Full title of project
Better guidelines for better care: accounting for multimorbidity in clinical guidelines

Aims and objectives
The aim of this study is to test the methodological feasibility of new approaches to summarising and creating evidence for guidelines for the management of people with multimorbidity. There are two specific objectives:

1. To systematically collate and summarise the evidence of benefit, harm and cost effectiveness for guideline recommendations for three common conditions, including where recommendations are mutually reinforcing or contradictory, in order to examine the value and feasibility of making existing evidence and guideline recommendations more useful for people with multimorbidity.
2. To develop and evaluate exploratory modelling methods to estimate expected benefit, time to benefit, risk and healthcare costs for people with selected multiple conditions, in order to examine the value and feasibility of new approaches to evidence creation for guidelines for people with multimorbidity.

Background
Guidelines have significantly improved the care of people with chronic disease, but they usually focus on single diseases and seldom explicitly account for people with multiple conditions. This reflects the way in which clinical evidence is created, but generates problems in using guidelines in everyday practice where multimorbidity is common (and is the norm in older people). We are currently examining the prevalence of multimorbidity using data on the presence of 40 chronic conditions from a large primary care clinical dataset for 1.75 million people. Figure 1 shows the number of conditions that people with selected common morbidities have (in press). The majority of people with any common chronic condition are multimorbid. For example, 81,586 (4.6%) people in the dataset have coronary heart disease (CHD), of whom 93% have at least one other chronic condition. People with CHD have a median of 3 other conditions, and 21% have 5 or more. Some of these other conditions are cardiovascular (52% have hypertension, 22% diabetes, and 14% cerebrovascular disease) but many are not (25% have a painful condition, 20% have active depression, and 13% chronic obstructive pulmonary disease [COPD]).

In parallel with multimorbidity, polypharmacy is also common. Using a database of all community dispensed prescriptions for the ~400,000 residents of the Tayside region of Scotland, we have shown that 30.2% of over-65s are currently prescribed 5 or more drugs, and 10.0% are prescribed 10 or more (20% and 4.5% of those aged 45-64 – unpublished data). Of the 86,665 people in Tayside currently...
taking any cardiovascular drug (defined as those in BNF chapter 2), 62% are taking 5 or more drugs in total, and 19% 10 or more. 46% are co-prescribed one or more central nervous system drugs (BNF chapter 4, most commonly analgesics 31% and antidepressants 18%), 38% a gastrointestinal drug (BNF chapter 1), 33% an endocrine drug (BNF chapter 6), 14% a musculoskeletal drug (BNF chapter 10, most commonly NSAIDs 8%) and 13% a respiratory drug (BNF chapter 3). Decision making for people with multimorbidity is therefore difficult.5 There is often no clearly ‘correct’ course of action, because of complex trade-offs between the benefits and risks of different treatments in a particular individual, and between clinical evidence and patient preference. 6, 7

In the UK, NICE guideline recommendations for individual diseases are rational in that they are based on robust synthesis of clinical and economic evidence. However, although each recommendation may be rational, the overall treatment regime may be harmful or impractical,7 because guidelines rarely attempt to account for other conditions except where there is major overlap in targeted outcomes (as happens with diabetes and CHD guidelines), or where there is specific trial evidence (as is the case with beta-blocker use in people with heart failure and COPD).8, 9 As a result, for an individual with several conditions, guidelines may make multiple, sometimes contradictory recommendations to prescribe chronic drug or non-drug therapy. Boyd et al have demonstrated this for US guidelines by examining recommendations for an older person with 5 conditions - COPD, type 2 diabetes, osteoporosis, hypertension, and osteoarthritis. Only one of the five US guidelines examined explicitly acknowledged potential co-morbidity, and they cumulatively recommended 12 drugs with a number of predictable drug-drug interactions, as well as sometimes contradictory non-pharmacological treatments.9 Additionally, although multimorbidity is strongly associated with higher mortality and the benefits of many preventive treatments accrue relatively slowly, guideline recommendations rarely explicitly consider applicability to individuals with limited life expectancy.

There is therefore a need to design new forms of clinical guidelines and evidence summaries that support informed treatment initiation and cessation in people with multimorbidity. The main target audience is clinicians with overall responsibility for a patient rather than a disease focus (currently more often doctors than nurses, and usually generalists like GPs and geriatricians). Guideline methodology work in the past has focused on robustly and transparently turning evidence into evidence-based single recommendations. How best to summarise evidence and present recommendations to different audiences has only recently received comparable attention. Examples include NICE work on developing treatment algorithms to display individual recommendations for a single condition more coherently, and the €2.9M EU-funded DECIDE project led by ST with PA as a co-applicant, which is developing and evaluating new guideline evidence summaries appropriate for different users, including clinicians, policymakers and the public. However, this work has been single disease focused, and therefore typically does not address multimorbidity or facilitate comparison of the evidence base across conditions. This study will extend existing work by exploring the methodological feasibility of alternative approaches to guideline development, and specifically will examine the extent to which existing guideline recommendations are synergistic or contradictory, and explore how best to model benefit and harm in the context of multimorbidity. This will inform future NICE guideline development and implementation of guidelines for people with multimorbidity.

**Need for the research**

A major health services policy concern worldwide is how best to manage the increasing number of people with long term conditions resulting from ageing populations and increased survival with chronic disease (sustained interest and intent). 2, 3, 8, 10 The majority of people with any chronic disease are multimorbid, and rates of multimorbidity are rising.2 Multimorbidity matters because it is strongly associated with higher mortality, lower functional status, worse health-related quality of life, and
higher levels of healthcare service use and costs (including emergency and potentially preventable admissions).\textsuperscript{3,11,12} Managing people with multimorbidity appropriately is therefore a requirement of a high-performing healthcare system. However, because the evidence base that underlies clinical guidelines remain largely organised by disease,\textsuperscript{8} there is a mismatch between guidelines and decision making for individuals with multimorbidity. Although individual guideline recommendations are rationally developed, their cumulative effect may not be in an individual’s best interests because recommendations are sometimes contradictory,\textsuperscript{9} drug interactions can cause harmful effects or reduce benefit,\textsuperscript{13,14} and the burden on patients of attempting to adhere to complex treatment and care regimes can be overwhelming.\textsuperscript{5,15} Additionally, people with high mortality and limited life expectancy are unlikely to benefit from treatments with relatively long ‘pay-off’ times (\textit{health need}).\textsuperscript{9,10,16}

The study will focus on developing methods necessary for creating guidelines that are tailored to individual patients and the multiple conditions they have, rather than disease focused.\textsuperscript{8} To our knowledge, this has not been systematically attempted by any organisation developing guidelines, although NICE has identified it as a priority for development (\textit{capacity to generate new knowledge and expressed need}). The study will therefore address the NIHR HSR priority to make better use of existing knowledge by carrying out research to improve the use of evidence in services (\textit{organisational focus consistent with HSR mission}). The project is a multi-disciplinary collaboration between academics, NICE and NHS clinicians which will ensure both rigour and a clear focus on NHS needs and longer term implementation (\textit{generalizable findings and the prospects for change}).

\textbf{Methods}

The aim of this study is to test the methodological feasibility of new approaches to summarising and creating evidence for guidelines for the management of people with multimorbidity, by examining the extent to which existing guideline recommendations account for multimorbidity, the value of consistently summarising existing evidence in terms of benefit and harm to allow more explicit comparison, and how best to model benefits, harms and healthcare resource use and costs in the context of multimorbidity. The findings will inform future NICE guideline development. A Guideline Development Group (GDG) will be convened using existing NICE procedures for ensuring inclusion of an appropriate spectrum of professional and public representation with expertise across the included conditions. The GDG will have between one quarter and one third lay members to ensure that public/patient perspectives are robustly represented. The GDG will form the overall project steering group, will have significant public representation, will make decisions about the focus of the study and which guideline recommendations to focus on for each objective, and inform interpretation of the findings and their implications for future NICE guideline development. The GDG will be chaired by one of the NICE recruited members, independent of the research team. The first GDG meeting will define the scope in terms of the phase 1 work and the treatments to be included for the three selected guidelines, with subsequent meetings reviewing the evidence collated and created, and examining their usefulness in guideline development.

\textit{Methods overview}. A key problem faced by clinicians is that current NICE guideline summaries recommend treatments without usually or consistently providing data on relative benefit and harm. The latter are usually detailed to varying degrees in the full guideline, but few clinicians use this, partly because it is intended to be a comprehensive account of guideline development rather than a summary document. When making decisions for people with multimorbidity, clinicians are therefore faced with a set of recommendations that do not distinguish between treatments with very large benefit and those with smaller benefits, and therefore do not help clinicians and patients to prioritise treatments in the face of multiple morbidities, high treatment burden and contradictory recommendations.
Objective 1 work will collate evidence of relative benefit and harm for chronic treatment recommendations in the selected guidelines and explicitly identify where recommendations are mutually reinforcing or incompatible, in order to allow different recommendations to be more directly compared in a way which supports clinical decision making. This will be valuable in itself, but implicit in this approach is that existing evidence applies equally to patients with and without multiple co-morbidities which is unlikely to be true. Rather, the presence of other conditions may mean that treatments are more effective (for example, because the baseline risk of future events is higher) or less effective (for example, because life expectancy is significantly reduced). For selected key treatment recommendations, objective 2 work will use economic modelling to extend this approach to more formally estimate relative benefit, harm and healthcare resource use in people with co-morbidities, in order to examine the feasibility of incorporating such modelling into guideline development.

**Guideline and recommendation selection.** The study will use guidelines for type 2 diabetes, heart failure and depression. These three conditions:

- Are individually important because they are common and are associated with a large burden of population morbidity and health service resource use;
- Are commonly co-morbid (table 1);
- Have a recent NICE guideline with economic modelling carried out for at least some of the individual treatment recommendations;\(^{17-20}\)
- Include both physical and mental health conditions where co-occurrence is known to worsen outcomes of both conditions,\(^{21}\) and where there are some published trials of the effectiveness of treatment of physical and mental health conditions in the presence of the other;\(^{22}\)
- Include a physical condition where treatment is commonly long-term and preventative (type 2 diabetes) and one where life expectancy is much reduced but treatment has major benefit over short periods (heart failure, particularly moderate/severe left ventricular systolic dysfunction).

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<tr>
<th>Condition (prevalence %)</th>
<th>% of row condition who also have:</th>
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<td>Heart failure (1.1)</td>
<td>Heart failure</td>
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<td>Diabetes (4.3)</td>
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<td>Depression (8.2)</td>
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* Based on GP morbidity coding and prescribing data from 315 practices with 1.75 million registered patients

To ensure that we focus on an important and feasible set of recommendations during the whole study, we will use the GDG in the initial phase of the study to select key recommendations from all three guidelines for detailed examination in objective 1 (for example, focusing on chronic treatment recommendations that are applicable to all or nearly all people with the condition rather than diagnostic recommendations or treatment recommendations for small subsets), and to select a small number of recommendations for the economic modelling in objective 2 (for example, focusing on those for which there are existing models and reasonable data available).

**Methods for objective 1 (to systematically collate and summarise the evidence; months 1-18, led by the pharmacist with support from the economist)**

*Design.* Structured collation, summarising and cross-referencing of clinical and economic data from selected guidelines with focused literature review where necessary.

*Data collection and analysis.* For each included guideline, we will initially identify and cross-reference guideline recommendations. For chronic treatment recommendations and other
recommendations where comorbidity is likely to be important, we will retrieve all referenced studies and relevant systematic reviews used to support the key pharmacological and non-pharmacological chronic treatment recommendations identified for examination by the GDG. Data will be systematically extracted using a structured data extraction form, and stored in database format to support objective 2.

(1) Cross-reference guideline recommendations. To allow explicit cross-referencing across guidelines, we will identify where there is synergy (recommendations are consistent or reinforce each other), inconsistency (recommendations do not agree, or there are potentially important interactions), or contradiction (recommendations contradict each other or if followed would lead to high-risk interactions). For each recommended chronic treatment, we will additionally identify important drug-drug and drug-condition interactions for commonly prescribed medicines and common conditions not explicitly considered in the included guidelines.

(2) Summarise estimates of benefit, harm and cost effectiveness using the evidence referenced by the guideline. For each recommendation for a treatment (a drug, a drug class, a non-pharmacological treatment), we will summarise estimates of absolute benefit and risk, likely time to benefit, absolute QALY gain and incremental cost per QALY. For each recommendation we will define key treatment benefits identified in the guidelines and estimate the absolute benefit of treatment for each outcome, using the guideline where these numbers are explicit, systematic reviews where available and the original reports of trials where not. For selected recommendations where the risk of harm is judged significant by the GDG, we will additionally estimate harms of treatment using trial and observational data, although data will often be limited. Estimates of absolute benefit and risk of treatment for key outcomes will be converted to numbers needed to treat and numbers needed to harm over a defined period. Estimates of the absolute QALY gain and incremental QALYs will be tabulated alongside the estimates of absolute costs and incremental costs for the intervention and comparator treatment within a recommendation.

(3) Systematically record the strength and generalisability of the evidence referenced by the guideline. Information relating to the quality of the clinical and economic evidence underlying guidelines, and the population studied will be systematically recorded with a summary of key data uncertainties, and tabulated alongside the summary of benefit, harm and cost effectiveness. The applicability of the evidence to the UK population of people with the condition will be examined, and to people with multimorbidity in particular (for example, in terms of trial inclusion and exclusion criteria23), and limitations in the evidence in terms of data quality, and the type and degree of uncertainty systematically recorded. Requirements for future research stated in existing guidelines will also be summarised.

(4) Combine collated data into a single table to allow comparison of guideline recommendations. Existing guidelines do not make it easy to compare relative benefits and harms of different treatments, but deciding what to prioritise is a key element of decision making in people with multiple conditions, or people overwhelmed by treatment burden. The GDG will be used to examine the potential usefulness of systematic and careful summaries of existing data, and how best to make it interpretable to clinicians and patients.

**Objective 1 outputs.** Systematic comparison across the three conditions studied of (i) the coherence of chronic treatment recommendations including when they are synergistic, inconsistent or incompatible; (ii) relative benefits and harms as estimated during the guideline development process, by existing systematic reviews, or in the original trials; and (iii) the strength and generalisability of the
underpinning evidence cited by the guidelines. As well as having value in its own right, this process will support the conduct of the objective 2 economic modelling for selected recommendations.

**Methods for objective 2 (to develop and evaluate exploratory modelling methods to compare multiple disease-based guideline recommendations; months 7-30, led by the economist supported by the pharmacist)**

Current NICE guideline development already uses decision analytic modelling methods to estimate the incremental costs and QALYs gained (or lost) by different treatment options. Existing models look at a defined intervention and comparator for a patient population with a single disease/condition. Generally, these studies assume an NHS perspective and aim to model the life-time costs and benefits of the intervention and comparator. The most commonly used decision analytic model structures used to estimate incremental costs and benefits are Markov models that are generally constructed to represent discrete health states for single conditions. Using these model structures means there is no systematic or robust way to consider the impact of treating a patient population with co-morbidities. To provide information relevant for decision makers allocating healthcare resources it is important to recognise that patients often have co-morbidities and account for this in the model structure and subsequent model input parameters. Patients with co-morbidities are likely to experience different benefits, harms and costs compared with people with a single condition. Current modelling approaches do not account for these differences. Therefore, this study aims to develop existing economic modelling methods to conduct exploratory analysis of the incremental costs, benefits and harms for treatment options in patient populations with multiple morbidities. These models will aim to recognise and quantify that the benefit and harms of treatment may be higher or lower, or life expectancy may be significantly reduced by the presence of other conditions.

**Design.** We aim to explore the feasibility of re-structuring existing models using adaptations informed by relevant literature and clinical expert opinion to represent the health states for co-morbidities and subsequent pathways of care that patients with (i) single conditions and then (ii) patients with co-morbidities will follow, with pathways simplified as necessary to make modelling feasible. We will focus analysis on key general problems in accounting for multimorbidity in guidelines that are likely to apply to many conditions. Examples include accounting for worse treatment outcomes in the presence of other morbidities (for example, worse physical and mental health outcomes in the presence of depression), and accounting for limited life expectancy when treatment benefit typically accrues over relatively long periods (preventive treatment in type 2 diabetes in the presence of life limiting left ventricular systolic dysfunction). The choice of guideline recommendations to model in detail will be made by the project Guideline Development Group informed by model and data availability.

**Data collection.** The required adaptations to model structures will be identified using a two-round classical Delphi process with 10-15 clinicians who have expertise in the clinical conditions being modelled. This process will focus on first of all defining the most suitable model type, which may or may not be a Markov model structure. Once the most appropriate model type is defined then the model will be structured to represent the conditions, treatments and care pathways under evaluation. For each selected treatment recommendation, we will then use systematic review methods to summarise the available published literature on how event rates and treatment benefit and harm vary with multimorbidity. For some outcomes such as mortality, we expect there to be reasonably good evidence available, but for others we envisage that the data required for modelling (e.g. resource use and utility data) will not be available. Therefore, we will use a structured expert elicitation approach, using mathematical aggregation methods to define parameter values and address current gaps in the
evidence base. Such elicitation methods allow the systematic capture of expert knowledge about uncertain quantities in terms of mean or median values, and also variation and distribution of parameters. We will use the expert knowledge of study GDG members, supplemented by topic experts where necessary to elicit unknown parameters for modelling (for example, the increase or reduction in benefit expected from the presence of other conditions). Facilitated elicitation will take place in GDG meetings (using SHELF software21), with structured briefing material sent to members beforehand including a summary of available published data. Supplementary elicitation exercises with topic experts will be conducted using the SHELF software on-line with telephone support from the study health economist. This process has worked well in previous studies to enable contact with geographically disperse expertise.

**Data analysis.** The base case analysis will take the perspective of the NHS and a lifetime horizon. An exploratory analysis will also explicitly consider the ‘time to event’ (ie when benefits are realised) within this time horizon. Because existing models do not allow time to be explicitly considered, adaptation will therefore be required of these starting model structures to allow an estimate of ‘time to event (benefit)’ to be explicitly modelled. We will identify, synthesise and analyse data to estimate the expected benefit and costs within each recommendation for selected interventions treating (i) single and (ii) multiple conditions. Similar methods are applicable to synthesise evidence of harm, although we expect data to be much sparser. Data will be summarised in terms of the incremental costs and benefits for each treatment-comparator. An extensive sensitivity analysis will be included to understand the type and degree of parameter (probabilistic sensitivity analysis) and structural (scenario analysis) uncertainty affecting resulting summary measures of incremental costs and benefits. To better understand the impact of reduced life expectancy among people with multimorbidity, we will examine the feasibility and applicability of the proposed model structures and outputs for estimating and applying a proposed framework for calculating the impact of the ‘pay-off’ time17 for treatments (the time required for cumulative benefits of treatment to outweigh cumulative hazards). The expected pay-off framework has previously been described for colorectal cancer screening and tight glycaemic control.26

**Objective 2 outputs.** The innovative outputs for this objective are the development of modelling methods to (i) account for multiple conditions and (ii) understanding the impact of considering expected time to benefit given predicted life expectancy. This exploratory analysis will generate summaries of expected benefits, costs and harms for intervention-comparators, which will be useful for expert consideration within NICE and GDGs.

**Contribution to collective research effort and research utilisation**

The study will contribute new knowledge on how to account for multiple morbidity in clinical guidelines, by assimilating and summarising multiple sources of evidence on benefits, harms and cost-effectiveness, and by the use of economic modelling to address key areas of uncertainty. Specifically, the study will create new knowledge in terms of the generalisability of trial findings and guideline recommendations to real populations including people with multimorbidity (objective 1), and methods for modelling benefit and cost for people with multimorbidity (objective 2). The findings will additionally have direct relevance to clinical guideline design and implementation in the UK and internationally. From a research perspective, we will disseminate findings via a comprehensive final report, presentations at academic conferences and articles in high-impact peer-reviewed journals. Dissemination to a policy and NHS audience to influence guideline design and implementation is equally important, and will be facilitated by the senior NICE staff co-applicants, and additional collaboration with the Scottish Intercollegiate Guidelines Network (SIGN) and NHS Evidence. We
will produce and disseminate short summaries for policymakers, managers and clinicians, and offer seminars to relevant policy stakeholders in NICE, SIGN, and the four UK health departments.

**Plan of investigation and timetable**

Sponsorship, ethical review, and R&D approvals will be organised prior to the study starting. Objective 1 will be delivered in months 1-18 led by the Dundee-based pharmacist and supported by the Manchester-based economist researchers. Objective 2 will be delivered in months 7-30 by the economist supported by the pharmacist.

**Approval by Ethics Committees**

Objective 1 will not require ethical review. Objective 2 will require ethical review, but we do not foresee any difficulty obtaining a favourable opinion since the research only involves professionals and members of the public in their professional role as GDG participants.

**Project management**

BG will have Chief Investigator responsibility for project progress and delivery, and will provide day to day supervision of the Dundee based pharmacist, supported by ST and CM. KP will have responsibility for supervision of the Manchester based economist, supported by MS. Ensuring close collaborative working between the three sites (Universities of Dundee and Manchester, and NICE in Manchester) will be critical, and we plan weekly teleconferences of the employed researchers involving relevant senior staff, plus 4-6 weekly teleconferences of the whole team with ~4 monthly face to face meetings over 2 days. We have budgeted for the pharmacist and economist to additionally meet between these whole team meetings on a regular basis. PA and TS will facilitate convening a Guideline Development Group on the NICE model to provide expert advice and to ensure that guideline development and implementation combines innovation with fidelity to current best practice in stakeholder involvement.

**Public Contributor / Public Involvement**

The NICE convened Guideline Development Group will be central to the conduct of the project and production of outputs, and will include public representatives recruited and reimbursed using standard NICE procedures. We expect the GDG to have 8-10 members in total, of whom 2-3 will be public representatives with expertise in the selected conditions, ideally drawn from public members of the Guideline Development Groups of the underlying NICE single disease guidelines. GDG members will be acknowledged in project outputs, and we will encourage GDG public and professional members to be part of writing groups for publications where appropriate and where they meet criteria for contributorship and authorship.

**Expertise**

The core project team is a strong collaboration between university academics (health services research, economics, guidelines development), NICE guideline development experts, and clinicians working within NHS (more detail is provided in section I of the main application form). The team has research expertise in multimorbidity (BG), prescribing quality and safety (BG, CM, KP), economic (KP, MS) and statistical (PA, BG) modelling, guidelines development (ST, PA, TS), data presentation and information design (BG, ST, PA, TS, CM), clinical expertise from the two main generalist medical disciplines (general practice and geriatrics – BG, TS, MW), and NHS guidelines development and implementation expertise (PA, TS). The academic-NHS collaboration proposed will ensure both methodological rigour and the alignment of the research to NHS needs. Moray Nairn (Programme Manager at the Scottish Intercollegiate Guidelines Network) and Andrew Fenton (Chief Information Officer, NHS Evidence) have additionally agreed to be collaborators, ensuring that the main UK
Guideline development and implementation organisations are actively involved. This will facilitate dissemination beyond conventional academic outputs and translation to implementation.

References