Incorporating multi-morbidity into clinical guidelines: a health economics perspective

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Abstract
Multiple morbidities is the norm rather than the exception, yet existing clinical guidelines are formulated for single conditions. Multiple morbidities can generate economies and diseconomies of scope because of their influence on both the costs and benefits of treatment. This paper aims to promote discussion on whether multi-morbidity can be accommodated within the current framework for providing clinical guidance and more broadly, the impact on methods for economic evaluation. We describe how health economics evidence has been used in clinical guidelines published by NICE, provide a broad thematic discussion on how the concept of multi-morbidity fits into the current single-disease paradigm, and discuss how health economic principles could be used in future guidelines when evidence for patients with multi-morbidity is likely to be poor and when decisions by guideline developers need to be made in a timely fashion.

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1. **Introduction**

Clinical practice guidelines (also called ‘clinical guidelines’) are a series of recommendations for the care of people by healthcare and other professionals. Clinical guidelines assess the clinical and cost effectiveness of treatments and ways of managing a particular condition and are based on the best available research evidence and expert consensus [1]. Policy-makers believe undesirable variations in care can be reduced and clinical outcomes improved through effective implementation of clinical guidelines into routine practice [2]. Alongside Technology Appraisals, The National Institute for Health and Care Excellence (NICE) is most well known both nationally and internationally for developing clinical guidelines. To date, NICE has developed 160 clinical guidelines on appropriate care of patients with different conditions for the NHS in England, Wales and Northern Ireland [3].

A key principle underpinning the work conducted by NICE is the requirement for health economics evidence, typically in the form of cost-effectiveness analysis, to be incorporated into decision-making [4]. For clinical guidelines, this explicit social value judgement requires that decision-makers must take into account evidence on the incremental costs and benefits of an intervention as well its possible effectiveness or harms [1]. The level of influence of cost-effectiveness analysis on the clinical guideline production process at NICE is unique amongst large guideline producing bodies and combined with its reputation for rigour and transparency, NICE is recognised as a world-leader in guideline methodology and development [2]. However, there is a growing recognition within the organisation [2], by guideline developers and by users that the current single-disease approach for creating guidelines is problematic [5]. As suffering from multiple diseases or ‘multi-morbidity’ [6] is the norm rather than the exception, there is a demand for guidance produced by NICE which accommodates for the complex needs of these populations [7]. Consequently, the health economics methods within clinical guideline methodology may also need to be re-considered in order to meet this new demand.

This paper is structured around three key objectives. After providing an overview of the NICE process used to develop clinical guidelines, the first objective is to describe how health economics evidence has been used in single-disease clinical guidelines published by NICE. This objective will be achieved by describing the key health economics processes that feed into the production of clinical guidelines and by the analysis of an exemplar guideline published by NICE in 2009 as a case study: “Chronic Heart Failure: The Management In
Primary and Secondary Care”. These guidelines provide a useful example of a single-disease
document designed for a population that is highly likely to have multiple morbidities [6]. The
second objective is to provide a broad thematic discussion on the purposes of clinical
guidelines including how guidelines integrate into different models of health care and how
the concept of multi-morbidity fits into the current single-disease paradigm. The third
objective is to discuss how health economic principles could be used in future guidelines
when evidence for patients with multi-morbidity is likely to be poor and when decisions by
guideline developers need to be made in a timely fashion. Overall, the primary purpose of the
paper is to promote discussion on whether the characteristics of multiple disease can be
accommodated within the current framework for providing clinical guidance by NICE and
more broadly the impact this has on methods for economic evaluation.

2. Health economics in current NICE guidelines

2.1 Stakeholders

The production of clinical guidelines by NICE follows a set of well-established processes that
are covered at length in what is labelled by NICE the ‘Guidelines Manual’. This publicly
available manual is published on the NICE website and undergoes periodic updates, with the
most recent version being published in November 2012. Similarly to Technology
Assessments (TA) and public health guidance, clinical guidelines topics are referred to NICE
from The Department of Health (DoH) and National Assembly for Wales. Once a referral has
been made, NICE commissions the guideline topic and nominates one of four National
Corroborating Centres (NCC) or the Internal Clinical Guidelines team (within NICE) who
take ownership of the production and publishing of the guideline. The decision making body
of guideline production is the Guideline Development Group which is composed of
healthcare and other professionals, both specialists in the topic and generalists, patients
and/or carers, and a “technical secretariat” (systematic reviewer, project manager, health
economist), provided by the NCC. The technical secretariat provides assistance to the GDG
members and presents clinical and health economic evidence to the GDG to aid evidence-
based decision-making.

2.2 Clinical Review Questions
The building blocks of a NICE clinical guideline are Clinical Review Questions (CRQ). CRQs describe key decision points in the patient care pathway that will be covered by the clinical guideline. Answers draw on the most robust clinical and cost-effectiveness evidence available. The CRQ is typically drafted using the PICO (population, intervention, comparator, outcome) format [1]. An example of a common arrangement for a CRQ for an intervention is: ‘what is the clinical and cost-effectiveness of drug A compared to drug B in patient group X in the treatment of condition Y’. This CRQ would be identified where there is uncertainty and variation in the decision point to offer drug A or B to patient group X in condition Y. The answer to this CRQ may form the basis of a recommendation and provide improved certainty at this particular decision point in the care pathway. Sometimes CRQs do not appear in this format when presented to the GDG, however the associated evidence search protocol (which is approved by the GDG) would explicitly define the CRQ in terms of the PICO.

In practice, approximately 15 to 20 CRQs are created per full-length clinical guideline. The CRQs are drafted during the scoping stage of guideline development process and are used to define the boundaries of what is to be covered in the final clinical guideline. The use of CRQs is carried through into the final ‘Full Guidelines’ document that is produced by the NCC after recommendations have been agreed and drafted by the GDG. The ‘NICE Guidelines’, often used by clinicians in their day-to-day practice, are a shortened version of the ‘Full Guideline’ and are edited in such a way as to be accessible. Therefore, the CRQs that underpinned the clinical guideline development are not always visible when viewing a NICE-version of a guideline

2.3 Planning

The need to produce health economics evidence is considered early in the scoping process through the use of an economic plan which is initially drafted by the health economist from the NCC who is part of the GDG as a member of the technical secretariat. The importance of prioritisation is recognised within the guideline manual as evidence on cost-effectiveness from the literature will rarely be of sufficient quality and relevance for decision-making for the NHS and numerous CRQs would ideally receive further analysis. The economic plan gives detail as to which CRQs have been identified as being high priority for de-novo, or new, economic analysis, as well as the quality of the current evidence base. NICE takes the view that developing new economic analysis to inform clinical guidelines derives from the
potential added value based on: (1) ‘importance’ which is a function of the population and the expected incremental costs and benefits [8]; and (2) the level of uncertainty in the current evidence base and the likelihood that new analysis will resolve this. If a CRQ is deemed to be important (judged using the criteria of either: being relevant to a large population or large incremental benefits versus costs) and further analysis is likely to reduce current uncertainty then de-novo modelling is likely to be prioritised. However, no formal analysis to understand the potential value of generating new evidence, such as Value of Information Analysis, is conducted at this stage. Instead, the GDG (acting on advice from the health economist) ultimately decides on which CRQs to study using a deliberative and qualitative process that usually occurs in one of the first GDG meetings.

2.4 De-novo economic analysis

Following the generation of the economic plan, the health economist will produce de-novo analysis in order to provide economic evidence to the decision making body for the particular CRQs which have been identified as being a high priority for further work. Health economic models tend to take the form of decision trees, Markov models or Discrete Event Simulation. The specific methods used to produce the de-novo analysis is described in the NICE ‘reference case’ (departures from the reference case requiring justification) as detailed in the methods for technology appraisal [8]. NICE uses a common reference case to ensure continuity between decisions made by Technology Appraisal committees and Guideline Development Groups. Consequently cost-effectiveness analysis is the preferred form of health economics evidence with the QALY as the preferred measure for health benefit.

2.5 Health economics in guidelines: decision-making and implementation

Ultimately, decisions on recommendations included in the clinical guideline are made as a collective view of the GDG reached during a deliberative process. The evidence on health economics (either from the literature or de-novo analysis) is presented within committee meetings alongside evidence on effectiveness, harms and risks. Once the evidence has been discussed and the uncertainty within the evidence has been understood, the wording for recommendations are drafted and then fine-tuned. Generally NICE uses informal consensus techniques and the use of more formal methods, such as multi-criteria decision analysis, are not currently used [1]. When health economic evidence for a particular CRQ is not available and the CRQ has not been prioritised for synthesis of health economic evidence by the health
economist, the GDG will make a qualitative judgement of the cost-effectiveness of a particular recommendation.

3. The use of economic evidence in clinical guidelines: a case study of chronic heart failure (CG108)

3.1 Background and methods

The use of economic evidence was explored using a case study of a published clinical guideline: chronic heart failure (CG108) [9]. This guideline was chosen because a clinical guideline on chronic heart failure is likely to be a high priority in terms of considering the implications of suggested treatment options for patients with multiple morbidities. A study published in The Lancet found that 93% of patients with coronary heart disease (CHD) have at least one other disease, whilst 15% have over 5 chronic diseases [6]. Chronic heart failure occurs when the heart is unable to sufficiently pump blood around the body to meet its needs. No single cardiac disorder accounts for heart failure; however, most heart failure is caused by coronary heart disease (CHD), with a third of heart failure in the UK being caused by hypertension.

Health economic evidence within the guideline was analysed by one researcher (AT) searching systematically through the ‘Full Guideline’, the associated evidence-tables, the appendices and the initial ‘economic plan’. All of these documents were publically available on the NICE website, with the exception of the economic plan which was requested from personal correspondence with NICE. Three categories for the incorporation of economic evidence were summarised: none; review of existing evidence; creation of a de novo model. If health economic evidence was used, either in new analysis or from the existing literature, then the primary evidence was screened to see if: (1) utilities were adjusted for co-morbidity or multi-morbidity; and (2) the underlying datasets (RCTs or longitudinal data) reported some measure of co-morbidity or multiple disease.

3.2 Results

The clinical guideline for chronic heart failure (CG108) was found to have 12 CRQs, of which, 4 related to diagnostic strategies and 8 were interventions. Table 1 summarises the key findings of this structured assessment of the clinical guideline. Appendix 1 contains further details on the CRQs and classifications.
Table 1: Level of health economics evidence identified in CG108 (chronic heart failure)

<table>
<thead>
<tr>
<th>CRQs</th>
<th>Total</th>
<th>Any health economics used?</th>
<th>De-novo economic analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Intervention</td>
<td>8</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

The economic plan identified three CRQs as being ‘high priority’. However, only one new health economic model was developed (CRQ: 4). This model was highly influential in the decision-making: sub-group analysis found the ‘monitoring’ method, the topic of the CRQ, to have differential cost-effectiveness in patients above 75 and below. Consequently, the recommendation drafted in the guideline was also stratified according to this sub-group.

There was an encouraging amount of health economics evidence used within the decision-making for clinical guideline CG108, with 11 out of the 12 CRQs including some aspect of cost-effectiveness evidence. This may in part be explained by NICE CG108 (2010) being a partial update of a previous guideline (NICE guideline 5, 2003), enabling previous be-spoke analysis developed by the NCC to be used in one CRQ (CRQ: 9) as well as the guideline including evidence from technology appraisals for two CRQs (1,2).

Despite evidence being used for virtually all CRQs, the applicability and quality varied. Some aspects of the health economics evidence for the CRQs came from studies which had been graded as being only partially applicable to the clinical guidelines or having potentially serious limitations as assessed by standardised applicability and quality-assessment checklists included in The Guidelines Manual (appendix G of the manual). None of the health economics studies explicitly considered populations with multiple morbidities although the underlying evidence sourced from RCTs for the de-novo analysis did include details on the characteristics of patients, including the percentages of patients with co-morbidities as well as sub-group analysis for older patients. However, in the de-novo model, mean population inputs were carried through and were not stratified according to levels of multiple morbidity.
4. **Discussion**

This discussion section will describe five key areas that emerged from the case study looking at how economic evidence had been included in a clinical guideline for chronic heart failure, which is a condition in which multiple morbidity is likely to be important due to the high prevalence of multiple conditions in patients with this disease.

4.1 **The single disease paradigm**

Underpinning the use of current disease-specific clinical guidance lies the predominance of a conceptual model, commonly labelled as the ‘biomedical’ model, which characterises a distinctive theory of what health and illness is [10]. In this framework, health is defined negatively; it is the absence or complete freedom from any disease. Where individuals present with illness, it is attributed to a *single* underlying pathology, the removal of which, will return the physical (or mental) loss of function back to normality. The framework has been the dominant paradigm of Western medicine for at least the last 100 hundred years and guides what medicine ought to be, how it is to be practised and consequently, how clinical guidance is structured [10, 11]. Economic evaluation, as a sub-discipline of health economics, has also evolved within the biomedical model of disease and thus shares many of its epidemiological methods for gathering evidence including a preference for probabilistic evidence sourced from systematic reviews, meta-analyses and RCTs as well as a focus on populations with a single index condition. Therefore, economic evaluations commonly address one particular physiological condition rather than a decision problem that involves a patient with multiple morbidities.

4.2 **Purpose of guidelines**

The purpose of evidence-based clinical guidelines is to link and further encourage the practice of medicine with evidence from clinical research, ultimately to lead to better quality of care for patients. To serve this purpose, guidelines have to present evidence in such a way so that they are relevant and usable to their target audience whilst still retaining the complexity of the underlying evidence-base. The purpose of health economics within guidelines is to ensure that recommendations, made in the context of a constrained health care service, make allowances for the opportunity cost and provide guidance on how scarce healthcare resources can be used most effectively. If this is not the case, then ‘health’, as
encapsulated by the estimates of QALYs gained or lost as a result of the clinical recommendations in the NICE guidelines, will be displaced elsewhere within the health care system. When robust health economics evidence is incorporated into the production of clinical guidelines, it is likely that resources are being efficiently used and that health is being maximised. This is viewed as a good thing in itself as it represents the best use of NHS resources, given current knowledge.

4.3 Defining and understanding multiple morbidity

Against the backdrop of disease-specific guidance and a disease specific research framework, is the rise in the prevalence of patients with multiple morbidities. Instead of being the exception, this is rapidly becoming the norm [12, 13].

Two terms are used predominantly to define patients with multiple concurrent diseases: ‘multi-morbidity’ and ‘co-morbidity’. Confusion still exists within the literature about the appropriateness of the terminology and when and where the terms should be used [14]. Often this results in the terms being used synonymously, although it has been argued that they provide different conceptual frameworks for the notion of multiple disease [15]. The seminal definition for co-morbidity has been described as “any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study” [15]. This definition seems to be firmly rooted in a biomedical perspective of disease. No such consensus for a definition has yet emerged for multi-morbidity [14] but it is increasingly being defined (and recommended as such [16]) as the co-existence of multiple diseases without an index diagnosis [15]. By not specifying an index condition, multi-morbidity can therefore be viewed as being outside of the biomedical model – a concept with different philosophical foundations. This is in contrast to the term co-morbidity, which assumes the presence of an identified index condition (eg. Diabetes) together with another disease (eg. Depression) that is in addition to the index condition.

4.4 Why multi-morbidity in guidelines matter

Whichever concept for multiple diseases or conditions is ultimately favoured, multiple morbidities that are not accounted for in economic models are likely to be detrimental to the purpose of clinical guidelines and the validity of health economics evidence within
Work in progress Multi-morbidity in clinical guidelines.

guidelines. From a clinical perspective, a single-disease guideline, making recommendations that take no account of the cumulative burden from other diseases, is likely to be of limited use. Such documents, if followed rigidly, can create problems of polypharmacy (drug-to-drug interactions and drug-to-disease interactions) and can create treatment regimens that are overly burdensome leading to potential adherence problems [17, 18]. Evidence based recommendations incorporated within guidance is useful only insomuch as the evidence relates to the populations that is seen in consultations day-to-day, which is commonly patients with multiple diseases [19]. By not accounting for these patients, guidelines will lack usefulness and recommendations (rightly or wrongly) will not be adhered to. Therefore, in light of formal incentive mechanisms being increasingly implemented (‘quality standards’, QOF, COF), which use clinical guidance as the evidence base [20], policy-makers need to be increasingly sensitive to multiple diseases.

For health economics, significant co-morbidity or multi-morbidity within a population could undermine the validity of statements on whether interventions are likely to be cost-effective or not. For example, on the cost side there could be economies of scale or scope when treating diseases that are concordant (similar pathogenesis) therefore permitting for overlaps in management or treatment. Evidence for this hypothesis has been found on a macro scale for primary care costs in England with a recent observational study finding that hypertension associated with other cardio-vascular diseases was ‘cost-limiting’ [32]. On the other hand, discordant conditions requiring different management or treatments can lead to increased costs, with the same study finding depression associated with other conditions to be ‘cost-increasing’. On the benefit side, it is known that patients with increasingly more diseases generally have lower HRQoL but this relationship is far from simple with the impact varying dependent on the nature and combination of disease. Decision-analytic models which overlook these properties are unlikely to give representative estimates for the true costs and benefits for patients with multiple morbidities. Therefore, even if analysis on cost-effectiveness is correct on the average population, if certain sub-groups with multiple diseases have differential cost-effectiveness estimates then there is potential for resources to be used more efficiently by stratifying recommendations accordingly [21].

4.5 The problem of evidence
NICE, like other guideline developers, have a preference for certain types of evidence representing the validity and authority of the clinical research. The gold standard of evidence in this hierarchy currently remains the randomised controlled trial, which, if properly conducted, provides strong inferences on incremental outcomes, such as cost and QALYs, of interventions within trial populations. However, historically, older patients have been systematically excluded from RCTs [22, 23] whilst patients with co-morbidities are also highly likely to be excluded [24]. Therefore, any movement beyond single-disease clinical guidelines is likely to be constrained by a lack of available evidence. Given this constraint, it is not surprising that current guidelines, rooted conceptually within a single-disease paradigm, fail to adequately accommodate for co-morbidities [17, 18], let alone the more complex concept of multi-morbidity.

In order to tackle the binding constraint of a lack of evidence, NICE, like other guideline developers, may have to adjust its preference for RCTs and sacrifice internal validity in favour of evidence which is available and generalisable to populations with multiple diseases. Observational data where outcomes for patients with multiple conditions can be captured, already provide evidence for life expectancy in decision-analytic models and so this type of evidence could also be extended for outcomes such as HRQoL and health care resource use. Where HRQoL data for populations with multiple morbidities cannot be found, then health state utility values can be obtained utilising the methods in an emerging literature seeking to combine utility values from single-disease populations [33]. For the longer-term however, an emphasis for research must be to include older patients and patients with multiple diseases into clinical trials to allow future guidelines access to important and robust data on the outcomes of interest.

5 The future of clinical guidelines?

The extent to which health economics evidence can influence future guidelines accommodating multiple conditions will ultimately be based on how these future guidelines would be organised in order to aid clinical decision-making. Many potential models could be adopted for future guidelines; however, the distinction between co-morbidity (having an index) and multi-morbidity (without an index) is a useful reference point in which to base thoughts about the potential structure that future guidelines could take. The following section
will briefly introduce some potential approaches for the inclusion of multi-morbidity in guidelines.

### 5.1 Including multi-morbidity?

One potential multi-morbidity approach would be to create guidelines based around clusters of disease that have physiological associations and which are commonly seen in clinical practice. This would be an ambitious departure from the current single-disease paradigm and it would require a classification system to prioritise and select diseases which would appear together within a guideline. Within such a document, it would be feasible for the GDG to create a CRQ that defined ‘condition Y’ as multiple conditions without a specific index. New health economics evidence would then be required to answer questions on cost-effectiveness in populations with multiple conditions before recommendations could be made on the basis of being cost-effective.

A major limitation of this approach from a clinical perspective would be the numerous separate guidelines that would need to be issued and whether this would be useful for day-to-day decision-making. A further significant problem, from a health economics perspective, is the impact of breaking away from the single-disease paradigm on the available evidence base. Such a complex approach is unlikely to be catered for currently in the evidence base and so the required inputs for decision-analytic models are likely to be difficult to source. Moreover, it is unknown how interactions between multiple diseases would be incorporated into model pathways and whether such models, which are simplifications of reality, would be able to incorporate such complexity whilst actually reducing uncertainty in the decision-problem – ultimately a binary decision on whether an intervention is likely to be cost-effective or not and consequently whether a recommendation should be made.

An immediate problem faced by guideline producers at NICE with a CRQ within a multi-morbidity format, would be a preliminary evidence search that fails to yield any useful trial data on that particular defined population with all defined conditions. Due to a lack of evidence, some if not all of the input parameters would then be required to be modelled (or require expert elicitation using robust methods, for example see [25]) which in turn increases the uncertainty associated with the model inputs. As the choice to create de-novo analysis for each CRQ is fundamentally constrained by time and resources, the likely failure of any
potential model to reduce uncertainty may lead to the question being assigned low priority within the economic plan. In response, the format of the original CRQ may revert back to a more conservative single-disease population dragging the guideline back to being single-disease focused, or alternatively, decisions will be made without any robust cost-effectiveness evidence.

Due to the complexity of interacting diseases, a potential longer-term solution would be to move away from decision-analytic models. Instead, a trial-based approach could be adopted for specific populations with multi-morbidity, which have been identified as being high priority. Whilst trial-based RCTs evaluations are argued to provide the most robust evidence for primary data on health outcomes and resource-use, the use of model-based evaluations is preferred by NICE. Decision-analytic models can incorporate all the available evidence from data sources other than RCTs (e.g. longitudinal data), can capture an appropriate time horizon for the follow-up and can include all relevant comparators [26]. However, decision-analytic models require the structuring of model pathways which, for multiple diseases, are likely to become extremely complex. Trial-based evaluations do not require the specification of pathways and could therefore avoid the problems of non-linearity in the way that diseases interact. Clearly this approach would only be available on a limited basis and is not feasible for current decision-making within clinical guidelines.

5.2 Use co-morbidity, not multiple morbidity?

A less ambitious approach would be to modify current guidelines to more explicitly highlight common co-morbidities whilst retaining an overall guideline topic based around an index disease. This approach would therefore remain within the single-disease paradigm meaning that continuity would be maintained with the other work conducted by NICE, such as HTA. Again, it would be entirely feasible for GDG within the NICE process to create a CRQ investigating the impact of an intervention on ‘condition Y’ as the index and then list potential co-morbidities which are of interest for further analysis.

Just as the analysis of CG108 revealed that cost-effectiveness analysis resulted in different findings for different age sub-groups, a stratified approach to a single-disease guideline would be able to assess the cost-effectiveness within individuals with one or more co-
morbidities in sensitivity analysis. Where there are differential changes due to co-morbidity in for example absolute risk, then this could lead to differential cost-effectiveness results and ultimately different recommendations for different populations who share those observable characteristics. For this approach to work, strong assumptions would have to be made regarding the impact of co-morbidities on pathways of care as well as the timing of the onset of the co-morbidity in relation to the index condition. At the most simple level, a co-morbidity approach would adjust HRQoL, and as a consequence QALYs, for patients with multiple diseases whilst retaining model structures and costs of the original disease-specific model.

5.3 Generic ex-post adjustment

Another approach would be to produce general adjustment factors to the incremental costs and benefits for multiple morbidity, which could be applied retrospectively to current models. Underpinning current models, are assumptions about discounted quality-adjusted life expectancy for treated patients which could be lower for patients with multiple morbidities. Also, inherent are figures on costs, which might be lower or higher for patients with multiple morbidity because of economies or diseconomies of scope and scale. Rather than investigating these factors for each possible morbidity combination, it might be possible to produce general adjustment factors for the costs and benefits. This approach would ignore the effects of multiple morbidities on model pathways. However, by basing the adjustment factor on the number, type (e.g. whether the co-morbidity is pathophysiologically similar) and severity of co-existing conditions, a generic approach may be a workable simplification to a complex problem.

5.4 Patient-centred care

Patient-centred care has no common definition but it is associated with an approach to medicine which considers the needs of patients as a whole and not just the underlying pathologies or disease [27]. This approach to care, which has its roots in a bio-psychosocial perspective [28], recognises that health is inherently complex, a function of many interdependent factors which can only be properly understood by focusing on ‘the patient’s total experience of illness’ [27, 29]. Appropriate treatment and management can be chosen
through a doctor-patient relationship which integrates the preferences of the patient, the social context and the psychological impact of treatment into a tailored package of care.

It has recently been argued that the incorporation of multiple diseases in clinical guidance is counter-productive and that more emphasis should be placed on patient-centredness, patient-preferences and integrated care rather than increasing the numbers of clinical guidelines to cover all the possible permutations of disease [30]. This argument is rooted in a more fundamental question as to whether medicine is an art or a science [31]. Guidance provides scientific evidence on populations and the clinical art is applying it to the individual given their history, characteristics and preferences. The use of sub-group analysis can swing the pendulum further towards providing evidence-based individual recommendations. However, individualised evidence-based care can never be fully realised so patient-centred care and patient preferences remain a vital counter-point for the constant need for recommendations based on evidence.

How health economics should influence this ‘pendulum’ is up for debate. What is apparent however, is that current theories underlying economic evaluation would suggest that a failure to stratify recommendations, when cost-effectiveness varies among groups, will ultimately lead to a displacement of health that is not accounted for in single disease analysis [21]. Therefore patients with multiple diseases in the form of co-morbidities need to be explicitly considered when recommendations are made in clinical guidelines. This will require the development of further methods and further evidence for these populations if stratified cost-effectiveness evidence can be presented to guideline decision makers. However, the boundaries of knowledge, the appropriate medium to convey knowledge and the incremental cost of procuring further knowledge, must also be given due consideration.

6. Concluding remarks

This preliminary discussion paper has introduced a relatively un-explored concept about how evidence is used in current single disease guidelines to prompt a discussion on the principles to be considered if guidelines are to accommodate multiple morbidities. An initial screen of an exemplar clinical guideline for chronic heart failure (CG108) found that a substantial quantity of health economics evidence is being used in this single disease guideline.
However, decision-making based on health economics evidence was constrained by an evidence base that was not always appropriate and a lack of time for new analysis to be produced. Due to the nature of the way research has been historically conducted, any new guidance, which incorporates multiple morbidities and health economic evidence, is even more likely to be hampered by a lack of evidence and the simultaneous need to produce new analysis, whilst constrained by time.

Some commentators have argued from a clinical perspective that guidance should not be changed to incorporate multi-morbidity and should stay as they are – in a single-disease paradigm – but instead that patient-centred care should be further encouraged. For NICE, the role of cost-effectiveness is to promote an efficient use of resources within the NHS and to maximise health. Ignoring the impact of multiple disease on clinical guidance, when it is likely to influence cost-effectiveness, is therefore misplaced irrespective of the merits of patient-centredness in a clinical context. Therefore, bodies such as NICE may need to reconsider the preference for certain types of evidence whilst in the longer-term, encouraging the incorporation of patients with multiple diseases within clinical trials in order to provide improved evidence on cost-effectiveness. For the health economics in clinical guidance, a key decision will need to be made as to whether multi-morbidity requires a paradigm shift in the way that economic evaluation is conducted or whether current methods, such as sub-group analysis, can accommodate such a complex problem.

7. **Suggested points for discussion**

This is work in progress and we would like to suggest some starting points for discussion at the meeting:

- Would it be useful to extend the analysis of CG108 to other clinical guidelines and would this then be suitable for a publication that describes the current state of play in how economic evidence is used to develop clinical guidelines?

- Should economic models take account of multiple morbidity or is it just ‘too difficult’?

- How could economic models take account of multiple morbidity?

- Are there any special equity implications for stratifying medicine by co-morbidities/multi-morbidity over and above those considered by NICE already?
8. References


## Appendix 1: Clinical review questions and quality of health economic evidence

<table>
<thead>
<tr>
<th>CRQ ID</th>
<th>Type</th>
<th>Question</th>
<th>Evidence found (1)</th>
<th>Evidence found (2)</th>
<th>Relevance (1)</th>
<th>Quality (1)</th>
<th>Relevance (2)</th>
<th>Quality (2)</th>
<th>Co-morbidity in model</th>
<th>Co-morbidity reported in evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>108-01</td>
<td>Diagnostic</td>
<td>What is the diagnostic accuracy of a collection of symptoms and signs, including any scoring systems vs gold standard in the diagnosis of heart failure?</td>
<td>Previous HTA submission</td>
<td>Nil</td>
<td>Directly applicable</td>
<td>Minor limitations</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>108-02</td>
<td>Diagnostic</td>
<td>What is the accuracy of natriuretic peptides v gold standard in the diagnosis of heart failure?</td>
<td>Previous HTA submission</td>
<td>Nil</td>
<td>Directly applicable</td>
<td>Minor limitations</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>108-03</td>
<td>Diagnostic</td>
<td>What is the accuracy of echocardiography v natriuretic peptides in the diagnosis of diastolic dysfunction?</td>
<td>Nil</td>
<td>Nil</td>
<td>N/A</td>
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<tr>
<td>108-04</td>
<td>Diagnostic</td>
<td>Does serial BNP monitoring (guided therapy) improve outcome compared to standard care in adults with chronic heart failure?</td>
<td>De-novo</td>
<td>Lit</td>
<td>N/A</td>
<td>N/A</td>
<td>Partially applicable</td>
<td>Potentially serious limitations</td>
<td>No</td>
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</tr>
<tr>
<td>108-05</td>
<td>Intervention</td>
<td>What is the efficacy and safety of ACE inhibitors in people with heart failure and preserved left ventricular ejection fraction?</td>
<td>Lit</td>
<td>Nil</td>
<td>Minor Limitations</td>
<td>Directly Applicable</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
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<tr>
<td>108-06</td>
<td>Intervention</td>
<td>What is the efficacy and safety of using an aldosterone antagonist in addition to optimal medical management compared to placebo plus optimal medical management in adults with chronic heart failure?</td>
<td>Lit</td>
<td>Lit</td>
<td>Directly applicable</td>
<td>Potentially serious limitations</td>
<td>Partially applicable</td>
<td>Potentially serious limitations</td>
<td>No</td>
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<tr>
<td>108-07</td>
<td>Intervention</td>
<td>What is the efficacy and safety of angiotensin-II receptor antagonists (ARBS) in comparison to placebo in the medical management of adults with heart failure?</td>
<td>Lit</td>
<td>Nil</td>
<td>Directly applicable</td>
<td>Potentially serious limitations</td>
<td>N/A</td>
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<tr>
<td>108-08</td>
<td>Intervention</td>
<td>What is the efficacy and safety of a) angiotensin-II receptor antagonists (ARBs) plus an Angiotensin Converting Enzyme Inhibitor (ACEI) in comparison to ACE inhibitor plus placebo b) ARBs + ACEI + BB vs placebo + ACEI + BB in the medical management of ad</td>
<td>Lit</td>
<td>Nil</td>
<td>Directly applicable</td>
<td>Potentially serious limitations</td>
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<tr>
<td>108-09</td>
<td>Intervention</td>
<td>What is the efficacy and safety of beta blockers in comparison to placebo, optimal medical management or other beta blockers in people with chronic heart failure?</td>
<td>Lit</td>
<td>2003 Guideline evidence</td>
<td>Directly applicable</td>
<td>Minor limitations</td>
<td>N/A</td>
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<tr>
<td>108-10</td>
<td>Intervention</td>
<td>What is the efficacy and safety of isosorbide/hydralazine in comparison to a) placebo b) ACE inhibitor, c) placebo + optimal medical management in the medical management of adults with heart failure?</td>
<td>Lit</td>
<td>Nil</td>
<td>Partially applicable</td>
<td>Minor limitations</td>
<td>N/A</td>
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<tr>
<td>108-11</td>
<td>Intervention</td>
<td>What is the efficacy and safety of patient telemonitoring in comparison to outpatient monitoring for adults with chronic heart failure?</td>
<td>Lit</td>
<td>Lit</td>
<td>Directly applicable</td>
<td>Minor limitations</td>
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<td>Very serious limitations</td>
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<td>108-12</td>
<td>Intervention</td>
<td>What is the safety and efficacy of exercise based cardiac rehabilitation in adults with chronic heart failure?</td>
<td>Lit</td>
<td>Nil</td>
<td>Partially applicable</td>
<td>Potentially serious limitations</td>
<td>N/A</td>
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1 Clinical review question.