IMPROVING THE MANAGEMENT OF PATIENTS WITH MULTIMORBIDITY IN GENERAL PRACTICE

The 3D Study: Improving whole person care

Funder	NIHR Health Services and Delivery Research Programme (HS&DR)
Funder Ref Number	12/130/15
Sponsor	University of Bristol
Sponsor Ref Number	2148
REC number	14/SW/0011
ISRCTN number	ISRCTN06180958
CSP number	139520
Chief Investigator	Professor Chris Salisbury
Version number, Date	V6.1; 02/06/2016

History of version changes and amendments

Version No.	Version Date	Pages	Description of change
2.0	04/03/14	17-18	Change to exclusion criteria. Adults lacking capacity to consent excluded in Scotland only.
		19	For patients lacking capacity in England only, assent from consultee will be sought.
		33	ISRCTN number added Ethically differences in England and Scotland over adults lacking capacity to consent
3.0	24/11/14	6	Update affiliation for Ardiana Gjini
		8	4 changed to 3 pilot practices
		9	4 changed to 3 pilot practices with 1 in Manchester instead of 2 in Glasgow 1383 participants – due to rounding error
		11	Tran measure of Treatment burden replaced with Boyd Healthcare Task Difficulty and Brief Treatment Burden Questionnaire Addition of Brief Treatment Burden Questionnaire for carers
		15	4 changed to 3 pilot practices
		18	Replace now extant PCRN and disease specific research networks with NIHR Clinical Research Networks.
		19	Explanation and process for selecting maximum number of patients per practice in order to reduce variability in cluster size.
		20	Clarification that practice randomisation performed by registered trials unit
		21	4 changed to 3 pilot practices with 1 in Manchester instead of 2 in Glasgow
		22	Addition of process for dealing with practice withdrawals
		25	Boyd HCTD and Brief Treatment burden questionnaire replaced Tran measure
		26	Addition of Brief Treatment Burden Questionnaire for carers
		27	Further details provided for management and outcome databases For details of qualitative data collection directed to section 7.6
		28	Reference back to section 2.5.2 regarding cluster sizes
		29	Addition of using anonymised records linkage data for hospital admissions and deaths
		30-36	Updating and expansion of Process evaluation section of protocol
		38-39	Inclusion of deaths and if the event is related to the research processes, added to processes concerning SAEs
		42	Claire Henry no longer works at NHS Improving Quality. Therefore Jane Whittome as her replacement as Head of Programme for Long Term conditions has been invited to be on the study Advisory panel.
		44	Further details provided of publication policy
		52	Timetable has been updated in Appendix B
4.0	23/03/15	12	Removal of the Boyd Healthcare Task difficulty scale Stating that some questions are taken from the LTC6 QIPP Footnotes associated with Boyd scale and BTBQ removed.
		18	Marital status removed from socio-demographic data collected and Education has been included Changes in QOF LTC conditions. However, given that the management of CKD is similar to CVD, it was decided to include CKD under the grouping of CVD as one condition. Osteoporosis has been removed from the inclusion criteria conditions list. Explanation provided in text.
		20	11 changed to 10 practices taking part in Bristol for the main trial

		26	Updating the outcomes by removing Boyd Healthcare Task difficulty scale and stating some questions from the LTC6 QIPP Marital status is removed from the subgroup analysis and education has been included
5.0	26/03/15	19 20	Patients will be consenting to being offered the new approach should their practice be randomly allocated to the intervention arm. Removal of decline form and requesting that patients return a blank questionnaire should they not wish to take part in the study,
5.1	13/04/15	23	Clarification of participant withdrawal options following patient consent changes as detailed in v5.0.
6.0	05/01/16	9-13, 21-22, 26-27, 29, 32 54-55 12 33-35 38-41	All references to 6 and 12 month follow-up replaced with 9 and 12 months follow-up. Explanation of change in follow-up times Updated data collection procedures for process evaluation protocol Definition and clarification of SARs and their reporting
6.1	02/06/16	34-35	Increasing the number of consultation recordings from approximately 20 to approximately 60. This may include intervention and usual care practices as well as case study practices.

Contents

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Abbreviations

AE	Adverse Events
BHF	British Heart Foundation
BNF	British National Formulary
CARE	The Consultation And Relational Empathy measure
CBT	Cognitive Behavioural Therapy
CCG	Clinical Commissioning Group
CI	Confidence Interval
CKD	Chronic Kidney Disease
CLRN	Comprehensive Local Research Network
CONSORT	CONsolidated Standards Of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRN	Clinical Research Network
CVD	Cardiovascular Disease
DMC	Date Monitoring Committee
EQ-5D	Euroquol 5D Questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety Depression Scale
ICC	Intra Cluster Coefficient
LTC	Long Term Conditions
MMAS	Morisky Medication Adherence Scale
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
OR	Odds ratio
PACIC	Patient Assessment of Chronic Illness Care measure
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
PPI	Public and Patient Involvement
PSS	Personal and Social Services
QALY	Quality Adjusted Life Years
QOF	Quality and Outcomes Framework
QoL	Quality of Life
R&D	Research and Development
RCGP	Royal College of General Practitioners
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RM&G	Research Management and Governance
SAE	Serious Adverse Event
SMI	Serious Mental Illness
SOP	Standard Operating Procedure
SSC	Service Support Costs
TMG	Trial Management Group
TSC	Trial Steering Committee
WISE study	Whole systems Informing Self-management Engagement study

1 Introduction

1.1 Summaries

1.1.1 Lay Summary

An increasing proportion of the population have long term health conditions. The current approach to managing patients with long term conditions is based on guidelines and treatment for each specific condition. Patients are regularly called to clinics in general practice (eg. diabetes clinics) to see a nurse who follows guidelines on managing that particular disease. However, there is an increasing awareness that many patients have multiple long term health conditions. This is known as multimorbidity. Patients with multimorbidity often have to attend several clinics which can be repetitive, inconvenient and inefficient. They see different nurses and doctors who may give conflicting advice. These patients may have to take a large number of drugs which can be confusing, difficult to remember and some combinations could be potentially dangerous. These patients frequently get depressed and they also sometimes complain that no-one treats them as a 'whole person' or takes their views into account.

To address this problem, this study aims to develop and test a new approach to how GP practices manage patients with multimorbidity. Instead of focussing on each disease in isolation, the aim is to treat the whole patient in a consistent, joined-up manner in order to improve their overall quality of life. GP practices testing this new management system (intervention group) will be compared with GP practices following the current treatment system (usual care or control group).

Specifically, patients in general practices allocated to the intervention group will be identified and flagged on their GP computer systems. A named nurse and doctor will be allocated to them to manage their care. These patients will be given a card to identify them to reception staff who will offer longer appointment times. Patients will also be invited for a comprehensive '3D' health review every 6 months designed to cover all of their health issues. The patient will first see their named nurse who will identify the patients' concerns and priorities (**Dimensions of health**), as well as perform any routine checks required by each of the patients' conditions. The patients' **Drugs** will be reviewed to check they are being correctly prescribed (without dangerous interactions), taken properly and where possible, to try to simplify the patients prescriptions e.g. by arranging for all of them to be taken once a day. The named GP will check for and treat symptoms of **Depression**. The practice will also have a linked 'general physician' at the local hospital whom they can contact easily for advice about patients with complex problems.

Patients in general practices allocated to the usual care group will continue having their care managed by their GPs and practice nurses using current management practices of multiple appointments and clinics for each separate condition.

We will first try out the new approach in three practices and use this experience to improve it. Then we aim to recruit 32 GP practices from in and around Bristol, Manchester and Glasgow to take part in the main study. These practices will be randomly assigned to the intervention or usual care group. A target of 1383 multimorbid patients from these practices will be followed up over a period of 15months.

Before the practice randomisation and at 9 and 15 months into the study, participants from both groups will be asked to fill in questionnaires about their wellbeing, illnesses and treatments, their experience of their care, and what health resources they use. The research team will review the notes of patients in both groups to record the number, type, duration and quality of consultations within general practice as well as their use of other health and social services.

We will compare the cost of the old and new approaches (both the cost to the NHS and the cost to the patient) and relate this to the benefit in a cost-effectiveness analysis.

We will check whether the care provided in the intervention practices actually changed the way intended. Through interviews with patients and care staff, and by direct observation, we will explore how well the approach was implemented and how it could be improved.

1.1.2 Scientific Summary of research

AIM: The aim is to optimise, implement and evaluate an intervention to improve the management of patients with multimorbidity in general practice

Design: Pragmatic cluster randomised controlled trial with nested process evaluation and economic analysis of cost effectiveness.

Setting: 3 practices (2 in Bristol and 1 in Manchester) will participate in a pilot phase followed by approximately 32 GP practices in Bristol, Glasgow and Manchester. Only practices with a minimum of 3 GP partners and minimum practice list size of 4,500 patients will be approached in order to ensure an adequate number of participants per practice.

Participants:

A target of 1383 participants from 32 GPs will be recruited to the study. Eligible participants will be 18 or over with multimorbidity, defined as having three or more long term conditions (LTC) from a predefined list of conditions.

Interventions

GP practices will be randomised to the intervention or usual care groups.

A. Intervention group:
This is also described as the 'new approach' group. The intervention is designed to address the problems of illness burden (poor quality of life, depression) treatment burden (multiple unco-ordinated appointments, polypharmacy, poor primary/secondary care co-ordination) and lack of patient-centred care (low continuity, disregard of patients' priorities) experienced by patients with multimorbidity.

There are 4 main components of the intervention

1. Identification and prioritisation of patients with multimorbidity – given '3D' card + flagged records.

2. Improving continuity of care – defined usual GP and usual practice nurse. Offered longer appointment times.

3. Reducing the burden of illness and treatment – comprehensive assessment every 6 months. Each 3D assessment consists of 2 appointments approximately 1 week apart. At the first appointment, the patients' usual nurse will complete a bespoke computerised template to address all of the 3D elements, collect relevant data in relation to the patient's combination of LTCs, and organise necessary tests. At the second appointment, the usual GP will review all the information, conduct a thorough review of medication and agree an written care plan with the patient for them to take away. The '3D' label provides a mnemonic for health professionals. It refers to:

    - Dimensions of Health – patient's concerns and priorities, addressing quality of life issues first
    - Depression – Assessment and treatment
    - Drugs – Doctors will seek to simplify treatment regimes and improve medication adherence, aided by prior pharmacist review of patient's medication regime

4. Improving integration – each practice has a designated general physician who is readily available to discuss multimorbidity patients with complex needs and help co-ordinate hospital investigations.

To ensure the intervention is effectively implemented, it will be incentivised as if it were an Enhanced Service or included in the Quality and Outcomes Framework (QOF), with payment against targets for completion of two 3D assessments per annum. Practices will train in local collaboratives to share ideas. We will allow local adaptation, appoint a practice champion, provide training and monthly feedback on performance e.g. number of patients with care plans.

B. Control group:

Practices in the care as usual group, will continue their usual practice following disease specific computerised protocols focussing on data related to QOF targets.

Outcomes

Outcomes will be collected at baseline, 9 months and 15 months after patient recruitment. This choice of follow-up time-points was made to reflect the fact that practices are randomised following individual patient recruitment, and then it takes approximately 3 months for intervention practices to be fully trained and able to make the organisational changes (e.g. appointment booking and clinic re-organisation) ready to deliver the intervention. Therefore collecting the first patient follow-up data 9 months after the date of consent represents about 6 months from when practices begin to deliver the intervention.

The primary outcome will be Health Related Quality of Life as measured by the EQ-5D-5L at 15 months post recruitment.

Secondary outcome measures will include:

Burden of illness measures:

- Self-rated health
- Bayliss measure of illness burden in multimorbidity
- Quality of disease management (composite measure of QOF achievement)
- Hospital Anxiety Depression Scale (HADS)

Burden of Treatment measures:

- Brief Treatment Burden Questionnaire
- Morisky Medication Adherence Scale (MMAS, 8 item)
- Number of drugs prescribed
- Reduction in high risk drug combinations

Experience of patient centred care:

- CARE measure and how well you know your doctor
- Coordination of care (Questions from LTC6 QIPP)
- Management of LTCs (PACIC)
- Overall satisfaction (single item)

Use of resources:

- Hospital admission and outpatient rates
- Use of health services in primary, community and secondary care
- Investigations
- Prescribed medication

Socio-demographic measures (measured at baseline only):

- Number of long term conditions
- Age
- Gender
- Education
- Ethnicity
- Deprivation status
- Work status

Measures of strain on patient's carers:

- Carer Experience Scale
- EQ-5D-5L completed by carers.
- Brief Treatment Burden Questionnaire for carers

Alongside the trial, a parallel mixed methods process evaluation combining quantitative and qualitative methods will be conducted in order to provide understanding of trial delivery, intervention implementation, current management practices and the responses of targeted participants.

An economic evaluation will be undertaken from the perspectives of (a) NHS and personal social services (PSS) and (b) patients. In a cost-consequences analysis we will relate the cost of the intervention or usual care to changes in a range of outcomes. In a cost-effectiveness analysis from the NHS and PSS perspective we will estimate the incremental cost per QALY gain. Uncertainty will be addressed in sensitivity analyses and by using bootstrapping to estimate the net monetary benefit and a cost-effectiveness acceptability curve.

Sample size: based on 32 general practices, 108 eligible patients per practice, 40% providing consent, we aim to recruit 1383 patients (1555 including pilot practices). With 80% follow-up at 15 months, and ICC at practice level of 0.03, the study will have 90% power to detect a difference between trial arms of 0.274 SDs in the EQ-5D.

Benefits and potential impacts: There is widespread interest in how to improve care for patients with multimorbidity. If successful, this intervention could improve the quality of life of patients and their experience of care and reduce NHS and patient costs. By working with RCGP, we will ensure that if the intervention is effective, it can be implemented widely, quickly and effectively.

1.2 Background

In an attempt to improve the quality of care of individual long term conditions in general practice, care has become increasingly driven by protocols delivered using computerised templates by practice nurses. These nurses often have extra training in specific diseases and provide care within disease-specific clinics (e.g. diabetic clinics) which focus on one disease at a time. Primary care clinicians are incentivised through the QOF to achieve against targets relating to a limited range of specific long term conditions. Disease pathways for specific long term conditions are being developed to improve vertical integration across primary and secondary care.

These developments fail to take account of the fact that many people have multiple long term conditions (multimorbidity) [1,2]. Sometimes these co-morbid conditions have a bigger impact on the patient's quality of life than the specific condition being addressed at a nurse led chronic disease management clinic. The priorities and incentives for the health professionals dealing with a specific disease may or may not align with the priorities of the patient [3].

As the population ages this problem is becoming increasingly important, since multimorbidity is much more common in older people [1,2]. Multimorbidity matters because people who have multiple conditions have poor quality of life [4], increased morbidity [5], reduced life-expectancy [6], and increased rates of depression [7]. Patients with multimorbidity are also a priority for the health service because they account for a high proportion of resource use in both primary and secondary care (including having high rates of hospital admissions) [8-10].

Failing to improve care for multimorbidity will also lead to increased inequalities in health. Multimorbidity is more common in deprived areas [2], and patients with fewer material and personal resources are particularly disadvantaged by having to attend multiple appointments for each of their long term conditions, and being expected to follow a series of different care plans

[11,12]. Their care is also more likely to be complicated by other medical and social factors, such as poor mental health, poor housing, and smoking [13].

The consequences of a single disease approach for the health service potentially include duplication and also gaps in services (e.g. conditions included in the QOF are prioritised but others are neglected) [14], inefficiency (because the same topics are addressed repeatedly by different specialist practice nurses), and waste (because of non-adherence to medication and non-attended appointments) [15]. If taken to its logical conclusion, the disease pathways approach would mean that one patient with multimorbidity would have their care managed by several specialist services (each crossing primary and secondary care), but there would be little co-ordination between these specialist services and no one professional who has an overview and takes responsibility for the patient as a whole.

For patients with multimorbidity, the single disease approach is inconvenient and inefficient, because they are repeatedly invited to different disease-focused appointments in general practice, where they are asked the same questions and given the same advice (or sometimes conflicting advice which can be confusing) [3,12,16,17]. Patients may receive less good quality care if the specialist nurse is not aware of the impact of the treatment of one disease on other diseases, which can be a particular problem with drug interactions. Alternatively, the disease-focused nurse or doctor may slavishly follow guidelines without recognising that the evidence underlying those guidelines is not necessarily applicable to the individual patient in front of them with multimorbidity (since most guidelines are based on research which excluded patients with comorbidities) [18,19].

If all the recommendations for each long term condition are considered in isolation and followed, patients with multimorbidity are likely to have numerous investigations and to be prescribed large numbers of drugs [20,21]. This polypharmacy can be burdensome for patients, increases the likelihood of interactions and adverse effects (including those causing hospital admissions), and may reduce medication adherence [19,22-24].

It is also well recognised that multimorbidity is associated with an increased prevalence of depression [7]. This association is strongest in deprived areas [2]. The relationship between physical and mental health works in both directions – people with chronic illnesses are more likely to be depressed, and those who are depressed are less likely to manage their long term conditions well, leading to worse disease control and poorer health outcomes [25]. People with multimorbidity and depression are also more likely to have unplanned hospital admissions [9]. The prevalence of comorbid depression and physical health problems is much higher in deprived areas than affluent areas [2]. Therefore improving mental health in people with multimorbidity is also a priority.

Most importantly, patients with multimorbidity can feel that no one treats them as a ‘whole person’ rather than ‘a disease’ [3]. Patients say that they want to have a relationship with one health professional that they can trust, and who listens to them, helping them make appropriate decisions in the context of their life circumstances and values [3]. Given the large number of health problems they face and the number of potentially relevant investigations and treatments, they may want to set priorities and make trade-offs so that medication regimes are not excessively burdensome and they are not over-investigated. For patients, improving quality of life (which might include not spending too much time in contact with the health service or suffering side-effects of medication) might be a higher priority than achieving improved indicators of disease control with a view to greater longevity.

In summary, patients with multimorbidity experience problems of illness burden (poor quality of life, depression) treatment burden (multiple unco-ordinated appointments, polypharmacy) and lack of

person-centred care (low continuity, little attention paid to patients' priorities). This research is designed to test the hypothesis that an intervention in general practice designed to address the needs and priorities of patients with multimorbidity will improve their health related quality of life (primary outcome), reduce their burden of illness and treatment and improve their experience of care, while being more cost-effective than conventional service models. This will be tested using a cluster RCT, with economic evaluation and mixed methods process evaluation.

1.3 Rationale

There is a growing body of literature and commentary on the scale and consequences of multimorbidity [1,2,5,13,15,19,21,26]. Commissioners, professional bodies, academics and other stakeholders have all recognised the growing tension between the single disease focus of medicine and the needs of patients with multiple long term conditions [27]. This is evidenced by recent reports from the Royal College of General Practitioners [28], the Royal College of Physicians [29], NICE [30], and others [31]. There is a long term challenge to redesign the NHS to reflect the needs of patients with multiple long term conditions[32] in light of the ageing population.

A recent Cochrane review however, highlighted the paucity of research on interventions to improve the outcomes of patients with multimorbidity in primary care[33]. Ten studies were identified examining a range of complex interventions which demonstrated mixed effects. The interventions that proved most effective were organisational interventions focussed on areas of concern for patients or where they have difficulties, such as functional ability and medication management. No studies included an economic analysis of cost effectiveness although a trend towards improved prescribing and medication adherence suggests the potential for cost savings. The conclusions of the systematic review called for further pragmatic studies based in primary care settings, using clear definitions of participants and appropriate outcomes.

There has been considerable research on the scale of the problem and the needs of patients with multimorbidity [3,11,26,34-37]. Qualitative studies of patients with multimorbidity have identified several barriers to their self management (including depression, poor patient-clinician communication, poor physical function and greater financial constraints [11])as well as identifying what services these patients desire (including greater access, individualised care plans, continued care by a single coordinator of care who will listen and respond to their shifting priorities [3]).

There are isolated examples of individual general practices trying out some of the ideas described above, e.g. co-ordinated assessments, although these typically focus on rationalising appointments rather than the extended assessment and holistic approach proposed here[38]. There is a pressing need for rigorous research to test the benefits and costs of a new approach to managing multimorbidity.

The issues identified by the qualitative studies were confirmed by patient and carer forum meetings held prior to the development of the current study proposal and which informed the design of the intervention for the current study. The resulting complex healthcare intervention requires a large scale randomised controlled trial to evaluate the clinical effectiveness, cost effectiveness and implementation of this service.

1.4 Study Aims and Objectives

AIM: The aim is to optimise, implement and evaluate an intervention to improve the management of patients with multimorbidity in general practice

HYPOTHESIS: An intervention in general practice designed to improve the management of multimorbidity will improve patients' health related quality of life, reduce burden of illness and treatment and improve their experience of care whilst being more cost-effective than conventional service models.

OBJECTIVES:

- To optimise an intervention to improve the management of multimorbidity in general practice through **piloting** in three practices.
- To implement this intervention in a representative range of general practices
- Through a **cluster randomised controlled trial** and **economic evaluation**, to assess the impact on health related quality of life, illness burden, treatment burden, patient experience, carer's burden and quality of life, and cost-effectiveness.
- Through **mixed methods process evaluation**, to explore how and to what extent the intervention was implemented, the advantages and disadvantages of different models of care for patients with multimorbidity, and how and why the intervention was or was not beneficial. We will also characterise usual care and explore any changes to management practices over the duration of this study in usual care GP practices.
- To **design educational materials and commissioning guides** to ensure that the intervention is delivered consistently in practices in the trial and that if beneficial, it can be speedily rolled out nationally.

2 Trial Design

2.1 Study Design

2.1.1 Study outline

This is a multi-centre pragmatic, two-arm, practice-level cluster randomised controlled trial, with parallel mixed methods process evaluation and economic analysis of cost effectiveness.

2.1.2 Design

The overall design is a pragmatic cluster randomised controlled trial comparing a new approach to the management of multimorbidity in general practice versus usual care, with process evaluation and economic analysis of cost-effectiveness.

In line with the MRC framework for the evaluation of complex interventions [39], we will first conduct a pilot and optimisation phase and then conduct a parallel mixed methods process evaluation alongside the trial to examine how the intervention is implemented by intervention practices and to characterise usual care. This will help to gain understanding about why the

intervention worked (or did not work), and will inform and facilitate commissioning and other implementation of the intervention if appropriate.

Economic evaluation will be undertaken from the perspectives of (a) NHS and personal social services (PSS) and (b) patients. In a cost-consequences analysis we will relate the cost of the intervention or usual care to changes in a range of outcomes; cost-effectiveness analysis from the NHS and PSS perspective will estimate the incremental cost per QALY gain.

2.1.3 Theoretical/Conceptual Framework

The underlying theoretical basis for the intervention is the Patient Centred Care Model, described by Stewart et al [40]. This is strongly valued by patients[41] and there is some evidence that it is associated with improved health outcomes [42-45]. A recent report from the American Geriatric Society has recommended the Patient Centred Care Model to improve care for multimorbidity [31].

The concept of patient centred care has been reviewed and developed by later authors [46,47] but it broadly includes four key components:

- A focus on the patient's *individual disease and illness experience*: exploring the main reasons for their visit, their concerns and need for information.
- A *biopsychosocial perspective*: seeking an integrated understanding of the whole person, including their emotional needs and life issues.
- Finding *common ground* on what the problem is and mutually agreeing management plans.
- Enhancing the *continuing relationship* between the patient and doctor (the therapeutic alliance).

As shown in the flow diagram in Appendix C, the conceptual framework for our intervention draws on the existing research evidence about the main types of problems experienced by patients with multimorbidity and their preferences for care, and uses strategies based on the Patient Centred Care Model to seek to address these problems. For example, there is evidence that patients with long term conditions particularly value relational continuity of care[48], therefore the intervention includes strategies to improve relational continuity and one of the outcome measures (CARE) collects data about whether this is achieved.

Our conceptual framework also draws on the Chronic Care model[49] and experience in related initiatives such as Year of Care [50], for example the importance of promoting patient engagement in self-care through care plans, improving communication between primary and secondary care, and the recognition that organisational change needs to be accompanied by attitudinal change amongst clinicians, enhanced by training, appointment of local GP champions, collaborative working, incentives, support and feedback.

2.2 Study setting

This study is based in primary care involving General Practices serving different patient populations in 3 geographical areas; in and around Bristol, Manchester and Glasgow. Practices will be selected from areas within a range of socioeconomic deprivation levels as well as urban, suburban and rural areas.

2.3 Eligibility criteria for Practices

General practices with the following criteria will be approached:

- A minimum of three GP partners
- Minimum practice list size of 4,500 patients
- Uses EMIS GP computer system

2.4 Eligibility criteria for participants

2.4.1 Inclusion Criteria

- Aged 18 and over (on date of invitation to participate)
- Three or more long term conditions from the following list of conditions:
    - Cardiovascular disease (CVD) or Chronic kidney disease (CKD): including coronary heart disease, hypertension, heart failure, peripheral arterial disease, chronic kidney disease stage 3 to 5.
    - Stroke
    - Diabetes
    - COPD or asthma
    - Epilepsy
    - Atrial fibrillation
    - Severe mental health problems (eg. Schizophrenia, psychotic illnesses)
    - Depression
    - Dementia
    - Learning disability
    - Rheumatoid arthritis

In the above list we have grouped a number of cardiovascular conditions together, along with CKD, as management of them is very similar, and similarly grouped asthma and COPD together. Therefore these only count for one disease if patients are coded with more than one disease within these categories.

The research team will maintain awareness over developments concerning updates to QOF clinical indicators and any changes to the QOF list will be reflected in the inclusion criteria for the study.

The 2015/16 QOF rules have removed osteoporosis and Chronic kidney disease from the disease list. However, given that the management of CKD is similar to the management of hypertension, it is clinically appropriate to still include CKD as an inclusion criteria, but to include this as counting towards one disease condition of ‘CVD or CKD’ as a single entity.

2.4.2 Exclusion Criteria

In order to maximise generalizability of this intervention, the exclusion criteria have been kept to a minimum. These patients are often excluded from other research and it is these patients with the greatest burden of illness that have the most to gain from this intervention. Therefore the very elderly, patients in nursing homes or housebound, those with mental health problems and those with multiple comorbidities, are all included.

In **England only**, where patients lack capacity, we will seek consent from their legal guardians or consultees. The Scotland A REC board ruled that under Scottish Law, adults who lack capacity to consent should not be included in research studies if not essential. Therefore for practices in **Scotland only**, adults lacking capacity to consent will be excluded. If participants are unable to complete questionnaires themselves, carers can do so on their behalf. We will undertake sensitivity analysis of the impact of including or excluding responses provided by carers on the main results.

Patients who will be excluded:

- Life expectancy of less than 12 months
- Serious suicidal risk
- Known to be leaving practice within 12 months
- Cannot complete questionnaires in English (themselves or with the help of carers, which may include excluding those with visual or hearing impairment)
- If actively taking part in other research involving extra visits to GP or other health services.
- Adults lacking capacity to consent (Scotland only)

2.5 Recruitment procedures

2.5.1 Recruitment of General Practices

Local contacts from the Clinical Research Networks (CRN), Primary care and Scottish Primary Care Network will be approached to assist in identifying and accessing GP practices who are interested in taking part in the trial.

Interested practices will be contacted by local researchers who will arrange a meeting(s) with the practice manager, GP partners and practice nurse(s). It is important to get the acceptance and understanding of all the key stakeholders at the practice since the study involves randomisation at the practice level, which therefore requires a commitment to organisational and procedural change. Practice representatives will be asked to sign a practice agreement consenting to the practice taking part in the study.

Since this is a cluster randomised trial, all eligible patients within one practice will be treated in the same way, subject to their consent. Patients will be asked to give consent to being offered care

based on the new 3D approach, if their practice is allocated to the intervention arm, and also to complete questionnaires and to allow researchers access to their medical records.

We plan to recruit 32 practices for the main trial: 12 near Glasgow, 10 near Bristol and 10 near Manchester. However we will seek to recruit at least two more practices in each of these areas to act as 'reserves' in case a practice drops out after initially agreeing to take part. In this way we can ensure that practices are blind to which arm of the trial they will be in at the time they are recruited.

2.5.2 Identification and consent of patients

General practices agreeing to participate in the study will be asked to search their practice database using an electronic search strategy devised by the research team based on pre-defined Read-Codes to identify potentially eligible patients who have three or more long term conditions as defined above. GPs will be given the opportunity to screen the resultant list for the above exclusion criteria. The practice will then send out patient invitation packs which will contain an invitation letter from the GP, a patient information sheet explaining about the study, an acceptance/consent form, a baseline questionnaire, and a freepost envelope. Patients will be asked to respond by returning the consent form and completed baseline questionnaire to the research team, using the freepost envelope. Patients who do not wish to participate will be invited to return a blank questionnaire. Practice staff will also send one postal reminder to individuals who have not responded approximately 10 days after the initial mailing. This may be supplemented with a telephone reminder by a member of practice staff or a researcher with an honorary contract acting on behalf of the practice if necessary.

Maximum statistical efficiency within a cluster trial is achieved if all clusters are of equal size; large variation in the number of patients participating across practices will therefore reduce the power of the trial. For this reason the maximum number of patients within a practice invited to participate will be restricted. This will also reduce the burden on larger practices of potentially having to re-organise care for a large number of patients, and hence limit the cost of the study. The sample size calculation estimated the average number of eligible patients to be invited per practice to be 108 (see section 5.1). We will initially select a maximum of 150 patients in each practice, randomly selecting those to invite from all potentially eligible patients. After GPs have screened and excluded further ineligible patients we anticipate that we will invite up to about 130 patients in larger practices, with the aim of recruiting about 43 patients per practice. These numbers are provisional and may be modified in the light of our experience about the number of potentially eligible patients and the proportion that return questionnaires. Those patients who provide consent to participate in the study form the group of patients who will receive the intervention in the intervention arm practices. If patients wish to talk to someone about the study, they can contact a research contact at their GP practice or a member of the local research team whose details are on the patient information sheet and invitation letter.

This is an individual-cluster trial where the unit of experimentation and the unit of observation is at the level of the individual. Therefore individual level consent is sought to participate in the study, to complete questionnaires and to allow the research team to collect relevant information from their medical notes.

2.5.3 Permission of Patient's Carers

We are also interested in the views and experiences of carers. Therefore as part of the invitation pack to patients, we will also include a form for carers requesting contact details, permission to contact them and consent to complete a separate carers questionnaire at baseline, 9 months and 15 months.

If the GP assesses that a patient lacks capacity to consent, in England, we will obtain the assent of the patient's carer, legal guardian or consultee on behalf of the patient for them to take part in the study.

2.5.4 Baseline data collection

Participants will be sent a postal baseline questionnaire as part of the invitation mailing. The questionnaire will include questions on socio-demographic factors (age, gender, ethnicity, marital status, work status and deprivation status (via postcode) and details of health conditions) as well as baseline measures for all study outcomes. Personal ID and contact details will also be elicited so that the research team can acknowledge receipt of completed questionnaires and provide a £5 gift token in appreciation of the patient's help.

On receipt of a completed questionnaire, the researcher will mail a letter confirming receipt and a £5 gift token in appreciation of the patient's help. This will be followed this up 1 week later with a telephone call from the local research team to confirm receipt of the letter and voucher and to provide an opportunity for any questions from the participant.

2.6 Randomisation

GP practices will be the unit of allocation. Practices will be randomised using an automated web randomisation system run from the Bristol Randomised Trials Collaboration (BRTC, UKCRC registration ID: 2) on a 1:1 ratio to receive either the intervention or continue care as usual (control group). Randomisation will be stratified by area (Bristol, Manchester, Glasgow) and minimised by deprivation level and practice size.

In order to minimise post-randomisation selection bias, practices will not be randomised until after patients have been identified and after the initial patient invitations have been mailed.

2.6.1 Control group

Practices allocated to the control arm will continue care as usual. In most practices this will mean patients are recalled to different clinics to see different practice nurses to review each of their long term conditions. The nurses will usually follow disease specific computerised protocols for their management, and will mainly focus on collecting data related to QOF targets rather than quality of life or patients' priorities.

2.6.2 Blinding

Is it not possible to mask participants or health care professionals to the group allocation of their practice. It is also not feasible to blind all members of the study team actively involved in the execution of the study. However, as far as possible, analysis of outcomes will be performed blind.

2.7 Procedure optimisation and pilot

Prior to commencing the main trial in 32 practices we will recruit 3 practices (2 in Bristol and 1 in Manchester) and will use this to optimise the intervention and pilot procedures for the trial. We will implement the intervention as described in all 3 practices. Through direct observation of the training events, observation of some 3D patient reviews and interviews with a sample of patients, GPs, practice nurses, receptionists and practice managers we will seek to improve the training programme, learn from stakeholders about how the intervention can be improved, refine the intervention to improve the likelihood of it being implemented as planned in the main trial, and ensure that the IT infrastructure (computerised search routines and new 3D data collection template) works smoothly in a range of practices. This phase will also enable us to pilot aspects of the trial, including checking that our estimates about the recruitment rate are reasonable, test our patient documentation, pilot data collection mechanisms, and assess follow-up rates. Although the main trial will have started before the patients in pilot practices complete the 6 month follow-up measures, there will be an opportunity to improve follow-up procedures for the main trial because of the time lag between pilot and main trial practices.

2.8 Follow-up procedures

Follow-up data will be collected at 9 and 15 months post recruitment with the primary outcome time-point being at 15 months. The primary method of self-reported data collection will be via postal questionnaires, however alternative completion methods including online, phone or via a home visit will be offered in order to maximise response rates.

Prior to being sent follow-up questionnaires, the research team will attempt to telephone or email participants to pre-notify them. This is particularly important for those participants reliant on carers/guardians or representatives, if they lack capacity or require help completing the questionnaires. It provides the opportunity for participants to ask questions, remind participants that they are taking part in research (e.g. if they are in a control practice group) and pre-notification has been shown to improve response rates [51].

Two reminders, the first by letter or e-mail (approximately 10-14 days after posting the questionnaire) and the second by phone (approximately 10-14 days after the first reminder), will be conducted for participants who have not returned their questionnaire.

Patients will be given £5 gift vouchers for completion of questionnaires. However, the research team would like the option of performing a sub-study examining the timing of providing vouchers pre- and post questionnaire completion. We envisage submitting this substudy as a substantial amendment to the protocol for REC approval at a later date.

2.9 Withdrawal

2.9.1 Practice Withdrawal

A practice can decline to take part at any time during the initiation and set-up phase of practice recruitment.

Once a practice has been randomised, they may withdraw from the study only under extreme circumstances. If a practice wishes to withdraw the situation should be discussed with the local team, TMG members and CI. All avenues should be explored to try to resolve the problems and concerns of the practice.

If a practice must be withdrawn, then time permitting an additional site will be allocated to the same randomisation group from the 'reserve' practices originally recruited. The new site will be from the same area (Bristol, Manchester, Glasgow) and if possible the same deprivation level (high/low) and practice size (small/large). If there is more than one feasible practice, the replacement practice will be randomly selected.

If a practice must be withdrawn after having signed the study agreement and after their patients have given consent to participate, we will still seek to obtain outcome data on the practice's patients if at all possible. It is likely that withdrawal will be due to practice difficulties in delivering the intervention rather than an unwillingness to allow us to collect data from their patients' records.

Any practice withdrawing, which is replaced, will not be included in the primary intention to treat analysis, but will be included in sensitivity analyses if outcome data are available.

2.9.2 Participant withdrawal

If the participant has already consented, but later decides to drop out, they have several options:

a) Withdrawing from just the data collection (i.e. completing questionnaires and/or allowing researchers to access their medical records), whilst still continuing to receive the intervention if their practice is in the intervention arm.

b) Withdrawing from receiving the intervention from their practice, if their practice is in the intervention arm, but still completing the data collection

c) Withdrawing from both data collection and intervention if their practice is in the intervention arm.

Any data collected from the patient prior to withdrawal will still be included in the final analysis of the data. Withdrawal from the study does not affect the patients' treatment or access to NHS services.

A notification of withdrawal can be directly from the patient, their carer, GP, or other practice staff. On receipt of such notification, a member of the research team will contact the patients to confirm the request and explain the withdrawal options.

Patients do not have to give a reason for withdrawal if they choose not to although possible reasons could include being too busy, or does not wish to complete any more questionnaires. If the withdrawal is due to the participant experiencing an adverse event, a worsening of their symptoms or has died, the researcher will follow the standard operating procedures (SOP) for adverse events in addition to the withdrawal SOP.

This information will be passed onto the participants' GP in order for their records to be updated.

3 Intervention

This is a complex intervention, with four main components:

1) Identification and prioritisation of patients with multimorbidity: These patients will be identified on practice database systems and 'flagged' in order to prioritise them for a different model of care. These patients will also be provided with a '3D' card in order to identify them with practice staff (see below).

2) Improving patient-centred care: Patients will be prioritised for enhanced continuity of care. Each patient will be allocated a named usual GP and usual practice nurse, who will be identified in the patient's notes and between them will have responsibility for co-ordinating their care. Patients will identify their 3D status to receptionists when booking appointments and will be offered longer appointments with their usual doctor or nurse whenever possible. Other elements of the review of their long term conditions described below (for example the emphasis on care planning) will also enhance patient centred care.

3) Reducing the burden of illness and treatment: '3D' patients will be offered a comprehensive assessment every 6 months, instead of separate reviews for each of their LTCs. Each 3D assessment consists of two appointments a week apart, the first with the patient's usual nurse and the second with their usual doctor. Both will follow the same '3D' assessment structure, supported by a bespoke computerised template:

DIMENSIONS of health. First elicit patients' concerns and priorities for improving their quality of life (e.g.mobility, pain) before collecting data about disease based indicators e.g. weight, BP.

DEPRESSION. The template will include questions to identify depression (PHQ9).

DRUGS. Before the baseline assessment, a pharmacist will review the patient's medication list to try to identify ways to simplify the patient's drug regime, potentially unsafe drug combinations, drugs which are indicated according to guidelines but are not being prescribed, and drugs which may be indicated but are potentially inappropriate or are low priority for this patient in view of their comorbidities. They will be supported in this by computerised 'rules' applied to the patient's electronic medical record. A note of the pharmacist's recommendations will appear in the 3D review template, for consideration by the GP. This pharmacist review will occur once a year i.e. at alternate 3D reviews. In addition, the template will prompt the nurse and GP to check at every 3D review whether patients are taking the drugs they have been prescribed, using questions designed to detect problems with adherence, and whether they understand what the drugs are for.

At the first 30 minute appointment, the practice nurse will collect information to complete the template and organise all relevant blood tests/investigations. Following the nurse appointment the patient will be given a letter summarising their assessment which details their top priorities for change. This will set the agenda for the second appointment, approximately one week later, with the patient's usual GP. At this 20 minute appointment the GP will review all the information collected by the nurse and from the test results, undertake a through medication review with the help of the pharmacist's recommendations, use evidence based strategies to address the patient's priorities and problems identified in the assessment, and agree a written care plan for the patient to take away.

For example, if depression was identified, treatment will be based on stepped care to antidepressants and/or psychological intervention according to severity [52]. An important focus of the GP appointment will be evidence-based approaches to simplifying medication regimes, stopping high risk or low priority drugs and promoting medication adherence [53,54]. Doctors will be trained in these strategies and will be guided by the pharmacist's recommendations [55].

Following the 3D review, follow-up will be determined by the patient's needs and plan.

4) Improving integration. Each practice will have a designated 'general physician' whom they can contact to discuss individuals with complex problems,[56] and to help co-ordinate use of hospital investigations and appointments where patients are attending numerous different specialist clinics or having multiple hospital based tests on different days.

Supporting practices to provide the intervention

Working with commissioners, we will use financial incentives to encourage clinicians to attend training and complete 3D assessments, as if the intervention was included in a Local Enhanced Scheme[57] or part of the QOF.

We will provide training to help practices to implement the intervention as intended. All GPs and all practice nurses involved in LTC management will be asked to attend two half days of training, with practices training together to share ideas. Practice nurses and GPs will be trained to use the 3D assessment template, to focus on addressing issues relating to quality of life, depression, and medication adherence as well as disease management, and how to create a written care plan with the patient. A substantial element of the training will be devoted to promoting attitudinal change amongst clinicians towards identifying and responding to patients' own priorities and problems with broader quality of life, as organisational change is unlikely to be effective unless clinicians 'buy into' the underlying philosophy of the new approach [50].

Following initial training, we will appoint a local GP champion in each practice to monitor and maintain adherence with the intervention amongst practice staff and to promote the research. GP champions from intervention practices in each area will meet together in local collaboratives to share good ideas and experiences. We will allow local adaptation of the intervention to reflect local context while ensuring the key elements of the conceptual framework are maintained.[58] We will provide regular feedback about implementation e.g. the number of patients who have had a 3D assessment (which we will monitor through regular searches in the intervention practices, with the help of practice champions).

GP Receptionists will be offered training at their own practice. Receptionists will have a key role in ensuring that patients are offered longer appointments with their usual nurse or GP. They will be trained in strategies and forms of words to achieve this.

4 Data Collection

Participant study data will primarily comprise of self-reported questionnaires and GP patient records. Research teams at each site will be responsible for data collection including sending the questionnaires, collating, logging the data and entering the data onto the trial database and

collecting data from GP records. Letter and email reminders will be sent to participants who do not return questionnaires within 14 days. Participants may receive a further phone reminder or may be called if the primary outcome is incomplete.

4.1 Quantitative Outcome Measures

All outcomes are at the level of the individual patient and will be collected at baseline, 9 months and 15 months post recruitment.

4.1.1 Primary Outcome

The primary outcome is health related quality of life, measured using the EQ-5D-5L [59] at 15 months. This is a self-report measure which will be collected by paper questionnaires.

4.1.2 Secondary Outcomes

These patient reported outcome measures will be collected at baseline and 9 and 15 months post recruitment from patient questionnaires.

Burden of illness measures to assess quality of life, disease control and depression:

- Self-rated health (single item)
- Bayliss measure of illness burden in multimorbidity [60]
- Quality of disease management (composite measure of QOF achievement) [61]
- Hospital Anxiety Depression Scale (HADS) [62]

Burden of Treatment measures to assess the problems of poor coordination of care, multiple appointments and polypharmacy:

- Brief Treatment Burden Questionnaire
- Morisky Medication Adherence Scale (8 item) [64]
- Number of drugs prescribed
- Reduction in high risk drug combinations[65]

Experience of patient centred care, to assess the lack of holistic patient centred care:

- CARE measure and how well you know your doctor[66]
- Coordination of care (questions from LTC6 QIPP)
- Management of LTCs (PACIC) [67]
- Overall satisfaction (single item)

4.1.3 Socio-demographic measures

The following socio-demographic measures will be collected from self-reported paper questionnaires at the baseline timepoint only (prior to GP practice randomisation). These measures will allow comparison of population composition between study groups and study centres, and will also be used for subgroup analyses.

- Number of long term conditions

- Age (on date of invitation to participate)
- Gender
- Education
- Ethnicity
- Deprivation status – based on postcode which maps onto the index of multiple deprivation.
- Work status

4.1.4 Carer outcomes

The role of the carer in supporting a patient with multimorbidity is often neglected. In order to assess whether the change in GP management affects other aspects of the participant's care we request that the participant's carer also complete questionnaires about their experience and how it affects their wellbeing. Carer contact details and consent to complete brief surveys will be requested in a form which will be included as part of the initial patient invitation mailing pack. Carers will be requested to complete the survey at baseline, 9 and 15 months follow up.

Measures of strain on patient's carers:

- Carer Experience Scale [68]
- EQ-5D-5L [59] completed by carers
- Brief Treatment Burden Questionnaire for carers

4.1.5 Resource use

Resource use will be compiled from a combination of self-report measures in participants' follow up questionnaires at 9 and 15 months and electronic GP records examined at the end of the study. Participants will be asked to provide information concerning:

- Hospital admission and outpatient attendance.
- Use of health services in primary, community and secondary care

To simplify data collection, the questionnaires will ask whether participants have been admitted to hospital. If so, the researcher may phone the participant to obtain more detailed information about reason, length and place of stay if the information is not available in their GP notes.

GP records will confirm participants' resource use over the course of the 15 months that they were in the study. Researchers will request access to patients' records after 15 month follow-up data collection has been completed. In addition to the above data, the following information will be collected from GP records:

- Any health investigations the participant underwent

- All medications prescribed for the patient over the course of the study

Resource use information is required for the economic evaluation of the service. It is also a way of demonstrating changes in the process of care.

4.2 Data Management

4.2.1 Source data

Data will primarily be in the form of participant self-report paper questionnaires, logs collated from GP/nurse 3D computer template usage, extractions from patient records and case report forms. Research teams at each recruitment site will be largely responsible for the collection and monitoring of data from participants and practices within their areas. Overall responsibility of the study data will be with the Chief Investigator which can be delegated to the Trial Manager and Data Manager.

Patient, carer and practice staff contact details needed for day-to-day trial management will be held on a bespoke management database, designed and managed by the BRCT and held on secure servers at the University of Bristol. Since ID numbers will be accessible from this system, researchers will have unique logins and restricted access to the appropriate recruiting centre data only.

All paper questionnaires and records will be entered into a separate tailor-made database held on a central university server. The data is entered via a securely authenticated, web-based, commercial software system called REDCap. This database will only store anonymised questionnaire and CRF data. Study researchers will be given a unique login in order to access and input on this database. At least 10% of questionnaire data from each site will be subject to double entry and second checking to ensure quality and inter-rater reliability.

Qualitative data collection will be conducted and analysed by the qualitative researcher (CM) and will involve a variety of mixed media. Full details are provided in the Process Evaluation section of this document (section 7.6)

In accordance with REC requirements, regulatory authorities including monitors and auditors from NHS Trusts may request access to source data and documents for cross checking. This will be explained in the participant information sheet and a statement included as part of the written consent form to be signed by the participant.

4.2.2 Data Storage

Where possible, personal identifiable details will be removed from hard-copy documents and replaced with the participant's unique trial identification number. During the study, all hard copy documents containing patient identifiable data (e.g. consent forms) will be stored in (as a minimum) locked filing cabinets within alarmed, access restricted University buildings of each of the research centres. Only local research teams will have access to these locked cabinets.

Electronic data will only be accessible via a password protected database held on a secure server.

See section 11.3 for long term storage procedures at the end of the study.

5 Data Analysis of quantitative trial outcomes

5.1 Sample Size calculation

The study is designed to detect an effect size of 0.274 standard deviations in the primary outcome of the EQ5D-5L. Data about the variability of the new 5 level (5L) version of the EQ5D is currently more limited than for the well-established 3 level (3L) version. The standard deviation of the EQ5D-3L in the UK general population is 0.23, rising to 0.27 in the oldest respondents (aged over 75).[69]Hence an effect size of 0.274 would equate to a detectable difference of (0.274*0.27) = 0.074 on the EQ5D-3L, previously deemed to be the minimum important difference.[70] Although there are less data about the variability in the 5L version of the EQ5D than the 3L version, it seems wise to use this latest version of the EQ5D as it is likely to have greater sensitivity to change.

Based on data available from our previous studies, we estimate that 2.3% of adult patients will have multimorbidity in terms of 3 or more LTCs as defined in this study. This equates to about 108 patients in an average sized practice of 6000 patients i.e. 3456 potentially eligible patients in 32 practices. Assuming 40% of patients agree to participate (n=1382), 80% are followed up to 15 months, and an ICC of 0.03 for clustering at the practice level (based on the WISE trial)[31] this sample provides around 90% power at a 5% significance level to detect an effect size of 0.274 standard deviations in the EQ5-D measure between the intervention and control groups. This is considered a small effect size.

In practices with large numbers of potentially eligible patients we will randomly select a maximum of 150 potential participants, as described in section 2.5.2. After GPs have excluded ineligible patients we anticipate inviting about 110 patients per practice, on average. The number of patients initially selected will be reviewed following the optimisation phase

Efficacy data analysis

Data will be analysed in accordance with CONSORT principles and its extension for cluster randomised trials. Descriptive statistics will be used to summarise characteristics of both practice and patients and compare the balance across groups. We will take account of clustering by practice in all analyses using multi-level regression models. A full statistical analysis plan will be developed and agreed by the Data Monitoring Committee (DMC) and Trial Steering Committee (TSC) after the pilot phase and prior to undertaking any analyses of the main trial.

5.1.1 Primary analysis

Intention to treat analysis will compare groups using a linear multi-level regression model adjusted for baseline values, stratification/minimisation variables, clustering and other important co-variates such as age, number of long-term conditions, deprivation, depression. The results will be presented as the difference between group means and corresponding 95% confidence intervals will be derived.

5.1.2 Secondary and subgroup analysis

Multi-level regression models will be applied to evaluate differences between groups for the pre-planned analyses of secondary variables. These will be based on logistic or linear regression as appropriate.

We will use sensitivity analysis to examine the effect of missing data on outcomes based on different assumptions. We will conduct subgroup analyses using appropriate interactions terms to explore the effectiveness of the intervention in relation to age, number of long term conditions, index of deprivation and presence or absence of depression alongside physical health problems. These subgroup analyses will be hypothesis generating and will focus on interpretation of 95% confidence intervals rather than P-values. Subgroup analyses are likely to be insufficiently powered since the trial was not powered to specifically test these effects.

5.1.3 Use of anonymised data

Anonymised data will be used for the following:

i) Comparison of descriptive data for consenting vs. non-consenting patients

ii) Comparison of QOF performance in patient with LTCs with and without multimorbidity. This is to assess for any unintended consequences, ie. whether concentrating effort on patients with multimorbidity has any positive or negative impact on the care of other patients.

iii) Comparison of hospital admissions and deaths. We will explore the feasibility of obtaining data via anonymised records linkage (HES data and death registry) in order to examine the impact of the intervention on all eligible patients in participating practices, and also to compare the impact on patients with or without multimorbidity, without needing individual patient consent or access to identifiable patient data. Without these data, we will only be able to collect this information for patients who return questionnaires, and this analysis would lack power since the events (particularly deaths) are relatively rare.

6 Economic Evaluation

Economic analysis will be undertaken from the perspectives of:

a) NHS and personal social services (PSS)

b) Patients

We will also measure and value the time off work and usual activities.

Resource use data will be collected from self-reported patient questionnaires from questions of utilisation of primary, community and secondary care services and personal costs (including travel, loss of earnings and dependent care costs). These data will be supplemented by GP records and trial records where appropriate. Unit costs will be valued using national published sources such as Curtis [71] , NHS reference costs and the British National Formulary (BNF).

The set-up and training costs of the intervention will be identified and estimated separately from the running costs. The costs of each component of the intervention will also be estimated separately

from each perspective and when related to changes in a range of outcomes will give the cost consequences.

Cost effectiveness analysis from the NHS and PSS perspective will estimate the incremental cost per Quality Adjusted Life Year (QALY) gain. A QALY is a composite measure of health combining quantity and quality of life. QALYs will be estimated using the EQ-5D-5L.

Uncertainty will be addressed in sensitivity analyses and by using bootstrapping to estimate the net monetary benefit and a cost-effectiveness acceptability curve.

7 Process Evaluation

7.1 Background

Process evaluations of complex intervention trials are recommended by the MRC Framework [39] and have many potential purposes [72], but there is relatively little guidance on how best to design them. One of the applicants has recently published a framework for process evaluation design which emphasises the importance of explicitly stating the aims of the evaluation and the choice of processes to examine [72]. The aims of the mixed methods process evaluation in this project are:

- If the intervention is effective, to identify and document examples of good practice and strategies for successful implementation, and also practical difficulties in implementation and maintenance, in order to inform commissioning and other long-term implementation.
- If the intervention is ineffective, to identify if this is due to problems with the intervention (failure of intervention concept despite the intervention being delivered as intended) or problems with intervention delivery (implementation failure, which may occur at multiple points) [73].

The process evaluation will therefore explore issues of representativeness, intervention implementation, reach at patient level, nature and fidelity of intervention delivery, maintenance of the intervention over time, and patient perceptions of how care has changed. This will help to gain understanding about why the intervention worked (or did not work), and will inform and facilitate commissioning and other implementation of the intervention if appropriate.

The process evaluation will also include practices in the usual care group, in order to clarify what are the current practices in the management of multimorbidity patients. Given the recent changes in the NHS and GP contracts and structures, it is necessary to characterise what usual care is at the start of the trial and whether this changes over the intervention period so that we define what we are comparing the intervention to. This can also help to inform of ways of future delivery of the intervention.

7.2 Design

The process evaluation will be mixed methods, combining analysis of quantitative process data (such as patient characteristics, number of consultations, number of drugs prescribed) from all practices with an in-depth, comparative case study [74] in up to five purposively selected intervention practices, chosen to represent those in different settings and with different prior levels of

organisation of care for patients with LTCs. Data will be supplemented by interviews with commissioners.

There will be an optimisation study preceding the process evaluation of the main trial. The aim of the optimisation study is to help the main trial team optimise the intervention. This will be achieved by evaluating implementation of the different elements of the intervention to identify any implementation problems or divergence from the intentions of the trial. It will also allow the process evaluation methods to be used in the main trial to be piloted and evaluated. The methods will be as described below for the main trial but in smaller numbers i.e. 2 case study practices and some supplementary interviews and observations in the other 2 pilot practices

7.3 Methods and Setting

Up to five purposively selected case study practices will be chosen, to represent different settings and with different prior levels of organisation of care for patients with LTCs. Additional data regarding some processes may be collected from other practices participating in the 3D trial depending on fidelity and implementation issues identified during the course of the process evaluation. Information regarding usual care will be collected from all practices at the start of the trial and at the end of the intervention period, by questionnaire supplemented by interview if necessary.

Quantitative methods will involve the analysis of routinely available data on practice characteristics and data collected as part of the trial.

Qualitative methods will involve semi-structured interviews, focus groups and direct observation of these case study practices. If necessary, qualitative data will be collected from some other practices taking part in the 3D trial in response to particular issues that arise during the trial. These methods are described in detail below.

7.4 Sampling

Practices: Up to 5 study practices will be purposively selected to take into account geographical region, socioeconomic deprivation levels and different prior levels of organisation of care for patients with LTCs. Practices will be the main unit of sampling and within these case practices, we will sample a range of people (patients and staff) and events (consultations, appointment bookings) over a period of 15 months.

Practice staff: We will undertake approximately 40 interviews sampled purposively to reflect a range of relevant professionals including receptionists, practice nurses, GPs and Practice Managers. These will mainly be in the case study practices but may also include some interviewees from other practices taking part in the 3D trial.

Patients: Approximately 6 patients per case study practice and some from other practices participating in the trial (n= 30 total approx.), will be purposively sampled for heterogeneity in age, sex, socio-economic status and LTCs.

7.5 Recruitment

Staff: We will write to practice staff in case study practices and some other participating practices asking for consent to participate in an interview, and in some cases, to participate in recording and observation of a consultation with a patient. We will include an information sheet and consent form.

Patients: When consenting to participate in the trial, participants will be asked if they are willing to be approached by a member of the research team at a later stage to consider taking part in an individual or focus group interview and in the observation and recording of a consultation. If they agree, we will write to them with an information sheet and relevant consent form if they are sampled for interview.

7.6 Data Collection for Process evaluation

7.6.1 Quantitative data

Quantitative data on practice recruitment and representativeness, reach at patient level (whether or not patients receive the intervention), implementation of intervention elements and whether or not the actual process of care is different from usual care from the patient's perspective will be gathered as part of the main trial data collection (Box 1). Data on recruitment will be used to examine representativeness of participating practices to inform judgements about generalisability.

Box 1 Process evaluation quantitative questions and methods	
PROCESS: RESEARCH QUESTION	**DATA COLLECTION**
Recruitment: How representative are recruited practices?	Analysis of routinely available quantitative data on practice characteristics (comparing characteristics of recruited and non-recruited practices)
Reach at patient level: What proportion of targeted patients receive the intended assessment?	Analysis of quantitative data collected as part of trial (for practices in the intervention arm): Number of patients given a 3D card, receiving a comprehensive 3D assessment and components of this (e.g. quality of life discussion, mental health assessment, care plan, treatment for depression).
Evidence of intended changes in care. Is the process of care in intervention practices different from that in control practices?	Analysis of quantitative data collected as part of the trial (comparing practices in the intervention and control arms) e.g. number of appointments per patient; Continuity of care (COC measure of longitudinal continuity [75]); Number of contacts with hospital general physician; provision of pharmacy advice, number of drugs prescribed.

7.6.2 Qualitative data

We will collect qualitative data in the following ways see Box 2.

1. Observation/recording of training sessions for intervention practices
2. Interviews and focus groups involving patients/carers
3. Observation of practice setting and reception
4. Observation/recording of 3D consultations
5. Interviews with practice staff

Up to 8 interviews will be conducted with a range of practice staff in each case study practice over the course of the trial and some interviews in other practices approx. 40 in total

i) Semi structured interviews of lead GPs lead nurses and lead administrators will occur at two time-points

a. Early in the implementation, approximately 4 weeks after initial training to reveal whether and how practices plan to reorganise care to deliver the different elements of the intervention, appraise care at baseline, evaluate the adequacy of the training and attitudes towards the change in care processes.

b. Towards the end of the trial in order to elucidate whether and how practices maintain the reach and fidelity of the intervention over time, appraise how the intervention was delivered in the practice and how it affected their individual roles. In addition what where the barriers and facilitators of successful maintenance?

ii) Additional practice staff including receptionist, practice nurses and GPs (will also undergo semi structured interviews at 2 time points.

a. Soon after initial training to appraise care at baseline and to evaluate the adequacy of the training and attitudes towards the change in care processes.

b. After 3D reviews have been begun to appraise how the intervention was delivered in the practice and how it affected their individual roles. For nurses and GPs, also to evaluate a recently recorded 3D review.

Approximately 6 patients per case study practice and some from other participating practices (approximate total n = 30) will be invited to one focus group per practice during the intervention period. Some of these will be patients from usual care practices to assess how they perceive existing care. Patients from intervention practices will be asked about their perceptions of the intervention and whether it has changed their care. Towards the end of the intervention, some patients of intervention practices will undergo a semi-structured interview, which may be after a recorded consultation to assess how patients perceive the 3D reviews and to evaluate a recently recorded consultation. These interviews will be conducted at a time and place agreed by the participant and can include the patient's home or University building. At the end of the interview, participants will be offered a £5 gift voucher as a goodwill gesture for their time.

Non-participant observation of the training delivered to practices and completion of evaluation forms by participants and trainers will assess the response of practice staff to the intervention and the adequacy of the training.

Non-participant observation of appointment booking at the reception desk and by telephone will examine if and how the appointment system has been reorganised for participating patients.

A sample of 3D assessment appointments in case study practices and some in other practices, both intervention and control (up to 60 in total) will be audio or video recorded and/or observed to evaluate the nature and fidelity of this aspect of intervention delivery. Where possible, follow-on

interviews will also be conducted with the nurse or GP who delivered the consultation and the patient who received it to evaluate the consultation from their perspectives.

Box 2 Process evaluation qualitative questions and methods	
PROCESS: RESEARCH QUESTION	**DATA COLLECTION**
Usual care: How does organisation of care for patients with multi-morbidity vary across practices and over the timeframe of the trial?	Descriptive data about organisation of care and appointment arrangements collected from informal interviews at time of recruitment and by contact with practice representative later in trial
Initial response of practices to training: What is the response of practice staff to the intervention training? Whether and how do practices plan to or initially reorganise their care to deliver the different elements of the intervention?	Participant and trainer evaluation of all training sessions. Non-participant observation of some training sessions. Semi-structured interview with GP practice champion for 3D, lead administrator for 3D and lead nurse in case study practices and some other participating practices, soon after the initial training.
Nature and fidelity of the intervention: How is the appointment system reorganised (or not) to deliver continuity? What is the actual content of 3D assessments, and does it match what was intended by the research team? What aspects of the intervention seem to be most (and least) effective, and how does this vary with patient circumstances and practice context? How could the intervention be improved?	Non-participant observation of appointment booking at the reception desk and by telephone in case study practices. Audio or video recordings and/or observation of a sample of 3D assessment appointments in case study practices and some in other participating practices, including usual care practices Semi-structured interviews at 1 or 2 time points with practice champion, lead administrator, receptionist, practice nurses and GPs Review of log of contacts with hospital physician supplemented by brief interview if indicated
Maintenance: Whether and how do practices maintain the reach and fidelity of the intervention over time? What are the barriers to, and facilitators of successful maintenance?	Semi-structured interview with GP practice champion for 3D, lead administrator and lead nurse towards the end of trial.
Patient perspectives: How do patients perceive the changes to their care and what is their experience of the 3D consultations?	Semi-structured interviews and focus groups with up to 6 patients per case study practice and some other practices participating in the trial, purposively sampled for heterogeneity in age, sex, socio-economic status and LTCs. Interviews will in some cases follow observed consultations in order to evaluate the consultation.

7.7 Commissioners

We recognise that implementation of findings from health services research can be problematic, but will seek to facilitate implementation by designing our intervention to be highly pragmatic and potentially commissionable. We will therefore additionally interview a sample of 6 commissioners (2 from each study area) both before and after the intervention is introduced. Before, we will interview them about ways to ensure that the intervention is introduced in a way which lends itself to commissioning, to identify barriers and facilitators to commissioning this type of service, how the new approach would fit with current commissioning models which are likely to be mainly in disease-

specific service silos, and the advantages and disadvantages of different approaches to incentives (e.g. QOF-type targets, Local Enhanced Services etc.). Towards the end of the study we will interview the commissioners again, showing them the findings from our research, in order to discuss with them the most important messages, potential barriers to implementation and how to mitigate them, current commissioning priorities and policy changes and implementation tools to help to ensure that (if effective) the intervention is commissioned in future. This may be supplemented by interviews with additional commissioners at later workshop/dissemination events.

7.8 Data Analysis

Data analysis for the process evaluation will initially focus on the individual datasets. Quantitative recruitment/ representativeness from all practices will be analysed using chi-squared tests for categorical variables and t-tests or non-parametric tests for continuous variables, and will inform judgements about the generalisability of the findings. Failure to deliver the intervention to target patients is an important potential cause of lack of effectiveness for any intervention, and will be examined by determining what proportion of the target population actually received any or all of the intervention components, and how this varies between practices. Differences between intervention and control practices in terms of process of care will be analysed using the same regression analysis as for main trial outcomes (described above). These data (for example about number of appointments, continuity of care, patient centred care) will also help to characterise 'usual care' in the control arm practices.

For the optimisation phase, the focus of the qualitative data collection and analysis will be on practices' response to the intervention, any issues they have with implementation, and fidelity of their intervention delivery to patients. Analysis will employ the 'framework' method [76] in order to quickly feed into improvements to the intervention and analysis that may be required for the main trial.

For the qualitative data from the case study practices and other participating practices, analysis will take place alongside data collection to allow early analytic insights to inform ongoing data collection. Field notes from observation of training, appointment bookings and consultations will be coded alongside transcripts from recorded 3D consultations, interviews and focus groups, and used to characterise organisation and delivery of care in different contexts, as well as responses to, and implementation to the intervention. Emerging themes and theoretical ideas will be discussed and refined at team meetings throughout the research. The qualitative data from multiple sources, alongside the quantitative data, will allow us to build up a 'thick description'[77] of each case study site, helping us to understand whether, how and why the intervention worked in each practice. Analysis of these data will enable us to elucidate the internal processes and interactions (e.g. staff-staff, staff-patient) that impact the delivery, implementation and maintenance of the intervention. Across the cases, analysis of both qualitative and quantitative data will allow us to identify factors which are plausibly and/or consistently related to successful or unsuccessful delivery of the components of the intervention and changes to the experience of care by patients.[73,74] As analysis progresses, the fit of the data with models of patient centre care[40] will be evaluated, for example, giving attention to whether and how the intervention enhances the therapeutic alliance between patient and doctor. The final stage of analysis will be to draw together the findings from the broader quantitative analysis and the in-depth case studies to create an understanding of why

the intervention did (or did not) work, why this happened, and identify implications for longer-term implementation if appropriate.

7.9 Unintended consequences

There is a theoretical concern that focusing effort on one group patients (in this case multimorbidity) could lead to reduced efforts and reduced quality of care in the other patients.[14] In order to compare performance in terms of the QOF in patients with and without multimorbidity, we will collect anonymous data about the performance against QOF targets for all patients in participating practices with *any* of the index conditions (individually or in combination) that are included in our definition of multimorbidity, using electronic download from medical records. We will compare QOF performance in patients with and without multimorbidity in the year before and the year after the intervention, to check whether concentrating effort on patients with multimorbidity has any positive or negative impact on the care of other patients.

Similarly, we will explore whether it is feasible to obtain anonymised data about deaths and hospital admissions for all patients in participating practices, as this would enable us to compare these outcomes in patients with and without multimorbidity in intervention and control practices (see section 5.1.3)

8 Research Governance

The trial will be conducted to protect the human rights and dignity of the participant as reflected in the 1996 version of the Helsinki Declaration. Patients will not receive any financial inducement to participate. In order to protect the trial participants the following provisions will be made/upheld; the trial has been designed to minimise pain, discomfort and fear and any foreseeable risk in relation to the treatments involved; the explicit wishes of the participant will be respected including the right to withdraw from the trial at any time; the interest of the patient will prevail over those of science and society; provision will be made for indemnity by the investigator and sponsor.

The trial will be registered with a publicly accessible trial register (Trial registration number: ISRCTN06180958)

This study will be conducted in accordance with principles of good clinical practice (GCP) and a favourable ethical opinion from the appropriate Research Ethics Committee and local NHS R&D approvals from the appropriate trusts will be obtained prior to commencement of the study.

8.1 Ethical conduct

We are aware that patients with multimorbidities require quite complex care. However patients will not be denied any form of care that is currently available in the NHS by participating in this study. Patients from usual care practices will still have access to NICE recommended treatments and local provision of services. Whereas patients from intervention practices will still have full access to their GP and secondary care services in addition to their 6 monthly 3D assessments.

This study raises the following ethical issues:

(i) Cluster level randomisation: This is a complex organisational intervention, therefore randomisation needs to be at the level of the organisation, ie the practice. If one tried to randomise by individual patients, there would be problem of contamination (GP trained in the new way of working would change their 'usual' care practices and the study would not be able to test the effect of practice re-organisation).

(ii) The role of individual consent: Cluster randomised trials have the issue that all eligible patients in 'intervention' practices will receive the intervention even though they will not be asked to give individual consent. This is justified because the intervention has few risks, and it is normal for general practices to try out new ways of working with the aim of improving patient care, without needing individual patient consent. However, patients will be asked to give consent to complete questionnaires and to allow researchers to have access to their notes, and only consenting patients will be included in the analysis of the main trial outcomes.

(iii) Use of anonymised data: Anonymised data will be used for some analyses e.g. comparisons of consenting and non-consenting patients.

(iv) Patients lacking capacity to consent: Because we wish to have broad inclusion criteria we will ask carers to help with completion of questionnaires where appropriate. In England, we will seek assent from legal guardians or consultees where potential participants do not have capacity to give consent themselves. In Scotland, adults lacking capacity to consent will be excluded from the study

8.2 Safety Assessment and Adverse Events

The study will monitor the occurrence of any serious adverse event/reaction which arises whilst the participant is taking part in the trial.

8.2.1 Definitions

An **adverse event** is any **unexpected** effect of an untoward clinical event affecting the participant. This is classed according to severity i.e.

a) Non-serious adverse event (AE) – which includes discomfort or a slight worsening of symptoms

b) Serious Adverse Events (SAE) – which may be particular harmful, dangerous or require hospitalisations.

An SAE is defined as one of the following:

1. results in death;
2. is life threatening;
3. requires hospitalisation or prolongation of existing hospitalisation;

4. results in persistent or significant disability or incapacity;
5. consists of a congenital anomaly or birth defect;
6. is otherwise considered medically significant by the investigator.

Given that patients with multimorbidity may be heavy users of secondary care services, new medical diagnoses, hospital admissions and deaths are expected. New medical diagnoses and hospital admissions will not be investigated in detail unless it appears that they may have been related to the intervention of the research process, although the number of admissions will be collected, reported and monitored. We aim to investigate every death formally by writing to the participants GP asking for information about the circumstances of the death and whether there is any possible connection with the study intervention or research processes.

Hospitalisations and deaths will be counted as part of the service use data and reported as part of the trial analysis.

Serious Adverse Reaction (SAR) – is an SAE which is thought to be related to the study intervention or research processes.

Where any person related to the trial (participant; friend, carer or relative; GP or other clinician; research team member) believes that a SAE may have been related to the intervention or the research process, this will be investigated as a potential SAR (see below).

8.2.2 Detecting and recording AEs and SAE/Rs

Adverse events and reactions may be reported by several methods:

1. Directly by the participant (ie by email, phone call or voice mail message)
2. From the participants follow up questionnaires
3. Indirectly from family members, carers, guardians or representatives
4. From the participants GP practice (following the patient's 6 monthly assessment or information passed on from hospitals).

Participants and GP practice staff will be asked to notify their local research team of any serious adverse reaction which they believe may have occurred **as a result of** the trial intervention or the research process. On notification of any such a potential serious adverse reaction which may be related to the research process or intervention, a researcher should complete serious adverse event/reaction reporting form within 5 working days, paying specific attention to information regarding the timescale of events i.e. when the event started, were there any specific changes to medication or behaviour preceding the event. Further information should be requested from the participant or GP/practice nurse as necessary.

The research team may become aware that a patient has died having been notified by a clinician or relative, or through regular checks of the general practice records. They will send the deceased

patient's GP a SAE/R reporting form as above, which includes information about the cause and circumstances of the death.

All completed forms should be securely sent to the Trial Manager who will pass them onto the trial clinician to review.

8.2.3 Assessment of relatedness and expectedness

The trial clinician will make the following decisions

1. Whether the adverse event is an AE or SAE or SAR

2. How related is the event to the study intervention and/or research processes, according to the following definitions:

Unrelated – where an event is not considered to be related to the study intervention or research processes

Possibly – although a relationship to the study intervention and/or research processes cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible

Probably – the temporal relationship and absence of a more likely explanation suggest the event could be related to the study intervention and/or research processes

Definitely – Known effects of the study intervention and/or research processes, or based on challenge testing, suggest that study intervention is the most likely cause.

3. Expectedness of the event. Is the event an anticipated medical event even if the research had not been taking place?

4. Is further action required?

8.2.4 Reporting requirements for SAE/Rs

All reporting of SAEs of a related and unexpected nature (i.e. SARs) will follow regulatory reporting requirements as set out in article 17 of the EU directive 2001. These will be reported to the sponsor immediately and will be reported to the REC within 7 days of the Trial Manager becoming aware of the event. Any relevant further information will be subsequently communicated within 8 days. In addition all investigators will be notified.

The TSC will be notified immediately of all SARs thought to be treatment or research related. Potential SAEs which after review are not thought to be treatment or research related will be brought to the TSC's attention at their next scheduled meeting. The numbers and details of all AEs SAEs and SARs will be reported regularly to the Trial Management Group, Trial Steering Committee and Data Monitoring Committee.

8.3 Monitoring

Research procedures and progress will be constantly monitored by the Trial Management Group.

The research team will establish processes to enable practices to regularly monitor the extent to which they are implementing the intervention as planned. This will include regular audits of the number of patients who have been invited to a 3D assessment, the proportion that have attended both assessments, and the continuity of care provided. In addition, each practice will have a 'GP champion' who will informally monitor progress in order to ensure that the intervention is delivered as intended.

By participating in the trial, patients will receive a more intensive level of monitoring than that normally received in primary care.

All aspects of the study will undergo regular external monitoring by the independent Trial Steering Committee (see section 9.5) and Data Monitoring Committee (section 9.6). It may also be open to audit and monitoring from local NHS R&Ds.

8.4 Patient and Public Involvement

During the development of the proposal, two patient and carer open forum meetings were held whereby several support groups for various LTCs, carers and patients groups from GP practices were invited. Patient and Public Involvement (PPI) coordinators facilitated discussions aimed at asking patients directly what their health issues and concerns were and what services they would like in order to improve management of their conditions. This helped to inform the design of the intervention.

15 people were willing to continue being involved in the research and these will form a patient involvement group. The aim would be to meet approximately 4 times a year to advise on study patient information leaflets, questionnaire design, ethical issues, recruitment approaches, dissemination of results and impact. This group will be facilitated by CM and will be funded to attend PPI training workshops. Reimbursement will be provided in line with INVOLVE guidance.

Two members of this patient group, along with Prof James Goodwin, Head of research at Age UK will sit on a research advisory group and Trial Steering Committee whose role is to oversee the management of the research. Another member will be invited to contribute to the qualitative data analysis by helping to identify themes and commenting on findings. Therefore service users and patients will be directly involved in the research design, management, and analysis of the study.

We will take advice and use contacts within long term conditions groups to help reporting of results and dissemination of the research findings on their newsletters and websites, which will greatly enhance the relevance and reach of the study.

8.5 Confidentiality

All eligible participants will be allocated a unique trial identification number. This number will be used to identify patients throughout the study. Where possible, personal identifiable data will be removed from all collected data and replaced with the trial id number, thereby providing a level of pseudo-anonymisation. Only researchers needing to make direct contact will have access to the password protected database which links patients' personal details with their identifier.

Clinical information about identifiable patients will not be released without written permission from the participant. The exceptions are a) if the researcher is concerned for the participant's safety or well-being or b) if required for monitoring and auditing by the sponsor, regulatory authorities or by the REC or c) release of information to clinicians who are entitled to be aware of it as part of the patient's direct clinical team e.g. their GP or GP practice staff.

8.6 Data Protection

All collection, storage, processing and disclosure of personal information will be performed in compliance with the Data Protection Act 1998. All investigators and study staff will uphold the Act's core principles. Any communications, reports or published results will not contain any personal data that could allow identification of individual participants.

All computers used to collate data will have limited access measures via user names and passwords. Electronic mobile devices used to collect data will be encrypted. Databases and servers are stored in right-restricted areas with limited access. All data will be stored in locked facilities within secure offices.

9 Trial Management

9.1 Funding

Research funding has been secured from NIHR Health Services and Delivery Research Programme.

9.2 Sponsorship

The University of Bristol will act as sponsor for the trial. The sponsors contact is Dr Birgit Whitman, University of Bristol, Research and Enterprise Development, Senate House, Bristol, BS8 1TH.

9.3 Insurance and Indemnity

Normal NHS indemnity procedures will apply. The University of Bristol will also provide relevant public liability cover, as detailed in the certificate of insurance.

9.4 Trial Management Group (TMG)

The Trial Management Group will meet regularly (every 6 -8 weeks) in order to ensure that the three study centres are working consistently, meeting study targets and adhering to the study protocol. The group will consist of the CI, Trial Manager, PI and researchers from each of the recruiting centres with input from other members of the research team where necessary. Regular progress regarding study recruitment, retention, issues or complaints and adverse events will be reported and discussed.

9.5 Independent Trial Steering Committee (TSC)

An independent Trial Steering Committee will be convened comprising of an external academic chair (who is also an academic GP), at least two other independent members (including an independent statistician or trial methodologist and an independent clinician with relevant experience or interests), two patient representatives, the CI, PIs and other key members of the study research team. The TSC will meet at least annually (face-to-face or by teleconference) or more frequently at the request of the chair. The TSC will provide external supervision to the study and monitor the overall trial progress, adherence to the protocol and the implications of any new information (e.g. research articles or policy changes).

9.6 Data Monitoring Committee (DMC)

This committee will comprise of an independent chair and at least two other independent members including an independent statistician and a clinician with relevant interests. The CI, Trial Manager and Trial statistician will report to the DMC. The remit of the DMC is to monitor the trial data, in particular to quality control and quality assurance of data collected; the progress of the trial, including recruitment and retention rates and adherence to the trial protocol. A key role is to ensure that the dignity, rights, safety and well-being of the study participants are maintained at all stages of the trial. All adverse events will be reported to the committee which can have direct access to source data and documentation. Where possible the DMC will convene prior to the TSC and will report their recommendations to the TSC.

9.7 Advisory Group

An advisory group will be convened to ensure the research takes account of developments in the NHS. Prof James Goodwin (Head of Research, Age UK), Ms Jane Whittome (Head of Programme for Long Term Conditions for NHS Improving Quality), and Dr Kevin Gruffydd –Jones (RCGP) have agreed to join this advisory group, which will also include the chair and lay members of the TSC and will meet on the same day as the TSC to minimise costs and make best use of people's time.

9.8 Investigator responsibilities

Prof Chris Salisbury is the Chief Investigator with overall responsibility for the conduct of the trial as well as specific responsibility for the local running of the lead recruiting site. In addition, principal investigators will be responsible for the local running of the study at the remaining two recruiting centres (Pete Bower and Steward Mercer).

Sara Brookes (Senior Lecturer in Medical Statistics) will supervise the statistical analysis and provide trials methodology expertise. Sandra Hollinghurst (Senior Lecturer in Health Economics) will lead on economic methods. Cindy Mann (Senior Research Nurse) will conduct the process evaluation under supervision of Ali Heawood (Senior Research Fellow) and Bruce Guthrie, and will co-ordinate the PPI and advisory groups.

Stewart Mercer (Professor of Primary Care, Univ. of Glasgow) is an academic GP who will act as PI for Glasgow practices. Bruce Guthrie (Professor of Primary Care, Univ. of Dundee) is an academic GP

with an interest in multimorbidity, guidelines and polypharmacy. He will co-lead the process evaluation with Ali Heawood.

Pete Bower is Professor and Head of the Centre for Primary Care at University of Manchester. He has expertise in trials and mixed methods research and a focus on mental health, multimorbidity, and service delivery. He will be PI for Manchester practices.

Other co-applicants Imran Rafi (Chair of Clinical Innovation & Research Centre, sits on RCGP council) and Adriana Gjini (NHS England, Public Health Consultant) will advise on the direction and progress of the study.

Investigator responsibilities (such as obtaining informed consent, investigator documentation and data collection) may be delegated to an appropriate member of study site staff such as Trial Manager or Trial Coordinators. Coordination between the sites is the responsibility of the Chief Investigator and Trial Manager.

10 Dissemination and projected outputs

This project will demonstrate whether or not the new approach to managing multimorbidity in general practice is effective and cost-effective. Our hypothesis is that the new approach will improve patient outcomes in terms of health related quality of life, reduced illness and treatment burden and improved patient experience of well-coordinated person centred care. We anticipate that the intervention will be broadly cost neutral or even reduce costs for the NHS as a whole. There will be an increased cost from longer consultations in general practice and the financial incentive to practices to provide these, but this may be offset by fewer recall appointments for different individual conditions, fewer prescriptions and possibly fewer hospital appointments or admissions.

The project will seek to maximise the impact of the research by adopting a model of knowledge transfer based on the WHO knowledge transfer framework for ageing and health. This identifies 6 critical factors which are known to influence research impact. These factors will be addressed by constructing an advisory group consisting of academic leads from the study and potential users, to create an early and continuous dialogue between investigators and beneficiaries. Age UK have agreed to support this group. The academic members of this group will have expertise in the presentation of evidence to a wide range of audiences at national and international conferences focused on multi-morbidity; they will be complemented by users from the health and social care sectors, interested charities and the policy sector who have experience in the care of those with multi-morbidity, plus older people themselves, in accordance with the guidelines of the NIHR Age and Ageing Group. The group will identify and develop opportunities for the dissemination and exploitation of research findings and insights from the study, to a wide variety of audiences as described above.

As part of this research project we will produce guides for commissioners and for practices to enable them to implement the new approach speedily and widely throughout the country, if it is effective. Our collaboration with the RCGP Clinical Innovation and Research Centre will facilitate wide

dissemination to practices, and the backing of the RCGP will help to generate momentum to encourage practices to take up this new approach.

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

10.1 Dissemination to Patients

We will produce a short newsletter of the study results which can be distributed to all trial participants. The study results will be made available on the study website. With the help of the University of Bristol press office, we will design press releases and distribute then to local and national newspapers, websites and patient organisations for long term conditions (e.g. Diabetes UK, British Heart Foundation). We will take advice from our patient representatives an engage their support in disseminating findings. This includes the use of social media such as Twitter which can point people to the results on the study website.

10.2 Dissemination to Health Care Professionals

One of the co-applicants (IR) is a member of the Royal College of General Practitioners (RCGP) Clinical Innovation and Research Centre (CIRC). In addition to helping to identify practices to participate and advising on the development of the intervention, CIRC will also help to publicise the study findings to the RCGP's 42,000 members. This can be achieved through its communications network, hosting a page about the study on the RCGP website and the production of paper and online good practice aids and tools. In addition, a national workshop on Multimorbidity will be hosted by CIRC to highlight the research and disseminate the study findings.

10.3 Dissemination to Commissioners and Policy Makers

Commissioners and policy makers will be invited to the CIRC national workshop as described above. They will be made aware of articles in the lay, professional and academic press. Policy and key decision makers will be targeted using co-applicants individual networks. A guide for commissioners will be produced and published with the help of the RCGP. The full NIHR project report will include an executive summary and a set summary powerpoint slides aimed at NHS managers.

10.4 Dissemination to academics

The results of this study will be submitted to peer reviewed, high impact medical journals and presented at academic conferences. We envisage, as a minimum, research papers on the study protocol, the randomised trial outcomes, an economic analysis of cost effectiveness, patient experience of the new intervention and usual care, and the process evaluation. It is the intention of the trial team to publish the main study results within a year of study completion. The final project report will be made available on the NIHR website and published in the NIHR journal series.

11 Study conduct and end of study responsibilities

11.1 Protocol Amendment

Any changes in research activity procedures, except those necessary to remove an apparent, immediate hazard to the participant, will be reviewed and approved by the Chief Investigator.

Amendments to the protocol will be submitted to the REC and NHS R&Ds for approval. The sponsor will also be notified at this point.

Protocol amendments may be substantial (requiring full review and favourable ethical opinion from the REC) or minor (not requiring review). Only once the amendment has been approved by REC and trust R&Ds (or acknowledged in the case of a minor amendment) can the amended protocol be implemented.

11.2 Protocol Violations and Deviations

Researchers or investigators should not implement any deviation from the protocol without agreement from the Chief Investigator and with REC and R&D approval, except where necessary to eliminate an immediate hazard to trial participants.

In the event that a researcher inadvertently or needs to deviate from the protocol, the nature and reasons for the deviation will be recorded in a CRF or filenote to be kept in the study site file and a copy sent to the trial manager for the Trial Master File. If this necessitates a subsequent protocol amendment, this will be submitted to the REC and trust R&Ds for review and approval if appropriate.

11.3 End of study Archiving

All study documentation will be kept for a minimum of 5 years after the end of the final analysis of the study. All paper records will be stored in secure university storage facilities. Personal identifiable paper records (hard copy consent forms) will be kept separate from anonymised paper records (questionnaires) and will be stored in locked filing cabinets in locked offices. All electronic records will be stored on password protected servers on secure computer networks in the University of Bristol.

11.4 End study

Investigators and/or the TSC have the right at any time to terminate the study for clinical or administrative reasons.

The investigators, with the advice of the DMC will establish a set of criteria for stopping the study prematurely.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is stopped early. The investigators will inform participants and ensure that the appropriate follow-up is arranged for all involved.

A draft final report and a final summary report is required by the funder within 14 days after the completion date of the programme or date of termination.

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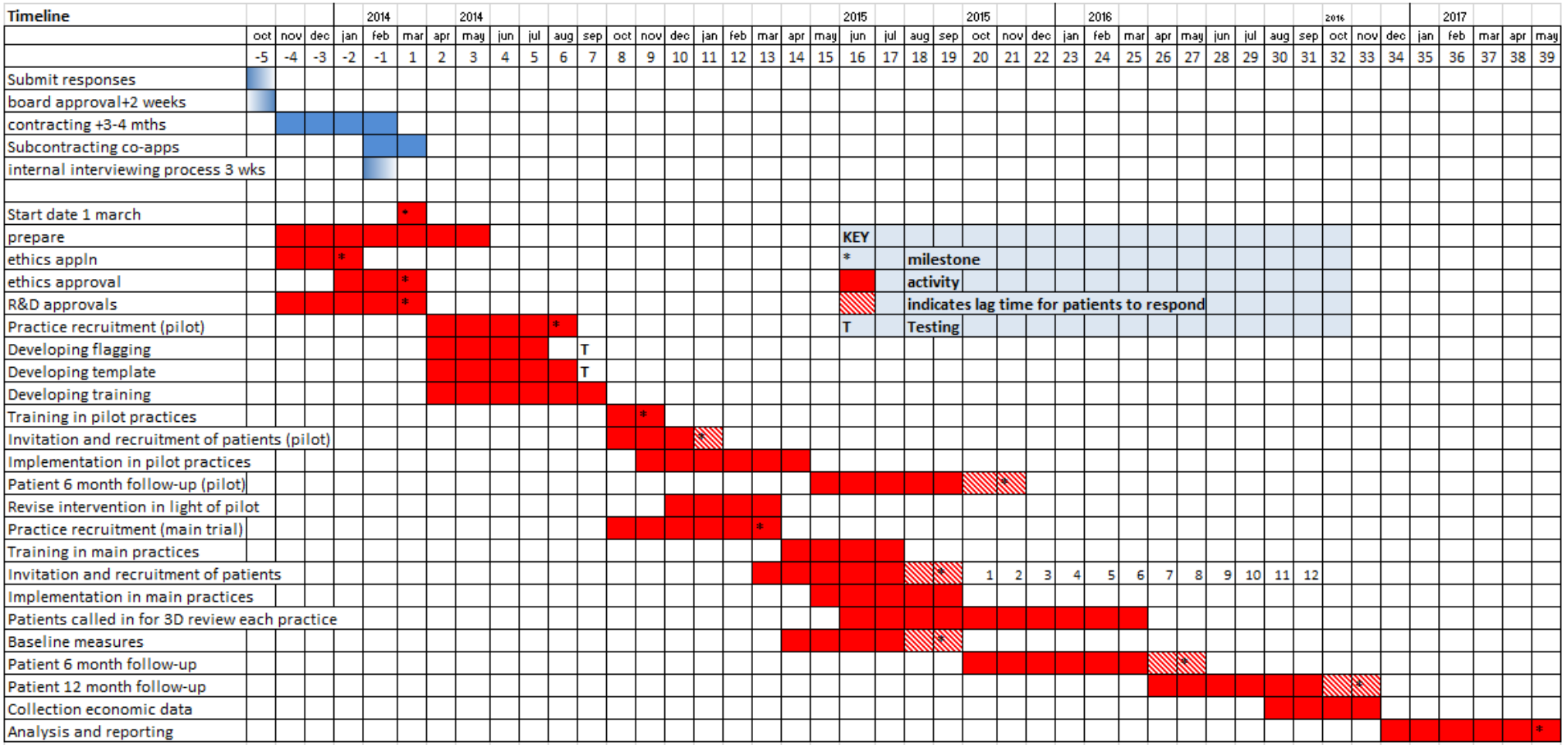
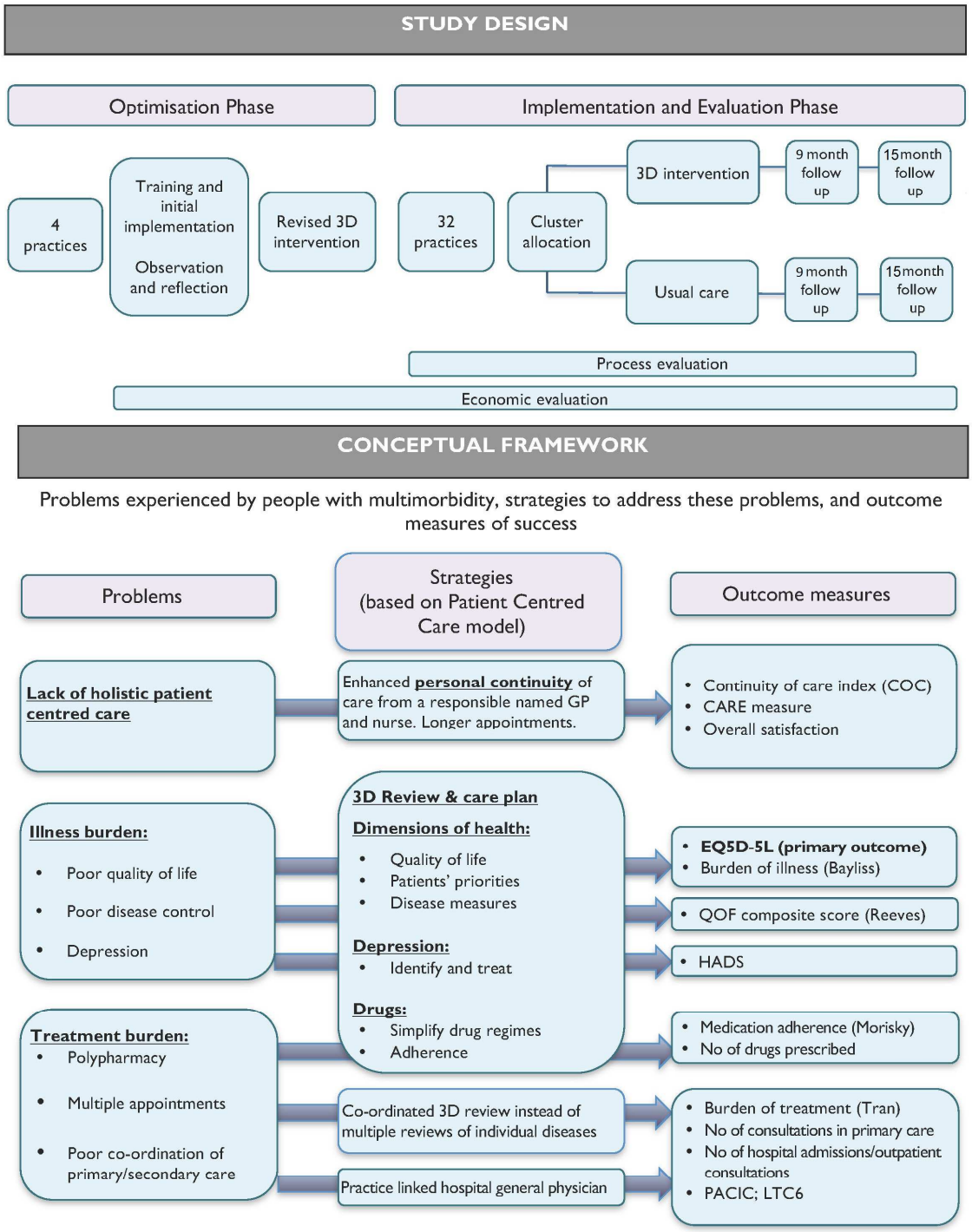
Appendix B – Trial Timeline



Appendix C – Study Flow Diagram & Conceptual Framework

Flow Diagram. HS & DR project 12/130/15
Improving the management of patients with multimorbidity in general practice. Salisbury et al.



Appendix D – Participant flowchart