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Optimising a whole-person-centred approach to stopping medicines in older people with multimorbidity and polypharmacy: The Tailor Medication Synthesis

1. SUMMARY OF PROPOSED RESEARCH

The Tailor Medication Synthesis will provide clinicians with the evidence base they need to safely and effectively stop medication in older people living with multiple long term conditions and at risk of problematic polypharmacy.

Our previous research in this field [1,3], the wider literature [4,5], and a preliminary search conducted in preparing this bid [flowchart] suggests that a single synthesis will be insufficient to provide the relevant data to answer this research question, signpost future research and support changes to clinical practice. Therefore, we are proposing two evidence syntheses.

The first will be to conduct a formal systematic scoping review using the methodology recommended by the Joanna Briggs Institute [8]. Our preliminary search has highlighted variety in the interventions being used, the patient populations being targeted, the outcomes being measured and the methods being adopted to capture this information (e.g. quantitative, qualitative). We will therefore start with a scoping review which will describe a taxonomy of approaches for stopping medicines (their defining characteristics, presumed mechanism of action); along with their impact – effectiveness, safety and acceptability to patients and professionals alike. There are several advantageous to using this approach. A scoping review will support the identification, mapping and drawing together of the current evidence base on strategies to support safe medication withdrawal in this population. It will signpost health care professionals and policymakers to the quantitative and qualitative data they need to support decisions about when, if and how to stop medications. It will provide valuable information to researchers and funders on the gaps in the current evidence base, upon which new research can be prioritised. It is also a necessary part of our second work stream, to conduct a realist synthesis.

There is a clear justification for a realist review. Clinicians have indicated a need [1] for a framework that will support them in delivering the necessary compromise on [5], individual tailoring [4] or stopping of, medication use to address problematic polypharmacy. Realist review is a robust methodology used to examine what works for whom in what circumstances [6]. It is particularly useful for examining the process and impact of complex interventions [6,7]. This will deliver the framework (in the form of a programme theory) clinicians need to put deprescribing into practice – that tells them how, for whom and in what contexts they can stop medicines medication safely. We will follow the RAMESES standards [9] in using a robust iterative cross case analysis approach to critically examine how and why the actions of stopping medication, and beneficial/harmful outcomes, occurred in different studies [6,10].

We have identified two research questions:

> RQ1. What quantitative and qualitative evidence exists to support the safe, effective and acceptable stopping of medication in older people with multimorbidity and polypharmacy?
>
> RQ2. How, for whom and in what contexts can safe and effective individual tailoring of clinical decisions related to medication use work to produce desired outcomes?

To answer these questions our research design includes the two described, interlinked and simultaneous evidence syntheses, conducted from a shared search strategy - collectively called the Tailor Medication Synthesis. We will use a structured approach to identify relevant literature from as many relevant sources on the complex intervention that is stopping medication in the context of individual (whole-person) tailoring of medication use.

We will deliver 3 key outputs including : 1) a reference data set for clinicians working in this area detailing a classification of approaches used to stop medication, and what is known on effectiveness, safety and acceptability; 2) a framework for best practice in individual tailoring of medicines based on our realist programme theory of tailoring prescribing – a set of recommendations to support clinicians making decisions about stopping medication; 3) application for funding for an implementation study of a revised version of our PRIME prescribing complex intervention that incorporates the new findings from this study. Our structured dissemination strategy will deliver a range of formats for different users.

The Tailor Medication Synthesis will be delivered through a collaboration of experts in the fields of: problematic polypharmacy (the PRIME prescribing team including patient partners Ranson and Dickenson); clinical pharmacology (Walley, Aronson); multimorbidity (Fahey, Wallace); evidence synthesis (Mahtani, Wong, Roberts); primary care (Reeve, Mahtani, Wong, Fahey); secondary care (Aronson, Walley, Barnett) and the acute ambulatory care interface (Lasserson).

To ensure our proposal builds sustainable future research capacity, the Tailor Medication Synthesis will partner the new £1.9M NIHR School for Primary Care Research Evidence Synthesis Working Group (ESWG) [86]. The ESWG is a collaboration of all nine primary care member departments of the School of Primary Care Research, incorporating 45 leading researchers. Two members of this proposal (KM, GW) are Co-PIs within the ESWG, and have secured the partnering relationship. Knowledge gaps identified by our scoping review, will feed into the prioritisation process for new reviews delivered by the ESWG. In addition, knowledge gaps may form the basis of future collaborative bids to the NIHR Health Technology Assessment funding stream, in the form of new primary research. The Tailor Medication Synthesis will also use this relationship to build future cross boundary evidence synthesis networks across the UK, Ireland and Canada.

To provide reassurance on the lasting impact of our research, we will work closely with key stakeholders including patient and clinical (RCGP, NIHR CLAHRCs, Royal Pharmaceutical Society, NICE, SAPC, Clinical Commissioning Groups and other local networks) partners throughout the project to ensure our analysis is grounded in the needs of end users; and to optimise the impact of our dissemination strategy.

2. BACKGROUND AND RATIONALE

The NHS faces a growing challenge of dealing with problematic polypharmacy. Polypharmacy, the concurrent use of multiple medicines in a single person, is on the rise; driven by an expanding population living with multiple long term conditions (multimorbidity). It is estimated that around 1 in 5 patients take

five or more medicines a day [5]. Polypharmacy can be appropriate, extending life expectancy and improving quality of life [5]. However ~40% of people taking 5 or more medicines a day report feeling significantly burdened by their medication [11]. The latter are experiencing what has been described as problematic polypharmacy [5] – the use of multiple medicines on a long term basis when the intended benefit of the medicines is not achieved.

Dealing with problematic polypharmacy means knowing how to safely and effectively taper, withdraw or stop medications [1]. Clinicians are regularly required to stop medicines that are causing acute harm to patients – for example following an acute adverse reaction. However, discontinuing long-term-medicines is a process that causes anxiety and concern for clinicians and patients [1]. This year's Prescribing and Research in Medicines Management (PRIMM) Conference (at which several of our co-applicants/advisory group were speakers/organisers – Krska, Reeve, Barnett) was dedicated to looking at deprescribing- the process of supervised withdrawal of inappropriate medication [12]. Delegates discussed research highlighting that clinicians remain concerned about the safety and impact of stopping medicines – including the potential consequences for them as the decision maker.

Guidance on stopping inappropriate medicines (eg Beers criteria [13], STOPP/START[14]) has been around for a number of years. But clinicians report a broader problem in knowing how and when to stop medication that may be 'appropriate' from a clinical perspective but potentially not right for this individual patient [1]. Both recent research and policy reviews highlight the need to rethink how we understand 'optimal' prescribing – particularly in recognising that the perspectives and priorities of the medicines taker (patient) and indeed their family and carers may, or may not match the priorities of the prescriber [4,5]. The 2013 Kings Fund report on Polypharmacy described a need to recognise/support a "compromise" between patient and prescriber when defining best practice [5]. Denford et al.'s recent scoping review of approaches to individualised care related to medicines concluded a need to recognise a process of Mutually Agreed Tailoring of medicines – balancing benefits and harms from medication use [4]. Decision making processes that allowed patients to be able to input their specific needs, experiences and strategies for using their medication, and clinicians to be able to use their professional judgement to adjust medication use for the individual.

Our research highlights that professionals often feel unable to tailor medical care [3], including medication use [1], in this way. Multiple factors contribute to this problem, reflecting problems at both an individual level, and within the organisation of systems of practice [1]. Our research indicates that a significant barrier to individual tailoring of medicines use, including – where appropriate – stopping medication, results from a perceived problem in making 'defendable decisions' with regard to individual tailoring of medicines.

Therefore to support the safe and effective tapering and stopping of medications in vulnerable groups, we need to support professionals in making defendable, individually tailored decisions about prescribing. Clinicians describe needing data which helps them to discuss with patients and other stakeholders the process and impact of medication use [1,15]. Practitioners have a wealth of data on the process and impact of starting medication, but less on stopping it. This study will address that gap through a scoping review to summarise the current available evidence in a format that makes a useful reference source for clinicians.

Clinicians also need a validated framework against which to judge and defend complex decision making – compromise decisions that are inevitably interpretations, rather than adherent to protocols [16]. A realist programme theory for tailoring medication (including stopping medicines) would provide such a robust

account of what works, for whom, in what circumstances; and so provide a critical framework for recommendations on best practice in stopping medication. Our PRIME Prescribing team have completed preliminary work [1,17-19] to describe a draft programme theory, as part of the wider development of a whole-system complex intervention for whole-person-tailored prescribing in primary care practice. The currently proposed Tailor study will deliver a validated programme theory through completion of a realist review – providing immediate recommendations to clinicians about practice, as well as refining the PRIME prescribing model in preparation for a formal intervention study.

2.1. The evidence that this research is needed now

The success of social, societal and health care changes mean more people are living longer, but with more chronic illness. In addition to managing the burden of illness [20,21], patients are also dealing with the emerging challenges of treatment burden [22-24], "too much medicine" [25], over- as well as under-diagnosis [26]. For the growing numbers of people living longer with multiple long term conditions (estimated 3 million in the UK by 2018 [27]), health systems have become part of their health problem.

The RCGP have highlighted a need to "describe the benefits, harms and optimal strategies for the safe withdrawal of medication in older people with multimorbidity to reduce polypharmacy and treatment burden" [15]. The Tailor Medication Synthesis proposes that to address this problem, we need to focus on individual tailoring of medication use from a whole person (person centred) perspective. Our position derives from key research examining the impact of current practice and policy from patient, professional and health service perspectives; including offering clarification of how we understand 'optimal', and 'strategy'.

2.1.1. From the patients' perspective

Research shows patients define benefit from medicines differently to clinicians– prioritising the impact of care on their continued daily living [22,23,28-30], over the management of disease [31]. From a patient-focused perspective, non-guideline care may be understood as 'rationalised non-adherence' [5,31]; addressing, for example, the recognised growing treatment (including medication) burden [5,22,32] faced by patients living with chronic conditions.

To date, medicines optimisation seeks to minimise risks of problematic polypharmacy through safe delivery of care that maximises medical benefit [5, 33-35]. But problematic polypharmacy also refers to the impact of a burdensome effect of multiple medicines use that goes above and beyond adverse effects. 40.6% of people taking five or more daily medicines report experiencing a burden on daily living [11]. Patients describe the difficulties of managing, monitoring, and making sense of (often complex) healthcare plans, especially in trying to match regimens to their own context and priorities[36-39]. Research shows patients tailor medicines according to personal perceptions of relative benefit and harm in an effort to regain control over their healthcare[34] ; seeking to reduce medicines by adopting non-medical approaches to managing health [31,41] , and/or prioritising management of 1 condition over others [42,43] . There is an expressed need from patients for individually tailored prescribing, including the capacity to withdraw medication.

In Tailor, we therefore define 'optimal' prescribing with reference to the concept of personalised/whole person medicine – medical decision making that optimises health-related capacity for daily living through individual tailoring of care. Optimal strategies for medication use are those that recognise the goal of health care being to support the capacity of the individual living in their lifeworld context [17,30,44-47].

2.1.2. From the professionals' perspective

There has been limited research examining how patients tailor medicines; but even less on professional behaviour [1,48,49]. For practitioners, achieving 'compromise' [5] can mean deviating from the recognised route of 'best practice' described in guidelines [1]. Our research has identified professional perceptions of key barriers to delivering individually tailored care - including a lack of skills and confidence in using clinical judgement to make beyond-protocol defendable decisions; inappropriate prioritisation of workload; and lack of supportive feedback [1,3]. Professionals report feeling frustrated and demoralised by perceiving themselves to be unable to deliver the individual care that they would want to [1]. A continuing mismatch between professional values and practice may be contributing to low staff morale, burnout and so to challenges of recruitment and retention of staff.

Professionals need help with confidently and safely exercising professional judgement for different patients in different contexts. They want a framework that supports and validates clinical judgement, rather than a tool that takes over the decision [1]. Any strategy must support evidence informed practice in a manner that is contextually appropriate (works for patients, professionals and services) [50]; deal with the variability, complexity and changing nature of the task involved in supporting individuals in different contexts [4,31]; support the stated priority of delivering personalised care [30,51]; and ideally enhance, certainly not worsen, alignment of professional and patient priorities for the consultation [52].

The complexity of the task involved in achieving the compromise [5] or mutually agreed tailoring [4] necessary for individually tailored prescribing to address problematic polypharmacy requires evidence informed practice [7] combined with robust professional clinical judgement [16]. We therefore recognise 'strategies' as robust frameworks of principles to guide practice, rather than prescriptive tools/pathways. Realist review, informed by a robust scoping review, is the most appropriate methodology to develop and deliver this output.

2.1.3.From the system's perspective

The biggest challenge facing 21st century healthcare is to refocus our work around the patient [30,45,53-55]. Strong primary care designed and delivered around person-centred care delivers effective, efficient and equitable health care [45,56,57]. International policy recognises concerns about the potential negative impact of health systems increasingly designed for the "command and control of disease" [45,47]. We see international recognition of a need for a resurgence in whole person medicine [45,47,53,58 60]; strategies that support the tailoring of care to the individual living in their personal context [30]. We need the evidence and implementation strategies that support individual tailoring of prescribing decisions.

3. AIMS AND OBJECTIVES

This work directly supports a key policy and practice agenda of improving person-centred care [30,45,54] in the specific field of medication use and prescribing.

A critical consideration of the policy, research and practice contexts thus reveals two research questions (RQ):

> RQ1. What quantitative and qualitative evidence exists to support the safe, effective and acceptable stopping of medication in older people with multimorbidity and polypharmacy?

- What types of strategies are used to support the safe stopping of medications in older patients with multimorbidity and polypharmacy? (Who is implementing the strategy? What are

they doing: clinician-led, patient-led, or shared decision making? balancing of risks and benefits? What is the duration of the strategy? Type of patient follow up?)

- In what context are these strategies being implemented? (e.g. primary or secondary care, urgent or non-urgent care settings, clinic or home setting, the person implementing the strategy, duration of strategy and type of patient follow up)
- What outcome measures, reported in the both the quantitative and qualitative literature, are used to measure the success of these strategies? (e.g. acceptability to patients and prescribers, measurements of patient benefits and harms, adverse events, health-related quality of life, treatment burden).

RQ2. How, for whom and in what contexts can safe and effective individual tailoring [4,5] of clinical decisions related to medication use work to produce desired outcomes?

We will answer these questions through delivering a combined scoping review (RQ1) and realist review (RQ2), providing clinicians the evidence and knowledge they need to support individual tailoring of clinical decisions about medicines use for older people living with multimorbidity and polypharmacy.

Wen will deliver tools that will support clinicians and patients in tackling the emerging challenges of problematic polypharmacy and medicines-related treatment burden.

Our study has four objectives:

i. Complete a robust scoping review of the literature on stopping medication. We will systematically identify current evidence on the approaches, benefits, harms and acceptability of interventions to taper/tailor and stop medication in older people living with multimorbidity and polypharmacy. We will describe a taxonomy of stopping approaches (their defining characteristics, presumed mechanism of action); along with their impact – effectiveness, safety and acceptability to patients and professionals alike.
ii. Undertake a realist review to develop a realist programme theory on stopping medication – examining how, when and for whom tailoring of medicines works in order to describe and explain the heterogeneity in approaches to individual tailoring (specifically stopping) of medicines. This programme theory will form the basis of recommendations for supporting defendable individually tailored clinical decision making.
iii. Disseminate the findings of both reviews in formats that are directly useful to clinicians, patients and policy makers.
iv. Use the findings to refine into our team's developing model of a complex intervention to support individually tailored prescribing practice (PRIME prescribing). We will use this information to prepare and submit a funding application for feasibility, pilot testing and full randomised trial of PRIME prescribing.

4. RESEARCH PLAN

4.1. HEALTH TECHNOLOGY BEING ASSESSED

Strategies for medication withdrawal in older patients with multimorbidity and polypharmacy

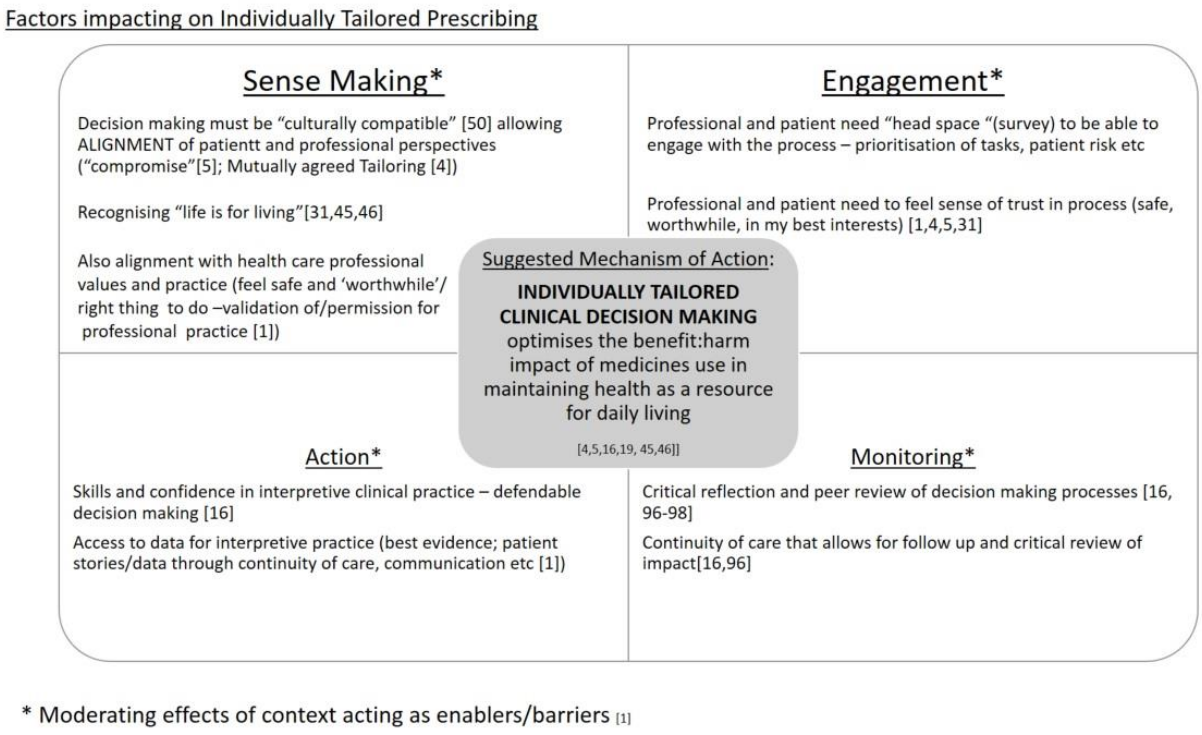
4.2. THEORETICAL FRAMEWORK AND JUSTIFICATION OF THE DESIGN

4.2.1.Work leading to this proposal

We recognise tailoring or stopping medication in order to address or prevent problematic polypharmacy as a complex intervention [1]. An intervention is defined as complex (rather than complicated) because it consists of a numerous components interacting in non-linear ways and is sensitive to context [61]. Uncontrolled and uncontrollable variation is inevitable; the active ingredient(s) may behave differently in varying contexts and for different people [62]. Complex interventions include constant and variable components [63,64]. Constant components are what makes the intervention distinct – in this case individual tailoring, and prescribing. Variable components are the elements that support flexibility and fit to context [63,64].

The PRIME Prescribing research team (including coapplicants Reeve, Krska, Byng, Ranson, Britten) have been working for 3 years on the development of a complex intervention to support safe, effective and acceptable person-centred individual tailoring of medication. The overarching aim of this work being to address emerging challenges of treatment burden and problematic polypharmacy. Based on service development work, literature review, new and existing empirical work within the team and stakeholder discussion [1, 4, 17-19, 65], we have described likely key components of a whole-system (primary care) complex intervention – which we refer to as PRIME prescribing (see Figure 1). Within that model, we recognise the core (constant) component to be the capacity for individually tailored clinical decision making. With variable components being the factors which act as enablers or barriers to delivery in different contexts.

FIGURE 1: Describing the ekements of the complex intervention that is PRIME Prescribing



The current Tailor study focuses specifically on the constant component of the PRIME Prescribing intervention – namely the process of individually tailored clinical decision making related to medication use. Decisions to stop medication are a form of interpretive clinical practice [16]. Reeve, PI for this study, has previously described a conceptual framework for supporting individually tailored defendable decision making, grounded in the work of Doucet & Mauther, Maxwell, Lincoln & Guba and others [16]. She has subsequently published a consultation model based on this framework [66]. The SAGE consultation model describes 5 elements that need to be present to support 'defendable' (trustworthy) clinical decision making in generalist practice [Box 1]

Box 1: SAGE consultation model – 5 principles of trustworthy decision making [16,66]

For the clinician viewing (interpreting) a health-related problem from the perspective of its impact on the whole person – an individual in the context of their daily life – the decision making process should demonstrate adequate:

- Collection of data (*that the clinician collects/uses data from the patient perspective, the biomedical perspective (evidence informed), and their professional perspective*
- Exploration of the problem *(that the clinician works with the patient to examine and interpret/understand the illness problem from the patient's perspective)*
- The 'fit' of the decision/explanation (interpretation) *(considering how well the decision made fits with the individual's account of their illness in the context of daily living)*
- Safety netting *(That the clinician checks for any 'cognitive/emotional biases' that may have adversely impacted on the decision making – for example age)*
- Follow up and evaluation of impact *(That the clinician follows up on the decision making process to assess the impact – and so utility – of the decision made)*

By integrating the background work to develop PRIME Prescribing described and this conceptual account of interpretive practice, we propose a draft programme theory outlining the factors predicting/explaining the successful or otherwise individual tailoring of medication related clinical decision making – see Figure 2. This is the outline that we will critically explore and develop through a realist review approach - so as to understand and explain in what contexts, for whom, to what extent how, why and when PRIME prescribing and these principles are likely to work for clinicians and patients to result in stopping medication.

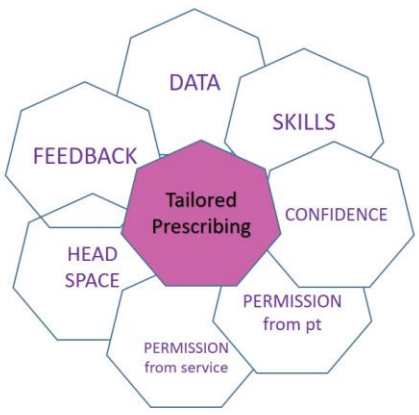


Figure 2: Draft programme theory describing elements needed for individual tailoring of medicines

(For both Stopping and Starting medicines)

DATA: the data/evidence on impact and safety that informs practice, along with patient and professional narratives

SKILLS: intellectual skills in defendable IT decision making (see Box 1)

HEAD SPACE: capacity to apply intellectual skills (time, energy, prioritisation of tasks etc)

CONFIDENCE: in applying skills

PERMISSION: from PATIENT (mutually agreed tailoring), and from SERVICE (legitimation of the role)

FEEDBACK: from multiple sources that reinforces/doesn't undermine work

4.3. STUDY DESIGN

Our goal is to deliver outputs that will be most useful to clinicians, patients and policy and decision makers in supporting clinical practice, and as soon as possible. We have therefore elected to focus on two interlinked reviews: a scoping review, and a realist review – both undertaken from a shared search strategy [6,66-67].

4.3.1. Justification for a scoping review

There are several advantages to conducting a full scoping review before considering further evidence synthesis. Firstly, our preliminary searches suggest that the current body of evidence on this topic is disparate. By this we mean the variety of interventions being utilised, the patient populations being targeted, the outcomes being measured and the methods being adopted to capture this information (e.g. quantitative, qualitative). For example, Reeve's [12] systematic review of definitions of stopping medication (deprescribing) highlights significant heterogeneity in understanding of the nature of the task, with implications for work to synthesise findings from studies. A scoping review will allow us to identify, map and draw this evidence together into a useable form. Secondly, a scoping review will help determine the feasibility of conducting further evidence synthesis, as well as steer the types of synthesis needed (e.g. meta-analysis of effectiveness, meta-synthesis). By mapping the existing evidence, subsequent synthesises will be able to target information more efficiently. Scoping reviews are recognised to be the most appropriate methodology when reviewing the evidence on complex interventions, in order to allow for the variability and complexity of the intervention and evaluation methods [2]. A scoping review is also a helpful step in the realist review approach – combining the two offers an efficient way to optimise the output from the review process. Finally, a scoping review will provide valuable information on the gaps in the current evidence base, upon which new research can be targeted.

4.3.2. Justification for a realist review

Realist reviews ask "what works, for whom, in what circumstances, to what extent, how and why?" and considers the interaction between context, mechanism and outcome i.e. how particular contexts (e.g. people, practices) trigger or interfere with mechanisms to generate the observed outcomes [10] [60] . The realist review methodology is particularly useful for understanding and illuminating the relationships and impact of the interaction between component parts in a complex intervention [6,7]. It generates explanations about the mechanisms by which stopping medication may (or may not) achieve impact in different settings, and within different subgroups. (Some people with multimorbidity and problematic polypharmacy may respond well to stopping medication, whilst others might respond better to a different approach, or not at all).

Our realist review will follow the stages set out by Wong et al. [69]. We will also follow the quality and publication standards for realist reviews [70]." The realist approach, when done well, is widely recognised

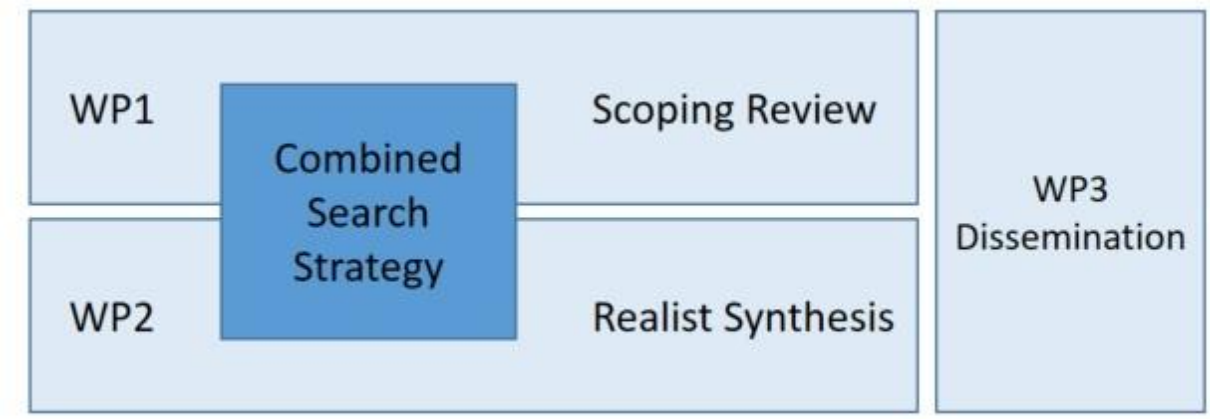
as a robust methodology which is particularly appropriate when seeking to explain and understand the outcomes observed under different contexts in a complex intervention [6].

4.3.3.Considering other forms of evidence synthesis

In preparing this bid, we have carefully considered the appropriateness and possibility of other forms of evidence synthesis. Our background expertise, and preliminary scope of the literature, suggested that a single review of effectiveness could not be justified. However, should our formal scoping review suggest otherwise, we have built sufficient capacity into this bid to take advantage of this and will complete this through matched funding from the host institution (Hull and York Medical School) HYMS have undertaken to fund the anticipated additional 3-4 months researcher time needed to complete this work. Our partnership with the NIHR SPCR Evidence Synthesis Working Group, will provide us with the opportunity to seek further funding for other forms of evidence synthesis, or economic evaluation, should this appear a relevant research need.

4.4. OVERVIEW OF WORKSTREAMS

The TAILOR project will consist of 3 interconnected workstreams:



The HYMS team will lead WP1 and the Oxford team WP2, with close interworking across both streams – including the use of a combined search strategy.

4.4.1. WP1: Scoping review

A variety of scoping review methods have been identified[71,72]. We will use the methodology for conducting a scoping review as set out by the Joanna Briggs Institute [8,73]. This draws on the methodological framework from Arksey and O'Malley [74] and enhanced by Levac et al. [75] Their framework includes the following 6 stages:

4.4.1.1. Stage 1: Setting the research question

We will review and refine our stated research question with our Stakeholder and Advisory Group in the first 2 months of the study prior to starting the search.

4.4.1.2. Stage 2: Identifying studies – a combined search strategy

Our search strategy describes a comprehensive, structured approach to identifying relevant literature from as many relevant sources on the complex intervention that is stopping medication (in the context of individual tailoring of medication use). Petticrew describes that a search strategy for a review of a complex intervention needs to adopt broader eligibility criteria than those used in traditional systematic reviews [2] - going beyond PICO to include context, processes and theory (mechanisms of action). Similarly, Peters et al [76] propose that scoping reviews need also to consider populations (i.e. types of participants), context, and 'concepts' (the interventions being examined and the outcomes used to assess their success). We have combined these approaches to describe the search eligibility criteria we will use in the Tailor study (Table 1).

Table 1: Search criteria for TAILOR study

Inclusion criteria	Explanation/justification
POPULATIONS: all participants aged 50yrs and over with multimorbidity (2 or more long term conditions – NICE) and polypharmacy (5 or more long-term medications). EXCLUDING response to acute adverse reactions/toxicity	Aged 50+ as this is age when multimorbidity starts to rise, 20% have >2 long term conditions, and 10% have more than 3 [77]. A growing group facing the challenges of problematic polypharmacy so inclusion in this study future proofs our work Medication burden – problematic polypharmacy – does not correlate directly to disease burden or number of medications [11,65]. We therefore keep a broad definition of multimorbidity Polypharmacy as 5 or more medicines as this is a common approach used by researchers and so will ensure we capture the key studies.
INTERVENTIONS (concepts/process and theory) – any systematic intervention process used to safely withdraw medications in older people with multimorbidity and polypharmacy and the outcomes used to measure the effectiveness of these strategies. EXCLUDING: no comparator group	Including deprescribing, individual/mutually agreed tailoring, medicines optimisation assessments, stopping medication, personalised prescribing, including individual/mutually agreed tailoring). involving discrete/multifaceted/blended strategies [78] Noting details of comparators; theories of mechanisms of actions; and outcomes used to measure success (may include patient benefits and harms; acceptability to pts and prescribers; health related quality of life/functional status; treatment burden; safety including adverse events; service use For the scoping review, we will exclude studies without a comparator group. However these studies will potentially be used within the realist review
CONTEXT: studies conducted in any appropriate setting	Including primary care (general practice, pharmacy, home settings), acute/interface care; secondary or tertiary care. Noting details of settings to inform explanation of variability in mechanisms of action and outcomes
STUDY DESIGN: Any comparative studies including RCTs, cohort or case control studies, qualitative studies	We will use a modified version of the 6S Pyramid [79] to frame the types of included evidence which will include both quantitative study designs [80] (experimental, before and after studies and observational studies); as well as qualitative studies with

EXCLUDING: Single case reports, case series, studies where results for intervention and control groups not presented separately	recognised methodological frameworks. We will include studies using any recognised structured review methodology and scan reference list of reviews for previously unidentified studies. We will include any national or international clinical guidelines that provides information on the safe withdrawal of medications in multimorbid patients with polypharmacy. Again, excluded studies will be re-considered for inclusion in the realist review

Using the criteria described in Table 1, we will produce a detailed search strategy (examples of anticipated key words are shown in our appended flow chart – scoping search) in conjunction with our information specialist (NR, coapp). We will test and refine our initial search to the Ovid MEDLINE, Cochrane Library and EMBASE databases: analysing text words contained within the title, abstract, and index terms of identified studies to refine our search strategy.

We will then apply our refined search terms to the following databases: Ovid MEDLINE, Embase, CINAHL, the Cochrane Library (including the Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Reviews of Effects (DARE)), Cochrane Effective Practice and Organisation of Care (EPOC) Group Specialised Register, Campbell Collaboration Library of Systematic Reviews, JBI Database of Systematic Reviews and Implementation Reports, PsycINFO, Allied and Complementary Medicine Database (AMED) and CAB Abstracts.

We will also search:

- trial registries: https://clinicaltrials.gov/; http://apps.who.int/trialsearch/
- grey literature, including: Google and Google Scholar websites; websites of relevant stakeholders (including RCGP Bright Ideas; National Clinical Guideline Centre; Royal Pharmaceutical Society; conference abstracts eg PRIMM). We will also use personal communications to contact experts in the field who may be able to signpost us to further relevant information
- forward and backwards citation tracking of the reference lists of any included evidence for further studies of relevance

4.4.1.3. Stage 3: Selecting studies

We will screen titles, abstracts and clipped web pages of all studies for eligibility and relevance (with reference to Table 1 above). If any uncertainty exists, we will err on inclusivity for this stage of our review. The full texts of eligible studies will be retrieved and reviewed by one of our two researchers. A random sample of 10% of all studies will also undergo double review to check for consistency. Studies that appear to meet the inclusion criteria will be presented to the Project Working Group (see page 20), who will agree a final decision on their inclusion. Where any disagreements occur, the principal investigator will take a consensus view for the final decision.

A master database of the literature searches will be constructed by amalgamation of all the citations from various database sources. The results of our search strategy will be organised into the EndNote X8 (Clarivate Analytics, USA) software. Duplicate citations will be identified and removed. Relevant web

pages will be “clipped” and stored using the Evernote organising and archiving tool (Evernote Corporation, USA).

We will provide a descriptive analysis of our search presented in the text narrative and summarised in a PRISMA flow diagram. This will include the total number of citations identified (before and after removal of duplicates), the number of full text articles retrieved and read, and the final number of included articles.

4.4.1.4. Stage 4: Charting the data

We will use a systematic process to extract data from each eligible study. All studies will be reviewed by one of the two research fellows, with a random sample of 10% of studies being double reviewed to check for consistency

Studies’ findings will be extracted using pre-designed and piloted data extraction forms using Excel (version 7.0, Microsoft, USA) , based on amended forms developed in our previously completed reviews [6]. Any disagreements will be resolved by consensus and/or arbitration involving a third reviewer (member of the Advisory Group). Missing information will be obtained from investigators if it is crucial to subsequent analysis. To avoid introducing bias, unpublished information will be coded in the same fashion as published information. In addition to using multiple coders in a sample of studies to ensure the reproducibility of the overview, sensitivity analyses around important or questionable judgements regarding the inclusion or exclusion of studies, the validity assessments and data extraction will be performed.

Data extraction will include the following details:

IDENTIFIER	Country of origin, year of publication, data source
POPULATION	Age; Gender; Socioeconomic status if known
CONTEXT	Primary/secondary care; home/clinic
INTERVENTION	Description of what - characteristics; categorisation of type
OUTCOME	What captured; patientt benefit and harms
STUDY DESIGN including quality	Scoping reviews provide a broad overview of evidence relevant to answering a given question, and do not traditionally assess methodological quality.

4.4.1.5. Stage 5: Collating and reporting

We will summarise our results under the following subheadings:

- Categorisation of the described approaches to stopping medication

- Descriptive statistical analysis to summarise the impact (benefits and harms) and acceptability of each approach. Including correlation with explanatory variables.
- Types of included evidence, including subcategorization according to study design
- Country of origin
- Year of publication
- Source of publication (e.g. journal, website)
- Population being examined (e.g. age, demographic, types of long term conditions incurred, nature of polypharmacy)
- Types of strategies being examined (e.g. single, multifaceted)
- Characteristics of the strategies (e.g. frequency of delivery, duration, dose, follow up, personnel involved)
- Outcomes assessed in relation to the strategies being examined (e.g. patient benefits and harms, acceptability to patients and prescribers, health-related quality of life, treatment burden, adverse events)
- Contexts in which strategies for drug withdrawal were being implemented and evaluated

We will undertake planned sensitivity analysis to assess the impact of any persisting areas of concern in data extraction that couldn't be dealt with by discussion within team [6]

4.4.1.6. Stage 6: Stakeholder consultation

See our dissemination plans.

4.4.2. WP2: Realist synthesis

Following the methodological standards described by the RAMESES group [81], we recognise the following key stages to a realist review: i) the research problem ii) understanding/applying principles of realist review iii) focusing the review iv) constructing and refining a programme theory v) developing a search strategy vi) selecting and appraising documents vi) data extraction vii) reporting. We have outlined i) and ii) in our justification for this study [see page 9]

4.4.2.1. Focusing the review

Our Stakeholder meeting (at 2 months) and Advisory Group discussions will critically re-examine the research question and thinking developed for this proposal

4.4.2.2. Constructing and refining a programme theory

A realist review begins with an initial 'draft' theory of how any intervention is understood to work – also known as a programme theory. Our pre-study draft programme theory is shown in Figure 2 and will be further developed in stakeholder discussion in the first two months of the project.

4.4.2.3. Search strategy

We have described a search strategy to systematically identify the current literature on the approaches used, impact, safety and acceptability of interventions for stopping medication. The realist review specifically examines the mechanism of action in different contexts. Two additional search elements will be therefore be needed for this workpackage:

- "Sister papers" (i.e. qualitative studies, process evaluation etc.) for any studies identified in the above search [6]; along with purposive searching to find relevant data that would enable us to develop and then confirm, refute or refine ('test') aspects of the draft programme theory.
- For each theory area in our draft programme theory, we will generate a sequence of search questions. For example, Figure 1 highlights 'sense making' as a concept in our draft programme theory. Emerging questions might include: What impact does the interaction between individual (patient and professional) beliefs and values and setting have on individual tailoring of medicines? From this, we draw up a series of specific search terms – a systematic search strategy that seeks to identify research (as 'data') related to the targeted programme theories [7]. This searching will capture the additional relevant data necessary for our developing programme theory that has not captured within existing specific studies of stopping medications.

4.4.2.4. Selection and appraisal of documents

When considering whether an identified study is suitable for the realist review, the researchers will apply the RAMESES identified principles of *relevance* (does the study illuminate the RQ) and *rigour* (is the data contained within trustworthy). A random sample of 10% of studies will be double appraised.

4.4.2.5. Realist analysis

Data on study characteristics for included documents will have been extracted in the search process outlined in WP1. For the realist review, full text documents will be uploaded into a qualitative data analysis software tool – e.g. NVivo. Relevant sections of texts that we have interpreted as relating to contexts, mechanisms and/or their relationships to outcomes will be coded. This coding will be both inductive (codes created to categorise data reported in included studies) and deductive (codes created in advance of data extraction and analysis as informed by the draft programme theory). Each new element of data will be used to critically challenge, examine and so refine the draft programme theory using the following specific analytic techniques:

- juxtaposing (e.g. when one study provides process data which help make sense of outcomes noted in another study)
- reconciling (identifying differences which explain apparently contradictory sets of findings)
- adjudicating between findings in different studies (e.g. in terms of providing data that enables judgements to be made on the credibility of data from studies which have been used to inform the programme theory)
- consolidating (producing multi-faceted explanations of success, failure and partial success)
- situating (this mechanism in context A, that one in context B)

In practice, this involves achieving immersion (reading and re-reading papers to really understand what was done and why), developing theory iteratively as emerging data are analysed, seeking data disconfirming cases and alternative explanations; critical reflexive thinking including defending our interpretations to researchers within and outside the team [82].

Interpretive cross case analysis /comparison is used to understand how and why stopping medication actions, and beneficial/harmful outcomes occurred in different studies. A realist logic of analysis – which may be summarised as context + mechanism = outcome – will be used to understand how mechanisms have behaved under different contexts described within the studies included in the realist review to generate reported outcomes.

As the review progresses we will iteratively refine our programme theory into a realist programme theory, that contains multiple context-mechanism-outcome-configurations within it that are able to explain the multiple more proximal and final desired outcomes of stopping medications. Where necessary, we will undertake additional purposive sampling of additional cases to critically test and examine emerging programme theory. Our finalised programme theory will describe the intervention strategies, steps and the contexts that need to be present for clinicians to enable them to make defendable decision making in the individual tailoring (including stopping) of medication use to support a "life for living".

Our iterative analysis will continue until the emerging final programme theory meets the criteria set out by Haig and Evers [83]. Namely that a theory is 'good enough' based on its ability to explain. Explanatory power is judged using 3 criteria: consilience (the theory is able to explain as much of the data as possible); simplicity (the theory has few if any ad hoc provisions – exceptions); and analogy (the theory fits with what we already know)

4.4.2.6. Reporting

We will comply with the RAMESES publication standards for realist syntheses [9] in reporting the production process of our programme theory (establishing rigour and trustworthiness

5. DISSEMINATION AND PROJECTS OUTPUTS

We anticipate three outputs from the Tailor Medication Synthesis project:

- A reference data set for clinicians involved in stopping medication: detailing a classification of approaches used, and what is known on effectiveness, safety and acceptability.
- Recommendations describing the key components of best practice in individual tailoring of medicines which clinicians, patients, policy and decision makers can use to support defendable decisions about stopping medication based on our realist programme theory.
- Submitted application for funding for a rigorous and theoretically informed intervention in an implementation study – i.e. potentially as a feasibility, pilot and randomised clinical trial of a complex intervention (PRIME prescribing) that incorporates the reference set and validated framework into a whole system approach.

Our dissemination strategy uses the principles of translational scholarship [84] to support knowledge mobilisation and so optimise impact. Translational scholarship Translational scholarship draws on the thinking of Bertrand Russell in recognising that 'the challenge to a thinker the 'challenge to a thinker is to state the problem in a way that allows [other people to be part of] a solution'. In practice, this means producing audience specific resources from our research outputs targeted at each of patients, professionals, policy makers and academics.

- Clinicians: freely accessible documents summarising best evidence on impact and safety of stopping medications (similar to reference source provided with multimorbidity guidance from NICE) – e.g. through RCGP website; freely accessible practical resources describing a framework of best practice for individually tailored care related to medication decisions. Envisaged as an animation/infographic or podcast with downloadable slide set. Supported by running of a one day Essentials in Problematic Polypharmacy event at RCGP. Similar engagement with Royal Pharmaceutical Society.
- Academics: open access publication on methods as well as outputs; conference presentation.

- Public: working with PPI partners and College to produce a short animation for patient/public to describe the principles and reasons for stopping medications.
- Research led teaching: generate methodological and clinical education resources based on the learning from this research.

6. PLAN OF INVESTIGATION AND TIMETABLE

The Project Working Group (PWG), consisting of Site leads (JR, LM in Hull York; KM, GW in Oxford) and both Research Associates (RAs) (from 3months onwards) will meet weekly for the first 2 months then monthly by Skype/video link to manage the day to day implementation of the work plans.

The Academic Advisory Group consisting of the PWG plus all co-applicants will meet on average on a 3 monthly basis. Key tasks will be to develop and agree the working programme theory; review and agree the search strategy; comment on discrepancies/inconsistencies arising in search strategy and scoping and realist reviews; receive and comment on emerging findings from both analyses; support preparation of report and dissemination plans.

The Stakeholder group – including patient, clinical, policy and commissioning partners, will meet twice a year, as described as part of the stakeholder group.

If funding is confirmed by November 2017, we anticipate being able to commence work in March 2018.

Time (months)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Set up: finalise protocol, stakeholder meet, recruit RA (PWG - JR KM DL LM GW)	x	x	x																		
Search and data extraction				x	x	x	x	x													
Scoping review						x	x	x	x	x	x	x	x	write up					opt. extn*		
Realist synthesis			prog theory			x	x	x	x	x	x	x	x	x	x	write up					
Targeted dissemination																			x	x	x
Stakeholder meetings			x									x							x		
Advisory Group		x		x		x			x			x		x			x			x	

6.1. Key milestones

Month 3: Academic Advisory Group (AAG) met to review research question, draft programme theory and search plan. Stakeholder Group (SG) met to review project plan. RAs recruited.

Month 6: Search strategy has been tested, refined, protocol submitted for publication. Searching and data extraction ongoing. AAG met (skype) to review search strategy

Month 9: Data extraction completed, analysis ongoing. AAG meet face to face to review emerging findings

Month 12: AAG (skype) review results scoping review, progress of realist review. SG virtual meeting to review progress both reviews. Start discussions with Hull Health Trials Unit. Start to plan GP education (dissemination) events

Month 15: Scoping review analysis near completion, decision on meta-analysis/extension. Realist synthesis near completion – tested with AAG (face to face)

Month 18: RAs finish. Both reviews in near final draft form. Patient dissemination work commissioned.

Month 21: Final reports submitted. Final AAG and SG meetings held to discuss findings and next steps. Dissemination events completed. Bid writing for follow on work in progress.

7. PUBLIC AND PATIENT INVOLVEMENT

Our PRIME Prescribing group have been working on this topic with patient partners over a number of years [1,17,19, 87]. The need for individual tailoring of healthcare was first identified at a participant stakeholder meeting following a former research project exploring living with long term conditions [85]. Ranson (co-applicant) and Dickenson (PPI member) have helped us apply these discussions to the current work. Both have personal experience of polypharmacy and being NHS patients and have been active participants in project development meetings, reviewing and commenting on emerging documents, and in discussing our emerging ideas with wider public groups e.g. at practice Patient Partner Group meetings. Feedback from these discussions highlighted the importance not only of an academically rigorous description of the outcomes of our work but also a patient-focused narrative – which has been incorporated into our dissemination strategy (WP3). Our commitment to collaborative working included the preparation and publication of a shared position paper [19].

Ranson will be actively involved in the running of this project as member of the Academic Advisory Group. Reimbursement for time, and training in research and ethics, committee work is fully costed. Ed will provide a critical patient voice in discussions on all stages of the project – searching, analysis and dissemination. In addition we will invite patient partners, including Dickenson and new members from the Humber region, to join our Stakeholder meetings to be held twice a year. Ranson will help us prepare these meetings to ensure all materials and organisation aspects are suitable for our mixed audience. Our PPI partners will help is in preparing emerging project documents and reports, and in particular any patient or public targeted resources.

8. EXPERTISE AND JUSTIFICATION OF SUPPORT PROVIDED

The Tailor Medication Synthesis will be delivered and supported by three sub-groups:

- Project working group – responsible for the day to day delivery of the research
- Academic advisor group – responsible for increasing academic expertise to the research outputs
- Stakeholder group – responsible for ensuring the research remain relevant and for supporting the dissemination of the outputs

Ultimate responsibility will lie with the principle investigator (Reeve).

Details of the three subgroups are provided below.

The PROJECT WORKING GROUP (% FTE indicated)

Reeve (10%)	Principle Investigator – responsible for delivering project on time and budget. Expertise in individual tailoring of clinical decision making/prescribing; complex interventions.
Mahtani (10%)	Oxford site lead – methodological oversight. Expertise in evidence synthesis, technology assessment in systematic reviews.
Wong (5%)	Realist synthesis expertise
Mitchell (5%)	Evidence synthesis. Line manage HYMS RA
Krska (2%)	Academic pharmacist; expertise in medication burden; evidence synthesis
Lasserson (2%)	medication tailoring in ambulatory care/secondary care context
Byng (2%)	complex intervention development and evaluation; person centred care
Ranson (hourly rate)	Patient partner
Roberts (3%)	Information Specialist, Oxford. With particular expertise in Realist Synthesis
Research Associate #1 (HYMS) (15m 100%)	leading the scoping review and supporting realist review
RA #2 (Oxford) (15m at 100% FTE)	leading realist review and supporting scoping
Administrative support (5%)	to provide administrative support to the PI, coordinate meetings between sites, project manage

Academic Advisory Group (non funded): as above plus

Nina Barnett	Secondary care, pharmacy, deprescribing
Tom Fahey	Multimorbidity, beyond UK
Emma Wallace	Multimorbidity, evidence review, beyond UK
Dee Mangin	Primary care, leads a deprescribing trial in Canada (McMaster Uni)
Tom Walley	Clinical pharmacology, secondary care
Jeff Aronson	Clinical pharmacology, secondary care, drug interactions

Stakeholder Group confirmed members include

Taz Dhanani and Roaslyne Payne	Coventry CCG (community pharmacy, care homes)
PenCLAHRC	[87]
CLAHRC Yorkshire & Humber managing Frailty stream	Contact John Young
Yorkshire & Humber AHSN – Medicines Optimisation stream	Contact Tony Jamieson
RCGP Humber and the Ridings	Contact David Rose
RCGP Innovation and Research Board	Contact Ali Marsh

9. REFERENCES – uploaded separately