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

FULL/LONG TITLE OF STUDY

Reducing Health Inequalities through General Practice: A Realist Review (EQUALISE)

SHORT STUDY TITLE/ACRONYM

Reducing Health Inequalities through General Practice

PROTOCOL VERSION 1.0   04 March 2021

SIGNATURE PAGE

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

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

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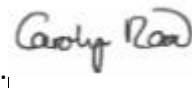
For and on behalf of the Study Sponsor:

Date: ..18/02/21

Signature:

....
Name (please print): Vivienne Shaw

....
Position: Head of Research & Development, Cambridgeshire and Peterborough Clinical Commissioning Group...

Date: ..18/02/21

Signature: ....
....

Name (please print):Carolyn Read ....

Position: .Research Governance Officer, University of Cambridge...

Chief Investigator:

Date: .18./..02./2021.

Signature: ....
Name: (please print): ………… Dr John Ford.............................

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KEY STUDY CONTACTS

Chief Investigator	Dr John Ford, Clinical Lecturer in Public Health Department of Public Health & Primary Care, University of Cambridge Tel: 07969850109 Email: jf653@medschl.cam.ac.uk Dr Geoff Wong, Clinical Research Fellow Nuffield Department of Primary Care The Chancellor Masters and Scholars of the University of Oxford Email: geoffrey.wong@phc.ox.ac.uk Tel: +44 (0)1865 289300 Fax: +44 (0)1865 289287
Study Co-ordinator	Dr John Ford (contact details as above)
Sponsor	Cambridgeshire and Peterborough CCG and University of Cambridge
Joint-sponsor(s)/co-sponsor(s)	N/A
Funder(s)	Secretary of State for Health and Social Care National Institute for Health Research (NIHR) Health Services & Delivery Research Programme (HSDR) Tel: 023 8059 4304 Email: hsdrinfo@nihr.ac.uk
Key Protocol Contributors	Dr John Ford, Clinical Lecturer in Public Health Department of Public Health & Primary Care, University of Cambridge Tel: 07969850109 Email: jf653@medschl.cam.ac.uk Dr Anna Gkiouleka Research Associate Department of Public Health & Primary Care, University of Cambridge Email: ag2192@medschl.cam.ac.uk Dr Geoff Wong, Clinical Research Fellow Nuffield Department of Primary Care The Chancellor Masters and Scholars of the University of Oxford Email: geoffrey.wong@phc.ox.ac.uk Tel: +44 (0)1865 289300 Fax: +44 (0)1865 289287

	Dr Fiona Head Associate Director Department Clinical Outcomes, Population Health Strategy and Hosted Research NHS Cambridgeshire and Peterborough Clinical Commissioning Group Email: fiona.head@nhs.net Ms Isla Kuhn Head of Medical Library Service University of Cambridge Medical Library Email: ilk21@cam.ac.uk Dr Sarah Sowden NIHR/HEE ICA Clinical Lecturer and Hon Consultant in Public Health Population Health Sciences Institute University of Newcastle upon Tyne Email: sarah.sowden@newcastle.ac.uk Prof Clare Bambra, Professor of Public Health Institute of Population Health Sciences University of Newcastle Upon Tyne Email: clare.bambra@ncl.ac.uk Ms Rebecca Harmston PPI Representative Ms Annie Moseley PPI Representative Sukaina Manji PPI Representative
Committees	N/A

STUDY SUMMARY

Study Title	Reducing health inequalities through general practice: a realist review (EQUALISE)
Study Design	Realist Review
Planned Study Period	1 January 2021 - 30 June 2022 (18 months)
Research Question/Aim(s)	What types of interventions or aspects of routine care in general practice increase or decrease inequalities in outcomes of cardiovascular disease, cancer, diabetes or COPD, for whom, why, in what circumstances and how? The aim of this review is to undertake a higher-level theory-driven review of the evidence to identify common cross-cutting causal processes which can be used by those re-designing and delivering general practice services.

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
Secretary of State for Health and Social Care National Institute for Health Research (NIHR) Health Services & Delivery Research Programme (HSDR) Tel: 023 8059 4304 Email: hsdrinfo@nihr.ac.uk	£282,061.36

ROLE OF STUDY SPONSOR AND FUNDER

Progress of the Research will be reviewed periodically by the Funder's Representative against the specifications detailed in the contract signed by the Chief Investigator and the Funder. The Funder will receive an interim written report on the progress of the research according to the schedule agreed. During the research period, the funder has the right to receive verbal or written reports on any aspect of the research. The Funder will also receive a draft final report of the research findings and send it for external peer review. The comments received will be given to the Chief Investigator and will be expected to be integrated to a final report and its summary. Other than monitoring and reporting, the Funder will not have other involvement in study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. The sponsors will be kept appraised on the progress and consulted if there are proposed changes to protocol or if any barriers or difficulties are encountered in delivering the project to NIHR timelines. They will

be informed if there are any deviations to protocol. They will also advise on any regulatory issues, and have financial and contractual oversight.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Research Team
The Research Team will be responsible for the day-to-day co-ordination and delivery of the research. The research will be jointly led by Dr John Ford (JF) and Dr Geoff Wong (GW) and will comprise of Prof Clare Bambra (CB), Dr Fiona Head (FH), Ms Isla Kuhn (IK), Sarah Sowden (SS), Rebecca Harmston (RH), Annie Moseley (AM), Sukaina Manji (SM) and Dr Anna Gkiouleka (AG). JF and AG drafted the current protocol which was then refined by all the research team members (GW, AG, CB, FH, IK, RH, AM and SM). JF supervises the research associate (AG) who contributes to all the phases of the implementation, co-ordination and dissemination of the research. Both JF and GW will be responsible for quality assurance of the screening, extraction and analysis. IK will be responsible for designing the initial search and any subsequent searches. CB will be instrumental in the design of the guiding principles because of her experience in health inequalities interventions. FH will be key in helping to interpret the data and ensuring the outputs are usable to GPs, PCNs and the wider health system. The two GPs on the research team, GW and FH, will resolve any uncertainty about which interventions are relevant to general practice. Drawing on her current NIHR/HEE fellowship looking at health care inequalities SS will be key to ensuring that the findings build on existing literature and that the outputs have greatest impact.

Expert Panel
The Expert Panel has been assembled to provide key input to identifying initial theories, support in developing guidance materials and ensure broad dissemination. The group members are not in any way influenced by the funders and study sponsors. Stakeholders will be first asked by the Investigators to identify any key theories of how general practice interventions could reduce or increase inequalities before showing the initial programme theory to avoid confirmation bias, then the initial theory from the scoping literature search will be shared. Feedback from both these discussions will be used to iteratively refine the initial programme theory.

The Expert Group will include academics, practicing and academic General Practitioners, NHSE/I representatives, Primary Care Networks representatives, and Healthwatch representatives.

Patient and Public Involvement Group
We will have three PPI representatives involved in the study; Rebecca Harmston, Annie Moseley and Sukaina Manji. Our PPI team members will ensure that a patient and public voice is maintained throughout the research. They will be an active member of the research team and contribute specifically to the design, interpretation of the findings and dissemination activities.

Research governance and financial management will be formally overseen by Cambridgeshire and Peterborough Clinical Commissioning Group. All data will be handled in accordance with the Data Protection Policies of our respective institutions.

STUDY FLOW/GANTT CHART

	2021												2022					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Agree research protocol - **MILESTONE 1**	■	■	■															
Establish Expert Panel	■																	
Expert panel meetings			■						■					■			■	
Step 1 – Locate existing theories and build initial programme theory - **MILESTONE 2**	■	■	■															
Step 2 – formal search, screening of reviews and obtain full text articles of the primary studies - **MILESTONE 3**			■	■	■	■												
Step 3 – Initial article selection - **MILESTONE 4**						■	■	■	■									
Step 4 – Initial cycle of extracting and organising data - **MILESTONE 5**								■	■	■	■	■						
Step 5 – Synthesising the evidence and drawing initial conclusions - **MILESTONE 6**												■	■	■	■			
Refine initial programme theory and additional searching as needed										■	■	■	■	■	■			
Deliberative workshop - **MILESTONE 7**																■		
Preparation of outputs, academic papers, report and dissemination - **MILESTONE 8**																■	■	■

STUDY PROTOCOL

Reducing Health Inequalities through General Practice: A Realist Review (EQUALISE)

1. BACKGROUND

The gap in life expectancy between least and most deprived areas of England is 9.4 years for men and 7.4 years for women [1]. Three quarters of this gap is caused by deaths in those aged 50 to 89 years [2]. In recent years the gap has increased, especially for women in the most deprived groups for whom life expectancy has reduced by 100 days between 2012-14 and 2015-17[1]. A report by the Institute of Health Equity found that cancer, heart disease, stroke, and chronic obstructive pulmonary disease (COPD) were driving health inequalities in life expectancy [3]. The Global Burden of Disease study estimates that these conditions were responsible for two thirds of premature mortality in England in 2017 [4].

Whilst some of these inequalities are driven by wider determinants of health, such as employment, education and income, the NHS has a vital role for three reasons: first, the NHS leads the debate in advocating for a reduction in health inequalities; second, health care services are often the first point of contact for vulnerable individuals; and third, the NHS can reduce the gap through more equitable prevention, diagnosis and treatment since it has been estimated that health care contributes 15-43% to health outcomes [5]. In particular, general practice is key to reducing health inequalities. Previous research exploring cancer pathways found that inequalities tend to arise due to late presentation and diagnosis in general practice, rather than the diagnosis to treatment pathway in secondary care [6]. However, the NHS does not yet have an awareness of which types of interventions or aspects of routine practice in general practices are likely to increase or decrease inequalities.

Interventions which increase inequalities by disproportionally affecting disadvantaged groups have been termed *intervention generated inequalities* or IGIs [7]. A scoping review of public health interventions found that media campaigns and work-based smoking bans tended to increase inequalities across socio-economic groups, whereas workplace interventions to increase employee control or participation and fiscal policies, such as tobacco price increases and folic acid supplementation, reduced inequalities [8]. Based on public health research, Adams and colleagues proposed agency, the extent to which individuals have to use their own resources to benefit from an intervention, as the key underlying mechanism [9]. They found that interventions which require high agency (i.e. individuals require considerable personal resources to benefit) tend to be favoured by governments but are more likely to lead to inequalities, whereas low agency interventions (i.e. individuals only require a small amount of effort to benefit) are more likely to reduce inequalities. The extent to which interventions increase or decrease inequalities may also vary over time. For example, research assessing inequalities in smoking found that population-based smoking interventions may increase inequalities in the short-term as they benefit the most-affluent in society, but over the long term reduce inequalities as the benefit moves more towards lower socio-economic groups [10].

The NHS recognises that there is both a moral imperative to address systematic, unfair differences in health outcomes and a financial rationale with socio-economic inequalities costing the NHS £4.8 billion/year in hospitalisations alone [11]. The NHS Long Term plan aims to take a "more concerted and systematic approach to reducing health inequalities" and has pledge about £1billion additional funding to areas of higher deprivation [12]. Details within the five year GP contract (2019-2024) state that Primary Care Networks (PCN) and Integrated Care Systems (ICS) will have to develop plans to reduce health inequalities [13]. However, the NHS still lacks a broad understanding of which types of interventions are likely to reduce inequalities [14] and, paradoxically which may inadvertently increase inequalities [6], [7], [15]–[17]. For example, there is some evidence that nurse-led behavioural counselling in primary care results in more physical activity for those with greater social support [18]. However shared-decision making interventions appear to benefit disadvantaged groups more because this group often have reduced health literacy [19].

This realist review study will examine the existing evidence on the types of interventions or aspects of routine care in general practice that are likely to increase or decrease health inequalities and will provide NHS organisations, such as Clinical Commissioning Groups (CCGs), NHS England Integrated Care Systems and Primary Care Networks with an evidence synthesis and a series of guiding principles on how and what should be commissioned for the reduction of health inequalities.

2. RATIONALE

The last systematic review looking broadly at health service interventions to reduce inequalities was published 23 years ago based on articles published 25 to 35 years ago [20]. The study focused on how to reduce inequalities but did not include interventions which may increase inequalities (i.e. intervention generated inequalities). Based on 94 included studies, the authors found that a multi-disciplinary approach using a combination of strategies was more likely to reduce inequalities. However, the evidence base and organisational landscape within the NHS has changed substantially over the past 25 years.

One important development is the PROGRESS Plus framework to conceptualise different types of inequalities, such as age, gender, sex, ethnicity and disability, or specific vulnerable groups, such as people who are homeless or belonging to the gypsy, Roma or traveller community. Proposed by the Campbell and Cochrane Collaborations the framework supports researchers to take more of a systematic approach to equity by categorisation of disadvantaged groups – Place of residence, Race/ethnicity/culture/language, Occupation, Gender/sex, Religion, Education, Socio-economic status, Social capital plus characteristics related to discrimination (e.g. age, disability), features of relationships (e.g. parents who smoke) and time dependent relationships (e.g. being a carer) [21].

Two reviews have taken an equity perspective to look at general practice interventions using the PROGRESS Plus criteria. Attwood and colleagues reviewed primary-care-based physical activity interventions using the PROGRESS Plus categories [18]. The review was limited to RCTs and the authors identified 24 RCTs in which differential effects of one or more PROGRESS Plus criteria were reported in the article. Gender (n=22) and age (n=16)

were the commonest PROGRESS Plus criteria to be differentiated in the results, followed by race (n=4), education (n=3), social capital (n=3) and socio-economic status (n=3). The authors found mixed effects for gender and some evidence of improved physical activity for those patients with higher baseline social support. The second review, also limited to RCTs, by Terens and colleagues explored quality improvement strategies to reduce inequalities in diabetes care using the PROGRESS Plus criteria [22]. The authors identified seven RCTs assessing quality improvement strategies in diabetes care and found that quality improvement strategy appeared to improve care for older people, African-Americans and those with low educational attainment.

There have been other equity focused reviews in specific conditions across primary care, secondary care and public health. Capewell and Graham reviewed the evidence for cardiovascular disease prevention in the reduction of health inequalities [23]. The authors compared the evidence for a "high-risk approach" where patients are categorised according to risk and treated as required with "population-wide programmes", such as the smoking ban. The authors argue that a high-risk approach is more likely to lead to an increase in inequalities compared to population-wide programmes. Durand and colleagues reviewed the impact that shared decision-making across primary and secondary care has on health inequalities [19]. The authors included 19 articles with 10 pooled in a meta-analysis and found that shared decision-making interventions seemed to benefit disadvantaged groups and therefore were likely to reduce inequalities. The authors suggested that disadvantaged groups benefited more because of reduced inequalities in knowledge, decisional conflict, uncertainty and treatment preferences.

Reviews have also been undertaken looking at the wider determinants of health. Bambra and colleagues undertook a review of reviews looking at interventions aimed at the wider determinants of health [24]. Based on 30 included reviews, the authors report that while the impact of the interventions was generally unclear, there did appear to be evidence that interventions in housing and the work environment appeared to reduce health inequalities.

In summary, this realist review is needed now to provide NHS England, CCGs, ICSs and PCNs with the evidence and guiding principles to commission general practice effectively to reduce inequalities. To date the evidence base is disparate and needs unifying into digestible and useable guidance. The previous primary care-focused reviews described above were limited to RCTs and it is likely that broadening the search to include non-RCT interventional or other studies will identify additional interventions which may increase or decrease inequalities. Our approach will not only provide a description of interventions which increase or decrease inequalities, but also for whom, in what circumstances, why and how these interventions reduce inequalities. Guiding principles will help the NHS take a health-inequalities-in-all-policy approach to general practice.

3. THEORETICAL FRAMEWORK

3.1 Health inequalities and their causes

In the frame of our study, health inequalities are understood as systematic differences in health outcomes (i.e. morbidity and/or mortality) between groups which are socially produced and therefore unnecessary and avoidable [25,26]. From this perspective, the drivers and causes of health inequalities have been located at the conditions that people live and work, what is commonly described as the social determinants of health (SDH) [24,27]. The pathways through which SDH result in health inequalities have been explored from various perspectives resulting in materialist [28,29], behavioural [30] and/or psychosocial explanations [31, 32]. In a nutshell, these explanations suggest that health inequalities between socially advantaged and disadvantaged groups are the outcome of their differences in terms of material resources, behaviours and cultures, or psychosocial stressors respectively.

However, more critical approaches stress that while all these explanations may stand true, social stratification is associated with health inequalities through multiple and complex pathways that involve individual characteristics but also structural and institutional factors which need to be addressed [33-35]. Recent work takes a step further and highlights that for a deeper understanding of health inequalities, an intersectional approach is needed [36-38] According to this stream of thought, health inequalities are context specific and are the outcome of multiple and intersecting social hierarchies that operate simultaneously at the micro, meso, and macro-level affecting people's social position, experience and health, like for example, socio-economic position, gender, sexuality, ethnicity or race. From this perspective, individuals and groups according to their intersecting social locations have differential access to social determinants of health but also, they are differentially affected by institutions, interventions and policies [39] affecting their health and its determinants.

3.2 Health Inequalities and primary care

During the last couple of decades, major public health actors like the World Health Organisation (WHO), have been stressing the importance of primary healthcare in addressing health inequalities [40]. Primary care services including general practice are at the frontline of effective healthcare involving a series of preventive, curative, and rehabilitating services as well as health education and advice. Importantly they function as the main referral systems that facilitate access to comprehensive healthcare for the population [41] and they are regarded as a key factor for the sustainability of entire healthcare systems [42]. In the UK, General Practice (GP) consultations represent almost 90% of all contact with healthcare professionals [43]. This massive rate highlights the importance of GP services in appropriate care access but is also telling of the vital role the GP services (can) play in the exacerbation or mitigation of health inequalities.

Tracing the mechanisms that produce these inequalities is a complicated task. Individuals and groups deal with different financial, geographical, cultural and organisational barriers in accessing GP services and primary health care according to their intersectional social locations [44]. At the same time, primary health care comprises itself a system that involves

multiple actors, domains, and contexts organized at different levels (i.e. micro, meso, macro) from individual GP consultations to system level policy making [42]. The consequence is that the health inequalities observed in this context are the outcome of the interplay between individual level patients' characteristics and structural factors operating at practice, organization and system levels. As stressed in the previous section, inequality producing hierarchies operate simultaneously across all these levels vertically but also horizontally; primary healthcare services, programmes and interventions are often regulated by different bodies with different priorities and guiding principles that are not necessarily aligned and can even contradict or cancel each other [45-46]. This interplay is why routine care that takes place in general practice is not equally accessible to and effective for different individuals and groups and also the reason why interventions aiming to improve the quality of care for a population/group can result in the increase of inequalities within this population/group [7].

Building on this broader understanding of intersecting inequality producing processes, in our review we will employ a realist methodology that will allow us to uncover the specific causal mechanisms that link GP services with the increase or decrease of inequalities in cardiovascular disease, cancer, diabetes or COPD and the relevant factors in order to produce a refined and contextualised theory for the phenomenon.

4. RESEARCH QUESTION/ AIMS

What types of interventions or aspects of routine care in general practice increase or decrease inequalities in outcomes of cardiovascular disease, cancer, diabetes or COPD, for whom, why, in what circumstances and how?

The aim of this review is to undertake a higher-level theory-driven review of the evidence to identify common cross-cutting causal processes which can be used by those re-designing and delivering general practice services.

4.1 Objectives

Our overall objective is to develop a broad and transferable understanding of the types of interventions or aspects of routine care which are likely to increase or decrease health inequalities through a realist review. Specifically, we will:

1. Identify existing systematic reviews, and the full text of their included primary studies, which assess interventions or aspects of routine care delivered in general practice for cardiovascular disease, cancer, diabetes or COPD.
2. Identify those studies which report clinical outcomes by socio-economic group, or other PROGRESS Plus group, and describe the inequalities arising from interventions or aspects of routine care delivered in general practice.
3. Undertake a realist analysis of the data to identify the context, mechanisms and outcomes for the types of interventions or aspects of routine care which increase or decrease health inequalities.

4. Develop guidance and a toolkit for NHS decision makers about how best to tackle health inequalities through general practice services.

4.2 Outcome

The findings will be a description and explanation of the general practice interventions which are likely to increase or decrease inequalities across the major conditions. We will specifically focus on the gap in life expectancy and what general practice can do about it in the short and medium term. Therefore, we are focusing on interventions or aspects of routine care in general practice aimed at adults with the major causes of mortality or their common risk factors.

5. STUDY DESIGN AND METHODS OF DATA COLLECTION AND ANALYSIS

5.1 Overarching study design

The aim of this research is to identify and understand why broad types of interventions or aspects of routine care delivered in general practice across the major conditions increase or decrease health inequalities and develop guiding principles, plus resources, for decision makers in the health care system. To do so, we will undertake a realist review. Our review will follow a detailed realist review protocol which will be written by the project team, informed by Pawson's five iterative stages in realist reviews and registered with PROSPERO[47], [48]. We have chosen to use a realist review approach because the existing research indicates that the interventions and routine care delivered in general practice is complex and has a range of impacts on inequalities in different settings. Furthermore, the inequalities that occur are context sensitive. We are also aware that what is being asked of the NHS and general practice is continually evolving, with for example, a drive to greater team working and integration. The influence of such changes on inequalities is at present unclear. Thus, any evidence synthesis that seeks to make sense of how to address inequalities for different groups must be able to consider the various contexts and changes that are likely to occur in the NHS in the coming years. A realist review would be able to generate the knowledge needed to address both these issues [49].

To identify the broad types of interventions, we will seek out existing systematic reviews published across cardiovascular disease, cancer, diabetes or COPD for interventions delivered in general practice. To search for primary studies would generate too many results and is unnecessary since the body of systematic reviews has already undertaken this task. It is unlikely that the systematic reviews will report the impact on socio-economic inequalities, therefore, we will examine the full text of the primary studies included within each systematic review to identify those which report or comment on inequalities. They will be subsequently described, categorised and synthesised using a realist logic of analysis. To conceptualise the clinical outcomes we will use the categories set out by Ramalho and colleagues [42]; type of care (acute, chronic, preventative), function of care (diagnosis, screening and prevention, follow-up and continuity, and treatment) and domain of care (effectiveness, efficiency, timeliness, patient-centred and safe).

5.2 Identifying existing theories

We will start by identifying existing theories that explain how, for whom, why and in what circumstances interventions delivered in general practice may increase or decrease health inequalities. To identify these theories we will first scope the literature on intervention generated inequalities, starting with existing reviews [8], [9], [18], [50], and second consult with key content experts in our Expert Panel. Scoping of the literature will be exploratory and use informal methods such as snow-balling and citation tracking [51]. These initial theories will contribute to the development of an initial programme theory. This initial programme theory will be refined through iterative discussions within the project team to synthesise the different theories into an initial coherent programme theory.

5.3 Searching for evidence

Formal search

The goal of the formal search is to identify the body of literature with which to further develop and refine the initial programme theory. The articles identified through this search will form an initial set of documentation, however additional searching will be required to identify potentially relevant evidence that was excluded, such as opinion and commentary articles.

To identify eligible articles, we will undertake an electronic search of MEDLINE, EMBASE, CINAHL, PsycINFO, the Web of Science and the Cochrane library. The search will seek to identify reviews of interventions delivered in general practice across cardiovascular disease, cancer, diabetes or COPD.

Screening

The purpose of screening is not to find every study assessing interventions delivered in general practice that reports on inequalities, but to find the relevant data that will enable us to undertake a high-level theory-driven review that identifies common cross-cutting causal processes within broad types of interventions which are likely to increase inequalities.

The titles and abstract of each identified systematic review will be screened for eligibility and marked as include, excluded or unclear independently by two reviewers. Disagreements and unclear studies will be resolved through discussion. A random 10% sub-sample of citations will be reviewed for quality control purposes. Any disagreements will be resolved through discussion. Our inclusion and exclusion criteria for the *reviews* will be broad as we seek to find a breadth of literature. The following criteria will be used:

Inclusion criteria
- Systematic reviews that use a comprehensive search strategy and appropriate quality appraisal tool
- Interventions which target cardiovascular disease, cancer, diabetes or COPD. Studies which are aimed at risk factors of these conditions will also be included, namely, smoking, hypertension, diet, exercise and cholesterol.
- Interventions which are delivered in general practice
- Only studies undertaken in high income countries, as defined by the OECD, will be included and there will be no language restrictions.

Exclusion criteria
- Drug effectiveness or efficacy studies will not be included, but prescribing interventions will be. For example, trials comparing different types of anti-hypertensive medications will not be included but trials assessing interventions to increase anti-coagulation treatment for patients with atrial fibrillation will be.
- Review articles which have been superseded by larger more comprehensive reviews
- Reviews which include children, mental health or disease areas not listed above

We will only include clinical outcomes relating to the type of care (acute, chronic, preventative), function of care (diagnosis, screening and prevention, follow-up and continuity, and treatment) and domain of care (effective, efficient, timely, patient-centred and safe)[28]. We will not include outcomes relating to general practice structure (e.g. general practice facilities). We will include studies which report both the differential effectiveness across groups and studies targeted at discrete disadvantaged groups.

The included primary studies from each of the reviews will then be identified and the full text of these studies retrieved. Referencing software will be used to electronically obtain the full text articles of the primary studies, such as the Find Full Text function in Endnote. Full text articles which cannot be obtained through the referencing software will be obtained through the university library. Inclusion and exclusion criteria for the primary studies, identified from the systematic reviews, will be as follows:

Inclusion criteria
- Interventions which report clinical outcomes by socio-economic group, or other PROGRESS Plus criteria, relating to the type of care (acute, chronic, preventative), function of care (diagnosis, screening and prevention, follow-up and continuity, and treatment) and domain of care (effective, efficient, timely, patient-centred and safe)
- Interventional studies, or interventions targeted at discrete groups.
- General practice interventions which target cardiovascular disease, cancer, diabetes or COPD. Studies which are aimed at risk factors of these conditions will also be included, namely, smoking, hypertension, diet, exercise and cholesterol.
- Any experimental study design will be included, such as randomised controlled trials, before-and-after studies, time series or service evaluations.
- Only studies undertaken in high income countries, as defined by the OECD, will be included and there will be no language restrictions.

Exclusion criteria
- Drug effectiveness or efficacy studies will not be included, but prescribing interventions will be. For example, trials comparing different types of anti-hypertensive medications will not be included but trials assessing interventions to increase anti-coagulation treatment for patients with atrial fibrillation will be.

We will focus on socio-economic inequalities (e.g. education, employment, income), however to get the most out of the research we will collect data on other PROGRESS plus criteria as well. Therefore, the full text papers will be screened to identify studies which report the results by any of the PROGRESS Plus criteria – i.e. to identify if the studies report

on one or more aspect of inequalities. Attwood and colleagues undertook a systematic review of primary-care-based physical activity interventions using PROGRESS Plus categories [18]. We will use these descriptions of the PROGRESS Plus to direct our inclusion criteria. Socio-economic groups may include reporting by occupational class, education, income or an index, such as the Index of Multiple Deprivation. We will only include studies which report the differential effect across PROGRESS Plus categories of clinical outcomes (such as mortality, myocardial infarction, cancer survival), clinical measures of risk factors (such as change in Hb1Ac, blood pressure or cholesterol, or smoking cessation) or health care process outcomes (such as number of hospitalisations or consultations). A further random 10% sub-sample of citations will be reviewed for quality control purposes.

Additional searching

More searches will be undertaken if we find that we require more data to develop and test certain sub-sections of the programme theory. For example, we may find we need relevant data about one or more of mechanisms and how these behave under different contexts. These additional areas that we will need to search will greatly increase the amount of relevant data available to us for the realist review. For each additional search the project team will discuss and set inclusion and exclusion criteria. The screening processes will be as described above for the initial search. These searches will be of a different nature to that mentioned above as they will be less well categorised and much more exploratory, purposive and interdisciplinary. Where applicable, we will follow the search strategies developed by Booth and colleagues developed for just such data [48].

Feasibility testing of the search strategy

We have undertaken an initial search to ensure that the review is feasible and achievable. A conservative search strategy is shown Appendix 1. The search identified 5,753 articles. An initial screen of a random sample of 200 of these articles identified nine review articles which would require full text review to assess eligibility. These nine articles had an average of nine included primary studies (range 2 to 23). Assuming all nine of these articles are included and there is a similar selection proportion across the whole search this would result in about 259 review articles. It is likely that a considerable proportion of these review articles would be excluded because they cover the same topic or have been superseded. However, assuming that all the review articles were included with an average of nine primary studies per review, there would be about 2,331 primary studies requiring review of full text to assess if they report outcomes by PROGRESS Plus criteria. Tugwell and colleagues looked at reporting of inequalities outcomes in musculoskeletal Cochrane reviews [52]. The authors found that six out of 147 studies (4%) reported outcomes by PROGRESS Plus criteria. Assuming we find a similar proportion of reported inequalities outcomes, we would estimate that about 95 articles would be included in data synthesis. This is less than some other previous realist reviews, for example, our realist review looking access to primary care included 162 articles [44].

5.4 Article selection

Documents will be selected based on relevance (whether data can contribute to theory building and/or testing) and rigour (whether the methods used to generate the relevant data are credible and trustworthy). Even when a document found from the initial search has

been screened and has met inclusion criteria, it may still not contain any data that is relevant for programme theory development and refinement. To illustrate how we will operationalise rigour, if relevant data have been generated using a randomised controlled trial, then the trustworthiness of the data would be considered to be greater if we have been able to ascertain that the trial meets current quality criteria for rigour. Documents may still be included even if judged to be of limited rigour, as we will also be making an overall assessment of rigour at the level of the programme theory[53]. We will employ the same decision-making process as outlined above.

5.5 Extracting and organising data

The full texts of included papers will be uploaded to NVivo. Relevant sections of texts which have been interpreted as relating to contexts, mechanisms and their relationships to outcomes will be coded in NVivo. This coding will be inductive (codes created to categorise data reported in included studies), deductive (codes created in advance of data extraction and analysis as informed by the initial programme theory) and retroductive (codes created based on an interpretation of data to infer what the hidden causal forces might be for outcomes). A random sample of 10% will be independently coded by the two PIs to improve consistency and quality. Key study characteristics, such as included patients, interventions and outcomes by socio-economic group or other PROGRESS Plus criteria, will be extracted from systematic reviews or primary studies that meet the eligibility criteria using an Excel pro forma. Each new element of data will be used to refine the theory if appropriate, and as the theory is refined, included studies will be re-scrutinised to search for data relevant to the revised theory that may have been missed initially.

Data from this step will allow us to generate a list of interventions which lead to inequalities in clinical outcomes from interventions or aspects of routine care delivered in general practice for socio-economic status, and where relevant other PROGRESS Plus groups (Objective 2).

5.6 Synthesis of data

Data analysis will use a realist logic of analysis to make sense of the data in light of the initial programme theory. We will undertake this step with support from the wider research team. We will use interpretive cross-case comparison to understand and explain how and why observed outcomes have occurred, for example, by comparing interventions which apparently widen inequalities and those which narrow them. We will use a series of questions about the relevance and rigour of content within data sources as part of our process of analysis and synthesis, as set out below:
- Relevance: Are sections of text within this document relevant to programme theory development?
- Rigour (judgements about trustworthiness): Are these data sufficiently trustworthy to warrant making changes to any aspect of the programme theory?
- Interpretation of meaning: If the section of text is relevant and trustworthy enough, do its contents provide data that may be interpreted as functioning as context, mechanism or outcome?

- Interpretations and judgements about Context-Mechanism-Outcome-Configurations (CMOCs): What is the CMOC (partial or complete) for the data that has been interpreted as functioning as context, mechanism or outcome? Are there further data to inform the particular CMOCs contained within this document or other documents? If so, which other documents? How does this particular CMOC relate to other CMOCs that have already been developed?
- Interpretations and judgements about programme theory: How does this particular (full or partial) CMOC relate to the programme theory? Within this same document, are there data which inform how the CMOC relates to the programme theory? If not, are there data in other documents? Which ones? In light of this particular CMOC and any supporting data, does the programme theory need to be changed?

Data to inform our interpretation of the relationships between contexts, mechanisms and outcomes will be sought not just within the same document, but across documents (e.g. mechanisms inferred from one document could help explain the way contexts influenced outcomes in a different document). Synthesising data from different documents is often necessary to compile CMOCs, since not all parts of the configurations will always be articulated in the same document. When working through the questions set out, where appropriate we will use the following forms of reasoning to make sense of the data:
- Juxtaposition of data: for example, where data about how one intervention widened inequalities in one document enables insights into data about outcomes in another document.
- Reconciling of data: where data differ in apparently similar circumstances, further investigation is appropriate in order to find explanations for why these differences have occurred.
- Adjudication of data: where there are conflicting data, plausibility of these data can be informed based on methodological strengths or weaknesses of the data collection methods.
- Consolidation of data: where outcomes differ in particular contexts, an explanation can be constructed of how and why these outcomes occur differently.

The realist review will follow current quality and publication standards[54].

5.7 Developing guidance and a toolkit for use within the NHS
The programme theory will be used to develop guidance and a toolkit for commissioners. An initial guidance document and toolkit will be developed by the research team. This will follow a similar toolkit that was produced based on our previous realist review (https://www.england.nhs.uk/wp-content/uploads/2017/07/inequalities-resource-sep-2018.pdf). This will then be refined within a one-day deliberative workshop led by a professional facilitator with the Expert Group, Research team and key stakeholders (e.g. NHS England, groups which represent disadvantaged communities such as The Kite Trust, Clare Lodge Secure Unit for Women, Traveller Health Team) to develop the resources and ensure they have maximum benefit within the NHS.

Deliberative techniques, including workshops, have been described as "discussions that provide participants with the opportunity to consider an issue in depth, challenge each other's opinions and develop their views/arguments to reach an informed end position".

The advantage of a deliberative workshop is that commissioners (e.g. NHS England and CCGs), practitioners, patients, researchers and third sector organisations are able to discuss the programme theory and the proposed resources. Models and resources will be provided in advance and discussed at the deliberative workshop. Based on the feedback from the deliberative workshop the existing resources and framework will be adapted for use within the NHS in England.

6. STUDY SETTING

The data collection will involve only documents which will be searched and retrieved online according to the guidelines of the realist review methodology. There will be no study participants and there are no specific requirements to run the searches and collect the data.

7. SAMPLE AND RECRUITMENT

The study will not involve participants, so there will be no sampling or recruitment processes. Similarly, no consent is needed.

8. ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and Management of Risk
Given that the study will not involve participants no potential risks or harm is identified.

8.2 Research Ethics Committee
Ethics approval is not required because this study does not include any primary research.

8.3 Peer Review Process
The project underwent an independent peer review process during the funding process and was also reviewed by the funding panel. No material changes have been made to the research proposal since funding approval.

8.4 Patient & Public Involvement
Patients and public involvement in the delivery of the research will be key. We will have two PPI representatives as part of the Research Team (Rebecca Harmston, who is a co-app) and Sukaina Manji, Annie Moseley. Our PPI team members will ensure that a patient and public voice is maintained throughout the research. They will be an active member of the research team and contribute specifically to the design, interpretation of the findings and dissemination activities. Recruiting individuals who belong to marginalised or seldom heard groups to research involvement is difficult. Our experience is that this is easier to recruit people when there is a specific event which people can attend. Therefore, we will work closely with HealthWatch who have agreed to help recruit a diverse range of individuals from across society to attend two Expert Group meetings and the Deliberative workshop.

8.5 Protocol Compliance
Accidental protocol deviations can happen at any time. In case, they happen they will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

8.6 Data protection and patient confidentiality

Patient confidentiality and data protection is not relevant because this study does not include any primary research.

8.7 Indemnity

Indemnity arrangements are not required because this study does not include any primary research.

8.8 Access to the final study dataset

The study's dataset will only involve secondary data so participants' consent or anonymisation procedures will not be necessary at any stage. The principal investigators will have access to the final dataset and be responsible for granting access to other investigators of the research team for purposes related to the study and to investigators outside the research team, if a formal request describing their plan is approved.

9. DISSEMINATION POLICY

9.1 Dissemination Strategy & Audiences

The findings of this research will inform general practice policy making and commissioning of efforts to tackle health inequalities. This in turn will help general practice to close the gap in care processes, risk factors, clinical outcomes and, in the long term, life expectancy.

Our dissemination strategy will capitalise on the stakeholder networks that we have established during the research. The NHS organisational landscape is changing, and our strategy has been developed to be flexible to respond to new or emerging organisations (such as Primary Care Networks and Integrated Care Systems) and policy requirements. A range of stakeholders will be interested in the findings and recommendations from our review. Different strategies are likely to be needed. We will draw on the advice and expertise of our Expert Panel to help; a) clarify who the main players are for dissemination for each audience; and b) to develop materials which are tailored and relevant to each audience.

Audience 1: Primary care policy makers and commissioners

This audience is central to implementing the findings and toolkit from our review. Key influencers and policy makers from NHS England are included in the expert panel and will contribute to the research throughout. We will draw on these individuals to ensure that the findings are presented to the relevant teams and groups within NHS England, such as the GP Contracting Team and General Practice Forward View team. We will also draw upon existing NHS England collaborations which have been developed through our health inequalities RightCare evaluation. To augment the toolkit we will produce a short animation to communicate the guiding principles in an accessible way. We envisage that the guiding principles, toolkit and animation will be included on the NHS England Health Inequalities Hub website. Clinical Commissioning Groups are important as they commission general practice. We will work with CCG members within our team to develop specific briefing

materials for this group. We will also produce policy briefing for other interested organisations, such as the Health Foundation, Nuffield Trust and Kings Fund.

Audience 2: General Practitioners
We will target general practitioners through tailored briefings for the Royal College of General Practitioners and presenting at the RCGP conference. We will also target Primary Care Network leads, who are mostly general practitioners, through the development of specific PCN briefing packs. These will be developed with support from members of our Expert Group who lead PCNs (e.g. Dr Rachel Harmer). We will produce a series of infographics to communicate the broad types of interventions which are likely to increase or decrease health inequalities. We will also work with the primary care work streams within the CRN to disseminate the findings to general practices.

Audience 3: Members of the public and third sector organisations
We will produce plain English summaries of our findings for the public and hold an afternoon dissemination event for members of the public and stakeholders. Plain English summaries will be published on the university websites and distributed via social media. Press releases will therefore be prepared for dissemination to both lay and medical press. We will provide summaries of our findings to all relevant charities and to Healthwatch England. We will engage with our PPI and Expert Panel to maximise dissemination opportunities to the widest possible public audience, for example through social media, ensuring our materials meet their needs.

Audience 4: Researchers
We will target publication in high impact journals, such as the British Medical Journal, and present at one national conference (RCGP) and one international conference (North American Primary Care Research Group (NAPCRG) conference.

Project outputs
To ensure that the findings have maximum impact we will produce a number of outputs.

a) Guiding principles and associate toolkit
We will produce a set of guiding principles to reduce inequalities for decision makers and commissioners to use in the NHS when designing general practice services. These guiding principles will be aimed at all general practice services, not just those specifically designed to reduce inequalities. For example, one guiding principle may be that low effort (or agency) services are more likely to reduce health inequalities but services which require high patient effort are more likely to increase inequalities. These principles will help decision makers to understand the likely impact of their services on health inequalities and give evidence-based suggestions of how services could be modified. Alongside the guiding principles we will produce a toolkit which explains in more detail and gives worked examples of how services can be modified to reduce inequalities. At present we expect that the main target audience of this toolkit will be NHS England, CCGs and PCNs, but we will modify it to reflect the organisational landscape at the time of completing the research.

b) Academic outputs

We will produce and submit for publication a protocol of our realist review. The findings from the review will be submitted for publication to an open-access high-impact peer-reviewed journal, such as the BMJ. We anticipate that such a publication is most likely to impact at an academic audience. Our final project report will also be available on an open access basis to those interested in the detail of our findings and the processes we used in the realist review.

c) <u>User-friendly summaries of the findings tailored to the needs of the different audiences</u>
The intended impact of this series of documents is to make relevant stakeholders aware of the 'headline' findings of the realist review. These outputs are thus closely linked to our dissemination strategy. We will again draw on the expertise within the review team and Expert Panel to produce summaries that are user-friendly and relevant to the audiences we have identified and disseminate them as described above.

9.2 Authorship and eligibility guidelines
All members of the research team will be granted authorship to the final study report as long as they have been engaged to the study according to their role and have contributed to the collection, analysis, interpretation of data and writing the report.
Individual and group authorship for academic publications will be granted according to the criteria of the International Committee of Medical Journal Editors (ICJME).

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11. APPENDICES

11.1 Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made