient/medication safety • Cost-effectiveness

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History of version changes and amendments- Study protocol

Version No.	Version Date	Pages	Description of change
1.0	08/02/2019		Submitted to ethics for review
2.0	29/03/2019	 Pg18 Pg 19	Removal of all references to identification and recruitment of individuals who lack capacity to consent requested by the Ethics Committee (to include details related to the use of a consultee declaration form) Subheading 'subject population' removal of 'those who lack capacity to consent (e.g. dementia).' Subheading 'Contact and consent of eligible patients' removal of the following : - 'If the GP assesses that a patient lacks capacity to consent, a consultee declaration form will be included within the invitation pack to enable the assent of the patient's carer, legal guardian or consultee on behalf of the patient.'

3.0	05/11//2019	Pgs 3, 18 & 23	At the joint TSC&DMC meeting July 2019, oversight committee members commented that the protocol was unclear with respect to who the primary end points apply and when assessment occurs. This has been clarified throughout the protocol as follows:- The primary outcome is the mean number of PIP indicators triggered per patient at 6 months following the pre review eligibility check (i.e. is not at a fixed date point or related to the actual time of the scheduled review). The primary outcome applies to consented patients in both arms.
4.0	02/07/2020		Adaption of the intervention to include telephone or video consultation as alternatives to face-to-face consultation for delivery the patient medication review component of the intervention. Necessary to restart the study after the enforced pause due to the COVID-19 pandemic and to 'future proof' the intervention so it remains relevant and applicable to primary care service delivery post COVID-19. TSC confirmed support for this amendment 18/06/20. KT details added as lead for the process evaluation.
5.0	14/07/2022		Amendments to the consent process for audio-recording and observation of the interprofessional discussions and medication reviews so that this process is consistent with the consent process for qualitative interviews. The consent processes are now full detailed on page 35-36. Other protocol amendments include; A change of Lead Statistician as Richard Morris has recently retired, and Peter Blair has taken on this role. Page 2 Updated title and contact details for Tobias Dreischulte who has recently moved to the University of Munich. Page 2 A typographical error related to the definition of multiple medicines has been corrected. The definition now reads as follows; Multiple medicines, defined as taking at least five regular medicines. Page 19. Clarification on page 28 that the additional training being offered to intervention practices is optional. A reduction in the number of practices required to power the study based upon analysis of pilot study data which revealed a narrower standard deviation than originally estimated (SD of 2.0 rather than SD of 2.4) meaning that 28 practices are required to achieve 80% power, and 37 practices to achieve 90% power. The patient recruitment target has been reduced accordingly within the protocol to 1850 (50 participants per practice). Amendments to practice recruitment target have been previously discussed and approved by the TSC, DMC and the funder. Pages 38. Finally, further details for the process for capturing safety data at 6 and 12 months have been added to page 47.

LIST OF CONTENTS

Table of Contents

LIST OF ABBREVIATIONS/TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
BlueBay	Third party software developer providing the trial informatics tool
BNF	British National Formulary
BRTC	Bristol Randomised Trials Collaboration
CAPC	Centre for Academic Primary Care
CAG	Confidential Advisory Group
CCG	Clinical Commissioning Group
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
DMSC	Data Monitoring Steering Committee
DSA	Data Sharing Agreement
DQIP	Data-Driven Quality Improvement in Primary Care study
EDC	Electronic Data Capture
EMIS Web	Clinical system for delivering integrated healthcare
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
HRA	Health Research Authority
HS&DR	Health Services and Delivery Research
HTA	Health Technology Assessment
IMPPP	Improving Medicines use in People with Polypharmacy in Primary Care
ICC	Intraclass correlation coefficient
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MRC	Medical Research Council
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 Research
NSAIDs	Non-steroidal anti-inflammatory drugs
PAG	Patient Advisory Group
P-DQIP	Pharmacist and Data-driven quality Improvement in Primary Care study
PI	Principal Investigator
PINCER	Pharmacist-led INformation teChnology intervention for medication ERrors
PIL	Participant Information Leaflet
PIP	Potentially inappropriate prescribing
PPI	Patient and Public Involvement
POEMS	Polypharmacy Enhanced Medication Summaries
PQ	Patient Questionnaires
QOF	Quality Outcomes Framework
RCT	Randomised Control 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
SF-12	Validated questionnaire of 12 questions of health-related-quality of life
SLA	Service Level Agreement
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UoB	University of Bristol

STUDY PROTOCOL

PLAIN ENGLISH SUMMARY

Prescribing medicines is one of the most important things doctors do to treat illness and improve peoples' health. The UK population is steadily ageing and people often have more than one health problem. This means more people are taking multiple medicines, which is called polypharmacy. Polypharmacy is common. It is often necessary to help a person keep well, but polypharmacy can also cause problems such as side effects or confusion about exactly what medicines are to be taken when. We need to find ways of improving the use of medicines in people with polypharmacy so we can reduce some of these problems. However, there is no good scientific evidence to help health care professionals decide how to most effectively do this. The aim of this study is to create an effective approach for improving the use of medicines in people with polypharmacy attending general practice.

We will develop a new approach (called IMPPP) to improve how we manage polypharmacy. IMPPP has several parts to it. It will improve how GP surgeries organise reviews of medicines for patients experiencing polypharmacy. It will encourage better care by providing GPs with training, payments, and information about how well their practice is performing. It will use a new computer program to help GPs and pharmacists make the right decisions about medicines. Patients' concerns and wishes about their medicines will remain central.

We will base IMPPP on similar approaches our team has used in Scottish general practices, called POEMS and P-DQIP. Unfortunately, POEMS and P-DQIP are both developmental, so we cannot tell if they will be successful in improving care. In developing IMPPP, we will be able to use and improve upon what we have learned from POEMS and P-DQIP.

This project has 3 parts:

1. Firstly, we will speak to health care professionals and patients with experience of POEMS and P-DQIP. This will tell us what they think of these existing approaches. We will use prescribing data gathered by the Scottish GP computer systems to help us understand which people with polypharmacy will benefit most from improved care. We will use this information to design the new IMPPP method, with the help of patients and other experts.
2. Secondly, we will test IMPPP in 3 Bristol-based general practices. We will interview patients and clinicians in these practices to find out about any problems with IMPPP so we can improve it.
3. Thirdly, we will carry out a clinical trial in Bristol and the West Midlands. The trial will compare 27 practices using IMPPP to 27 practices using current, normal care. We will test whether using IMPPP results in improved medicines safety, less use of health services, better quality of life and less burden of treatment for the patients involved. We will also check whether IMPPP is acceptable to patients and both GPs and pharmacists, and will find out the cost implications of IMPPP for the NHS.

This protocol only covers the second and third parts of the IMPPP study; there is a separate protocol for the first part.

The research will provide us with valuable information about which people with polypharmacy might benefit most from having improvements made to their medicines, and tell us what approaches work best for improving the use of medicines in people with polypharmacy, including how GPs and pharmacists can work together most effectively to achieve this. If it works, it should be possible to use the IMPPP approach across the NHS, helping many people with polypharmacy. We will work closely

with the public and other patient groups throughout this research, to make sure that we take on their views in the design of the IMPPP approach itself, the research more generally, and when publicising the findings.

BACKGROUND AND RATIONALE

Background

Polypharmacy is broadly the prescribing of multiple medicines to one individual, and although there is no single agreed definition, it is increasingly common. We have shown that ~6% of adults are prescribed 10 or more regular medications (and ~20% of people aged 70+ years), doubling between 1995 and 2010[1]. An ageing population and increasing multimorbidity are key factors driving polypharmacy, compounded by single-condition clinical guidelines recommending more intensive treatment[2]. Given that the majority of prescribing occurs in primary care, where long-term conditions are increasingly managed, polypharmacy presents a particular challenge to general practice.

Although not necessarily inappropriate, the use of multiple medications is often considered undesirable by patients [3], and can have a number of undesirable consequences[2,4-8]. Medication errors and potentially inappropriate prescribing are strongly associated with the number of medicines prescribed, and in turn can lead to adverse drug effects, increased health service utilisation (primary and secondary care), poor medication adherence (potentially compromising treatment efficacy) as well as reduced quality of life [2].

Importantly, there is a need to differentiate appropriate polypharmacy (where medication use is optimised) from problematic polypharmacy (where medications are used inappropriately or where the intended benefit is not realised) [9]. Our own work has shown that the adverse associations of polypharmacy are dependent on clinical context, and polypharmacy is not always hazardous [10].

Medication optimisation strategies for managing polypharmacy therefore need to balance expected benefits and risks with patient goals and priorities as opposed to just technical aspects of prescribing and should not only demonstrate reductions in potentially inappropriate prescribing but also benefits to patient outcomes.

Importance

This study addresses an unmet health need. Polypharmacy is widespread with ~6% of adults taking 10+ regular medicines[1]. It is associated with adverse outcomes as described earlier[2]. This research will develop and evaluate an intervention to optimise medicines in patients with polypharmacy with the potential to improve the appropriateness of medicines use, with a reduction in treatment burden and patient harms, and improvements in drug treatment effectiveness. Furthermore, there is the potential for cost savings, not just by decreasing medication waste and other costs, but also through reduced health service use.

There is an expressed need for research in polypharmacy and medicines optimisation. National guidelines on medicines optimisation and multimorbidity have been published by The National Institute for Health and Care Excellence (NICE), but a limitation of these guidelines is the lack of RCT evidence about intervention effectiveness. The medicines optimisation NICE guideline makes a research recommendation calling for evidence for the clinical and cost effectiveness of medication review conducted in the UK by practitioners other than community and hospital pharmacists[11]. NICE also calls for research into organisation of care for patients with multimorbidity[12]. Our research will address these knowledge gaps. The Primary Care Workforce Commission report on the future of primary care also called for greater involvement of clinical pharmacists to meet the needs of people on long-term medicines[13]; our proposal will help inform how GPs and pharmacists can best work together to minimise drug.

There is also sustained interest in this area. The prevalence of patients with polypharmacy has doubled over a recent period of 15 years[1], and given its association with age the number of people with polypharmacy is likely to greatly increase in future years.

The study has the potential to generate important new knowledge. NICE reports a lack of evidence-based interventions for medicines optimisation[11]. The proposed study will address this gap in knowledge by conducting a definitive, randomised controlled trial, providing evidence to inform best practice for medicines optimisation in NHS primary care. Our study will also establish the best approach to identifying those patients with polypharmacy most likely to benefit from medicines optimisation, as well as providing information on appropriate screening and recording standards.

Findings from IMPPP will be generalisable to the UK population, and with the potential to achieve change in health service delivery and outcomes. The intervention design will allow it to be delivered to harder-to-reach populations (e.g. frail elderly, housebound) who are potentially most at need, as well as the wider GP population. Results from the case-finding work will have the potential to be used separately from the specific intervention being evaluated by this project. The scalable nature of the IT tool and its compatibility with the leading UK primary care clinical system makes wider implementation relatively straightforward. Increasing availability of GP-based pharmacists will also facilitate future implementation and change.

Need for research

Substantial and increasing rates of polypharmacy in primary care, associated with a range of clinical harms, alongside a continuing shift in the management of long-term conditions from secondary to primary care, make addressing the problem of polypharmacy a priority. Recent national guidance in this area has been produced separately by NICE, Scotland and Wales, but it is not supported by high quality evidence of interventions that improve outcomes[11,12,18,19]. Furthermore, there has been significant recent investment in pharmacists working in general practice[13,20]. The proposed research is therefore extremely timely.

A Cochrane review in 2014 identified 12 interventions designed to optimise polypharmacy in older patients[21]. Most of these were multifaceted complex interventions delivered by pharmacists. Reductions in inappropriate prescribing (but not adverse clinical outcomes) were observed, but studies were of limited quality and focused on reducing medication count as opposed to addressing prescribing appropriateness. Nevertheless, a number of recent trials conducted in UK primary care demonstrate that primary care prescribing can be improved by targeted review of patients with a limited range of high-risk prescribing. The PINCER intervention trial tested a pharmacist-led intervention of 12 weeks duration in general practices and showed substantial improvements in targeted prescribing at 6 months, but the effect was attenuated at 12 months for all three primary outcomes[22]. The DQIP intervention comprised an informatics tool (which identified patients with high-risk prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) and antiplatelets for review, facilitated review and provided feedback on levels of high-risk prescribing), an educational outreach visit by a pharmacist (providing evidence and guidance around targeted prescribing) and financial incentives for review (a £350 one off payment and £15 per review). The DQIP trial found substantial reductions in high-risk prescribing at 12 months follow-up (which importantly were sustained in the year post-incentives) and provided some evidence of reductions in emergency admissions for gastrointestinal ulcer/bleeding and heart failure[15]. There is additional evidence that educational outreach has small but consistent and potentially important effects on prescribing[23]. Feedback can also lead to small but potentially important improvements in practice, particularly for prescribing[16,24].

A limitation shared by all of the above described interventions is that they focussed on a limited number (<20) of high-risk prescribing indicators of limited complexity, and it is therefore not known whether the same approach can be applied to optimising polypharmacy. In addition, in PINCER, the impact of a time limited pharmacist-led intervention appeared to wane after the pharmacist left the practice. However, the longer-term sustainability of interventions solely delivered by GPs is questionable, given the limited GP workforce and increasing prevalence of older people with polypharmacy. Ongoing collaboration between pharmacists and GPs (consistent with recent investment in clinical pharmacist posts in general practices) supported by an informatics tool (that identifies and facilitates the review of patients with polypharmacy who are at high risk of drug related harm or unrealised benefit), is therefore a potentially effective and sustainable approach to optimising drug therapy outcomes in this vulnerable group of patients.

The IMPPP study builds on academic-NHS collaborative work to develop and implement two related primary care polypharmacy informatics tools (POEMS, P-DQIP) to support existing polypharmacy programmes in two Scottish Health Boards. These programmes include clinical polypharmacy reviews together with a range of educational interventions and some financial incentivisation. The informatics tools are suitable for use by GPs or pharmacists, and share common elements including case finding and the ability to create printable patient-specific enhanced medication summaries relevant to polypharmacy medication review. Informatics tool design and technical implementation has been completed for both POEMS and P-DQIP, with pilot work establishing feasibility and acceptability. Both are currently in use, with planned evaluation using interrupted time series analysis.

POEMS and P-DQIP will provide some time-series evidence about whether implementation is associated with changes in potentially inappropriate prescribing. However, strong evidence of patient benefit or cost-effectiveness of the informatics tools, or indeed wider polypharmacy programmes, will remain lacking. However, the POEMS and P-DQIP informatics tools are not suitable for England due to important differences in IT infrastructure. We therefore have a unique opportunity to learn from our experience in Scotland to optimise a complex intervention for implementation throughout the UK and evaluate it in a definitive RCT.

AIMS AND OBJECTIVES

Aim

The aim of the IMPPP study is to develop, implement and evaluate an intervention to optimise medication use for patients with polypharmacy in a general practice setting. Only the implementation and evaluation phases are the subject of this protocol

Primary objective

- To optimise the implementation of the intervention for use in the NHS in England in a pilot-feasibility study
- To evaluate the clinical effectiveness and cost-effectiveness of the intervention in a cluster randomised controlled trial
- To examine the implementation of the intervention in the trial using a mixed methods process evaluation

OUTCOMES

Primary trial endpoint/outcome

- Number of potentially inappropriate prescribing (PIP) indicators triggered per patient over the previous 8 weeks.

Secondary trial endpoints/outcomes

The Implementation/Pilot phase will be used to determine which secondary outcome measure(s) will be most suitable for use in the main trial, for example by evaluating completion rates of questionnaires and sensitivity of different measures to change. We will attempt to minimise the number and complexity of measures at baseline and follow-up to improve response rates.

- Patient experience:
    - Quality of life (EQ5D[48], SF-12[49])
    - Medication adherence (MARS[50])
    - Burden of treatment (Multimorbidity Treatment Burden Questionnaire, developed for 3D study[17])
    - Medicines literacy (categorical)
- Health service utilisation
    - Unplanned acute hospital admission rate (all admission types) over previous 6 months
- Patient/medication safety
    - Number of medication-related admissions (derived from ICD10 codes T36-T50, X40-44, Y40-Y84 in primary diagnostic position) over previous 6 months
    - Inappropriate Polypharmacy Score (an automated score based on routine data being developed by our team as part of an ongoing project [NIHR SPCR FR12/330], based on composite of several factors (e.g. medication adherence, presence of contraindications, drug-drug interactions, complexity)
    - All-cause mortality

Cost-effectiveness

- Quality adjusted life years (QALY)
    - Service utilisation will be determined over previous 6 months

STUDY DESIGN AND SETTING

Phase 1 (intervention development)

Mixed-methods study in 2 Scottish Health Boards that are implementing novel informatics tools to support NHS polypharmacy reviews in a range of ways. Interviews with healthcare professionals (HCPs) plus patient focus groups will be used to understand implementation and their experience of polypharmacy review, and the strengths and limitations of the various intervention components implemented. Descriptive epidemiological analysis of practice data will be undertaken to explore the prevalence, variation and amenability to change in PIP. These findings will inform a detailed draft design of the intervention components, which will then be refined in consultation with HCP and patient groups in England. This work is covered by a separate protocol and is not detailed here.

Phase 2 (implementation/pilot)

Pilot-feasibility study in 5 Bristol-area general practices to optimise the intervention in the English NHS. A formative qualitative process evaluation will examine initial adoption and intervention implementation, including likely barriers/facilitators to implementation which will be addressed prior to the main trial. We will also pilot and evaluate trial processes including collecting quantitative data on patient recruitment/retention.

Phase 3 (evaluation)

Multicentre cluster-RCT comparing intervention vs usual care in the Bristol area and the West Midlands. The primary outcome is the mean number of PIP indicators triggered per patient at 6 months following the pre review eligibility check, which occurs in both the control and intervention practices (i.e. is not at a fixed date point or related to the actual time of the scheduled review). The primary outcome applies to consented participants in both arms and not the wider practice population.

Secondary outcomes are detailed above and include patient experience and quality of life, health service utilisation, and other aspects of patient safety. A cost-effectiveness analysis will be conducted. A parallel mixed-methods process evaluation will be undertaken to examine the implementation of the intervention to help explain the success, or otherwise, of the intervention, and to inform subsequent implementation in practice.

This protocol is for Phase 2 and 3 only.

TRIAL ELIGIBILITY CRITERIA

General practices with a minimum practice list size of 4,000 registered patients will be approached to participate by the Clinical Research Network (CRN).

Practices will need to have capacity to deliver the trial. They must have an EMIS clinical system compatible with BlueBay. If a practice does not have a pharmacist attached to it, a separate pharmacist will be provided to undertake the relevant parts of the study. If a practice already has a pharmacist, funding will be provided for the time necessary for the pharmacist to undertake the relevant parts of the study.

Subject population

Persons experiencing potentially problematic polypharmacy in primary care and community settings. This will specifically include “hard to reach” groups, including nursing home residents, housebound individuals.

The exact patient population will be defined as part of the case finding approach to be determined by the development phase (Phase 1) of the project. It is anticipated the case finding tool will identify older people (≥60 years) who are receiving 5 or more medications regularly on prescription. This is because people in this group are more likely than younger people on fewer medications to trigger at least one of the prescribing quality indicators (being defined within Phase 1) which will underpin the case finding approach.

Participant inclusion criteria

- Aged ≥ 18 years
- Willing to participate and able to provide consent for themselves
- Multiple medicines, defined as taking at least five regular medicines
    - This will be based on medicines 1) being currently available on the repeat prescribing system and 2) having been prescribed at least once in the previous 3 months
- Be identified by the case-finding tool developed by Phase 1

Participant Exclusion criteria

- Individuals receiving end-of-life care
- Patients judged by their GP to have chaotic medication use (e.g. history of drug or alcohol misuse)
- The GP deems contact to be inappropriate; for example, due to severe mental health problems, terminal illness, recent bereavement
- Participant is unable to complete the study questionnaires or medication review appointment (either themselves or with the help of carers)
- Individuals planning to move GP practice within the 6-month follow up period

A recent medication review outside the trial setting will not be considered an exclusion criterion, although it will be left to the GP screening for inclusion in the study to decide if a second review in a short time as part of the study would be inappropriate.

TRIAL PROCEDURES

A schematic representation of the trial activities/flow is shown in the figure below. The intervention design itself is described in the next section, followed in turn by a summary of usual care.

Practice recruitment

Practice recruitment and randomisation will be undertaken in blocks of intervention/control pairs in each area (Bristol, West Midlands). This will help minimise the gap between patient consent and practice randomisation. We will recruit 37 practices for the main trial. The pilot trial will recruit 5 practices, in two blocks (block one with one intervention and one control; block two with two intervention and one control; intervention practices will be purposively sampled to ensure we capture different models of pharmacist provision). The pilot trial will be external to the main trial, with practices participating in the former not able to participate in the latter.

Randomisation will be generated using a computer algorithm. Practices will not be informed of whether or not they will be intervention practices before agreeing to participate.

Recruitment of all practices will be followed by an initial set-up period to install the necessary software and provide basic training in the necessary administrative processes. Note that those practices in the control arm will not be able to access some of the functionality of the BlueBay software (e.g. the clinical review template).

Identification of eligible patients

Eligible patients will be identified by practices after practice recruitment but before randomisation. All potentially eligible patients meeting the inclusion criteria will be identified using the BlueBay informatics tool. A computer-generated random sample of these patients will then be considered for invitation. These patients will be screened by a GP for the exclusion criteria.

Provisionally, for the main trial, 260 eligible patients will be identified per practice; assuming a 20% exclusion rate (GP screening) and 20% drop-out (pre-review), and a 30% response rate. This provides 50 patients per practice undergoing a review. Due to the nature of the study, further drop-out will most likely be due to death (approximately 3% in 6-months) or patients moving; the primary outcome is not affected by non-response as this is captured automatically. The study remains adequately powered even in the unlikely situation that there is a post-review drop-out rate of 20% (see *Sample size calculation*). In the pilot trial, 25 patients will undergo reviews per practice. Response rates, drop-out rates and exclusion rates in the pilot trial will inform those of the main trial. During the main trial, practices will be randomised in blocks of intervention/control in each area (Bristol, West Midlands), Recruitment across all 37 practices will occur in a relatively short period. As such, the same number of patients will be identified in each practice, as adapting the number of patients according to response/exclusion rates in earlier practices is not feasible in the given timescales.

Contact and consent of eligible patients

All eligible patients will be contacted by post. An invitation letter and consent form will be sent by practices. Patients will also be asked at this point if they would like to receive subsequent questionnaires in a paper or online format.

Eligible patients who do not respond to the initial invitation to participate will receive a reminder invitation pack after approximately 2 weeks. Eligible patients who do not respond to the reminder invitation will not be contacted further regarding the study.

Randomisation

As soon as invitations have been sent in a pair of practices, the practices will be randomised, one to intervention and one to control. We will not wait for consent forms to be returned before randomising practices.

Baseline questionnaire

A baseline questionnaire will be sent to participants at the same time as the consent form.

Clinical training

Clinical training will be arranged for intervention practices only as soon as possible after randomisation occurs. We will allow up to 3 months because of the need to wait until two practices have been recruited and randomised.

Pharmacists will get more detailed training. All other clinicians involved in delivering the intervention would receive a shorter training package including the use of the BlueBay software in the clinical environment.

We will allocate training slots for *all* practices as soon as they sign-up, even though they are at this point unaware of randomisation status. By holding these slots over lunch and keeping them relatively short, we will minimise practices refusing to allocate time until post-randomisation. Control practices will be able to release unnecessary slots immediately post-randomisation. Longer slots will be necessary for the pharmacist, but it will be easier to negotiate such slots in advance of randomisation because it only involves a single individual (compared to multiple other practice staff including GPs).

Conduct of medication review

Summary

A 6-month period will follow completion of practice training, during which all eligible patients in the intervention arm will undergo a medication review. Pre and post review questionnaires will be sent to patients. Reviews will be distributed over the 6-month period. Participants in the control arm will not undergo a review, but a similar proportion of patients will be sent the “pre-review” questionnaire each month to ensure a spread over the 6-month period similar to that in the intervention arm.

Both arms

Each month, a random sample of one-sixth (N≈7 to 10) of consented patients will be selected to receive a medication review and the pre-review questionnaire. The ongoing eligibility of these individuals will be checked at this time; if a patient in the intervention arm is no longer eligible, they will not receive a review, but will still receive the pre-review questionnaire. Patients in the control arm will be selected in a similar manner, and their eligibility checked; they will not receive a review, but will still receive the pre-review questionnaire irrespective of eligibility. The random selection will be made by the trial team. This will continue over the 6-month period of the study until all consented patients have received an eligibility check. We anticipate the number of patients whose eligibility will have changed between consent and review will be small.

The eligibility check will involve using the BlueBay software to confirm patients still meet the inclusion criteria (based on prescribing). In addition, a practice administrator will ensure there are no other administrative barriers to ongoing participation (e.g. death). To minimise risk of GP selection bias, the GP will not be involved in this check. A similar model to this was successfully employed as part of the 3D trial.

Sending of the pre-review Questionnaire 2 will immediately follow the pre-review eligibility check in both intervention arms, and will coincide with the pharmacist case-note review in the intervention practices only.

6-month follow-up in both arms will include Questionnaire 4 being sent out 6 months after the pre-medication review eligibility check.

Intervention arm only

Practices will be allowed to decide how they wish to conduct the case-note review and collaborative discussion. Some may decide to do all the eligible patients for that month together, whereas others may decide to spread the work over the month. The pharmacist case-note review will coincide with sending Questionnaire 2, followed by the GP-pharmacist collaborative discussion to make a plan for the face to face review.

Once the collaborative discussion has taken place, the patient will be invited to make an appointment for a face-to-face, telephone or video review consultation with either a GP or pharmacist (based on the outcome of the collaborative discussion). This invitation will be by phone or letter, and will be no earlier than two weeks after Questionnaire 2 is sent out. The invitation will be sent irrespective of whether the patient has responded to Questionnaire 2.

All patients who have recently had an IMPPP medication review completed will be asked to complete a post review questionnaire (questionnaire 3). Questionnaire 3 will be sent to participants within 2 weeks of their medication review. This will contribute to the process evaluation, but because there is no comparison measurement in the control arm, it does not form a secondary trial outcome per se.

A follow-up appointment with the pharmacist or GP will be arranged at a time point deemed clinically appropriate by the clinician conducting the initial medication review. The timing of this appointment will vary considerably with clinical circumstances. There may be situations where no follow-up is deemed necessary. In this situation, a follow-up phone-call will nevertheless be necessary for practices to demonstrate that they have “completed” all steps in the review process.

Blinding

Practices will be recruited before randomisation. Since patients agree to take part in the study before the practice is randomised, patients will be blinded to the randomisation status of the practice at the point of consent. 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.

Intervention delivery

Not all practices that will be recruited will have an affiliated pharmacist. There are considerable regional differences, and numbers are generally growing with a national programme to encourage the use of clinical pharmacists in the general practice setting. At present, the majority of practices in the Bristol area employ a pharmacist, whereas a smaller proportion of West Midlands practices do so; recruiting in both locations thus has the advantage of including practices with varying experience with the use of practice pharmacists. Where a practice does not already have a pharmacist available, the study will provide a pharmacist to undertake the work in the practice (equivalent to 3 hours per week). Where a practice already has an affiliated pharmacist, the study will fund the additional time required for them to deliver the intervention. We will be alert to the possibility that pharmacists may work across more than one participating practice, and there is a possibility that these practices may fall into different trial arms; we will endeavour to recruit practices where this is less likely, but regardless

contamination will probably be small as many elements of the intervention will not be available in control practices.

Participant follow-up

Questionnaires

We anticipate questionnaires being sent out by the research team. This is dependent on the BlueBay clinical software being able to interface with the University REDCap trial management database.

Primary outcome measurement

The primary outcome is the mean number of PIP indicators triggered per patient at 6 months following the pre-medication review eligibility check (which occurs in both the control and intervention practices) determined by the BlueBay software using the data recorded in the GP electronic health record. For each consented participant, it will be measured at the time points corresponding to administration of Questionnaires 1 (baseline), 2 (pre-review eligibility check) and 4 (6 months following the pre-review eligibility check).

Measurement of service utilisation

We will seek to determine secondary care usage objectively using Hospital Episode Statistics (HES) data from NHS Digital on A&E attendances, in-patient and out-patient care (this will inform the secondary trial outcomes including economic analysis). This will be captured once the study has finished, for all practices and across the entire study period. Primary care usage will be determined using data from BlueBay. For the pilot trial, we will also seek information on primary and secondary care service utilisation using questionnaires. The pilot trial will be used to establish whether there are difficulties in acquiring the necessary data in an automated fashion, and the degree of concordance between automated measures and patient self-report; this will be used to determine whether patient self-report on service utilisation is included in the main trial questionnaires.

Schematic of trial activities

Month	Both trial arms		
	Install BlueBay software Training (protocol, informatics, admin)		
0	Identify eligible patients	→	Run computer case-finding GP screening of patient list
	Contact eligible patients	→	GP send invitation letter, consent form
	Send Questionnaire 1		
	Randomise practices		
1	↓ 3 months* to train practices →	Clinical training	→
2			
3			
4	↓ Conduct medication reviews →	Check eligibility (1/6 cases)	→
5		Check eligibility (1/6 cases)	
6		Check eligibility (1/6 cases)	
7		Check eligibility (1/6 cases)	
8		Check eligibility (1/6 cases)	
9		Check eligibility (1/6 cases)	
10	Ongoing follow-up		
11			
12			
13			
14			
15	End of follow-up		

Intervention arm	Control arm
Training of pharmacists	
GP training using BlueBay	

**3 months is maximum*

Time	Intervention arm	Control arm
Week 0	Re-run computer check Screening by practice administration staff	
Week 1	Send Questionnaire 2 Pharmacist case note r/v	Send Questionnaire 2
Week 2	Collaborative discussion Patient invited for r/v	
Week 3-6	Conduct r/v with patient	
Week 4-7	Send Questionnaire 3	
(variable)	Clinical follow-up appt	
Month 6	Send Questionnaire 4	

Measurement of trial outcomes and other quantitative data

The following table details the timing of different outcome measurements, including the source of data used. Time points correspond to pre-randomisation (T1), immediately pre-review (T2), immediately post-review (T3), and follow-up at 6 months (T4). Other qualitative data collection is detailed under the process evaluation section below.

Outcome/measure	Data source	Time point			
		T1	T2	T3†	T4
Participant demographics	Questionnaire	×			×
Primary outcome					
Potentially inappropriate prescribing	BlueBay	×	×		×
Patient experience					
Quality of life (EQ-5D, SF-12)	Questionnaire	×	×		×
Medication adherence (patient-reported)	Questionnaire	×	×		×
Medication adherence (prescription refills)	BlueBay	×	×		×
Burden of treatment (MTBQ)	Questionnaire	×	×		×
Medication literacy	Questionnaire	×	×		×
Health service utilisation					
Unplanned hospital admissions	NHS Digital*	×	×		×
Primary care consultation rate	BlueBay, Questionnaire	×	×		×
Other hospital utilisation data (A&E, O/P)	NHS Digital*	×	×		×
Other service use (social care, private, etc)	Questionnaire	×	×		×
Patient/medicines safety outcomes					
Medication-related admissions	NHS Digital*	×	×		×
Inappropriate Polypharmacy Score	BlueBay	×	×		×
All-cause mortality	GP practice				×
Other process measures					
Experience of medication review	Questionnaire	×		×	

† post-review "experience" questionnaire sent to intervention arm only

** to be captured using patient-reported questionnaire data if NHS Digital approvals cannot be acquired*

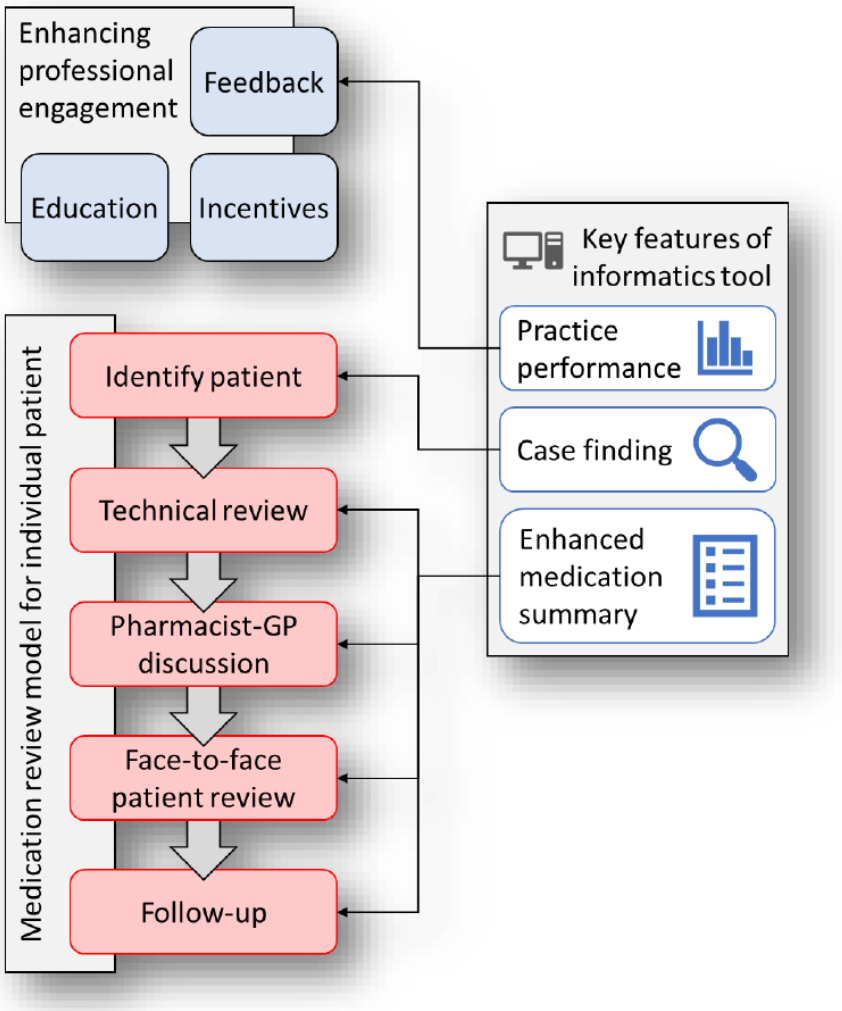
INTERVENTION DESIGN

Overview

The IMPPP intervention will be based in general practice, and will involve GPs and practice pharmacists working together, drawing on the specific skills of each professional sensitive to the context of each practice. This is a complex intervention and will comprise two key elements:

- a model for conducting a polypharmacy medication review (including pharmacist-GP collaboration and case finding)
- components seeking to enhance professional engagement (education, practice feedback, financial incentives)

An informatics tool integrated into GP clinical systems will help support the medication review element as well as the practice feedback component, as shown in the following figure:



Polypharmacy review model

The “review model” will comprise an organisational framework for implementing polypharmacy reviews, including a specific process for delivering the face-to-face component of the review. The framework emphasises a collaborative, flexible model of working between GPs and pharmacists, and the tailoring of care to best suit individual patient’s needs. The framework can be summarised in the following steps:

- **Identification of patients (case-finding):** Proactive case-finding will be undertaken to identify those patients most likely to benefit from the intervention, facilitated by an informatics tool described below.
- **Prescription case-note review:** For each patient, a pharmacist will conduct an initial review of the medication regimen based on the record alone, which will focus on more technical aspects of prescribing that may benefit from optimisation.
- **Collaborative discussion between GP and pharmacist:** Regular discussions will be held between the pharmacist and one or more GPs. This discussion will be used to address findings of the prescription case-note review, and any particular aspects that need to be considered as part of the subsequent medication review. A decision will also be taken at this stage about which health care professional is best placed to undertake the review with the patient (i.e. GP or pharmacist), and how best to follow the patient up, taking into account the specific expertise of each professional and the specific needs of each patient. Each discussion may address one or more patients, with the exact approach to implementation left to practices (see below).
- **Medication review with patient:** A 20-minute pre-arranged stand-alone (as opposed to opportunistic) polypharmacy review will be conducted face-to-face, via telephone or video consultation between a clinician (GP or pharmacist) and patient, ensuring enough time to enquire about patient concerns, goals and priorities alongside addressing technical issues. The review will follow the established patient-centred NHS Scotland/SIGN 7-step process[19]:
  1. Identify aims and objectives of drug therapy
  2. Identify essential drug therapy
  3. Does the patient take unnecessary drug therapy?
  4. Are therapeutic objectives being achieved?
  5. Is the patient at risk of ADRs or suffering actual ADRs?
  6. Is drug therapy cost-effective?
  7. Is the patient willing and able to take drug therapy as intended?

  To help prepare patients better for their review, the practice will send them a leaflet alongside the invitation to the medication review. This will comprise a list of the current prescribed medications that the practice has recorded them as taking, and opportunity for the patient to note any concerns or questions they may have for the pharmacist/GP. Patients will be asked to bring this to the face-to-face review or have it to hand during the telephone or video consultation.
- **Follow-up:** Follow-up and/or monitoring of patients after changes in medication is a recommended aspect of good medication optimisation practice. At the end of the face-to-face review, clinician and patient will agree a date for follow-up to assess clinical response, patient views, and evaluate any potential safety issues. Follow up will generally be undertaken by the pharmacist. This is potentially an additional opportunity to address issues not covered by the first medication review, as it often impossible or inappropriate to do everything at a single visit. If a formal follow-up appointment is not deemed clinically necessary, the clinical reasons for this must be documented and a telephone call arranged at around 4 to 6 weeks to confirm with the patient that no new issues have arisen; this will ensure that all patients still receive all components of the review process (i.e. maintenance of fidelity of function).

Implementation of review model

Practices will be required to complete each stage of the polypharmacy medication review framework (maintenance of fidelity of function). However, they will have autonomy in terms of the precise form each stage of the review takes, to allow practices to tailor the model to the local context. For example, the nature of discussions between GPs and pharmacists could vary in a number of ways, including the choice of face-to-face vs virtual meetings; discussion with a single GP versus multiple GPs, for example in practice meetings; and the choice of criteria and processes used to reach decisions about which health care profession should undertake face-to-face meetings. The review process will take a holistic approach to medicines optimisation, focusing on the overall medication regimen rather than specific, individual medicines. Again, clinicians will be allowed autonomy to make decisions guided by the priorities, values and goals expressed by patients as part of the face-to-face review.

Components seeking to enhance professional engagement

There will be three main components which will aim to change professional behaviour with respect to improving medication use in patients with polypharmacy. These are an educational outreach session, practice feedback, and financial incentives; these three components are outlined below.

Educational outreach

Educational outreach delivered to clinicians in each practice will cover broad issues implicit in the review model (including centrality of patients' goals/priorities) as well as technical aspects of common prescribing problems. Outreach sessions held within practices provide greater flexibility to fit around the commitments of busy staff, in contrast to workshops held on fixed days in locations remote to the practice. It also allows the informatics tool to be demonstrated and discussed using live/real data within the practice.

The educational outreach will comprise a fully-funded half-day training session provided to participating pharmacists to improve intervention delivery. This will be delivered by the research team. A subsequent shorter training session, ideally timed over a lunchtime to facilitate attendance, will be delivered by the pharmacist to other members of the clinical team (primarily the GPs delivering the intervention, although some aspects may be relevant to administrative staff). Engagement will be encouraged by ensuring the training session can count towards required continuing professional development for appraisal and revalidation. An additional optional lunchtime session will be offered to the practice and pharmacist after a 2-to-3 month period to discuss challenges with implementation and potential strategies to address practices' concerns.

This educational outreach will aim to achieve sustained improvements in prescribing post intervention. The exact nature of the sessions will be determined as part of the initial developmental work, but is likely to include the following:

- Suggestions/guidance on undertaking the collaborative discussion
- Training in undertaking a structured medication review (based around the SIGN 7-step model), focusing on patient priorities, key aspects of de-prescribing, and addressing in particular quality of life and treatment burden
- Instruction on use of the informatics tool
- Discussion of specific medication safety issues amenable to change which are identified by the informatics tool and of particular relevance to older people with multimorbidity (e.g. anticholinergic burden)
- Consideration of broader attitudes to prescribing (e.g. taking responsibility for medications when initiated by a specialist)

A separate training session in trial processes will be provided in all practices pre-randomisation. This will be delivered by the trial team to the pharmacist, lead GP and practice manager.

Financial incentives

Financial incentives will be provided for practices to deliver case-note reviews, collaborative GP-pharmacist meetings, medication reviews with patients, and clinical follow-up. These will be paid on a per-patient basis (£60 per patient completing all components of the review) and will reflect the kinds of contractual mechanisms (e.g. QOF) commonly used in UK general practice.

Feedback

The informatics tool (described below) will provide feedback to practices on a continuous basis. This will help ensure continuing engagement with the intervention. Feedback will include, firstly, data on relevant prescribing parameters (e.g. numbers of high-risk prescriptions) and, secondly, data on progress in delivering trial processes (e.g. number of case-note reviews completed, number of reviews with the patient completed, number completing follow up). Comparison will be made against practice baseline values, as well as against other (anonymised) practices within the study. Comparison with other practices at baseline may also help to motivate initial change; we will establish an appropriate benchmark using data from Phase 2.

Informatics tool

The informatics tool will be developed by a third party (BlueBay Medical Systems), but is referred to in short in this protocol simply as “BlueBay” or the “tool”. The tool will be based around an existing system developed by our team and trialled in GP practices in Scotland. All practices in the study will use the EMIS Web clinical system. EMIS have an approximate 50% market share in GP clinical informatics systems in the UK, which will facilitate future implementation. The tool will have three principal functions, outlined in more detail below:

- Case-finding
- Creation of an enhanced medication summary
- Feedback of performance data to practices

Provisional specification for the tool is outlined in the Appendix.

Case finding

The informatics tool will provide an effective, automated case finding process, based on routinely recorded electronic data. This will be modelled upon our existing Scottish IT tools, which already have the functionality required to identify people with polypharmacy who have clinically important potentially inappropriate prescribing (PIP), based on a panel of prescribing indicator “triggers”. The indicators to be used for the trial will be established as part of the work undertaken during the Phase 1 development work, and include high-risk prescribing, under-prescribing of highly effective medicines, and failure to conduct appropriate drug monitoring. Practice administrative staff will run the case finding feature pre-randomisation to identify potentially appropriate patients to invite to participate, as well as to check on-going eligibility immediately pre-review.

Enhanced medication summary

The tool will support medicines review and optimisation by providing an enhanced medication summary. This will bring together data from across the GP record in a structured way to summarise clinical context (e.g. recorded morbidities, blood pressure, renal function and other laboratory tests), flagging PIP (using >100 indicators of over-prescribing and under-prescribing which we have already implemented using GP data), identifying overlapping adverse drug effects (e.g. anticholinergic burden; sedative load; drugs causing hypotension, bleeding, or renal impairment) and summarising adherence. Summary information is provided about each separate drug, supplementing information such as dose and formulation with data on issues such as prescription refill frequency, key safety

indicators, or clinical test results. The option will be available to export this summary as a printable PDF, which makes it usable outside the surgery since the most at-risk patients are housebound or living in care homes. The printable summary will draw upon the model used in the POEMS intervention, an example of which is available in the Appendix.

Feedback of practice performance data

The informatics tool will feedback aggregated data to practices through a dashboard whose design will draw on our existing work in this area[16] and the Phase 1 development work. Two kinds of data will be fed back: (1) data on the prevalence of PIP in people with polypharmacy in the practice in total and by individual indicator; (2) data on progress in delivering trial processes (e.g. number of case-note reviews completed, number of face-to-face reviews completed, number completing follow-up). Data will be comparative, comparing current practice performance against practice baseline values, and comparing against other (anonymised) practices within the study.

The tool's ability to extract relevant data from the clinical system for the purposes of providing feedback, will also be used to extract data for trial evaluation of intervention effectiveness.

USUAL CARE COMPARATOR

There are no established management strategies for addressing the problem of polypharmacy in current English general practice. The nature of usual care for patients with polypharmacy in England is uncertain, but we believe it generally comprises brief, often opportunistic, largely unstructured medication reviews which are entirely records-based or conducted during routine consultations for other purposes, with variable reach and unknown effect. Pre-arranged follow-up subsequent to notes-based medication review is not typical. Guidelines are not available in England, GPs do not receive specific training in this area, and there are significant barriers to structured review including difficulties in identifying who would most benefit and the time needed to gather relevant information from an electronic record which is not designed to support the task. Although GP electronic health records contain most of the technical information required to support medication reviews (e.g. drug lists, problem lists, laboratory and clinical measurements), the data are spread across multiple parts of the health record with no easy means to identify problematic long-term prescribing or particular risks in individual patients. In addition, there are no accepted ways to undertaking case finding to identify patients with polypharmacy most likely to benefit from intervention.

The new NHS England 2020/21 GP contract lists “structured medication review and optimisation” as one of seven national service specifications, which will apply from April 2020. The contract does not specify how these must be delivered, although it is implied that clinical pharmacists will be expected to undertake most of this work. However, we expect that the more structured, integrated and patient-centred approach we propose for IMPPP, including informatics support, is unlikely to occur as part of these contractual changes.

Practices in the usual care arm will undertake their usual care for patients with polypharmacy. In most cases, we expect this will comprise occasional routine, unstructured medication reviews, but no specific management strategy focused on polypharmacy. Control practices will be aware that the patient has consented to a trial of a polypharmacy intervention. We consider this to be risk stratification, rather than specifically identifying a problem requiring intervention; changes to medications which trigger the review process are not mandated as part of the intervention. As such, the trial will not be withholding any intervention targeted at the specific prescribing indicators which would otherwise have triggered a review. We do not think there is substantial likelihood that control practices will improve care for these patients since they will not have access to the tools, strategies or support that we will be using to improve management in intervention practices.

PROCESS EVALUATION

Phase 2 (implementation/pilot phase)

We will conduct a formative mixed methods process evaluation in the Bristol area, drawing on a process evaluation framework we developed[39] and used in the DQIP [33,34] and 3D [40] studies, and on the MRC framework for process evaluation of complex interventions[25]. This will provide insight into context (particularly the initial context within which the IMPPP intervention is going to be implemented and the extent to which the intervention differs from "usual care"); initial response by practices to the intervention; and initial adoption and implementation of the intervention, including likely barriers and facilitators to implementation in the main trial.

Quantitative process measures

Quantitative measures will be used to examine delivery of the intervention itself, which will inform delivery of the intervention as part of the main trial.

- Examination of post-course evaluation questionnaire for educational outreach component
- Engagement with review process
    - Number and proportion of patients undergoing the different stages of the review process, including reasons for failure to complete each stage
- Nature of the review process
    - Time invested for each component of the review process (case-note review, collaborative discussion, medication review with the patient, follow-up appointment)
    - Person conducting the medication review with the patient (i.e. pharmacist vs GP)
    - Types of follow-up appointments (e.g. phone, face-to-face)
- Recommendations during review process
    - Nature of recommendations made at each stage of review process
    - Rate of implementation of recommendations, immediately post-review and at 6 months

Additional quantitative measures will examine the trial processes themselves, again allowing for these to be refined for the main trial.

- Recruitment rate (representativeness of recruited practices will not be assessed at the pilot stage, although will be explored for the full trial)
- Retention rate
- Patient completion of baseline and follow-up questionnaires
- Time between consent and review

Qualitative methods

- Pilot usual care survey, training evaluation forms, patients' post-review (questionnaire 3) and the medication leaflet used to prepare patients for the review (primer form)
- Semi-structured interviews (face-to-face or via telephone or video call) with key professionals in intervention and control practices, including GPs, practice pharmacists and practice managers (to understand usual care including models of pharmacist support to practices, the feasibility of implementation of the intervention, within the practice, initial acceptability of the intervention and areas for improvement and to refine usual care survey) (up to 10 interviews);
- Non-participant observation of training/educational outreach sessions with practice staff (to understand initial response to the intervention, particularly the educational outreach component and to pilot training evaluation forms) (3 sessions; intervention practices only);
- Think-aloud interviews [37] with practice staff during use of all aspects of the informatics tool (to explore the utility of each aspect, how the tool might support the implementation of the

medication review and practice feedback components, and areas for improvement) (2 think-aloud interviews conducted remotely or in person at the practice in each of the 3 intervention practices delivering the full intervention, i.e. 6 interviews);
- Audio-recording of the GP/pharmacist collaborative discussions (3 in each intervention practice i.e. 9 recordings)
- Non-participant observation and/or audio-recording of polypharmacy reviews with patients to examine how the review component of the intervention is being implemented (3 observations in each of the 3 intervention practices delivering the full intervention, i.e. 9 observations).
- Semi-structured patient face-to-face or telephone interviews to explore patient experience/engagement with the review process (utility of the primer form) 3 patient interviews in each intervention practice i.e. 9 interviews

Detailed field notes will be taken during observations of training sessions or reviews. These will be transcribed by the process evaluation researcher. Consent for face-to-face interview or recorded verbal consent for interviews conducted by telephone or video call will be obtained immediately prior to the interview. All interviews will be audio-recorded (where interviews are conducted using a video rather than telephone call, only the audio portion of the interview will be recorded and made available for transcription). Audio-recordings of the reviews will be transcribed by an approved transcription service. The qualitative data will be analysed thematically, using a mixture of deductive and inductive coding and adapted constant comparative techniques[41,42]. Analysis will be led by the process evaluation researcher with input from the senior qualitative co-applicants (KT, CC-G), who will read and provisionally code a sub-set of transcripts and agree the final coding framework.

The formative process evaluation will directly inform which intervention components require modification to optimise their potential impact by identifying potential barriers that will need to be overcome and key mechanisms of action of the intervention. This might include, for example, modification of the form or content of the educational intervention, restructuring of the financial incentive, redesign of the type and process of practice feedback, and modification to the informatics tool to increase usability and utility. Data gathered during the formative process evaluation will also inform evaluation and refinement of trial procedures and process evaluation methods (e.g. consent, data collection).

Phase 3: Main trial

The mixed methods process evaluation during the main trial will be guided by the same process evaluation framework [17,40] and MRC framework on process evaluations of complex interventions [25] as used in the formative process evaluation. It will examine key trial processes, giving insight into how the intervention is implemented in order to aid interpretation of the trial results. Analysis of data relating to the key hypothesised mechanisms of action identified in the formative stage will give insight into why the intervention was effective or not.

During the main trial, the process evaluation will examine five key trial processes:

- how practices take up the intervention and organise themselves to deliver it (**adoption**);
- what is actually delivered to patients and the extent to which this is as intended by the research team (**delivery** including fidelity);
- patients' experiences of receiving the intervention (**response**);
- GPs' and pharmacists' experiences of implementing the intervention (**response**)
- whether and how the intervention is maintained over time (**maintenance**);
- contextual factors that may influence implementation (**context**).

Quantitative measures

Quantitative data gathered for the purposes of the process evaluation will mirror that for the pilot phase. The following data will also be captured:

- Representativeness of recruited practices (e.g. list size, number of doctors, training status, availability of pharmacist, performance on external metrics [QOF, GP Patient Survey]) compared with non-recruited practices
- Survey to all practices on usual care policies (at baseline and at end of trial)
- Survey to all pharmacists to understand pharmacist/GP collaboration/interaction (end of trial).

Qualitative evaluation

Purposeful sampling of a subset of up to six intervention practices (representing different models of pharmacist provision and across both trial sites) will identify case studies for detailed qualitative evaluation, using a mixture of methods. In each case study practice, we will:

- Semi-structured face-to-face or telephone interviews with commissioners and medicines management managers (to understand context) (about 5 interviews);
- Observe the training/educational outreach session to examine how the practices respond to the intervention and the trial (6 observations, 1 per case study practice);
- Audio-record discussions between GPs and pharmacists to understand their interaction and the utility of the discussion (up to 4 discussions in each case study practice i.e. up to 24 observations). This may be particularly important for understanding mechanisms of action, such as priority accorded to meetings and professional role boundaries;
- Observe and audio-record medication reviews with patients to examine how this aspect of the intervention is being delivered, to include those delivered by GPs and pharmacists (5 observations in each of the 6 case study practices, i.e. up to 30 observations);
- Interview patients (face-to-face or via telephone or video call) who have received the intervention, and family carers if available, to evaluate their response, including their experience of the medication review process (up to 5 interviews in each of the 6 case study practices, i.e. up to 30 interviews);
- Interview (face-to-face, via telephone or video call) key practice staff regarding how they organise their systems to deliver the intervention, their views of different intervention components (e.g. educational outreach, medication review, financial incentives, IT tool), their response to and maintenance of the intervention over time and ongoing contextual issues (2 GPs, 1 pharmacist, 1 practice manager in each of the 6 case study practices, i.e. up to 24 interviews).

Patient and clinician participant consent will be sought prior to interviews and audio recordings for observation of interprofessional discussions and medication reviews. Written consent will be sought for face-to-face interviews and verbal consent will be audio-recorded at the start of interviews via telephone. The consent process will be similar for audio-recordings for observation of medication reviews with patients. The process evaluation researcher will send a postal invitation pack to patient participants who have given their consent to be contacted about the process evaluation and have been selected for interview and/or audio recorded observation of their review. The pack will comprise an invitation letter, a participant information leaflet, and the consent forms for an interview and for an audio recording of the IMPPP medication review. The researcher will telephone the participant 4-5 working days after the pack has been sent, to discuss the invitation and supporting materials, answer questions and confirm whether the patient wishes to take part in an interview and/or audio recorded observation of the IMPPP review. If the patient wishes to take part in an interview, a date will be arranged for the interview. Verbal consent to take part in interview will be audio recorded immediately prior to the interview commencing.

If the patient wishes to take part in audio recorded observation of the IMPPP review, the researcher will audio-record verbal consent to take part. The researcher will then let the reviewer (clinician) at the participating site know that the patient has given verbal consent to participate to confirm that the audio recorder can be used to capture the review.

At the start of the IMPPP medication review, the reviewer (clinician) at the site will ask the patient the following two questions;

- Have you spoken to [name of PE researcher] and given your verbal consent for audio recording of this medication review?
- Are you still happy for this review to be recorded?

If the participant confirms they are happy for this to take place, the recording continues. If the participant states they have not given verbal consent, or no longer wish to take part in audio recorded observation, the recorder is switched off and the review takes place without being recorded.

At the end of an audio-recorded review, prior to turning off the recorder, the reviewer will ask the participant to confirm they still agree to the recording being released to the University of Bristol research team for research purposes. If the participant agrees, the recording will be kept. If the participant does not agree, the audio recording will not be used within the analysis and will be deleted.

Verbal audio-recorded consent will be sought via telephone from clinicians wishing to take part in audio recorded observations of the interprofessional discussions and medication reviews with patients. Clinicians will be asked to also confirm at the point they start the recording that have given prior consent to the researcher.

At the end of the recorded session the clinician will state for the recorder that they agree to the recording being used for research purposes.

Given that usual care is both variable and may change over time, as part of the process evaluation we will also examine what usual care is in the two geographical settings, how it varies, how it overlaps with and departs from the intervention, and how it changes over the trial. This is to gain insight into the extent to which the intervention outpaces the ‘secular trend’ [56] and whether there have been movements in usual care towards the intervention. This will be evaluated through interviews (face-to-face or telephone) with health care professionals in a sample of practices from both arms of the trial. These interviews will be carried out at the start of the trial (both arms, before intervention implementation in intervention practices) and near the end of the trial (practices from both arms). We anticipate that up to 20 of these “usual care” interviews will be conducted, across both trial sites. Interview data will be supplemented with that from the practice surveys (see above).

The findings of the process evaluation will help us to interpret the main trial results, by giving insight into reasons why the intervention does or doesn’t work. For example, if the trial shows that the intervention works, how does the intervention work, what components are particularly helpful, for whom, why and in what contexts. If the trial shows that the intervention does not work, we will gain insight into whether this is due to intervention failure (flawed intervention concept) or implementation failure (poor intervention implementation)[57,58].

Qualitative data from the process evaluation will be analysed in parallel with ongoing data collection, so that emerging issues can be incorporated into future data collection. Data analysis will involve both within case and cross-case analysis, both rich description of implementation in individual case study practices, and cross-case thematic analysis[41] of recurring issues relevant to intervention implementation. Particularly for the thematic analysis, NVivo V.11 software (QSR International) will be used to facilitate both deductive and inductive coding, allowing the identification of both anticipated

and emergent themes. Themes relating to mechanisms of action and to the key components of the intervention including how they were adopted, delivered, received and maintained, will help to interpret trial results and give indication of reasons why the intervention worked or otherwise. Qualitative analysis will be led by the process evaluation researcher, with input from the two senior co-applicants with qualitative methods expertise (KT, CC-G), who will read and provisionally code a sub-set of transcripts, comment on the developing coding framework, agree the final themes and contribute in detail to writing up the qualitative findings. Involvement of more than one person in this process will enhance the trustworthiness and credibility of the interpretation and analysis[59]. Input from the Patient Public Involvement group regarding emerging themes will also help to ensure validity of the findings.

STATISTICS AND DATA ANALYSIS

Sample size calculation

We consider an average reduction in number of potentially inappropriate prescribing indicators (primary outcome) of 0.5 per participant to be clinically meaningful. Based on data on the distribution of these indicators in pilot work, the standard deviation of the average (mean) indicator count is 2.0. Previous related studies conducted by this group have found an intraclass correlation coefficient (ICC) of between 0.0126 (EFIPPS[16]) and 0.036 (DQIP[15]). Therefore, to detect a mean of decrease in number of indicators triggered per patient of 0.5 in 50 patients per practice, with a power of 90% at the 5% significant level, and assuming an ICC of 0.036, we require a total of 37 practices. Due to the automated manner in which primary outcome data is captured, we can expect ~100% follow-up; as the follow-up period is only 6 months, we expect few patients to move away or die during this time. Even if 20% of cases are lost to follow-up, power will still be 88% at the 5% significance level with the same number of practices. Participant engagement with the medication review process in the pilot study was ≥88%.

Implementation/optimisation evaluation

The pilot phase (Phase 2) will evaluate the trial processes, including the intervention itself, recruitment and consent processes, data recording, and data extraction. We will use this data to examine the feasibility of practice and patient recruitment, as well as response rates to baseline surveys and follow-up rates. This will be supplemented by qualitative data gathered during Phase 2. We will specifically evaluate the IT infrastructure in relation to being able to collect trial outcome and process data. This will include comparing the prevalence of PIP with Scottish data to identify outlier indicators for checking, as well as following up and correcting any errors which GPs identify when manually reviewing records during medication review. The evaluation will be carried out in both intervention and control practices.

We will also estimate between and within practice variance in the primary outcome.

Progression criteria

At the end of the 6-month pilot follow-up period a decision will be taken by the Trial Steering Committee to proceed to the main trial. This will be based on meeting all the following criteria:

- **Informatics tool:** Successful development of an informatics tool with no major outstanding problems.
- **Educational outreach:** Successful development of educational package based on >70% participant agreement on a post-course evaluation questionnaire
- **Recruitment:** We will proceed to the full trial if recruitment is >75% of that required (as outlined below for Phase 3). If recruitment is <50% of that required, we will discuss terminating the study with the HS&DR board.
- **Retention:** We will proceed to the full trial if data on >80% of primary outcome and >70% of secondary outcomes are available. If <70% of primary outcome data or <50% of secondary outcome data are available, we will discuss terminating the study with the HS&DR board. (Primary outcome data is captured automatically, and is therefore expected to be available for ~100% patients.)

- **Patient engagement:** We will proceed to the full trial if >60% of patients invited to a medication review have attended. If <40% of patients invited to a medication review have attended, we will discuss terminating the study with the HS&DR board.

If targets for recruitment, retention or patient engagement lie between the thresholds detailed above, the TSC will use findings of the implementation/pilot formative process evaluation to identify options for improving these figures, before discussing proceeding to the full trial with the HS&DR board.

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

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.

Main analysis – primary outcome measure

The main analysis will use a linear mixed effects regression model to compare number of PIP indicators triggered at 6 months post-review (the primary outcome at T4) between groups as randomised, adjusted for baseline (i.e. pre-randomisation, T1) values of the outcome, area (stratification variable), and elapsed time between T1 and T4, and will include a random effect for GP practice to account for clustering. The result of the regression model will be presented as an adjusted difference in mean between the intervention and control arms alongside the associated 95% Confidence Interval (CI) and exact p-value for the comparison. If the assumptions of the regression model do not hold then transformations of the data or alternative models (e.g. zero-inflated Poisson or negative binomial regression) will be explored.

Additional analyses – primary outcome measure

Additional analyses of the primary outcome will include further adjustment of the main analysis for any prognostic variables strongly related to outcome (identified *a priori* based on clinical expert opinion). A further additional analysis will be performed where baseline is taken from the pre-review time-point (T2), with adjustment for pre-randomisation outcome values. This is proposed as there is the potential for a considerable delay between randomisation and review; medication optimisation processes during this time may vary between arms (e.g. usual care may be more likely to take action to improve prescribing, as unlike the intervention arm these practices would be aware that no IMPPP review would be occurring later) resulting in differences in prescribing at T2 unrelated to the intervention itself.

Secondary analyses – secondary outcome measure

The effect of the intervention on the secondary outcomes collected at 6 months post-review follow-up will also be examined using appropriate mixed effects regression models (i.e. a linear model for continuous outcomes, logistic model for binary outcomes, etc) adjusted for baseline (pre-randomisation) values of the outcome being investigated, elapsed time between T1 and T4, area (stratification variable) and including a random effect to account for clustering by GP practice**.**

Sensitivity analysis

The sensitivity of the main analysis to the impact of missing data (where missingness is >5%) will be explored by imputing missing primary outcome data and repeating the primary analysis model using the imputed data. The imputation model will include all variables that are part of the ITT primary analysis, baseline and post-randomisation variables that are associated with missingness, and interim data on the primary outcome collected at 6 months follow-up. It is emphasised that levels of missing data are expected to be low, as the primary outcome is captured using automated processes.

Exploratory and sub-group analyses

Complier Average Causal Effect (CACE) analysis using a 2-stage-least-squares (2SLS) instrumental variable (IV) approach will be used to investigate the efficacy of the intervention in reducing PIP indicators at 6 months. The CACE methodology compares outcomes for those who “complied” with the intervention with a comparable group of “would be compliers” in the control group. CACE analysis provides an estimate of the efficacy of the intervention for comparison with the ITT estimate of the offer of the intervention, whilst respecting randomisation and avoiding biases inherent to crude per-protocol analyses where only individuals in the intervention arm are included. In this trial “compliance” will be defined as undergoing the face-to-face medication review.

To investigate potential moderators of treatment effect, interaction terms for treatment group by age, and treatment group by multimorbidity will be added (separately) to the primary analysis model.

Economic evaluation

Measure of outcome

There is little evidence to support the choice of any given preference-based measure of health-related quality of life in the polypharmacy population. The population itself is highly heterogenous with respect to the causes of ill health. During the Implementation/Pilot Phase we will randomise patients to collect responses to either EQ-5D-5L or SF-12, both of which have been used in polypharmacy related research. SF-12 has been shown to be sensitive to prescribing practices on the physical component score[52]. The EQ-5D-5L is currently being used in a polypharmacy-focused RCT although it is not certain if results will be reported before IMPPP begins recruitment (ISRCTN 42003273) [53]. We will assess completion rates and sensitivity to change to determine which measure will be most suitable for continued use in the main trial. Outcomes from the preference-based measure will be calculated as the difference in quality adjusted life years at six months post-review compared to baseline (pre-randomisation, T1), calculated using the area under the curve approach.

Resource use

We will assess the relative costs of the intervention compared to standard care. The intervention will lead to an increased cost from longer consultations in general practice, the addition of practice pharmacists, and the financial incentives to practices to provide reviews. Against this we anticipate that there will be fewer recall appointments to discuss management of single conditions, fewer prescriptions and possibly fewer hospital appointments or admissions. To minimise respondent burden, we will attempt to obtain primary and secondary care resource use data from routinely collected data sources, at the end of the trial for baseline and 6-month post-review follow-up (self-reported service utilisation data will be collected via questionnaire should this not be possible). Primary care data will be extracted directly from participating practices using the BlueBay informatics tool (again using questionnaire if automation should prove unworkable). Secondary care resource use data will be obtained from the NHS Digital. In an ageing population we anticipate some use of social care services and possible changes in patterns of use related to improved prescribing practices. We will ask respondents to complete a brief data collection tool at baseline and 6-month follow-up relating

to their use of social care services in the previous 6 months (e.g. home visits from social services, residence in a nursing or residential care home). We will also ask about additional support they have received from family or friends, such as help with cooking/cleaning or other tasks of daily living. Costs will be assessed from NHS and societal perspectives, including GP/other practice contacts, IT costs, identifying/contacting patients for review, pharmacist time, unplanned admissions, patient direct/indirect costs and informal care.

Analysis

The economic analysis will be performed using individual patient-level data from the trial. The primary outcome for the economic evaluation will be reported as quality adjusted life years, as derived from the EQ-5D-5L or SF-12 (as determined from Implementation/Pilot Phase results). If the SF-12 is selected, responses will be converted to SF-6D scores[54] using the validated scoring algorithm available online[55]. The analytical approaches will take the form of cost-effectiveness and cost-utility analyses. Results of the primary economic analyses will be reported as the net-benefit statistic; ICERs and cost-effectiveness acceptability curves will also be reported. The primary analysis will be from the perspective of the NHS and personal social services, with secondary analysis from a societal perspective. We will also estimate cost-effectiveness ratios based on the cost per incremental change in the primary outcome. The cost per unit of change in PIP indicators will also be calculated, using change in the count of PIP indicators from baseline (pre-randomisation,T1) when measured at 6 months post-randomisation. The association between change in PIP and change in QALY during the same period will be reported. The detailed analysis is presented in the separate Health Economics Analysis Plan (HEAP).

DATA HANDLING

Data collection and handling is discussed below. Further details are provided later under Ethical and Regulatory Considerations.

Data collection tools

Patient, carer and practice staff contact details needed for day-to-day trial management, including consent, will captured using paper forms. The data will be transferred to a bespoke trial management database, designed and managed by the research team and held on secure servers at the University of Bristol. These identifiable data will be kept separate to the other (anonymous) trial data.

A bespoke clinical software tool, developed as part of Phase 1 of the IMPPP study, will be used to capture clinical information directly from the GP's clinical electronic healthcare record system. These data will be downloaded over a secure network connection in an anonymised format on a regular basis, and stored on the secure University of Bristol Research Data Storage Facility (RDSF). This will be separate to the trial management database and individuals will be identifiable only by their unique study identifier.

Other quantitative trial data will primarily be in the form of participant self-report paper of online questionnaires and case report forms. Paper data will be anonymised and imported 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. Transcriptions will be undertaken by a service approved by University of Bristol and transferred in an anonymised format to the RDSF for analysis.

Data handling and record keeping

Data will be collected and retained in accordance with the General Data Protection Regulation 2018 (GDPR) (see section *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) .

Research teams at each recruitment site will be responsible for the collection and monitoring of data from participants and practices within their site.

At least 10% of paper questionnaire data will be subject to double entry to ensure quality/reliability.

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.

Access to data

The Senior IT Manager (in collaboration with the Chief Investigator) will manage access rights both to the participant contact data in the trial management database, and to the clinical data held in

REDCap. The trial manager (in collaboration with the Chief Investigator) will manage access rights to data extracted from the GP clinical information system, and to the qualitative research data.

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.

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 *Data protection and patient confidentiality*.

SAFETY

Overview

Given the nature of participants in the IMPPP trial (older with multimorbidity), new diagnoses, hospital admissions and death are to be anticipated.

Serious adverse events will be monitored, recorded and reported in accordance with the Good Clinical Practice (GCP) guidelines and the Sponsor's Research Related Adverse Event Reporting Policy. Assessment of intensity, relatedness and expectedness will be made for all serious adverse events.

The Principal Investigators at each research site will make the following decisions (based on the definitions outlined below):

- Is the adverse event serious or not?
- How related is the event to the study intervention or research processes?
- Would the event be expected even if the research had not been taking place?
- Does the event interfere with or prevent normal daily activities?
- Is further action required?

Serious adverse events may be identified by any person related to the trial (e.g. participant, carer, clinician, researcher).

Definitions

Serious adverse events

A **Serious Adverse Event (SAE)** is defined as any untoward medical occurrence in a participant subject to the IMPPP 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.

For the avoidance of doubt, an adverse event will be deemed to have occurred where a change to the prescribed medication is required at the medical review follow-up appointment to counter a change in medication made at the initial intervention (face-to-face review) appointment.

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.

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 IMPPP 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 IMPPP 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 IMPPP 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 every day activities
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities
- **Severe:** An event that prevents normal everyday activities.

Recording and reporting of adverse reactions

Participants and staff will be asked to notify the local principal investigator (GP) or University research team of any potentially serious adverse event (SAE) which they believe may have occurred as a result of the trial intervention or the research process.

For each SAE the following information will be collected by the research team using a SAE/SUSAR Initial Report Form; where necessary, further information will be requested from the participant or GP/pharmacist:

- 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 investigator;
- Whether the event would be considered expected or unexpected.

Forms completed by local PIs will be returned directly to the research team (trial administrator, trial manager). Local PIs must notify the co-ordinating centre of any events which they have assessed as possibly, probably or definitely related to the trial intervention or the research process via email using the SAE/SUSAR initial report form within 24 hours of becoming aware of the event. Where information is incomplete, including assessment of causality and expectedness, the forms will be passed to the CI for clinical review. The CI will take responsibility for obtaining any outstanding information to enable assessment to be completed. Each SAE will be reported separately and not combined on one form.

All SAEs, irrespective of whether or not they were considered to be expected and related (i.e. a Suspected Unexpected Serious Adverse Reaction, SUSAR), will be reported to the DMC at each scheduled DMC meeting. We cannot accurately capture all SAEs in the usual care arm, and thus comparison of adverse event rates across arms is not possible.

All SUSARs (but not other SAEs) will be reported to the sponsor. On notification of any potential SUSAR, the research team will inform the sponsor within 24 hours via email. An SAE/SUSAR Initial Report Form will be fully completed and sent to the sponsor within 5 working days, paying specific attention to information regarding the timescale of events (e.g. when the event started, were there any specific changes to medication or behaviour preceding the event). 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. This will then be forwarded to the sponsor.

The research team may become aware that a patient has died (e.g. notification by a clinician or relative). The researchers will send the deceased patient's GP a SUSAR initial report form, to collect further information about the cause and circumstances of the death.

All SUSARs will be reported to the REC within 15 days of the Chief Investigator becoming aware of the event, using the Health Research Authority Report of SAE form.

As there is a potential for ad hoc adverse events to be more readily identified in the intervention arm, the Principal Investigator at all research sites (irrespective of randomisation status) will undertake an additional proactive review of all participants' hospital admissions, adverse drug reactions and deaths during the study period at the end of study follow-up. This will help identify differences in adverse event rates between study arms.

The research team will send the site an email to notify them when a clinical review of the participants notes is required. The email will contain a link to an electronic Safety Assessment Report form V1.0, 21/11/2019. A Microsoft Word version of the report Safety assessment report form V1.0, 21/11/2019 will be attached to the email so that the site can choose how they wish to collect and report these data. A list of the unique study Id codes for IMPPP participants will also be attached.

Sites will record all Adverse Drug Reactions, unplanned hospitalisations and deaths occurring in the study participants between the date the participant provided their consent to take part and the current. These data will be recorded on the Safety Assessment Report form and return to the research team at least 1 week prior to the IMPPPP study Data Monitoring Committee meeting.

The researchers will collate the data for presentation to the Data Monitoring Committee.

TRIAL MANAGEMENT

The trial is supported by the Bristol Randomised Trials Collaboration (BRTC). The BRTC is an UK Clinical Research Collaboration registered Clinical Trials Unit. The trial will conform to the BRTC standard operating procedures. The research team in collaboration with BRTC will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators.

Day-to-day management

The CI will have overall responsibility for the project. A Trial Management Group (TMG) will meet monthly throughout the entire duration of the project to ensure smooth progress of the research; Dundee/Keele staff will generally join these meetings by teleconference. The TMG will be chaired by the Chief Investigator and will include all members of the named research team (see Co-investigator details).

The Development Phase of the study will be managed and coordinated in Scotland. Although not the subject of this protocol, due to the inter-related nature of the work, two face-to-face 1-day meetings of senior members of the research team will be convened to facilitate intervention design and implementation within the trial proper. In addition, a project team will be set up to facilitate working between the researchers and BlueBay. This will comprise members of both stakeholders, and will meet on a fortnightly basis either face-to-face or by teleconference to discuss progress.

The Implementation/Pilot Phase and Main Trial will be coordinated by the trial manager who will co-ordinate the research team on a day to day basis, in partnership with the Principal Investigator at each site, and supported by a senior manager in the Bristol Randomised Trials Collaboration. A junior trial coordinator will be employed to administer the main trial in Keele.

Principal Investigator/practice clinicians (GP, pharmacist)

Principal investigators (PIs) and clinicians at each site will be checking for SAEs when they have contact with participants. They will be responsible for:

- Using medical judgement in assigning intensity, seriousness, causality and expectedness.
- Ensuring that all SAEs/SUSARs are documented and reported to the research team as soon as possible after becoming aware of the event and providing further follow-up information as soon as available to enable full reporting to the sponsor within five working days.
- Ensuring that SUSARs are documented and reported to the Chief Investigator in line with the requirements of the protocol.

Chief Investigator

The Chief Investigator 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 SAEs where it has not been possible to obtain local medical assessment.
- Immediate review of all reportable SAEs including expedited reporting of SAEs to the Sponsor and REC within required timelines.
- Central data collection of SAE/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.

Sponsor

The sponsor will be responsible for overall oversight of the trial.

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 5 occasions to provide external oversight, supervision and advice about all aspects of the research.

Membership:

- Rupert Payne, CI, University of Bristol
- Chris Salisbury, GP and trials expert, University of Bristol
- Michael Moore, academic GP, independent Chair
- David Reeves, independent statistician
- Matt Hoghton, independent clinician (GP)
- Nina Barnett, independent clinician (pharmacist)
- Ayath Ullah, independent lay member
- Christina Stokes, independent lay member

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.

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:

- Greg Rubin, independent Chair/GP
- Julie Barber, independent statistician
- Beth Stuart, independent statistician

Patient Advisory Group (PAG)

Patient input informed the funding application and has already informed the design of this study, and 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 which has the potential to offer reduction of prescribed medications for patients. Two PPI representatives will sit on the trial steering committee

and contribute to writing key research documents (e.g. patient information sheets, guidance for clinicians on the review process, process evaluation topic guides, scientific papers).

A PPI advisory group (5-6 members) will be convened that will provide input at all phases of the study, including interpretation of process evaluation findings, input into educational practice and patient-facing materials (e.g. PILs, consent forms, interview schedules), consideration of ethical and regulatory aspects, identification of non-academic routes for dissemination and contribution to wider public materials.

The CAPC PPI coordinators will help facilitate and maximise PPI input throughout the project including provision of training to lay members.

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.

All University of Bristol studies that are registered on the Research Governance system will be eligible for monitoring by an independent service provider (an SLA is in place with University Hospitals Bristol to provide this).

Compliance with the GCP guidelines for monitoring is often interpreted as requiring intensive site monitoring. However, "the extent and nature of the monitoring should be proportional to the objective, purpose, design, size, complexity, blinding, endpoints and risks of the study." (GCP, section 5.18.3). This is of relevance to IMPPP, where the exact nature of implementation of the intervention will vary with individual practices, and the risks are relatively low.

The sponsor will delegate some of the monitoring to the research team, including the following checks:

- that written informed consent has been properly documented
- that data collected are consistent with adherence to the study protocol
- that CRFs are only being completed by authorised persons
- that SAE recording and reporting procedures are being followed correctly
- that no key data are missing
- that data are valid
- review of recruitment rates, withdrawals and losses to follow up.

On a regular basis we will monitor the percentage of patients that meet the eligibility criteria and report the percentage of patients who consent. To assess the generalisability of the participants, the characteristics of consenting participants and non-consenting will be compared. We will also report to the DMC if requested, preliminary data on rates of problematic prescribing, drop outs and SAEs, SUSARs and deaths observed in the trial population.

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.

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.

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 trial, 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.

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.

Research Ethics Committee (REC) review and reports

Ethical and Health Research Authority (HRA) approval will be sought through the HRA for the pilot and main trial, including the embedded qualitative work. We believe the proposed research raises some specific ethical issues detailed below.

Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIL, consent form) will be carried out by a UK Research Ethics Committee (REC). Any amendments to these documents, after a favourable opinion from the REC/HRA has been given, will be submitted to the REC/HRA for approval prior to implementation.

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.

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.

Ethical Issues

Firstly, to ensure broad inclusion criteria, we will ask carers to help with completion of questionnaires where appropriate.

Secondly, any medication optimisation strategy targeted at polypharmacy may result in a reduction in prescribed treatment (deprescribing). This is ethically acceptable assuming any such clinical decisions are made in agreement with the patient, are clinically justifiable, and are in the best interests of the patient. We will minimise any associated concerns about this by ensuring the issue is thoroughly considered during the intervention Development Phase (including obtaining patient input).

Risks and Benefits

Potential benefits:

- improved patient safety
- improved quality of life
- reduced health service use
- reduced drug expenditure
- reductions in medication waste

Potential risks due to changes in prescribing:

- medication errors
- adverse drug reactions (irrespective of errors)
- impaired medication adherence
- stopping potentially beneficial medications (and consequences thereof)

Indemnity

The necessary trial insurance is provided by the Sponsor. The PIL will provide a statement regarding indemnity for negligent and non-negligent harm.

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.

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. Identifiable data will also be deleted at any time if this is explicitly requested by a participant.

All non-essential data will be wiped within 3 months of the completion of the final analysis. Essential study documents and electronic data will be kept for up to 5 years, after which they will be deleted, and all copies destroyed in accordance with the University of Bristol policies on secure erasure of data.

After the final study analysis is complete, anonymised data 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.

Written data

Data in written form, such as written consent forms and reply slips which contain participant names and contact details (e.g. postal and email addresses, telephone numbers) 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 anonymised paper records (questionnaires).

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.

Recorded qualitative data

Audio and video recordings of participant or health professional interviews, or observations of educational outreach sessions, GP-pharmacist interactions, 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 optionally consent to the specific storage of anonymised interview data (transcripts only) on the ‘controlled access’ data repository.

Access to the final trial dataset

Anonymous research data 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.

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 (CI) holds various grants from NIHR related to polypharmacy. He is consultant editor for the journal Prescriber.
- Chris Salisbury has held grants from NIHR related to multimorbidity.

There are no other competing interests.

DISSEMINATION POLICY

We will disseminate findings from this research to the following audiences:

Patients and lay audience

We will co-produce press releases with PPI members and distribute via print media, websites and relevant patient organisations (e.g. Age UK). Design and promotion will be supported by Bristol and Keele University press offices and the CAPC communications officer 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. The trial website (www.bristol.ac.uk/primaryhealthcare/researchthemes/imppp/) will support this dissemination activity, and we will utilise our institution social media outlets to update and engage the public during and following the study.

Healthcare professionals

We will work with the Royal College of General Practitioners (RCGP) and Royal Pharmaceutical Society (RPS) to promote the research findings. The RCGP represents over 40,000 practising GPs, and the RPS over 40,000 pharmacists, and both have established communication networks including a strong social media presence. We will liaise with RCGP to contribute to its existing range of tools for supporting practices. Both RCGP and RPS hold national conferences, and have been working towards stronger collaboration, holding a recent meeting addressing joint working between the professions with a focus on polypharmacy. We will work with both to identify opportunities for workshops to disseminate findings and discuss implementation strategies.

Commissioners and policymakers

These stakeholders will be invited to national workshops, and will be influenced by articles in the lay, professional and academic press. We are working with Bristol and N Staffs CCG medicines management teams 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) to further influence policy. Our final NIHR report will include an executive summary, accompanied by relevant promotional material, targeting NHS managers.

Academia

Papers will be submitted to high impact medical journals and presented at academic conferences (e.g. SAPC, NAPCRG). The full project report will be available on the NIHR website and published in the NIHR journal series.

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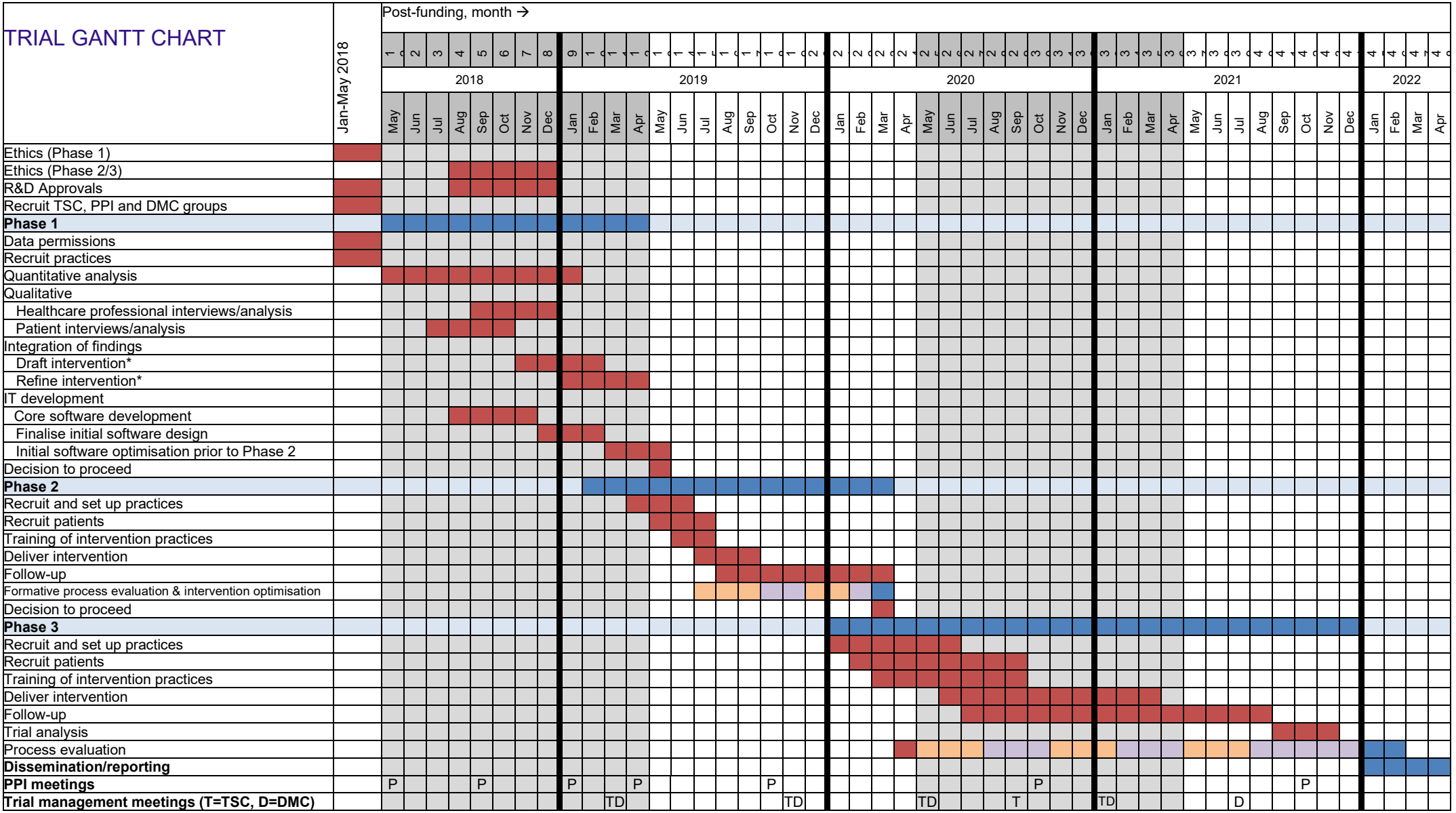
APPENDICES


TRIAL GANTT CHART
Jan-May 2018
Post-funding, month →
2018
2019
2020
2021
2022
May Jun Jul Aug Sep Oct Nov Dec Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec Jan Feb Mar Apr
Ethics (Phase 1)
Ethics (Phase 2/3)
R&D Approvals
Recruit TSC, PPI and DMC groups
Phase 1
Data permissions
Recruit practices
Quantitative analysis
Qualitative
Healthcare professional interviews/analysis
Patient interviews/analysis
Integration of findings
Draft intervention*
Refine intervention*
IT development
Core software development
Finalise initial software design
Initial software optimisation prior to Phase 2
Decision to proceed
Phase 2
Recruit and set up practices
Recruit patients
Training of intervention practices
Deliver intervention
Follow-up
Formative process evaluation & intervention optimisation
Decision to proceed
Phase 3
Recruit and set up practices
Recruit patients
Training of intervention practices
Deliver intervention
Follow-up
Trial analysis
Process evaluation
Dissemination/reporting
PPI meetings
P P P P P
Trial management meetings (T=TSC, D=DMC)
TD TD TD T TD D
* includes informatics, education and other aspects of the medication review process
TSC, trial steering committee; DMC, data monitoring committee; P patient and public advisory group
=Data
= Analysis
= Report

Updated trial timelines following variation to contract

	2022												2023											
TRIAL GANTT CHART V6.3 07/07/2021	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sep	Oct	Nov	Dec
Recruit and set up practices																								
Recruit patients																								
Training of intervention practices																								
Deliver intervention																								
Follow-up																								
Trial analysis																								
Process evaluation																								
Dissemination/reporting																								
PPI meetings									P							P				P				
Trial management (T=TSC, D=DMC)									T				D											

SPECIFICATION OF BLUEBAY INFORMATICS TOOL

	Essential	Desirable	Nice to have
Indicators			
• Implement up to 120 indicators in EMR (the indicators combine medicines, diagnoses and laboratory data, all from the EMRs, all specified by us for EMIS web)	X		
Practice level interface			
• List of patients determined by age, number of drugs and/or presence of 1 or more specific indicators	X		
• List of indicators with no. of patients triggering on each/any indicator			X
• Allow filtering of patients on specific indicators			X
• Run chart/dashboard (e.g. review activity, number of indicators) for practice		X	
• Run chart/dashboard (e.g. review activity, number of indicators) for practice comparing their data to other practices		X	
Patient level interface			
• Printable patient summary	X		
• Display clinical data - Problem list - Laboratory data - Weight, smoking status etc.	X		
• Display indicators triggered by patient	X		
• Allow recording of decisions against indicators (eg exception codes for indicators)		X	
• Allow recording of actions against drugs (start, stop, reduce dose etc)		X	
• Display timeline (e.g. issue dates) of prescription for repeat drugs		X	
• Display current medication (distinguishing between repeats and acutes)	X		
• Document that review has been done (in a retrievable format)	X		
• Document exception codes (in a retrievable format)		X	
• Take exception codes into account when calculating/displaying no. of pts triggering		X	
• Document review decisions (in a retrievable format)	X		
Data extraction			
• Remote extraction of specified data extract (e.g. CSV format) at different time points during trial	X		
Roll out of IT tool			

• Implement/activate tool in 27 intervention practices	X		
• Implement/activate only practice-level interface in 27 control (“usual care”) practices	X		
• IT help desk (or alternative software support)	X		

EXAMPLE OF POEMS MEDICATION SUMMARY


Acrobat Document